

Coming of age with Li-Fraumeni syndrome: perspectives of young people and health professionals

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This dissertation is submitted in total fulfilment for the degree of Doctor of Philosophy

Declaration

This is to certify that:

- The thesis comprises only my original work towards the Ph.D. except where indicated in the Preface;
- Due acknowledgement has been made in the text to all other material used; and
- The thesis is fewer than 100,000 words in length, exclusive of tables, figures and bibliographies.

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Abstract

This thesis is situated in the discourse of risk that defines our technology-driven modern society, wherein one's health is constructed as a personal and moral responsibility. A key contributor to the individualisation of risk in modern medicine is genomic technology. As genomics becomes progressively normalised in mainstream society, individuals of younger and younger ages are seeking to learn of their genetic risk of disease, including cancer. Young people occupy a formative and transitional life stage with complex processes of human development, making them a unique population for which genetic services are currently ill-equipped to serve appropriately. This research contributes to a new field of genetic counselling research that aims to explore and meet the distinctive developmental needs of young people with genetic disease.

This thesis comprises of three inter-related studies that explore the psychosocial implications of living with a devastating, early onset inherited cancer condition, Li-Fraumeni syndrome (LFS), from the perspectives of young people and health professionals in Australasia. Informed by a pragmatic-critical realist stance, this thesis uses a mixed-method approach divided into a qualitative and quantitative phase. The qualitative phase consists of two studies, the first is a systematic review and thematic synthesis of 39 studies investigating how young people experience inherited disease with similar implications to LFS. The second and principal study of this research is an interpretive description of how young people experience LFS in their daily lives. To develop findings, I conducted interviews with 30 adolescents and young adults (aged 15-39 years) with, or at 50% risk of, a pathogenic germline mutation in *TP53* from across Australia, and used reflexive thematic analysis. The quantitative phase consists of a survey of 43 Australasian health professionals who care for young people with LFS to document their current practices and how they meet the developmental needs of this population.

The first key finding is that experiences of cancer, either familial or personal, strongly influence how young people make sense and meaning of LFS, how they consider genetic testing, and their perceptions of cancer risk and mortality. The nature of LFS in terms of its high penetrance, early onset, and varied phenotype meant young people's experiences were unique in oncology and genetic settings and require in-depth exploration during genetic counselling. The second key finding was that young people's growing autonomy from family complicated the process of genetic testing, which was recognised by health professionals who worked to foster their autonomous decision-

making. Genetic testing and whole-body cancer risk management represented instrumental actions of control for young people to mitigate their cancer risk from LFS, a perspective shared and promoted by health professionals. Intensive risk management and risk-reducing surgery, however, was emotionally and logistically burdensome for some young people, constructing the body as a material object be scrutinised in great detail by health professionals and blurring boundaries between self and body.

The third key finding was that young people felt strongly about preventing the passage of their LFS- causing genetic variant to the next generation, reporting that pre-implantation genetic diagnosis was their preferred method for having a 'healthy' biological family. Few had reached a life stage, however, where they appreciated the ethical, financial and logistical burdens of this technology, and many deferred reproductive decision-making until they were 'ready'.

This research argues that young people with inherited disease have unique psychosocial and clinical needs that are directly tied to the formative developmental tasks of their life stage. They require specialist youth-friendly counselling that considers and appreciates their developmental needs both during genetic testing and beyond. Youth-friendly genetic counselling must therefore be longitudinal, incorporating psychosocial check-ups as a key clinical interaction. Further, youth-friendly models of care promote the distinct value of genetic counsellors in managing rare and complex inherited conditions. As the mainstreaming of genetic services begins to outsource tasks of genetic education and pre-test counselling, the genetic counselling profession must make better use of their psychosocial counselling skills to serve high-needs populations. In this context, young people stand out as a key focus.

Finally, this research argues that attending genetic counselling exposes young people to a discourse of risk bounded by an ethos of responsibility. Undergoing genetic testing, subjecting their bodies to intensive surveillance and risk-reducing surgery, and having a family with reproductive technology all stand out as the 'right thing' to do when living with genetic risk of disease. Yet, each presented complex psychosocial implications for young people that were intrinsically linked to the broader effects of our modern risk society defined by Beck (1992) and Giddens (1991). Young people's decision-making and preferences during this developmentally labile life stage therefore need to be interpreted in relation to normative societal pressures that dictate expected behaviour around risk.

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[Redacted]

To the young people and health professionals who participated in this research, thank you. You have taught me so much and your contributions were invaluable to this research.

Preface

For the duration of my candidature I was bestowed an Australian Government Research Training Program Scholarship, formerly a Melbourne Research Scholarship. During my Ph.D., I successfully published three chapters (Chapter 6, 7 and 11) in peer-reviewed journals. As per the University of Melbourne guidelines and for copyright purposes, they are presented verbatim in this thesis as the author-accepted versions. I also had the opportunity to present my research at several national and international conferences (Appendix 2). The following is a description of the publication status of Chapters 6, 7, and 11. As multi-authored publications, each description includes the contributions of all persons involved.

Chapter 6: A systematic review of how young people live with inherited disease: What can we learn for Li-Fraumeni syndrome?

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R. Forbes Shepherd designed the search protocol; retrieved and assessed all included literature; extracted and analysed relevant data, and wrote the manuscript. He developed all tables and figures. A. Lewis co-coded extracted data and contributed to snowballing additional literature. L. E. Forrest, A. Werner-Lin, L. A. Keogh, and M. B. Delatycki made substantial contributions to the design of the work and interpretation of data, and drafting or critically revising the manuscript for important intellectual content.

Chapter 7: 'I need to know if I'm going to die young': Adolescent and young Adult experiences of genetic testing for Li-Fraumeni syndrome

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R. Forbes Shepherd was involved in all stages of this work and manuscript preparation. He was the primary writer and developed all figures and tables. L. E. Forrest, A. Werner-Lin, L. A. Keogh, and M. B. Delatycki made substantial contributions to the design of the

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R. Forbes Shepherd was involved in all stages of this work and manuscript preparation. He was the primary writer and developed all figures and tables. L. E. Forrest, A. Werner-Lin, L. A. Keogh, and M. B. Delatycki made substantial contributions to the design of the work and interpretation of data, and drafting or critically revising the manuscript for important intellectual content.

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List of abbreviations and acronyms

AYA – adolescent and young adult (used interchangeably with ‘young people’)

LFS – Li-Fraumeni syndrome

TP53 – tumour suppressor gene *TP53*

PGT – predictive genetic testing

DGT – diagnostic genetic testing

TP53+ve – denotes an individual who has tested positive for a pathogenic germline mutation in *TP53*

TP53-ve – denotes an individual who has tested negative for a pathogenic germline mutation in *TP53*

WBMRI – whole-body magnetic resonance imaging

PMCC – Peter MacCallum Cancer Centre

FCC – familial cancer centre

CGS – clinical genetics service

GHP – genetic health professional

OHP – oncology health professional

HBOC – hereditary breast and ovarian cancer

ID – interpretive description

TA – thematic analysis

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1 Introduction

Extraordinary developments in genomic technology over the past decade have made genomics an increasingly integral part of clinical practice. While the full potential of genomics is far from being met, areas where transformative applications have been made include oncology and genetic disease diagnostics (i.e., genomic medicine) (Cunha 2017). In oncology, the prevention, diagnosis and treatment of cancer are now increasingly guided by one's genetic make-up and the adoption of comprehensive genome sequencing has led to a steady increase in the number of individuals identified with a genetic predisposition to cancer (Mattick et al. 2014).

The predictive nature of genetic information means individuals with a high genetic risk of cancer can avail themselves of life-saving and cost-effective cancer prevention measures, reducing cancer burden on their family unit and the health system more broadly. While genetic information has undeniable diagnostic and predictive power in medical terms, it also possesses significant psychosocial, ethical, relational, and reproductive implications. The most distinctive feature of genetic information that contributes to these implications is its hereditary nature; testing one family member for a genetic disease has implications for the whole family unit, including both close and distant biological relatives. Helping individuals and families understand, make meaning and adapt to their genetic risk of disease is a critical aspect to genomic medicine and since the 1990s, the undisputed domain of genetic counselling (Resta et al. 2006).

Genetic counselling as a discipline holds a remarkable position both as a clinical profession and as a field of research. The role of a modern clinical genetic counsellor is highly varied, but at its core involves working in the area of heritable disorders and related genetic testing, and translating genetic knowledge into the everyday lives of

individuals and families impacted by them (Abacan et al. 2019). This core task requires clinical genetic counsellors to have one foot in the fields of counselling, psychology, and social sciences, and the other in the fields of medicine and population health. This blended clinical role—encompassing psychosocial and biomedical perspectives—and the myriad issues that arise from introducing rapidly developing genetic technology into the lives of individuals and communities at genetic risk, forms the basis of genetic counselling research.

There are four broad fields of genetic counselling research: 1) genetic counselling practice, processes and outcomes; 2) genetic risk assessment; 3) public health and policy, and genetic service delivery; and 4) the ethical, legal, psychological, social implications of genetic technology, medicine, and information. This thesis examines a particular clinical problem that corresponds to the first and last fields of research. It explores the experiences of young people from families with a devastating, early onset inherited cancer condition—Li-Fraumeni syndrome (LFS)—and how health professionals care for them.

1.1 Defining the problem

To date, genetic counselling research focussing on young people has been limited (Godino et al. 2016; McGill, Wakefield, Vetsch, Barlow-Stewart, et al. 2019; Forbes Shepherd et al. 2018). Young people, defined as adolescents and young adults (AYAs) aged 15-39 years, are a unique population in healthcare (AYA Oncology Progress Review Group 2006; JAYAO 2011).¹ They are distinct because they occupy a transitional and formative life stage characterised by complex processes of human development. At the beginning of adolescence, young people experience rapid bodily changes during puberty, and by the end of young adulthood, many will have transitioned into normative social roles of adulthood: e.g., lifelong relationships, parenthood, and long-term employment (Sawyer et al. 2012). The gulf between the primary concerns of adolescence compared to those of emerging and young adulthood underscores the drastic changes that young people undergo during this period. Contending with these complex developmental changes is challenging for any young person, but is especially difficult to navigate for

¹ Although noticeably broad in age range, I have adopted this definition to be consistent with that endorsed by the National Cancer Institute (USA) and the presiding journal for AYA oncology.

young people affected by serious illness or disease (e.g., inherited cancer) (Sawyer et al. 2016; World Health Organisation 2003).

The increasing socialisation of genomics in public discourses (Patch and Middleton 2019; Metcalfe et al. 2019) means individuals of younger ages are making use of direct-to-consumer or health professional-recommended testing to clarify their genetic risk of disease (Savard et al. 2019). The rising numbers of young people attending genetic services poses two distinct, but interrelated problems that I will explore in this thesis. First, the evidence base describing the clinical and psychosocial needs of young people with genetic disease is only in the early stages of development (Godino et al. 2016; McGill, Wakefield, Vetsch, Barlow-Stewart, et al. 2019; Forbes Shepherd et al. 2018). Much of the research to date has focussed on the implications of adult onset conditions for young people, which are biologically and psychosocially dissimilar to early onset conditions like LFS, which have direct implications for the AYA years. As a result, robust evidence-based genetic counselling practices for young people with genetic risk of disease are lacking.

Second, the genetic counselling workforce has no formalised way to deliver ‘youth-friendly care’ (Sawyer et al. 2016; World Health Organisation 2003): i.e., genetic counselling that is orientated to the developmental tasks of young people’s life stage (Young et al. 2019; Sawyer et al. 2016; Tylee et al. 2007; Sawyer et al. 2012). While youth-friendly practices have become the norm in many fields (e.g., oncology, psychology, and adolescent medicine), how genetic counsellors meet the challenges of developmentally appropriate care in their practice remains relatively undocumented (Werner-Lin et al. 2015; Tse et al. 2013; Gaff, Lynch, and Spencer 2006). As a result, young people remain a high-needs and critically underserved population in genetic medicine and genetic counselling (Young et al. 2019; Duncan and Young 2013).

1.1.1 Aim and scope of the thesis

To continue building the evidence base of how young people experience inherited disease, and to better understand how genetic counsellors contend with the developmental needs of young people, the overarching aim of this thesis is:

- To explore the psychosocial implications of living with Li-Fraumeni syndrome for adolescents and young adults, and how they are cared for by health professionals.

To achieve this overarching aim, this thesis is divided into two phases: the first focusses on the experiences of young people from families with LFS, and the second on how they

are cared for by the genetic and oncology workforce in Australasia. There are three additional sub-aims to this overarching goal, which I outline and justify in Chapter 2 (refer to page 42 for a summary).

1.2 Significance of this thesis

By addressing the overarching aim of this research, this thesis makes a significant contribution to the field of genetic counselling in four different capacities. Firstly, this is the first study internationally to take an in-depth and comprehensive focus on the experiences of young people from families with LFS. It provides world-first knowledge of how young people interpret and make meaning of LFS, and how they navigate genetic testing, risk management, and reproductive decision-making. One intended outcome of this thesis is that, in collaboration with organisations like the Li-Fraumeni Syndrome Association, these findings will lay the groundwork for the establishment youth-specific support programs among the international LFS community. More generally, these findings contribute new knowledge to our understanding of how young people live with early onset inherited disease, and are transferrable to research addressing the psychosocial challenges of other complex, early onset conditions for which there is little empirical evidence.

Secondly, by providing an evidence base for the development of youth-friendly approaches to genetic counselling, this thesis helps to address the practical issues faced by genetic counsellors internationally who work with young patients. Specifically, this thesis adds an appreciation for the intersection of developmental and illness trajectories for young people with inherited disease. As the genetic counselling workforce moves to meet the challenges of working with younger patients, this research will provide a starting point from which to improve on. Thirdly, by producing a snapshot of LFS-related care in Australasia, this thesis provides important insight and evidence of oncology and genetic health professional practice when caring for this population. This research will help to inform Australasian health professional practice of LFS and be of use to other regions and countries internationally coming to grips with how best to manage complex inherited cancer syndromes.

Lastly, this research contributes to broader discourses of health sociology by framing the experiences of young people in this study as the bi-products of how we construct and live with risk in late modernity. This thesis illustrates that the risk society defined by Giddens (1991) and Beck (1992) is a key concept for understanding the impact

of genomics on the daily lives of young people with inherited disease, both now and into the future.

1.3 Overview of this thesis

This thesis consists of 13 chapters divided into three main parts. In Part 1 (Chapters 2-5), I situate the thesis within current literature and establish the research design and methodology. In Chapter 2, I discuss and critically appraise relevant literature to set the scene for the current research. I set out the shortfalls in our current knowledge of young people's experiences of inherited disease and argue for the need to investigate how young people experience LFS. I then pose the core aims of this research in line with this argument.

In Chapter 3, I outline the philosophical and theoretical framework of the research design. In the first section of Chapter 3, I argue that the position of critical realism is a welcome partner to my pragmatic methodology, and I disclose and describe how my personal biases and training have affected my research decisions. In the second section, I explain the core features of my theoretical framework and how they influence this research. I discuss the concept of risk as a sociocultural construct that bears meaning beyond its biomedical purpose in genetic counselling, I then discuss the critical importance of systems theories to understand the impacts of genetic information beyond the individual. Last, I critically review and define core concepts of developmental theory, specifically focussing on Erikson's (1963) psychosocial theory of human development and its implications for modern AYA development.

In Chapters 4 and 5, I describe and justify the mixed-method design and methods used for this research. The mixed-method approach first involves a qualitative phase, consisting of meta-data analysis of existing research on how young people live with inherited disease (Study 1), and the principal study for this research, an interpretive description of how young people experience LFS (Study 2). The second, quantitative phase consist of cross-sectional survey of current health professional practices for young people with, or at risk of, LFS in Australasia (Study 3).

In Part 2, the main body of the thesis (Chapters 6-11), I present the findings of both phases of research. Chapter 6 is the author-accepted manuscript for a systematic review of how young people live with inherited disease (Study 1). Chapters 7-10 present the salient qualitative findings from Study 2, the interpretive description of young people's experience with LFS. Chapter 7 is the author-accepted manuscript describing

the experiences of young people considering and undergoing genetic testing for LFS. Chapters 8 and 9 report the analysis of qualitative data on how young people make sense of LFS and how they perceive their options for cancer control. Chapter 10 explores the reproductive decision-making of young people with LFS. Chapter 11 is the author-accepted manuscript for the second strand of research, and signals a move away from focussing on young people's experiences. It presents the cross-sectional survey of health professional practices for young people with, or at risk of, LFS in Australasia (Study 3).

In Part 3 (Chapters 12 and 13), I discuss the main findings in terms of their implications and contribution to current genetic counselling practice and broader discourses of health sociology. In Chapter 12, I discuss the implications of our modern risk society described by Beck (1992) and Giddens (1991) for young people with LFS. I also outline a structure for longitudinal, developmentally appropriate care for young people with inherited disease using the Family System Genetic Illness model as a guiding framework. Lastly, in Chapter 13 I conclude the core arguments advanced in the discussion, before proposing an agenda for future research.

2 Literature review

2.1 Overview

The previous chapter established the context and research problem for this thesis. Specifically, it outlined that the implications of LFS for young people are poorly understood, and investigating the perspectives of young people with LFS and the health professionals who care for them will contribute to the evidence base for youth-friendly genetic counselling. While the introductory chapter established the broad context of this thesis, it is necessary to explore and critically evaluate current literature to further define the research problem. Reflecting this goal, this chapter consists of three main sections. The first section outlines the core clinical features and history of LFS that make it unique among inherited cancer conditions, and justifies why it was chosen as the condition of interest for this thesis. The second section outlines fundamental research on the psychosocial implications for individuals and families who live with LFS. The third section describes the state of developmentally appropriate genetic counselling practice, and the limitations to the current body of work that this thesis aims to address. Combining these three strands of literature—medical, psychosocial, and practical—I then outline the shortcomings of current research and the specific research aims for this thesis.

2.2 Clinical characteristics of Li-Fraumeni syndrome

This section broadly described the characteristics of LFS based on its origin as a clinical construct, its salient clinical characteristics, and the available cancer risk management options.

2.2.1 Origin of LFS and its relation to TP53

LFS is a rare autosomal dominant genetic condition that predisposes individuals to high, multi-organ cancer risk from childhood. Frederick Li and Joseph Fraumeni first defined LFS in 1969 to describe families with a clustering of soft-tissue sarcoma, brain tumours, breast cancer and adrenocortical carcinoma (Li and Fraumeni 1969). In a later prospective study of 24 LFS kindreds they established the ‘classic’ definition of LFS: a proband with a sarcoma before the age of 45, with a first-degree relative with a cancer before the age of 45 and a first- or second-degree relative with any cancer before the age of 45 or sarcoma at any age (Li et al. 1988). These continued to be the core diagnostic features of LFS until 1990, when two groups of researchers identified heterozygous germline mutations in tumour suppressor gene *TP53* (OMIM 191170) as the cause of LFS (Malkin et al. 1990; Srivastava et al. 1990).

Coined as the ‘guardian of the genome’, *TP53* plays a critical role in tumour suppression throughout the body (Lane 1992), and the *TP53* pathway is the most commonly affected in sporadic human cancer (Hollstein et al. 1991; Levine, Momand, and Finlay 1991). The *TP53* gene product, the p53 transcription factor, has a ubiquitous and wide-ranging role in integrating cellular responses to DNA damage, and without normal p53 functioning, the body is unable to effectively combat tumour development (Valdez, Nichols, and Kesslerwan 2016). Lacking the key protective functions of *TP53*, individuals with LFS have strikingly high cancer risk across a broad spectrum of organs from birth.

Most individuals inherit an LFS-causing *TP53* mutation from one of their parents (i.e., they inherit a mutant *TP53* allele), and have a family history of cancer consistent with LFS. Approximately 7-20% of individuals with LFS, however, have a *de novo* *TP53* mutation; i.e., they spontaneously acquired a germline mutation during embryonic development and do not have family history of cancer suggestive of LFS (Gonzalez, Buzin, et al. 2009; Renaux-Petel et al. 2018). In either case, for individuals with LFS, their cancer is caused by the somatic loss of function in their other, wild-type allele, subsequently leading to the first steps of tumourigenesis (Bougeard et al. 2008; Malkin et al. 1990; Srivastava et al. 1990; Levine, Momand, and Finlay 1991; Vousden and Lane 2007). After the identification of *TP53* germline mutations as the cause of cancer clusters in families diagnosed with LFS, practice moved away

from clinical definitions of LFS, and established genetic testing criteria for identifying individuals who are at high risk of carrying a pathogenic *TP53* mutation (Table 1, p. 9).

At this juncture it is useful to focus on an important historical limitation and quirk of LFS-related research. LFS is a clinically defined cancer-prone condition, necessarily involving the diagnosis of several tightly clustered (i.e., among first-degree relatives) cancers in a single family. Although germline mutations in *TP53* are identified in ~70% of individuals with cancer who meet the classic LFS definition (Varley 2003), an individual diagnosed with LFS is not the same as an individual identified with a *TP53* germline mutation, and the two are often conflated. An individual with a *TP53* mutation may be unaffected, may never develop a cancer associated with LFS, and may not have a family history suggestive of LFS. On the other hand, someone clinically diagnosed with LFS has necessarily been diagnosed with cancer and is from a family with a strong history, but may not have germline mutation in *TP53*. This difference has implications for the penetrance of *TP53* variants, which will be explained further below.

Table 1. Clinical diagnostic and genetic testing criteria for Li-Fraumeni syndrome
Criteria

‘Classic’ LFS (Li et al. 1988)^a

A proband with:

- A sarcoma before age 45; and,
 - A first-degree relative with any cancer before age 45; and,
 - A first- or second-degree relative with any cancer before age 45 or a sarcoma at any age.
-

Li-Fraumeni-like syndrome (LFL)^a

A proband with:

- Any childhood cancer or sarcoma, brain tumour, or adrenocortical carcinoma diagnosed before age 45; and,
- A first- or second-degree relative with typical LFS cancer (sarcoma, breast cancer, brain tumour, leukaemia, or adrenocortical carcinoma) at any age; and,

Birch definition (Birch et al. 1994)

- A first- or second-degree relative with any cancer before age 60.

Eeles definition (Eeles 1995)

- A first- or second-degree relative with two different typical LFS tumours at any age.
-

Chompret criteria (Chompret et al. 2001)^b

A proband with:

- A narrow LFS spectrum cancer before age 36; and,
 - At least one first- or second-degree relative with a narrow LFS spectrum cancer (other than breast cancer if the proband has breast cancer) before age 46 or multiple primary tumours; or,
 - A proband with multiple primary tumours, two of which belong to the narrow spectrum and the first of which occurred before 36 years, regardless of family history; or,
 - A proband with adrenocortical carcinoma at any age regardless of family history.
-

Table 1 cont.

Chompret (2009) criteria (Bougeard et al. 2008; Tinat et al. 2009)^b A proband with: • An LFS spectrum cancer (soft tissue sarcoma, osteosarcoma, brain tumour, pre-menopausal breast cancer, adrenocortical carcinoma, leukaemia, lung bronchoalveolar cancer) before age 46; and, • At least one first- or second-degree relative with a narrow LFS spectrum cancer (other than breast cancer if the proband has breast cancer) before age 56 or multiple primary tumours; or, • A proband with multiple primary tumours (except multiple breast tumours), two of which belong to the LFS tumour spectrum and the first of which occurred before 46 years; or, • A proband with adrenocortical carcinoma or choroid plexus carcinoma at any age regardless of family history.
Chompret (2015) criteria (Bougeard et al. 2015)^b A proband with: • A tumour belonging to LFS tumour spectrum (premenopausal breast cancer, soft tissue sarcoma, osteosarcoma, CNS tumour, adrenocortical carcinoma) before age 46; and, • At least one first- or second-degree relative with LFS tumour (except breast cancer if proband has breast cancer) before age 56 or with multiple tumours; or, • A proband with multiple tumours (except multiple breast tumours), two of which belong to LFS tumour spectrum and first of which occurred before age 46; or, • A patient with adrenocortical carcinoma, choroid plexus tumour, or rhabdomyosarcoma of embryonic anaplastic subtype, irrespective of family history; or, • A patient with breast cancer before the age of 31.

Abbreviations: CNS, central nervous system.

^a Criteria for clinical diagnosis; ^b *TP53* genetic testing criteria.

On a semantic note, the difference between LFS and *TP53* is also important to address because it affects my chosen terminology to describe young people in this thesis. Broadly I use the generic phrase ‘young people from families with LFS’ to describe young people with, or at 50% risk, of germline mutation in *TP53*. While this phrase does not strictly reflect the variety in the study sample, it serves as a useful simplification in text. Where possible in relevant chapters to follow, each participant has descriptors for their gene and cancer status.

2.2.2 Clinical characteristics

The unique clinical characteristics of LFS are centred on three core features: high cancer risk, variable phenotype and early age of onset. These characteristics, which are explained in turn below, make LFS unique among inherited cancer syndromes, and correspond to a uniquely exacerbated physical and psychosocial burden.

Perhaps the most striking feature of LFS is the high cancer risk associated with germline mutations in *TP53*: females by the age of 31, and males by the age of 46 with a *TP53*

mutation have a 50% risk of developing cancer of any type (Mai et al. 2016). Remarkably, cancer risk approaches 70-100% by the age of 70 for both sexes (Mai et al. 2016) (Figure 1, p. 11). The second significant feature of LFS is the variable phenotype observed among individuals with a *TP53* mutation who have developed cancer. Not only do individuals with LFS live with remarkably high cancer risk, the types of cancer they may develop are spread across a broad spectrum.

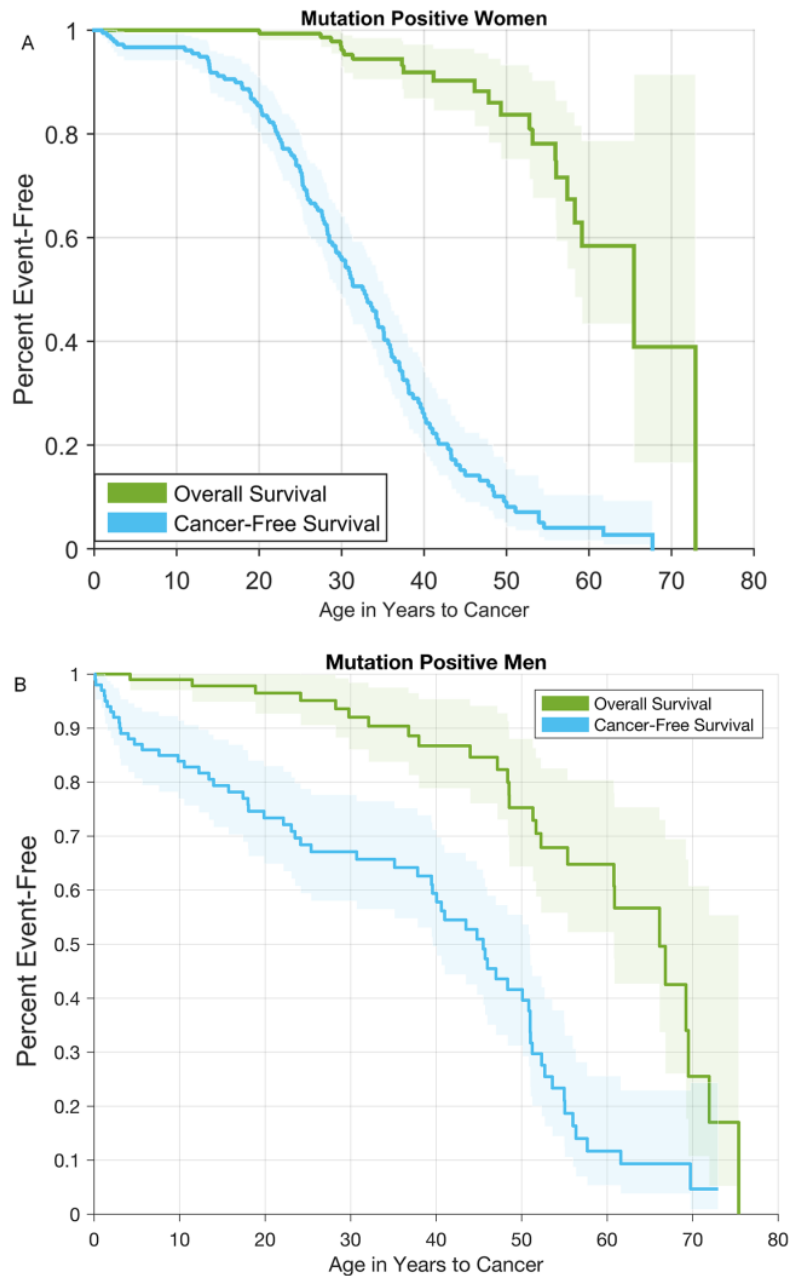


Figure 1. Overall and cancer-free survival among (A) *TP53*+ve females and (B) *TP53*+ve males

Source: Reproduced from Mai et al. (2016: 3676), © 2016, with permission from John Wiley & Sons, Inc. All rights reserved.

The most prevalent types of cancer associated with LFS, which account for 70-80% of the tumour burden among individuals with a germline mutation in *TP53*, are: breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system tumours (e.g., choroid plexus carcinoma), adrenocortical carcinoma, and haematological malignancies (Gonzalez, Noltner, et al. 2009; Nichols et al. 2001; Ruijs et al. 2010; Olivier et al. 2003) (Figure 2, page 13). Contributing to the extensive phenotypic heterogeneity of LFS, a wide variety of other tumours have also been reported among LFS kindreds (Nichols et al. 2001; Birch et al. 2001; Olivier et al. 2003; Ruijs et al. 2010; Gonzalez, Noltner, et al. 2009; Masciari et al. 2011) (Figure 2, page 13). These make up approximately 20-30% of the total LFS tumour spectrum and occur at earlier ages and more frequently in individuals with LFS compared with the general population (Nichols et al. 2001; Ruijs et al. 2010).

Importantly for this thesis, the tumour spectrum for individuals with a *TP53* mutation has a distinct temporal pattern consisting of three phases (Amadou, Achatz, and Hainaut 2018; Mai et al. 2016; Bougeard et al. 2015). The childhood phase (0-15 years), which accounts for 22% of the cancer burden in the LFS population, is mainly characterised by the incidence of adrenocortical carcinoma, choroid plexus carcinoma, rhabdomyosarcoma and medulloblastoma (Amadou, Achatz, and Hainaut 2018). These cancers are exceedingly rare in the general population and considered as cardinal features of LFS (Bougeard et al. 2015). The early adulthood phase (16-50 years), which accounts for 51% of the cancer burden, is mainly characterised by the incidence of breast cancer, osteosarcoma, soft-tissue sarcoma, leukaemia, astrocytoma and glioblastoma, colorectal and lung cancer (Amadou, Achatz, and Hainaut 2018). The late adulthood phase (51-80 years), accounting for 27% of the cancer burden, is characterised by a broad spectrum of cancers, but the most frequent incidences are pancreatic and prostate cancer (Amadou, Achatz, and Hainaut 2018).

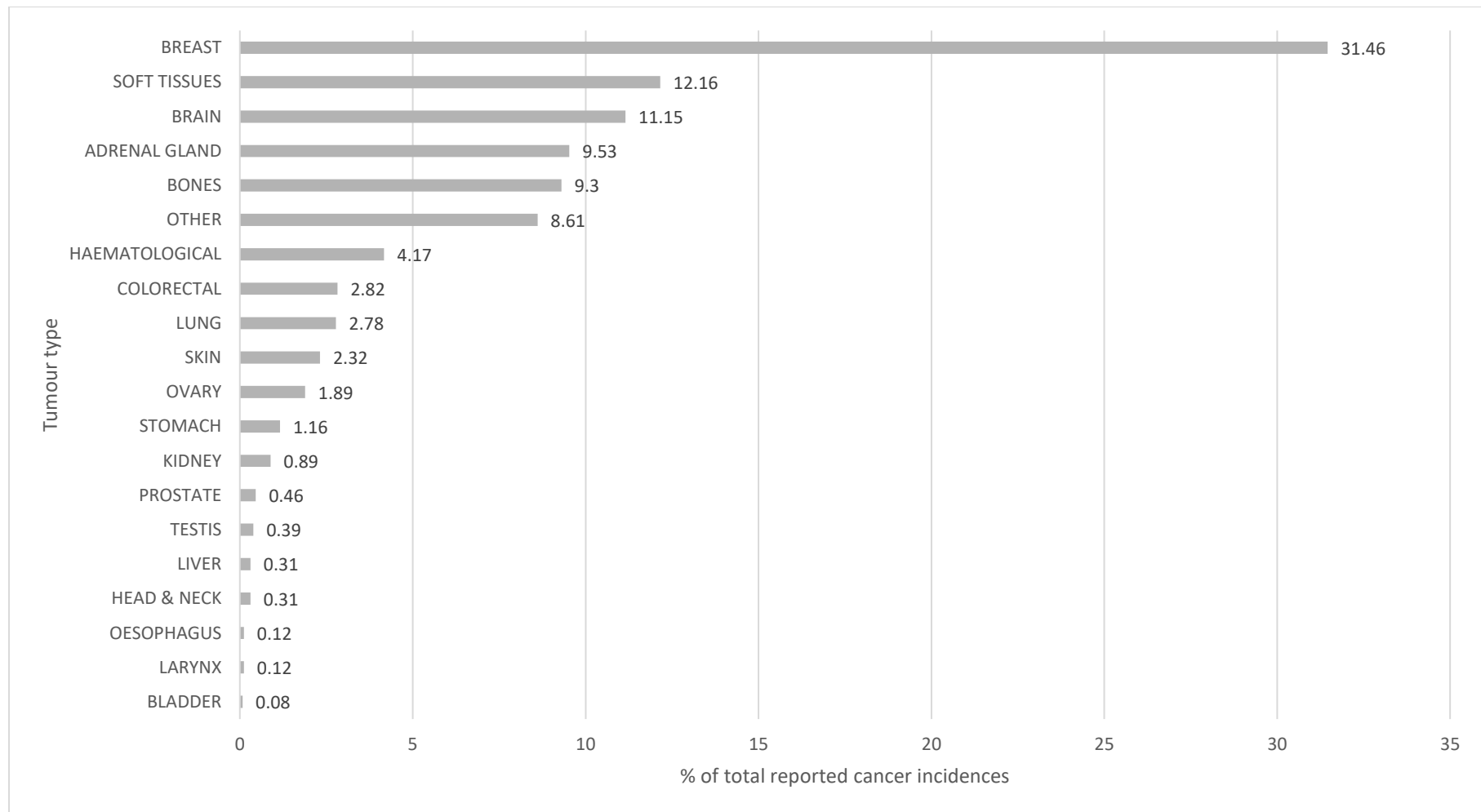


Figure 2. Tumours associated with pathogenic germline mutations in *TP53* (N=2591 tumours)

Source: Raw data retrieved from the International Agency for Research on Cancer (IARC) *TP53* database: R19, July 2019 (Petitjean et al. 2007 R18, April 2016).

As the temporal patterns suggests, the bulk of the cancer risk associated with *TP53* mutations manifests early in life (Gonzalez, Noltner, et al. 2009; Li et al. 1988; Lustbader et al. 1992; Mitchell et al. 2013; Nichols et al. 2001; Mai et al. 2016). Indeed, the French LFS working group demonstrated that among 322 individuals in their LFS cohort who had developed at least one malignancy, 22% had developed cancer by the age of 5 years and 41% by the age of 18 years (Bougeard et al. 2015) (Figure 3, page 14). The mean age of first tumour onset was 24.9 years (Bougeard et al. 2015), firmly situating LFS as an early onset inherited cancer condition with serious implications for young people.

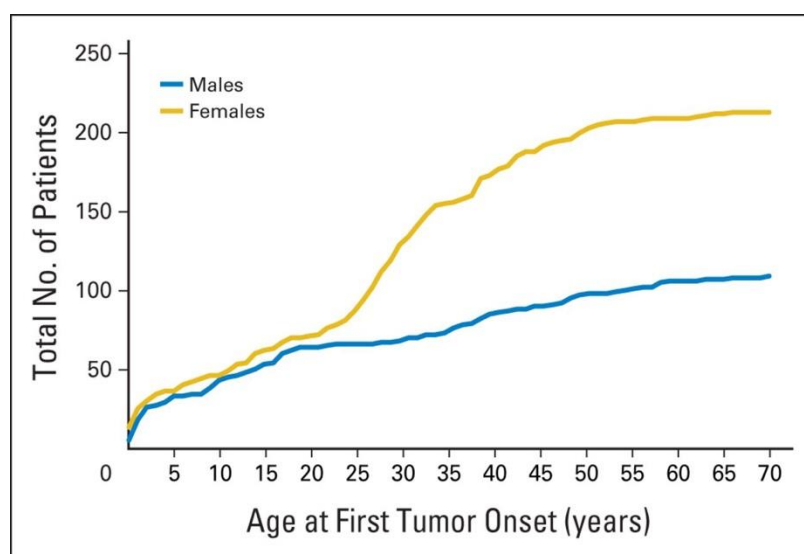


Figure 3. Age at first tumour onset in 322 affected individuals with a germline mutation in *TP53*

Source: Reprinted with permission. © 2015 American Society of Clinical Oncology. All rights reserved. Bougeard et al. (2015: 2346).

In addition, to these already burdensome features, approximately 40-50% of individuals with a *TP53* germline mutation affected by cancer develop a second primary malignancy within 10 years of their first (Bougeard et al. 2015; Chompret et al. 2000; Hisada et al. 1998; Hwang et al. 2003; Mitchell et al. 2013; Mai et al. 2016). Moreover, reports indicate some individuals with LFS develop multiple (up to six) primary cancers over their lifetime (Bougeard et al. 2015). There is some evidence to suggest a proportion of these additional primary malignancies may be due to exposure to ionising radiation and genotoxic chemotherapies, which individuals with a *TP53* mutation are unable to combat effectively due to a defective p53 pathway (Kasper et al. 2018). Therefore, it is recommended that those with a *TP53* mutation reduce exposure to these risk factors in surveillance and treatment (Kratz et al. 2017).

An important caveat to the description of LFS provided so far links back to how LFS and *TP53* are related. The high cancer risk estimates that have become synonymous with LFS are biased by the selection of cancer-affected families in research to date. In the context of samples ascertained on clinical LFS criteria, germline mutations in *TP53* have long been thought of as highly penetrant and rare events occurring at a rate of 1/50,000 to 1/20,000 in the general population (Malkin et al. 1990; Olivier et al. 2003; Srivastava et al. 1990; Bougeard et al. 2008; Levine, Momand, and Finlay 1991; Vousden and Lane 2007; Gonzalez, Noltner, et al. 2009; Laloo et al. 2003). However, more recently, estimates from studies agnostic to family history estimate the population prevalence of potentially pathogenic mutations in *TP53* to be as high as 1/2000 to 1/500 (de Andrade et al. 2017). This suggests the population prevalence may be up to ten times higher than previously thought, highlighting the presence of less penetrant *TP53* variants in the general population that do not confer the classic LFS phenotype (de Andrade et al. 2017).

The rhetoric commonly used to describe LFS as a devastating condition, a rhetoric I make use of in this thesis, masks what we know about the variable penetrance of *TP53* mutations. Addressing this is beyond the scope of the current thesis, and for the sake of simplicity, when I refer to *TP53* mutations from here on, I am referring to the highly penetrant, rare variants among families with classic LFS. Also, of note is the high prevalence of LFS due to a founder effect mutation in South-Eastern Brazil: the R337H variant (Achatz et al. 2007). This variant confers a similar but slightly different phenotype, and while it represents an important area of clinical and psychosocial research, it is also beyond the scope of this thesis.

In sum, the highly variable phenotype and distinct temporal pattern of tumour onset make LFS unique among other inherited cancer syndromes, and especially challenging to manage effectively in a clinical context.

2.2.3 Risk management

A critical aspect to genetic counselling practice is the discussion of risk management options for inherited disease. In the context of LFS, individuals who test positive for a germline mutation in *TP53* may have access to cancer risk management to mitigate their cancer related morbidity and mortality. Cancer risk management for inherited cancer usually consists of two main components: risk-reducing options (e.g., prophylactic surgery to remove at-risk organs or risk-reducing medication), or cancer surveillance/screening (e.g., organ-specific imaging) to improve overall outcomes by enabling early detection and treatment of mainly solid tumours. Due to the early age of

onset, the diversity of tumours associated with LFS, and the risk of additional primary malignancies from ionising radiation, cancer surveillance for LFS is especially complex and has important implications for this thesis.

Until recently, LFS was perceived as an intractable condition. Effectively managing the wide spectrum of LFS-associated cancers was technologically insurmountable and risk management protocols for LFS were made up of borrowed evidence-based approaches for common organ-specific inherited conditions. Core features included breast cancer surveillance and risk-reducing surgery based on protocols for women with a *BRCA1/2* mutation, and colorectal cancer screening borrowed from protocols for individuals with Lynch syndrome (Cancer Institute New South Wales 2010). While these approaches were arguably effective at managing breast and colorectal cancer risks, the main body of cancer risk associated with LFS was left unmonitored, and it remained an obstinate condition to manage clinically. Over the past five years, however, the introduction of the ‘Toronto protocol’ in 2011, and revisions in 2016, has dramatically shifted the perceived manageability of LFS.

The Toronto protocol is a multimodal, non-invasive biochemical and imaging screening protocol for the clinical management of LFS in children and adults (Villani et al. 2011; Villani et al. 2016) (Table 2, page 17). Centred on the novel use of rapid whole-body MRI, this seminal work provided the first evidence suggesting the potential survival benefits of whole-body surveillance among individuals with a germline *TP53* mutation. Using the protocol, a total of 40 asymptomatic tumours were detected in 32% (n=19/59) of patients who underwent surveillance, while 61 symptomatic tumours were detected in 88% (n=42/49) of patients who initially declined surveillance (19 of these subsequently crossed over to the surveillance arm). Importantly, there was a significant increase in 5-year survival for individuals in the surveillance arm compared (88%, 95% CI 78.7-100) to the non-surveillance arm (59.6%, 95% CI 47.2-75.2), ($p=0.0132$) (Villani et al. 2016).

While there are notable limitations to this study, especially the non-randomised study design and the crossover between study arms, it signalled an historical shift in how we conduct cancer surveillance for complex childhood onset inherited conditions (Malkin 2014). As a result, the Toronto protocol has been adopted, and versions thereof, by a consortium of international groups who are currently conducting trials of their own: the Li-Fraumeni Exploration (LiFE) Research Consortium (Mai et al. 2012). Notably, the Australian group is prominent in this consortium with the Surveillance study in Multi-

Organ Cancer-Prone Syndromes (SMOC+ trial; HREC/12/PMCC/17) being conducted out of Melbourne, Australia.

Table 2. The Toronto Protocol based on cancer type and age

Cancer type	Risk management
Adrenocortical carcinoma	Children (0-18 years) and adults (18-40 years) • Ultrasound of abdomen and pelvis every 3-4 months • Blood tests every 3-4 months: 17 OH-progesterone, total testosterone, dehydroepiandrosterone sulphate, androstenedione, 24-h urine cortisol
Brain tumours	Children and adults • Annual brain MRI
Soft-tissue sarcoma and osteosarcoma	Children • Annual rapid whole-body MRI Adults • Annual rapid whole-body MRI • Ultrasound of abdomen and pelvis every 3-4 months
Leukaemia or lymphoma	Children and adults • Blood tests every 3-4 months: complete blood count, erythrocyte sedimentation rate, lactate dehydrogenase
General assessment	Children and adults • Complete physical examination every 3-4 months • Prompt assessment with primary care physician for any medical concerns
Breast cancer	Adults • Monthly breast self-examination (age 18 years onwards) • Clinical breast examination twice a year (age 20-25 years onwards, or 5-10 years before earliest known breast cancer in the family, whichever comes first) • Annual mammography and breast MRI screening (age 20-75 years, or 5-10 years before earliest known breast cancer in the family, whichever comes first) • Consider risk-reducing bilateral mastectomy
Colorectal cancer	Adults • Colonoscopies every 2 years (start at age 25 years, or 10 years before earliest known colon cancer in the family, whichever comes first)
Melanoma	Adults • Annual dermatological examination

While many authors have stressed that whole-body risk management for LFS is distinctly multimodal (Kratz et al. 2017), the core modality is rapid whole-body MRI. To this end, a recent meta-analysis from the LiFE Research Consortium assessed the clinical utility of whole-body MRI at baseline for individuals with a *TP53* germline mutation (Ballinger et al. 2017). With data from 13 LFS cohorts in six countries, totalling 578 participants, the authors showed that baseline whole-body MRI effectively detected new, localised primary cancers at a rate of 7% (95% CI 5%-9%), and that all screen-detected malignancies were treated with curative intent (Ballinger et al. 2017). This landmark study demonstrated that whole-body MRI offers important clinical utility in the management of cancer risk among individuals with *TP53* mutations by enabling early detection and treatment of tumours. As a result, in early 2019, Australian risk management guidelines were updated to formally adopt recommendations for the use of whole-body MRI in the risk management for individuals with LFS (Cancer Institute New South Wales 2019), mirroring recommendations in the USA (National Comprehensive Cancer Network 2017).

Despite the growing evidence base for whole-body surveillance among individuals with a *TP53* mutation, there are important limitations and there remains considerable variability in guidelines internationally (e.g., UK guidelines only recommend annual breast MRI and consideration of mastectomy) (National Institute for Health and Care Excellence 2019). First, the long-term survival rates (over 5 years) are unknown, and current survival curves are based on non-randomised data (Villani et al. 2016). Second, having to attend surveillance in regular 3-12-month intervals to learn of potentially untreatable cancer anywhere in the body could be highly distressing (Kratz et al. 2017). Further, the high false-positive rate at baseline whole-body MRI (42.5%) could contribute to screening fatigue and drop out from regular invasive additional investigations (Ballinger et al. 2017). Indeed, the long-term psychological impact of intense comprehensive screening is largely unknown, and medicalising asymptomatic individuals, potentially from a young age, has understudied psychosocial implications. Preliminary work that addresses these implications are outlined in the next section (p. 30). Lastly, because whole-body protocols are largely experimental, access is currently limited to research protocols. Most countries internationally, including Australia, are still unable to offer whole-body surveillance on a routine basis. Families in regional areas and those without adequate insurance cover in the USA may not have ready access to clinical care that is in line with current recommendations.

2.2.3.1 Cancer surveillance does not reduce cancer risk

A more complex issue that remains unaddressed in the context of LFS is whether tumours can be prevented in the first place. Currently, the only form of risk reduction available to individuals with LFS is the prophylactic removal of breast tissue by surgery (i.e., bilateral prophylactic mastectomy [BPM]). Clearly, this approach only addresses one cancer among the broad spectrum of cancers associated with LFS and is only relevant to females with a *TP53* mutation. Moreover, BPM is a drastic surgical option with various psychosocial implications for body image, self-esteem, intimate relationships, and health insurance (Werner-Lin, Ersig, et al. 2018; Glassey et al. 2016). An ongoing phase one clinical trial sponsored by the National Institute of Health (NCT01981525) is assessing the use metformin as chemoprevention for individuals with a *TP53* mutation, but the primary outcomes are not geared towards measuring reduced tumour incidence (Malkin 2016). Moreover, while prevention is a hot topic of research in LFS currently, there remains few options available in clinical practice.

In sum, this section outlined important historical and technological turns in cancer risk management for LFS. It was important to do this because the participants from this project were involved in risk management in two main capacities: either as individuals with a *TP53* germline mutation enrolled in risk management (e.g., SMOC+, the Australian version of the Toronto protocol) or as a health professional who referred or administered risk management for LFS. Importantly, the shift in risk management practices means health professionals may face a discrepancy between what is recommended and what is clinically available. Exploring how health professionals navigate this tension is important for the clinical and psychosocial outcomes of individuals with LFS and is a key part of this thesis.

2.2.4 Summary

This section described LFS in terms of its clinical characteristics, epidemiology, and risk management. Although not an exhaustive review, this section clearly illustrated that LFS is a complex inherited condition defined by high, multi-organ cancer risk from a young age, which is difficult to manage. This complexity is conserved when appreciating the psychosocial landscape of individuals and families who live with LFS, which is the topic of the next section.

2.3 Psychosocial aspects of living with Li-Fraumeni syndrome

To date, few studies (<20) have addressed the psychosocial aspects of living with LFS. Because of the small size of the field, psychosocial research on LFS can be effectively organised into two main phases based on one historical event: the widespread uptake of the Toronto protocol in 2016. A summary of these studies is provided in Table 3 (p. 23).

2.3.1 Before the Toronto protocol

Before 2016, the earliest psychosocial work reinforced conceptions of LFS as a devastating inherited condition, conferring not only a heavy physical burden, but also a significant psychosocial burden to affected families. Families who experienced intergenerational LFS-related cancer and death were shown to be psychologically vulnerable in a landmark study of five French families with LFS (Oppenheim et al. 2001). Despite the absence of a clear analytical method and the selection of extreme cases with family conflict, Oppenheim et al. (2001) were the first to characterise the emotional, relational and familial problems faced by individuals from families with LFS. These mainly consisted of the influence of family history on perceived vulnerability to cancer, complex ideas about the origin of cancer in their family, and fear about passing on their condition to children (Oppenheim et al. 2001).

Oppenheim et al. (2001) suggested that the distressing experiences of being a part of family with LFS could explain participants' ambivalence towards learning their gene status and associated cancer risk. This was consistent with the initially low uptake of predictive *TP53* testing, which ranged from 25% (n=4/16) in a UK study (Evans et al. 1997), to 39% (n=22/57) in a USA study (Patenaude et al. 1996). Though these estimates were based on simple clinical audits of testing uptake, they are notably comparable to more robust estimates of low cumulative uptake (15.4%-17.4%) of predictive testing for Huntington disease over long periods (7-30 years), which is fully a penetrant, unpreventable and fatal neurological condition (Baig et al. 2016; Tassicker et al. 2009). Drawing comparisons with HD served to cement LFS as a devastating intractable condition at this time.

Extending Oppenheim et al.'s (2001) work, Peterson et al. (2008) offered important insights into the kinds of distress at-risk individuals may experience prior to genetic testing for LFS. From a sample of 92 individuals at 25-50% risk of a *TP53* mutation, those who had no cancer, had a strong family history (i.e., 2.8 first-degree

relatives who had died of cancer), and anticipated being *TP53*+ve were more likely to experience cancer-specific distress (Peterson et al. 2008). Although this was a cross-sectional assessment, it suggested that the ‘worried well’ (i.e., no personal history of cancer) with a strong family history of LFS, may present for genetic counselling and testing significantly distressed about developing cancer.

In the absence of effective risk management for LFS, there was a keen focus on the uptake of genetic testing and the potential adverse psychosocial impact of learning one’s gene status. A seminal Dutch study by Lammens, Aaronson, et al. (2010) showed that uptake of predictive *TP53* testing had increased from previous estimates (from 25-39% up to 55%, $n=65/119$), which is similar to the ~50% uptake of testing for other inherited cancer conditions (e.g., Lynch syndrome and HBOC) (Meiser 2005; Willis et al. 2017). A minority (23%) of the Dutch cohort of LFS families reported clinically relevant levels of distress during the process of genetic testing, which again is similar to rates of distress reported in other studies of genetic testing for inherited cancer (Douma et al. 2010; Bleiker et al. 2013).

Importantly, distress was not associated with genetic status, and the higher uptake of *TP53* testing contrasted prior suggestions that at-risk individuals would not want to learn their gene status due to potentially distressing findings (Lammens, Aaronson, et al. 2010). Importantly, the authors also identified that individuals with a lack of social support (measured by the Social Constraints questionnaire) were more prone to report clinically relevant levels of distress (OR, 1.3; 95%CI 1.0-1.5) (Lammens, Aaronson, et al. 2010). This study suggested that predictive *TP53* testing by in large does not cause psychological harm; yet, a substantial minority may require additional psychosocial services, especially those without well-established social networks of support.

In a sister study, Lammens, Bleiker, Aaronson, et al. (2010) also demonstrated a psychological benefit to cancer surveillance among 45 individuals with, or at 50% risk of, a *TP53* germline mutation. Notably, this was before an international consensus had been reached for the use of whole-body MRI in the risk management of LFS, and the surveillance advice reportedly received by participants was correspondingly varied (Lammens, Bleiker, Aaronson, et al. 2010). Nonetheless, the vast majority still reported early detection of cancers (90%) and feelings of control (84%) as perceived benefits to surveillance (Lammens, Bleiker, Aaronson, et al. 2010), suggesting that irrespective of

medical benefit, being enrolled in a dedicated risk management program provided a sense of safety for individuals with LFS.

Concurrent to the research investigating the uptake of genetic testing among adults at risk of LFS, two studies reported on health professional attitudes and experiences of providing predictive genetic testing for LFS among children (Fresneau et al. 2013; Evans et al. 2010). Both studies showed that health professionals from France (15%, n=3/20) and the UK (15%, n=4/26) rarely facilitated predictive testing among children, mainly due to there being no proven screening or interventions at that time for LFS (Fresneau et al. 2013; Evans et al. 2010). Both author groups suggested that predictive testing for children should be considered on a case-by-case basis to assess any potential psychosocial benefit, e.g., alleviating significant familial distress around uncertainty, until a clear medical benefit to knowing gene status during childhood was established (Fresneau et al. 2013; Evans et al. 2010).

From this near 15-year span of research, it is clear that LFS was considered a devastating condition with limited intervention and surveillance options. Despite this, uptake of genetic testing among adults slowly increased to over 50%, and only a quarter experienced clinically relevant levels of distress, which is similar to other inherited cancer conditions. In the face of high cancer risk, access to social support was flagged as a key resource to mitigate against cancer-related distress. Health professionals were reticent to offer predictive genetic testing to children because of a limited medical benefit.

Table 3. Summary of studies addressing the psychosocial implications of Li-Fraumeni syndrome

Author (yr., country)	Study aim(s)	Design and analysis	N (sample characteristics)	Mean age (range, yrs.)
Before the Toronto Protocol (prior to 2015)				
Oppenheim et al. (2001, FRA)	To explore the emotional, relational and familial problems of individuals from families with LFS	Psychotherapeutic interviews (clinical) No analytical framework, interviews not recorded	5 (4+ve, 1 married into family with LFS) 2/5 CA All males	Mean: n/a Reported ages: 11, 23, 24, 26, one not provided
Peterson et al. (2008, USA)	To determine the factors related to cancer-specific distress and perceived self-efficacy in coping with a positive <i>TP53</i> test result	Survey (measures: IES, perceived self-efficacy in coping, QLI, SSQ, perceived risk, CWS, DCS, pedigree data)	92 (AR); 22/92 CA M:F=31:61	49.7 (18-81)
Lammens, Aaronson, et al. (2010, NED) ^a	To evaluate the uptake of genetic testing and the psychosocial impact of undergoing or not undergoing a genetic test for LFS	Clinical audit Survey (measures: IES, SF-36, CWS, adapted Social constraints questionnaire)	Clinical audit: 142 (23+ve, 119 AR) Survey: 70/142 (27+ve, 18AR, 25-ve) 10/70 CA M:F=36:34	42.8 (17-75)
Lammens, Bleiker, Aaronson, et al. (2010, NED) ^a	To investigate which advice for regular surveillance, if any, is given to high risk LFS individuals, adherence to that advice, and any psychological gain or burden derived from surveillance	Survey (measures: study-specific questionnaire, IES, CWS)	45 (27+ve, 18 AR); 10/45 CA M:F=26:19	40.6 (17-75)
Evans et al. (2010, UK)	To describe the experience of providing childhood testing for LFS at a single centre	Clinical audit Case study	4/26 minors underwent <i>TP53</i> testing under the age of 18; four families used a cases for report	n/a

Fresneau et al. (2013, FRA)	To determine how onco-geneticists respond to parental requests for <i>TP53</i> testing, and to assess attitudes towards presymptomatic testing for minors	Survey (study-specific questionnaire, generic quantitative and qualitative analysis)	20 oncogeneticists	n/a
After the Toronto Protocol (2015 onwards)				
Alderfer et al. (2015, USA) ^b	To explore uptake and parent decision-making for predictive <i>TP53</i> genetic testing among children	Qualitative interviews (inductive content analysis) Clinical audit	46 parents with minimum one child (<22yrs) offered <i>TP53</i> genetic testing Of n=39 families in the sample: 14+ve, 23-ve, 2 unknown M:F=14:32	44.5 (29-68)
Peters et al. (2016, USA) ^c	To investigate the role of social, spiritual and emotional support of families with LFS	Qualitative family interviews (generic inductive analysis) Survey (measures: CEGRM and BSI-18)	66 (42+ve, 5-ve, 19 not provided) 28/66 CA M:F=27:39	Mean: n/a Stratified by age: 9 (<20); 26 (20-39); 25 (40-59); 6 (60+)
McBride et al. (2017, AUS)	To assess the psychosocial impact of engaging in multimodal screening for LFS (SMOC+-specific)	Qualitative interviews (inductive thematic analysis; n=9) Paper-based survey (measures: HADS, IoE-C, IoE-M, CWS) @ 2, 12, 26 and 52 weeks post WBMRI	17 (+ve); 11/17 CA M:F=9:8	43.3 (21-65)

Table 3 cont.

Author (yr., country)	Study aim(s)	Design and analysis	N (sample characteristics)	Mean age (range, yrs.)
Ross et al. (2017, USA)	To explore the psychosocial impact of multimodal screening for LFS	Qualitative interviews (grounded theory approach)	20 (+ve); 17/20 CA M:F=4:16	39.1 (18-61)
Alderfer et al. (2017, USA)	To explore the perspectives of PGT among AYAs from families with LFS	Qualitative interviews (descriptive content analysis) This sample was snowballed from parents enrolled in the Alderfer et al. (2015) dataset	12 (7+ve, 3-ve, 1 assumed +ve, 1 unclear) M:F=8:4	17.8 (12-25)
Schultz et al. (2018, USA) ^b	To explore how the developmental context of adolescence influences parental perspectives about genetic testing for LFS and discussions of cancer risk	Secondary analysis of existing qualitative data set: Alderfer et al. (2015) Inductive content analysis; authors selected all data relevant to questions of interest from interview guide for re-analysis	46 parents with minimum one child (<22yrs) offered <i>TP53</i> genetic testing 30/46 with adolescent children M:F=14:32	44.5 (29-68)
Valdez et al. (2018, USA) ^b	To investigate parent-child communication about genetic testing in families with LFS	Secondary analysis of existing qualitative data set: Alderfer et al. (2015) Inductive semantic content analysis; selected all data relevant to questions of interest from interview guide for re-analysis	14 parents from 10 families with a <i>TP53</i> +ve child M:F=4:10 In total, included participants were parents of 20 tested children (17+ve, 3-ve; 10 unaware)	Median 45 (36-56)

Young et al. (2018, USA) ^c	To evaluate couples' coping with LFS-related burdens	Qualitative dyad interviews (grounded theory and interpretive description) Sample drawn from n=64 family interviews at the same site as Peters et al. (2016); n=26 selected as they included only couple pairs.	26 couples (26+ve, 26-ve) M:F=26:26 21/26+ves were female; 5/26+ves were male	M: 43 (23-72) F: 40 (22-57)
Pantaleao et al. (2019, USA) ^c	To identify key health-related roles held by parents and members of the younger generation in families living with LFS	Qualitative family interviews (grounded theory and interpretive description) 2-5 family members/interview Sample drawn from n=23 family interviews from same site as Peters et al. (2016)	62 from n=23 family interviews, minimum one member <i>TP53</i> +ve	Mean: n/a Range: 7-81
Bancroft, Saya, Brown, et al. (2019, UK)	To report the short-term and medium-term psychosocial effects, health-related quality of life and acceptability of WBMRI scanning carried out as part of the SIGNIFY study	Paper-based survey (measures: HADS, CWS-R, IES, SSAI-B, HQ, SF36-II, SSQ) at baseline, arrival at MRI apt., pre-MRI, post-MRI results, 12, 26, 52 weeks post results Sex and age (+/- 5 yrs) matched case-control study. Case= <i>TP53</i> +ve carrier; control=healthy general population. Each group underwent MRI and received measures at each time point	44 cases (+ve); 6/44 CA M:F=17:27 44 healthy controls (no PHX of cancer, no FDRs <50 yrs with cancer) M:F=17:27	37.6 (19-58) 38.3 (22-59)

Abbreviations: n/a=not available; M:F=male : female participants; +ve=tested *TP53*+ve; -ve=tested *TP53*-ve; AR=at 50% risk; CA=clinically affected; FDR=first-degree relative; IES=Impact of Events of Scale; QLI=Quality of Life Index ; SSQ=Social Support Questionnaire; CWS=Cancer Worry Scale; DCS=Decisional Conflict Scale; SF-36=Short-Form 36 Health Survey; CEGRM=Coloured Eco-genetic Relationship Map; BSI-18=brief symptom inventory-18; WBMRI, whole-body MRI; HADS=hospital anxiety and depression scale; IoE-C=Impact of Events Scale-Cancer; IoE-M=Impact of Events Scale-MRI; SSAI-B=Spielberger State Anxiety Inventory-Brief form; HQ=Health Questionnaire; SSQ=Screening Satisfaction Questionnaire; PHX=personal history. ^{a, b, c} These studies share or are derived from the same sample.

2.3.2 After the Toronto protocol

Since the widespread adoption of the Toronto protocol, there has been a flurry of psychosocial research on LFS. The new wave of research can be broadly divided into four main groupings: the first is focussed on parental views of *TP53* genetic testing for children and parent-child communications about LFS (Alderfer et al. 2015; Schultz et al. 2018; Valdez et al. 2018); the second on the psychological outcomes and experiences of whole-body risk management for LFS (McBride et al. 2017; Ross et al. 2017; Bancroft, Saya, Brown, et al. 2019); the third on the impact of LFS on families as interdependent systems (Peters et al. 2016; Young et al. 2018; Pantaleao et al. 2019). The fourth type of research, which is directly relevant to this thesis, specifically focusses on the experiences of young people from families with LFS (Alderfer et al. 2017).

2.3.2.1 Parent-child communication about LFS and genetic testing

In the years immediately preceding the second landmark Toronto protocol publication in 2016 (Villani et al., 2016), there was a notable shift in the views of genetic testing among children for LFS. Alderfer et al. (2015) showed that 92% (n=159/190) of families with LFS in North America had undertaken *TP53* genetic testing for their children (aged <22 years). Uptake was significantly higher for diagnostic testing (95%) compared to predictive testing (79%; $p=0.008$) (Alderfer et al. 2015), and was much higher than previous estimates of testing for LFS in childhood (15%) (Fresneau et al. 2013; Evans et al. 2010). It is unclear from the authors' analysis how many families were recruited from the Hospital for Sick Children at the University of Toronto, a principal site in the study and the birthplace of the Toronto protocol. Therefore, it is open to question how many families may have had early access to versions of the Toronto protocol and what impact this may have had on parental genetic testing decisions.

What is clear though, from the second, qualitative arm of the study, was that parents (n=46 from 39 families) decided easily in favour of testing their children (Alderfer et al. 2015). Most parents described that promoting the health of their child and reducing their uncertainty about gene status were the primary advantages of testing, and had automatic (48%) or considered (49%) decision-making styles. Only a small number deliberated over testing (6%), stating psychosocial risk to their child as the primary disadvantage of testing (Alderfer et al. 2015). A caveat to this seminal research is that the upper limit of the age range to describe children was 22 years. This is notably high, especially as the age of legal majority in most countries is 18 years, which is a significant

milestone in the legal rights of young people to pursue or refuse testing of their own accord.

Extending the research on parent decision-making and attitudes to testing their children for LFS (Alderfer et al. 2015), there have been two notable studies. The first explored parent-child communication about LFS (Valdez et al. 2018); the second explored how the developmental context of adolescent children influenced parental perspectives of genetic testing and family communication about LFS (Schultz et al. 2018). Both studies used the same design and reported on secondary qualitative analyses of the Alderfer et al. (2015) sample, which consisted of interviews with 46 parents from 39 families with at least one child (under 22 years) who had been offered genetic testing for LFS (Schultz et al. 2018; Valdez et al. 2018) (Table 3, p. 23).

An important limitation to this body of work is that it reports on a sample with potentially substantial recall bias about genetic testing and discussions of LFS: the mean time between the offer of testing and interview was 5.7 years (range 3 months to 17 years) for the 46 parent interviews included in the sample (Alderfer et al. 2015). It is also critically limited in that it focusses exclusively on parental points of view and experiences; consequently, there still lacks first-hand data on how young people experience LFS themselves. Despite this, these studies bear particular importance to the current inquiry because they signal a shift of focus in the field towards the implications of LFS for young people.

Valdez et al. (2018) specifically focussed on 14 parents from 10 families with at least one child who had tested positive for a *TP53* mutation. All parents (n=14/14) felt that open communication about genetic testing for LFS, cancer risk, and risk management with their children was important, and nearly all (n=13/14) felt their familial and personal experiences of cancer provided opportunities for conversations about LFS with their children. Importantly, 10/14 parents felt their child's involvement in LFS-related discussions needed to be developmentally appropriate—i.e., they needed to select a level of detail that would inform them of LFS but not cause confusion or alarm—and none endorsed covering all information during one conversation (Valdez et al. 2018). To this end, 64% (n=9/14) of parents described staging their discussions of LFS over time as their children grew older, imparting smaller, more easily understandable pieces of information.

Of the 20 children (median age 8 years) from these families, 17 had tested positive for a *TP53* mutation, but only ten were aware of their gene status (i.e., their

parents had told them). Of the parents ($n=7/14$) who had not yet spoken directly to their children about LFS, or told them of their positive *TP53*+ve status, the main reason for non-disclosure was to avoid increased burden for their children at what they considered to be a young age (Valdez et al. 2018). All parents, however, still endorsed the importance of family communication with their children and were planning future discussions around times where their children showed an interest. A minority reported that conversations about LFS with their children were difficult and described avoiding them altogether in some cases due to fear of how the conversation may go, or personal discomfort at confronting intergenerational cancer risk (Valdez et al. 2018). Only three parents reported having support from a genetic counsellor or physician in the disclosure of LFS to their children, and parents expressed a lack of guidance or support about how best to initiate these conversations (Valdez et al. 2018).

Schultz et al. (2018) showed a similar pattern of parental concern for communication about LFS to their adolescent children. Their analysis specifically addressed interview questions on adolescence and its relevance to LFS from the original data set reported by Alderfer et al. (2015), and showed that most parents (72%, $n=33/46$) felt that adolescence as a life stage influenced the importance of genetic testing for their children and/or how they spoke about LFS as a family (Schultz et al. 2018). Similar to the Valdez et al. (2018) analysis, parents felt it was important to discuss LFS with their adolescent children because of the risk of cancer during this period, and the need to make plans for surveillance if their children were found to have a *TP53* mutation (Schultz et al. 2018). Parents mostly felt that adolescence was the right time to begin discussions about LFS as their children had the cognitive capacity to begin understanding the complexities and implications of LFS and genetic testing compared to when they were younger (Schultz et al. 2018). This adds to evidence showing that parents wait until their children are old enough to understand LFS before beginning conversations about cancer and cancer risk (Valdez et al. 2018).

These studies both suggest that the timing and considerations of parent-child communication about LFS vary based on the life stage of the child. For parents with young children (i.e., under 12 years), discussions about LFS are delayed or tailored to appreciate their child's cognitive ability to understand the information without causing undue alarm or confusion (Valdez et al. 2018). Whereas parental discussions with adolescents were laden with a different set of concerns. A core concern was fostering the independence and autonomy of adolescents to become advocates for their own health

from an early age (Schultz et al. 2018). A second parental concern was the impact of learning about LFS on adolescent identity and self-esteem, and subsequent risk-taking behaviours (Schultz et al. 2018). Some parents felt that learning of LFS was an unnecessary burden during a time of emotional and identity development, and could cause negative emotional reactions, leading to their child feeling different and isolated among their peers (Schultz et al. 2018). Some parents felt this could contribute to increased risk-taking behaviours (e.g., smoking), and interestingly, 12 parents described concerns about the implications of their children exploring sexual relationships for the first time with LFS, and the potential for passing on genetic risk to the next generation (Schultz et al. 2018).

In sum, this body of work showed that parents recognise the importance of open and developmentally appropriate communication about LFS with their children (Schultz et al. 2018; Valdez et al. 2018). An important tension for parents, however, is balancing the timing of discussions against concerns for heightened psychological vulnerability and social maladjustment due to learning of LFS at a young age (Schultz et al. 2018; Valdez et al. 2018). Exactly how this tension played out differed based on the age of children at the time of communication. Key parental concerns were focussed on the impact of learning LFS on their child's growing sense of identity, risk-taking behaviours, reproductive choices, feeling different among peers, and being burdened at a time in life that is already complex (Valdez et al. 2018). These studies mark an important shift in psychosocial research for LFS and begin to address some of the implications of LFS for young people, though not from the perspectives young people themselves.

2.3.2.2 Experiences of whole-body risk management for LFS

Running parallel to research into the clinical outcomes of whole-body risk management for LFS, there has been a concerted effort to also assess the psychosocial implications associated with screening. This is a growing field at present and has mostly focussed on the impact of using annual rapid whole-body MRI alone, not the full suite of surveillance techniques used in the Toronto protocol. Of note, due to the nascence of experimental whole-body screening programs, current evidence is unable to shed light on the long-term (over one year) psychosocial impact of screening.

2.3.2.2.1 *Psychological harm*

A primary concern of whole-body risk management for LFS is the potential for it to cause more harm than good: i.e., cause clinically significant psychological distress that outweighs any survival benefits from early detection. Quantitative research in this area

to date, using measures of psychological distress (e.g., the Hospital Anxiety and Depression Scale [HADS] and the Impact of Events Scale [IES]), has allayed some of the fears that intensive whole-body MRI is harmful, showing that it confers minimal short-term psychological distress (McBride et al. 2017; Bancroft, Saya, Brown, et al. 2019).

Preliminary evidence of the psychosocial impact of whole-body MRI was provided by the Australian LFS working group, who used a longitudinal mixed-method approach to evaluate psychosocial outcomes in a cohort of 17 adults with a *TP53* mutation (mean age 43.3, range 21-65) (McBride et al. 2017). The quantitative arm used measures of psychological distress at baseline, 2 and 12 weeks post whole-body MRI. Mean HADS scores were highest at baseline, but well below clinically significant cut-offs ($\geq 11/21$) for anxiety (5.3/21, SD 3.0) and depression (2.5/21, SD 2.1); though there was a significant decrease in mean anxiety scores between baseline and two weeks post-MRI (1.2, 95% CI 0.17-2.23, $p=0.025$) (McBride et al. 2017). While being statistically significant, this reduction was less than the minimally important difference for anxiety and depression scores on the HADS (i.e., a 1.5 point change in scores) (Puhan et al. 2008), suggesting it has limited clinical relevance. Interestingly, mean cancer worry scores for the cohort at baseline (14/32, SD 4.8) met the clinical cut-off for severe cancer fear (i.e., $\geq 14/32$) (Custers et al. 2014) and did not significantly reduce at 12 weeks post-MRI (mean reduction 0.21, 95% CI -1.26-1.69, $p=0.758$) (McBride et al. 2017).

From these key findings, McBride et al. (2017) showed that attending whole-body MRI did not cause a short-term increase to the already low levels of anxiety and depression in their small cohort of individuals with a *TP53* mutation, but nor did it help to lower clinically significant background cancer worry. The background of high cancer-related worry in their cohort, which is consistent with previous work (Lammens, Aaronson, et al. 2010; Peterson et al. 2008), means it is difficult to assess the psychological impact of engaging in whole-body MRI itself versus having LFS from this study (McBride et al. 2017). Without a control arm to compare psychological outcomes of whole-body MRI for individuals without LFS, the authors were unable to meaningfully evaluate its impact. Further, having a cut-off 12 weeks post-MRI meant long-term impact was also unable to be assessed.

Overcoming some of these limitations, the UK LFS working group recently examined the psychosocial outcomes of whole-body MRI for LFS in a cohort of 44 adults (mean age 37.6, range 19-58) with a *TP53* mutation and 44 sex and age (± 5 years) matched healthy population controls (Bancroft, Saya, Brown, et al. 2019). Controls had

no personal history of cancer and minimal family history (Table 3, p. 23), and underwent the same study procedures as cases (i.e., underwent MRI and received all survey measures). The authors used a longitudinal study design, administering psychological measures at seven time points: baseline, immediately pre-MRI appointment, pre- and post-MRI results, and 12, 26, and 52 weeks post-MRI results (Bancroft, Saya, Brown, et al. 2019).

Substantiating McBride et al.'s (2017) earlier work, the UK group also found that individuals with a *TP53* mutation presented to screening with a background of persistent, high cancer worry (Bancroft, Saya, Brown, et al. 2019). Individuals with a mutation had significantly higher levels of severe cancer worry (i.e., mean cancer worry scores $\geq 14/32$) compared to controls at baseline, 26 weeks and 52 weeks, and higher levels of clinically significant intrusive and avoidant thoughts about cancer across all time points compared to controls (Bancroft, Saya, Brown, et al. 2019). This, however, did not correlate with a prevalence of clinically significant anxiety or depression, as there were no differences between individuals with a mutation and controls at any time point using a HADS score of 11 and above, which is similar to other populations at high genetic risk of cancer (Bancroft, Saya, Page, et al. 2019; Brain et al. 2012).

Critically, Bancroft, Saya, Brown, et al. (2019) demonstrated that there were no differences in clinically significant intrusive and avoidant thoughts about MRI between individuals with a *TP53* mutation and controls across all time points. These findings strongly suggest that while individuals with a *TP53* mutation may have high, residual cancer worry, this is not impacted by whole-body MRI screening itself. A minority of participants (14% of individuals with a *TP53* mutation and 8% of controls), reported persistent, clinically significant levels of intrusive and avoidant thoughts about MRI 12 weeks post-results (Bancroft, Saya, Brown, et al. 2019). Suggesting that, similar to the minority (~25%) of individuals who experience clinically significant distress when undergoing genetic testing for LFS and may need additional support during genetic counselling (Lammens, Aaronson, et al. 2010), a minority of participants in screening programs may require targeted support for engaging in regular whole-body MRIs.

Consistent with McBride et al. (2017), highest mean anxiety scores on the HADS were reported at baseline for both individuals with a *TP53* mutation and controls, and there was a significant decrease in anxiety for those with a mutation between baseline and pre-results ($Z=-2.07, p=0.04$) (Bancroft, Saya, Brown, et al. 2019). There was also a significant decline in intrusive thoughts about cancer among individuals with a *TP53*

mutation between pre-results and 12 weeks after receipt of MRI results ($Z=-2.15$, $p=0.032$) (Bancroft, Saya, Brown, et al. 2019). This evidence suggests that participants are most distressed at baseline, perhaps because they are new to the processes and implications of intensive cancer screening and surveillance, which decreases over time as screening becomes normalised. It also suggests there could be a temporary increase in anxiety prior to whole-body MRI due to the anticipation of what may be detected, which also decreases over time after receiving results. This is broadly consistent with research on MRI for inherited breast cancer screening, that shows that high levels psychological morbidity at baseline significantly reduce after screening (Hutton et al. 2011).

2.3.2.2.2 *'Scan-xiety' and participant experiences of whole-body risk management*

While the assessment of psychological distress is important to establish the safety and acceptability of whole-body screening for LFS, the broader psychosocial implications are still under investigation. Only two qualitative studies have reported on the experiences of individuals enrolled in whole-body surveillance for LFS: a USA-based study using a one-off interview design with a sample of 20 adults (mean age 39.1, range 18-61) (Ross et al. 2017); and the qualitative arm of the McBride et al. (2017) mixed-method study, which interviewed participants at two time points ($n=14$ at baseline before commencing surveillance; $n=9$ at 6 months).

Broadly, both studies suggest that participants feel the perceived benefits of screening outweigh the perceived burdens (Ross et al. 2017; McBride et al. 2017). Consistent with research conducted prior to the Toronto protocol (Lammens, Bleiker, Aaronson, et al. 2010), reported benefits of screening for LFS consist of early detection of cancer, improved survival, and peace of mind, which participants attributed to worrying less about cancer and knowing their health status (Ross et al. 2017; McBride et al. 2017). Moreover, participants described LFS as being more 'liveable' with surveillance, because it provided them a way to cope with their high cancer risk and reframe their perceptions of LFS as not being a 'death sentence' (Ross et al. 2017). Having a 'clinical point of contact' and a dedicated team looking after their concerns also conferred a sense of safety for some participants (McBride et al. 2017).

A key burden of whole-body risk management for LFS described by participants is the experience of 'scan-xiety': anxiety in the lead up to screening stemming from the uncertainty of what may be found from a 'scan' (Ross et al. 2017; McBride et al. 2017). This patient-reported experience is consistent with, and helps to explain, the increasing trajectory of distress scores on the lead up to MRIs and decline in the period afterwards

(Bancroft, Saya, Brown, et al. 2019; McBride et al. 2017). How scan-anxiety plays out over longer periods of time, and for modalities other than whole-body MRI, however, is unclear. Anticipating a cancer diagnosis at potentially each screening appointment could contribute to long-term distress and may intersect with the developmental tasks of adolescents and young adults in ways we do not yet understand. This is of prime concern for individuals diagnosed with LFS from a young age as they stand to engage in screening over the course of their lifetime.

Other perceived burdens consisted of logistical constraints of attending MRI, mainly around insurance cover in the USA (Ross et al. 2017), and worry about access to subsidised MRI after the cessation of the experimental programs (Ross et al. 2017; McBride et al. 2017). Participants also reported that attending and waiting for results from additional investigations from MRI were stressful (McBride et al. 2017). Interestingly, this was not corroborated in the Bancroft, Saya, Brown, et al. (2019) study, where those who underwent additional investigations after MRI for an abnormality did not experience clinically significant anxiety or depression compared to those who did not.

In sum, research focussing on the psychosocial implications of screening among individuals with LFS has outlined three important points of relevance to this thesis. First, there is a notable lack of data addressing the broader psychosocial implications outside of measurable psychological distress. How screening for LFS as a whole program (not just MRI) may impact one's life is poorly documented, especially from a young age. Second, the long-term implications of engaging in a potentially cyclical pattern of distress from attending screening for LFS remain unknown. This is mainly due to the nascence of research programs, and with time, current protocols may be better placed to understand the long-term implications of screening. Third, and most relevant to this thesis, is that data specific to children and young people's experiences of whole-body surveillance are sorely lacking. The mean age of participants across the studies mentioned in this section ranges from 37.6-43.3 years (Table 3, p. 23) (Ross et al. 2017; McBride et al. 2017; Bancroft, Saya, Brown, et al. 2019). One of the main aims of the Toronto protocol is to address cancer burden among children and young people with LFS. It would therefore be remiss to conclude psychosocial research into screening for LFS without including the perspectives and experiences of nearly half the population it is designed for.

2.3.2.3 The impact of LFS on family systems

A collection of work originating from the first and largest continuing LFS study at the National Cancer Institute (NCI; USA) has provided important evidence on the impact of LFS on the family system (Peters et al. 2016; Young et al. 2018; Pantaleao et al. 2019). Although each study described here has a specific focus, they all stem from an ongoing program of interview-based research with individuals, couples and families participating in the NCI LFS cohort (Table 3, p. 23). One of the limitations of this NCI program is that it reports on a predominantly white adult population, who are well educated, heteronormative, mostly religious, and well supported by clinical and psychosocial services. Families with LFS from more diverse demographic backgrounds with less specific support may have vastly different experiences.

The first study of the program was conducted by Peters et al. (2016), who investigated prevalent types of social support among families with LFS using individual interviews (n=66) and co-construction of a Coloured Eco-Genetic Relationship Map (CEGRM), and examined emotional distress using the Brief Symptom Inventory (BSI-18) (n=59/66). Participants reported low global emotional distress, with no differences between gender, cancer or gene status (Peters et al. 2016). Only four participants showed clinically significant levels of distress, which from interview data was not due to LFS per se, but the intersection of multiple stressful life events (e.g., miscarriage, losing their job etc.). Contrary to findings suggesting lack of social support increased distress (Lammens, Aaronson, et al. 2010), Peters et al. (2016) showed there was no clear link between distress scores and the number and types social support described by participants.

This clearly suggests that not all families with LFS are psychologically vulnerable, as previously suggested by Oppenheim et al (2001), but also points to this particular cohort being resilient for reasons not related to social support. While it is unclear how long these families had been living with knowledge of LFS, they were recruited to the NCI study from 2011 (Peters et al. 2016). Perhaps this cohort was particularly resilient because they had long-term engagement with a dedicated team of multi-disciplinary clinicians and researchers at the NCI. This still remains an area for future research, but is broadly consistent with findings that suggest having a regular clinical point of contact may provide a sense of safety for individuals with LFS (McBride et al. 2017).

In terms of support networks, Peters et al. (2016) found that participants had a range of multi-dimensional support (i.e., informational, practical/logistical, emotional, and spiritual support) that was provided from friendship networks of 1-6 'good friends'.

Nearly half the cohort (48.5%, $n=32/66$) reported having no defined social group for support, but of those who did (51.5%, $n=34/66$), religious communities were the most common (29.4%, $n=10/34$). Considering one third of Australians have no religious affiliation (Australian Bureau of Statistics 2016), it would be interesting to assess the level of engagement with religious communities among Australians with LFS to compared to the USA in future research. Overall, these data mainly suggest that friends hold important roles of support in the context of LFS (Peters et al. 2016). In some cases, participants even felt their friends had the licence to speak more 'frankly' than family in emotionally fraught situations, as they were external to complex family dynamics related to multigenerational legacies of cancer and bereavement (Peters et al. 2016). One male spouse described:

With family dynamics, if you actually start talking about things that are real, it's uncomfortable. It's the opposite with my friend where I can be very vulnerable and talk about hard things. I can share my feelings and thoughts and get support and share my struggles or whatever (Peters et al. 2016: 536).

Notably, Peters et al. (2016) also showed that men reported smaller and less diverse support networks compared to women, with half as many confidantes (trusted friends) and more friends who provided no specific types of social support (Peters et al. 2016). Further, women more frequently nominated friends as confidantes whereas men nominated their spouse, suggesting men were more reliant on their spouse for support (Peters et al. 2016). Lammens et al. (2011) previously indicated that partners of individuals with LFS can also exhibit clinically relevant levels of distress, which is directly related to distress experienced by the high-risk spouse themselves. A cause for concern may be that, if highly distressed men with LFS regularly and disproportionately place their support needs on their spouse, it could lead to increased distress for them both as a couple.

A methodological drawback to Peters et al.'s (2016) description of social supports in families with LFS was the use of the CEGRM in data collection. While the CEGRM was effective at quantifying breadth and depth of support in the cohort, it was unable to explain how the relationships nominated by participants work to be supportive. A more recent study from the NCI characterised how couples helped each other to cope with LFS in more depth using couple interviews ($n=26$ dyads) (Young et al. 2018). Notably, in 21/26 dyads, the female partner had a *TP53* germline mutation. The authors showed that couples living with LFS experience a state of constant apprehension and ambiguous

danger from LFS-related uncertainties (i.e., high cancer risk and intensive screening) (Young et al. 2018). Couples that had joint ownership over challenges were more resilient than couples who coped independently of each other when facing the high cancer risk and screening burden associated with LFS (Young et al. 2018).

The most recent qualitative study from the NCI program showed that families with LFS commonly nominate a ‘family health leader’ who provides support to other members across generations when navigating the complicated healthcare decisions related to LFS (Pantaleao et al. 2019). From 23 interviews with family groups of 2-5 members (n=62 individuals, n=46/62 *TP53*+ve, aged 7-40 years), the authors showed the role of leader shifted over time based on the sickness or death of family members, or the maturation of younger generations (Pantaleao et al. 2019), suggesting a generational shift in support dynamics over the family life cycle. This study strongly suggests that providers must be attuned to family dynamics in the context of LFS, and while much of genetic counselling practice has the family unit in mind, in practical terms, it can be dominated by individualistic, client-centred approaches (Meiser et al. 2008). Broadening the scope of care to consider family-based approaches may be beneficial and is worthy of further investigation in the context of LFS.

In sum, this body of work demonstrates that not all families with LFS are psychologically vulnerable, though it is unclear whether having of a wide range of friends who offer different types of support promotes resilience. This makes for a complex mixture of findings regarding the interactions of social support and isolation with psychological distress due to LFS, and requires more research. More research on males would be beneficial to understand their social networks more clearly and how this contributes to couple coping if they are partnered. Lastly, these data strongly indicate that identifying family leaders and types of couple coping (independent or shared) during genetic counselling may be important considerations in offering targeted psychosocial support for individuals and families with LFS.

2.3.2.4 The experiences of young people from families with LFS

As outlined in the beginning of this chapter, the bulk of cancer risk associated with *TP53* mutations manifests early in life. Indeed, LFS has serious health implications for young people, with up to 50% of the tumour burden in the LFS population occurring by the age of 30 (Mai et al. 2016). Importantly, for young people with LFS, the physical and psychosocial burden of living with high, multi-organ cancer risk occurs at a formative and transitional life stage. During this life stage young people navigate—with varying

capacity—identity exploration, growing independence from family and increasing self-sufficiency, social role transitions, romantic relationships and family formation (Erikson 1963; Havighurst 1972; Arnett 2000; Patton and Temmerman 2016). As a result, young people with LFS face significant life cycle challenges that distinguish them from older individuals with a *TP53* mutation, who have been the focus of LFS research to date.

At present, the psychosocial implications of living with LFS as a young person are poorly documented. Given the intensity and variability of a young person's development, and the complex, grave, and variable health implications of LFS, a primary aim of this thesis is to explore how young people experience LFS. By investigating the interface between LFS as an illness and the core developmental tasks of adolescence and young adulthood, this thesis will generate important findings for developmentally appropriate genetic counselling. This rationale is also evident in the only study to date that has focussed on the experiences of young people from families with LFS (Alderfer et al. 2017).

Alderfer et al. (2017) explored how AYAs from families with a *TP53* mutation viewed predictive genetic testing for children in general (i.e., not just LFS). Sampled from their earlier work (Alderfer et al. 2015), the study consisted of 12 participants, aged 12-25 years (mean 17.8) at their interview, and aged 3-20 years (mean 11.4) when offered genetic testing. Seven participants were *TP53*+ve; three *TP53*-ve; one was assumed *TP53*+ve but untested; and, one was at 50% risk of a mutation and planning testing (Alderfer et al. 2017). Although novel, the mismatch between the aims of the study and a portion of the sample highlights a critical drawback to the research design.

If the intended aim was to explore how AYAs at high genetic risk of cancer viewed predictive genetic testing for children, the inclusion of three participants who were unaware of their *TP53*+ve status and of their family being diagnosed with LFS is highly questionable. First, being unaware of their high genetic risk of cancer, these participants were unsuitable for the aims of this study. Second, the implications of interviewing young people about topics related to their family condition, for which they had no knowledge, raises serious ethical concerns about the conduct of this research; namely, the provision of informed consent and the risk of harm from disclosing previously unknown genetic information to young people. In addition to this mismatch, the study was small ($n=12$), heterogeneous, and consisted of short interviews (16-40 minutes). Without the strength of a well-designed, small qualitative study (i.e., using in-depth interpretive or narrative methods), their content analysis was restricted to being cursory and did not reach their intended level of 'data saturation' (Alderfer et al. 2017).

Despite these limitations, Alderfer et al.'s (2017) study was still the first to show an interest in, and document, young people's experiences of LFS. The authors outlined the need to further explore how young people navigate genetic testing for LFS at an age where parents still play a major role in decision-making, and the need to further elucidate how LFS may intersect with developmental goals during this period of life: i.e., reproductive decision-making, relationships with family (e.g., siblings), career planning, intimate relationships, and developing identity (Alderfer et al. 2017). These hypothesis-generating findings offered important strands of enquiry for this thesis. The limitations of the evidence provided, however, meant a broader range of research was needed to adequately inform the project. One of the sub-aims of this thesis was therefore to conduct a systematic review and synthesise research investigating how young people live with inherited disease more generally (Chapter 6). This provided context for the current investigation into young people with LFS.

2.3.3 Summary

This section described the psychosocial aspects of living with LFS, dividing current research into two distinct phases: before and after the widespread adoption of the Toronto protocol. Before the Toronto protocol LFS was considered a devastating condition with limited intervention and surveillance options. As a result, predictive genetic testing was a highly distressing experience among ~25% of adults, and health professionals were reticent to offer predictive genetic testing to children because of a limited medical benefit. Families with LFS who had experienced multiple cancer diagnoses and deaths were shown to be psychologically vulnerable, cementing LFS as one of the most severe inherited cancer syndromes. More recent research, however, shows that some families with LFS are psychologically resilient and that friendship networks may be an important source of multidimensional support. Family also provided critical support: choosing family leaders that could guide relatives through the complicated healthcare decisions related to LFS stood out as an important family task, as did developing a shared approach to coping with the challenges LFS as a couple.

With the introduction the Toronto protocol, advances in whole-body risk management have triggered a shift in the perceived severity of LFS. Early evidence suggests that whole-body MRI for LFS confers a modest but important survival advantage from the early detection of resectable cancers, a sense of control over one's cancer risk, and minimal short-term psychological harm. But the long-term impacts and broader psychosocial implications of intensive risk management remain unknown,

especially for those who engaged from a young age, and for the full suite of cancer surveillance modalities used in the Toronto Protocol, not just whole-body MRI.

Nonetheless, among parents in North America with access to the Toronto protocol, decisions to test their children for LFS were newly motivated by an opportunity to promote the health of their child and reduce uncertainty about gene status, resulting in high uptake of testing (>90%). This sparked an interest in parent-child communication about LFS, and parents were found to tailor discussions to their child's developmental stage in spite of limited support from health professionals. Notably, for adolescent children, discussions of LFS were considerate of key developmental tasks such as their growing autonomy, identity development, risk taking behaviours and peer acceptance. Despite touching on the importance of youth development in the context of living with LFS as a family, the perspectives of young people themselves are critically lacking from this body of work, which forms a key part of the rationale for this thesis.

2.4 Developmentally appropriate genetic counselling

The surge in research exploring how young people live with, or at risk of, inherited disease over the past decade has led to widespread calls for models of developmentally appropriate care in clinical genetics (Duncan and Young 2013; Pichini et al. 2016; Godino et al. 2019; Godino et al. 2018; Godino et al. 2016; Vetsch et al. 2018). The unique skillset of genetic counsellors in helping individuals and families interpret, make meaning and adapt to their genetic risk of disease means they are best placed provide this specialised care. Yet genetic counsellors are in high demand as genomic medicine becomes increasingly popular in clinical practice globally (Ormond et al. 2018), resulting in a workplace shortage of genetic counsellors (Dobson DaVanzo & Associates 2016; Abacan et al. 2019).

To meet this shortage, there is renewed consideration of how genetic counsellors can 'work at the top of [their] scope of practice where [their] unique skills are most valuable within the changing landscape of genetics and genomic testing' (Abacan et al. 2019: 186). The field has begun to recognise that traditional models of genetic counselling that focus on the genetic testing episode are no longer feasible or desirable with all patient groups. Overseeing every patient for pre-test genetic counselling based on the model first proposed for predictive testing for Huntington disease is unsustainable with increasing patient numbers (Wexler 1992; Craufurd and Tyler 1992; Geller et al. 1997; Soldan et al. 2000). This model of practice overloads genetic counsellors with the task of

information provision pre-test, which for some patient populations can be effectively performed by other means (e.g., with artificial intelligence) (Kearney, Wojcik, and Babu 2020) or other health professionals (e.g., in mainstreaming for breast and ovarian cancer genetic testing) (George et al. 2016; Percival et al. 2016; Kentwell et al. 2017). Importantly, traditional models also pay little attention to structured long-term psychosocial follow-up, leaving some patients with continuing psychosocial needs without targeted genetic counselling support.

Instead, there must be a rationalised provision of genetic counselling services. Genetic counsellor skills need to be used more effectively and to their fullest extent with patient populations with the greatest need (Abacan et al. 2019). One such patient population consists of AYAs with high genetic risk of disease, a prime example being young people from families with LFS. With psychosocially and clinically complex inherited conditions that have implications for the AYA years and beyond, the AYA population requires specialised care and attention to navigate the complexity of their condition at a transitional life stage, and genetic counsellors are optimally positioned to provide it.

A collection of studies have demonstrated, however, that some genetic counsellors find it difficult to manage the life stage-related complexities of AYAs with a genetic condition (Werner-Lin et al. 2015; Tse et al. 2013; Gaff, Lynch, and Spencer 2006). Indeed, despite widespread support from the research community for developmentally appropriate genetic counselling methods, youth-friendly models of care in clinical genetics are lacking, and the intersection between AYA development and genetic risk remains challenging to navigate for AYA patients, their families, and health professionals alike (Duncan and Young 2013; Pichini et al. 2016; Godino et al. 2019).

To help address the unique challenges of working with young patients, Young et al. (2019) recently described the first framework for youth-friendly genetic counselling practice. The authors' framework was developed in the context of growing international recognition that health services deliver higher-quality care for young people when they are orientated to the developmental tasks of their life stage (Young et al. 2019; Sawyer et al. 2016; Tylee et al. 2007; Sawyer et al. 2012). The Young et al. (2019) framework integrates aspects of youth-friendly healthcare that are widely adopted in other disciplines (e.g., adolescent medicine, and adolescent and young adult oncology). Core aspects include:

- Engagement (i.e., specific approaches to building rapport and trust with young people);
- Consent, capacity and confidentiality (i.e., understanding the complexities of a young person's cognitive and legal capacity to make autonomous decisions regarding their healthcare, and a young person's right to keep their medical/psychosocial information confidential from their parents/guardians);
- Communication (i.e., specific communication skills for young people to effectively build a counselling relationship and provide age appropriate information about complex genetic concepts);
- Psychosocial risk assessment (i.e., the use of clinically validated assessment tools to holistically understand the circumstance of young person's life and identify sources of resilience and stress); and,
- The environment of their care (i.e., a physical environment that is tailored for young people and flexible administrative processes; personal communication, L. Holland, 20 September 2016).

Importantly, these aspects of youth-friendly care are not aimed at superseding well-established genetic counselling practices, but rather complement them to accommodate the needs of younger patients as distinct from adults (Young et al. 2019).

While the Young et al. (2019) framework is a landmark piece of work in the field, how health professionals meet the challenges of working with AYAs in their practice remains relatively undocumented, and entirely absent for the LFS population. Further, the Young et al. (2019) framework was not yet in wide use at the time of this research, and many genetic health professionals have stated they require additional training to work effectively and confidently with young people (Tse et al. 2013; Werner-Lin et al. 2015). Consequently, health professionals who care for young people from families with LFS may be unaware of the developmental needs of this population, which could have implications for their supportive care. Exploring how health professionals provide care to young people from families with LFS was therefore a core aim of this research.

2.5 Research aims

This literature review has shown that we lack experiential data on how individuals experience LFS over the life cycle, especially during the AYA period. Concurrently, we

have a limited understanding of how health professionals provide developmentally appropriate care to young people from families with LFS. In order to attend to these shortcomings in the literature, this thesis comprises of the following aims.

Project aim

To explore the psychosocial implications of living with Li-Fraumeni syndrome for adolescents and young adults, and how they are cared for by health professionals.

To address this overarching aim, the project is comprised of two phases:

Phase 1 – Qualitative inquiry

Aim 1: To explore the experiences of adolescents and young adults who live with, or at 50% risk of, a pathogenic germline mutation in *TP53*.

Phase 2 – Quantitative inquiry

Aim 2: To describe current Australasian genetic and oncology health professional practice for adolescents and young adults who live with, or at 50% risk of, a pathogenic germline mutation in *TP53*.

2.6 Summary

Li-Fraumeni syndrome is an early onset inherited cancer condition with severe implications for young people, both clinically and psychosocially. The Toronto protocol represented a sea change moment in the perceived intractability of LFS and precipitated a wave of psychosocial research for LFS that provides an important footing from which this research can progress. Key areas of this evidence base include parent-child communication about LFS, experiences of whole-body risk management, adult and parental experiences of genetic testing, and the intergenerational impact of LFS on families as systems. Missing from this groundswell in psychosocial, mainly qualitative research, however, has been a deliberate focus on young people's experiences. Considering the early age of onset and high cancer risk during the AYA years for young people with LFS, their experiences are likely unique and require empirical attention. Concurrently, youth-friendly models of care have only just begun to receive attention from the genetic counselling profession and are underdeveloped, leaving young people with LFS potentially at sea when attending clinical genetics services for supportive care. In outlining these key developments and shortcomings of LFS research to date, this chapter provides a strong rationale for addressing the two main aims of this thesis. In

order to address these aims, the next chapter outlines the philosophical and theoretical basis of the research design.

3 Philosophical and theoretical framework

3.1 Overview

The preceding chapter highlighted the need to explore the experiences of young people from families with LFS, and the experiences of the health professionals who care for them. In order to mount a well-founded investigation into these experiences it is important to understand the philosophical and theoretical basis of the research design. The aim of this chapter is to: 1) situate and describe the philosophical influences on the research design, stating the personal and systemic biases inherent to the approach taken; and 2) to provide background knowledge of the four main theories that have informed the research design. By gaining and understanding of these two critical aspects of the project, the purpose of the research design, and the strengths and limitations of this approach will be made clear.

3.2 Philosophical framework

3.2.1 Paradigms

Paradigms are ways ‘to summarise researchers’ beliefs about their efforts to create knowledge’ (Morgan 2007: 505). In the broadest sense, they are worldviews and philosophical stances that shape how we think about the nature of reality (ontology), the construction of knowledge (epistemology), and the nature of ethics and values (axiology) (Kuhn 1970). Paradigms provide a philosophical basis for research design choices and are a key component of any inquiry. There have been three major paradigmatic shifts in research: the first research paradigm consisted of positivist and post-positivist approaches; the second research paradigm consisted of critical theory and constructivist approaches; the third research paradigm consisted of pragmatist approaches (Table 4, p. 48) (Rapport and Braithwaite 2018; Guba and Lincoln 2005; Johnson and Onwuegbuzie 2004).

Fundamental differences between the first and second research paradigms have been the basis of the ‘paradigm wars’: all or nothing philosophical debates about the veracity of knowledge claims from broadly positivist compared to broadly constructivist approaches to inquiry (Gage 1989; Guba and Lincoln 2005). The prominent discourse resulting from the paradigm wars is the ‘incompatibility thesis’, which states knowledge gained from these different approaches to research are incommensurable (Howe 1988). That is, knowledge gained from under the banner of constructivism, endorsing researcher subjectivity and qualitative methods, is diametrically opposed and incomparable to knowledge gained from under the banner of positivism, endorsing researcher objectivity and quantitative methods (Biesta 2010). This deep opposition lead to an estrangement between the ‘scientist’ and ‘social scientist’, both with competing claims for the superior approach to research (Rapport and Braithwaite 2018).

An important practical limitation to the dogmatic paradigm divide is that it can preclude researchers from appreciating the distinct elements of research design in their own right. Drinking the Kool-Aid, so to speak, and adopting the conventional paradigm of one’s fellow researchers can obscure important research decisions ranging from the abstract (i.e., ontology, epistemology, and axiology) to the increasingly mechanical (i.e., methodology and methods) (Biesta 2010). In so doing, researchers may miss, or fail to make explicit, all the steps, decisions and values they have adopted when carrying out their research. A common confusion is to assume epistemology and method are synonymous: for example, constructivism necessitates qualitative data collection methods. Where in fact, epistemology

does not specify which data collection and analytical methods researchers must use, and is a critical research decision that must be considered in its own right (Johnson and Onwuegbuzie 2004).

It is not my intention to engage with the ongoing paradigm debate, although it is important to mention here because of its extensive impact on research practices. In brief, I have adopted a pragmatic approach, which is situated in the *Third Research Paradigm*. Pragmatism argues for methodological pluralism and for convergence of different types of knowledge over exclusivity (Rapport and Braithwaite 2018). In so doing, it skirts the metaphysical impasse symptomatic of the paradigm wars (Johnson and Onwuegbuzie 2004). In this section, I 'out' my assumptions lying behind the research design choices for this project, and show how they stem from my core beliefs about the world. First, I will outline my philosophical assumptions, and my personal values and beliefs. Second, I will provide a synthesis of pragmatism and why I adopted this approach for my project.

Table 4. Paradigms of research: principal features

	First paradigm		Second paradigm		Third paradigm	
	Positivism	Post-Positivism	Constructivism	Critical Theories ^a	Participatory	Pragmatism
Overview	Realists, 'hard science' researchers	A modified form of positivism	Gain understanding by interpreting human perceptions	Create change to benefit those oppressed by power	Transformation based on democratic participation between research and subject (post-modern)	Convergence of purist approaches, metaphysical pluralism, combinations of multiple methods
Ontology	Naïve realism: 'real' reality but apprehensible	Critical realism: 'real' reality but only imperfectly apprehensible	Relativism: local and specific co-constructed realities	Historical realism: 'virtual' reality shaped by social, political, economic, ethnic and gender values	Participative reality: subjective-objective reality, co-created by mind and given cosmos	Transactional realism: rejects mind-body dualism, physical and constructed worlds equally 'real'
Epistemology	Objectivist, findings True	Objectivist, critical tradition, findings probably true	Transactional/subjectivist; co-created findings	Transactional/subjectivist; value-mediated findings	Critical subjectivity in participatory transactions; co-created findings	Modified transactional, intersubjectivity; findings as warranted assertions
Axiology/values	Excluded – influence denied		Included - formative			
Nature of knowledge	Verified hypotheses established as facts or laws	Non-falsified hypotheses that are probable facts or laws	Individual and collective reconstructions	Structural/historical insights	Primacy of practical knowing; critical subjectivity; living knowledge	Co-constructed and based on 'real' world; findings are fallible

Table 4. cont.

Researcher position	Disinterested scientist, researcher is distant and should not influence decisions	Researchers are removed from the process, but concerns about its results	Co-constructor of knowledge; understanding and interpreting meaning of lived experiences	Researcher as activist and transformative intellectual: producing a fair society through social justice	Primary voice manifested through self-reflective action; secondary voices in illuminating theory and narrative	Pluralist, versatile
Data type	Statistical, Precise, Explanatory		Linguistic, Descriptive, Interpretive			Combined (Statistical and Linguistic)
Methodology	Randomised controlled trial, before and after study, time series, interrupted time series, cohort study, systematic review		Ethnography, case study, phenomenology, grounded theory, meta-ethnography, meta-narrative			Mixed-methods (verbal, visual and numerical), meta-synthesis
Methods	Scientific measurements and computational techniques		Focus Groups, Interviews, open-ended questionnaires/proformas, observations, participant observations			Quantitative and qualitative data that can be synthesised
Data characteristics	Set, precise, population-based, explanatory, generalisable		Interrogative, in-depth, rich, patterned, idiographic			Dichotomous, situational, pragmatic, triangulated
Hegemony	In control of publication, funding, promotion, and tenure		Seeking recognition and input; offering challenges to predecessor paradigms, aligned with post-colonial aspirations			

^aCritical theory includes critical feminist, race and queer theory.

Source: Adapted from Rapport and Braithwaite (2018); Guba and Lincoln (2005); Lincoln, Lynham, and Guba (2018).

3.2.2 Philosophical assumptions

3.2.2.1 Critical realism

Ontology, epistemology and axiology make up one's philosophical stance to research. My philosophical stance adopts the approach argued by critical realists, which retains a realist ontology while accepting epistemological constructivism (Maxwell 2012). This means that my ontological stance is realist, and I take 'the view that entities exist independently of being perceived, or independently of our theories about them' (Philips 1987: 205). Put simply, we are part of a physical world that is independent of our understanding of it: there is a real world 'out there'. In contrast, my epistemological stance is constructivist (or relativist). I believe that despite there being an objective world 'out there', we cannot possess an objective or certain knowledge of it. This is because our knowledge of the world is inevitably interpretive and coloured by our values, beliefs and biases: there is no one 'correct' understanding of the world that is independent of any particular view point. That is, our perceptions of reality are inherently subjective and not straightforwardly representational of the 'real world' (Maxwell 2012: 55). In this way, there are myriad valid perspectives on reality and we can accept alternative valid accounts of any phenomenon. Critical realism in this sense is a welcome partner to the pragmatic approach to research I will describe below and its appeal to 'warranted assertions' (Biesta 2010).

3.2.2.2 Axiology and values

Axiology, the branch of philosophy that addresses ethics, aesthetics, and religion, is a basic foundational dimension of one's paradigm (Guba and Lincoln 2005). My axiological stance is that we are not value-free, and that the role of personal, societal and cultural values in research must be made clear. Our values impact how we go about research in many ways, ranging from deciding what is important to study to more controversial, implicit values that may have unintended consequences. To avoid operating from an implicit value base that could greatly influence my research, I will explicitly describe my values and their origin here.

As a genetic counselling researcher, my value base is centred on the importance and utility of genetic information for individuals and families. Because of its predictive, familial and lifelong implications, it is unique among other types of medical information. Yet, I recognise that emphasising the uniqueness of genetic information is an extension of genetic exceptionalism (Green and Botkin 2003). The underlying value I ascribe to genetic information is a core value I bring to this research and a deliberate focus, and while other types of medical information nonetheless important, they are not the focus of this research.

More controversially, genetic counselling research is also influenced by the privileged position of genomic medicine. That is, presently, genomic medicine primarily benefits the ‘privileged few’, who are invariably of white European ancestry (Bustamante, De La Vega, and Burchard 2011). The overwhelming majority evidence for genomic medicine has been ascertained from white European populations, leaving populations of different descent (e.g., Asian, African, Hispanic and Latin American, Arab and Middle Eastern, Native peoples, and Pacific Islander ancestries) vastly underrepresented in research (Bustamante, De La Vega, and Burchard 2011; West, Blacksher, and Burke 2017; Popejoy and Fullerton 2016). Consequently, the extensive body of work undertaken in genomic research and its translation to clinical practice is almost exclusively applicable to people of white European descent, which has major implications for the equity of genomic medicine.

My project, focussing on how young Australians experience a rare inherited cancer condition (defined by families of white European ancestry) rests upon the message being broadcasted by genomic research currently: ‘the genomes of European descendants matter the most’ (Popejoy and Fullerton 2016: 163). Seen from a critical theory lens, this message is an extension of colonial values in genomic medicine, and exacerbates the systematic differences in health outcomes resulting from social disadvantage (West, Blacksher, and Burke 2017). I do not personally believe this message, nor does the aim of my project seek to contribute to this message. Nonetheless, the ascertainment bias with genomic research means the young people and families that are relevant to my research questions are mostly of white European descent. Consequently, in a small way, my project unintentionally contributes to the disparities in genomic medicine and the genetic counselling research that surrounds it, and I explicitly acknowledge that here.

In health research more generally, values that promote biomedical discourses are common and often unacknowledged. Recently, a formal report by Nesta, an independent innovation foundation, drew attention to the biases in funding mechanisms for health research in the UK (Jones and Wilsdon 2018). The authors stated: ‘too often, the biomedical bubble distracts attention and draws resources away from alternative ways of improving health outcomes’ (Jones and Wilsdon 2018: 66). In so doing, the authors shed light on the hegemonic position the biomedical sciences hold over knowledge gained from the social sciences, which seek to uncover the social, behavioural, and environmental determinants of health. I believe that biomedical knowledge is tremendously powerful and impactful, and plays a critical role in improving health outcomes for individuals with genetic disease. As a genetic counselling researcher though (who straddles the biomedical and social science

worlds), I contend that biomedical knowledge does not hold primacy over research that focusses on the psychosocial aspects of life. In this way, a key value I bring to my research is anti-hegemonic and pluralistic; I advocate for the convergence of disparate, purist paradigm positions such that social science is of equal standing with biomedical science.

To achieve this convergence, I have aligned with a core pillar of biomedical research: 'the fight to cure cancer'. This was a strategic choice because researching inherited cancer carries a certain currency within health research, and the 'fight to cure cancer' is a prestigious discourse within the biomedical sciences and among the wider public. This provides me a personal statement and strong rationale for my research, and shared value base with many researchers and the broader population affected by cancer.

The philosophical assumptions and values I have outlined are rooted in my training. My commitment to realism is borne out of my undergraduate training in medical science, where realism as a part of scientific method and inquiry were unacknowledged assumptions in my coursework. In my Honour's year, I moved into qualitative genetic counselling research under the guidance of a bioethicist. My first foray into qualitative research exposed me to many different ways of thinking and critically challenged my assumptions of realism in science and the validity of its claims to truth. By exploring the historical building blocks of genetic counselling and its varied disciplinary influences (e.g., psychology and counselling), and the complexities of qualitative research and its strong allegiances to social science, I moved to towards adopting a constructivist view of epistemology. My postgraduate training has solidified my view of critical realism and has blended my experiences of both medical sciences, genetic counselling, and social science perspectives into a coherent whole.

In sum, having experienced two forms of training, I have been exposed to different ways of thinking about how to do research, namely post-positivism and constructivism and their associated methods. For this project, I am able to blend them in a way that takes advantage of their attributes and capitalises on a mixed-method approach under the umbrella of pragmatism.

3.2.3 The pragmatic approach adopted for this thesis

The approach I have adopted for this project is pragmatism. Pragmatism sits within the *Third Research Paradigm* (Table 4, p. 48), which appeals to methodological pluralism and the deliberate coupling of quantitative and qualitative data (Rapport and Braithwaite 2018). As a philosophy, pragmatism was developed by several influential writers, namely John Dewey, William James, George Herbert Mead, and Charles Sanders Pierce, who each expounded their

own distinct versions of ‘classical pragmatism’ (Morgan 2007). What pragmatic philosophy offers, especially from John Dewey’s writings, is a shift away from traditional issues of philosophy in research (i.e., the incompatibility thesis) to an emphasis on transactions between humans and their environment. That is, pragmatism is based on a transactional philosophy (Biesta 2010). Explaining the origin and mechanics of a transactional world view is beyond the scope of this thesis, but suffice to say pragmatism as an approach to research is very powerful by virtue of its rejection of the world as either in the human mind or outside of it (i.e., mind-world dualism).

When thinking about research, pragmatism enables the researcher to disentangle their research efforts from abstract metaphysical debates centred in philosophy. Instead, pragmatism focusses on what difference philosophical views actually make when guiding inquiry, and prompts a middle-ground focus on methodology as a link between the metaphysical (philosophy) and the mechanical (methods) (Morgan 2007). The main application of pragmatism in research has come from the mixed-methods literature (Johnson and Onwuegbuzie 2004) and has become immensely popular because of its flexibility. It is important to note, however, that pragmatism is not a ‘magical methodological solution’, and if adopted without due consideration to its underlying philosophy, or the philosophies it seeks to combine, it runs the risk of leading researchers astray (Greene and Hall 2010).

To be clear about how pragmatism has guided this project, I have synthesised the main tenets of pragmatism as a philosophy and as an approach to research (Box 1, p. 54). Below I explain in more detail the key pragmatic concepts that have implications for this project, namely warranted assertions and metaphysical flexibility.

Box 1. Key tenets of pragmatism

- Rejection of the mind-world dualism (objectivism vs. subjectivism);
- Approaches to research are not primarily defined by philosophical considerations: equal weight is given to considerations about our practical efforts to produce knowledge and the nature of that knowledge;
- Researchers are free to employ different philosophies as practicable for the research question at hand;
- Research is always in political, historical and social contexts: any research is value-laden, and these must be acknowledged by the researcher;
- Knowledge is fallible, we can never be certain that our current knowledge will be appropriate for future enquiries;
- All human experiences are 'real'. Truth and falsity are borne out of the meaning we ascribe to experiences, not inherent qualities of the experience itself. Therefore, truth is always value-dependent and situation-dependent;
- The proposition of the term 'warranted assertions' to describe claims to knowledge;
- Endorsement of multiple methods to incorporate varying perspectives of phenomena and therefore reinforce our 'warranted assertions'; and,
- A problem solving, action-focussed process of inquiry.

Source: Adapted from Johnson and Onwuegbuzie (2004); Morgan (2007); Biesta (2010).

3.2.3.1 Warranted assertions and 'Truth'

The pragmatic concept of 'warranted assertions' rather than 'Truth' is important to consider, and closely aligns with my philosophical position of critical realism. Warranted assertions are perspectives gained from inquiry that are situation-specific and value-specific. What is possible in one situation may or may not be possible in another, and is irrevocably shaped by individual and collective values. Therefore, our assertions are only warranted in relation to the particular situation in which they were produced and are not 'warranted for all time and all similar situations' (Biesta 2010: 114). This notion links back to my critical realist position that posits we can never be certain of our knowledge or attain the one 'Truth' of a thing, but we can strengthen our assertions with rigorous enquiry. So, in this thesis, I will not be making truth claims, but warranted assertions with situation-specific evidence. These assertions may be applied more widely with careful consideration of how the evidence supporting them is pertinent to different, but similar situations.

3.2.3.2 Metaphysical flexibility

A key tenet to pragmatism is that it is not committed to one form of philosophy about reality and knowledge. It endows researchers with a metaphysical flexibility depending on the needs and purposes of enquiry. I have made use of this flexibility and adopted a critical realist approach for this research, which, in keeping with the pragmatic tradition, rejects the mind-world dualism and combines a realist ontology with a constructivist epistemology.

This has important implications for the project in that I believe and take what participants tell me about their life to be their perspectives of reality. How they think and what they think about are equally as real as what they do in a day-to-day capacity; the mental and physical worlds combine. Therefore, asking about their lived experiences is a window into their meaning making of life (a realist approach). Although, this window is not a neutral registration of reality, and is influenced by both myself as the researcher and the participants as the knower.

3.3 Theoretical framework

This section describes the four theoretical pillars that inform this research, namely: risk society as a central tenet of late modernity, ecological systems theory, the family system genetic illness model, and psychosocial human development theory.

3.3.1 Late modernity and risk society

A central premise of this thesis is that genetic technology can identify individuals, families, and populations at high risk of disease based on their genetic makeup. In the domain of public health, for example in genetic counselling, risk is commonly thought of as a term that refers to a neutral, measurable concept: i.e., the probability or mathematical likelihood of developing disease (Lupton 1993). As a result, a pillar of client-centered genetic counselling research has been to understand how individuals perceive and understand their genetic risk of disease in order to tailor risk information provision (Sivell et al. 2008).

Despite genetic counselling having historical roots in practices of information provision (Weil 2003; Austin 2010; Kessler 1997), especially providing probabilities pertaining to genetic risks, there is a wealth of evidence that shows the very concept of risk is subjective, and is not always processed rationally in terms numerical probabilities (Loewenstein et al. 2001). Indeed, ‘we do not *think* risk; we *feel* it’ (Rosenbaum 2014: 1550; italics in original). Rather, perception of disease risk is a multifactorial, intuitive and emotionally-driven process influenced by a host of relational factors (e.g., family history of disease), past experiences and

future expectations (Shiloh and Saxe 1989; Slovic 1987; Slovic et al. 2002; Slovic et al. 2004; Kahneman 2011; Loewenstein et al. 2001; Sivell et al. 2008; Hallowell, Statham, and Murton 1998). Indeed, since the early 1990s, there has been a counter discourse to conceptions of biomedical risk that contends risk is a complex sociocultural term. In modern society, risk has become synonymous with danger, and the pervading heuristic for risk assessment in health is that if someone is at high-risk, they are in high danger (Douglas 1990). The term of risk is therefore politically and socially produced, not discovered, which is implied in the case of genetic risk (Lupton 1993).

Lupton (1993) contends that there are two main conceptions of health risk in modern society. The first views risk as a danger to one's health that is imposed by external environmental factors (e.g., nuclear waste, pollution etc.); the hazard is external and the individual has little control over it. The second perspective views risk as a danger to one's health as a consequence of lifestyle choices made by individuals; the hazard is personally inflicted, emphasising the option for self-control (i.e., smoking, 'unprotected' sex, excessive sun exposure etc.). What differentiates these perspectives is the scope for individual control in mitigating their exposure to risk. The concept of genetic risk falls in-between the two perspectives outlined by Lupton (1993). While individuals have no control over their genetic make-up, they do have control over how they manage their genetic risk after being identified as an 'at-risk' individual. In modern society, when health risks can be avoided it is the responsibility of the individual to avoid them 'for the sake of his or her own health as well as the greater good of society' (Lupton 1993: 429). From this perspective, if an individual chooses to ignore their genetic risk, they are placing themselves in danger of illness, disability or disease, which removes them from a useful role in society.

The idea that modern society is defined and constrained by conceptions of risk is central to the view of late modernity described by both Giddens (1991) and Beck (1992). This 'risk society' is a society 'which is increasingly defined in terms of individual responsibility and agency rather than social constraints and collective responsibilities' (Hallowell and Lawton 2002: 424). Discourses of personal responsibility are made explicit in genetic counselling, which not only identify risks to an individual's health (and/or their biological children) with high precision, but by promoting risk management options, also promises a degree of control over these uncertainties (Hallowell 1999). Indeed, many authors have argued that by labelling individuals as 'at-risk', and by promoting genetic risk as manageable, genetic health professionals implicitly construct risk management and family communication of genetic risk as a personal responsibility (Forbes Shepherd, Browne, and Warwick 2017; Koch and Nordahl

Svendsen 2005). In this way, attempting to manage one's bodily risk becomes a moral exercise and those who fail to adhere are seen as morally irresponsible (Fitzpatrick 2000; Hallowell and Lawton 2002; Lupton 1993; Hallowell 1999).

The risk discourse promoted by genetic counselling is difficult to subvert because of its 'manifest benevolent goal of maintaining standards of health' (Lupton 1993: 433). Yet, while the discourse of risk promises individuals a choice with regards to their healthcare, the rhetoric in which the choice is couched leaves little room for manoeuvre:

[The body] has become a commodified and regulated object that must be strictly monitored by its owner to prevent lapses into health-threatening behaviours as identified by risk discourse. For those with the socioeconomic resources to indulge in risk modification, this discourse may supply the advantages of a new religion; for others, risk discourse has the potential to create anxiety and guilt, to promote hopelessness and fear of the future (Lupton 1993: 433).

For young people with LFS, who live with high, uncontrollable cancer risk, learning their gene status occurs in the context of the pervading risk discourse of modern society. Therefore, while the biomedical conception of genetic risk is an important aspect to defining the parameters of this project (i.e., the association between individuals with pathogenic mutations in *TP53* and multi-organ cancer risk), it is not the only conception of risk relevant to this thesis. Equally as important will be considering risk for young people with LFS in terms of its sociocultural meanings.

3.3.2 Ecological systems

One of the cornerstones of this project is the process of human development, specifically during the period spanning adolescence and young adulthood. In this space, the seminal work by Bronfenbrenner (1977) on Ecological Systems provides a strong foundation for understanding individual human development in a social context. As Bronfenbrenner astutely noted over 40 years ago, developmental research without attention to context or social relevance is an entirely peculiar exercise:

Much of contemporary developmental psychology is the science of the strange behaviour of children in strange situations with strange adults for the briefest possible periods of time (Bronfenbrenner 1977: 513).

While poking fun at his experimentally-minded contemporaries, Bronfenbrenner pushes a key concept that I want to echo for this project: the developing (young) person develops in context with their environment. His theory makes a global summation of the social

determinants that shape human development and mirrors deep currents running throughout sociology that speak to the social determinants of health. The major premise being that 'the conditions in which people live and die are shaped by political, social, and economic forces' (Commission on Social Determinants of Health 2008).

Bronfenbrenner (1977) defined his Ecological System as an open system: a person is continuously influenced by their interactions with the environment, but also concurrently creates and modifies the environment to preserve system functioning (Newman and Newman 2012). The ecology of human development is the study of these environment-person interactions going in both directions, where the ecological environment is a 'topologically nested arrangement of structures, each contained within the next' (Bronfenbrenner 1977: 514). I am using the principles of ecological systems here as a framework more than an explicit theory. It serves as a structure for housing different theories that I explain below (Syed 2015). The four main structures of the ecological system are explained here and depicted in Figure 4 (p. 59):

A microsystem is the complex of relations between the developing person and environment in an immediate setting containing that person. (e.g., home, university etc.). Settings are particular places with specific features in which the participants engage in activities while in particular roles (e.g., daughter, parent, student, etc.).

A mesosystem comprises the interrelations between two or more settings in which the developing person occupies at a particular point in life and actively participates in (e.g., for a young adult attending university and living at home: the relations among home, university, and social life). The mesosystem is a system of microsystems.

An exosystem is an extension of the mesosystem. It encompasses other social structures, both formal and informal, that do not directly involve the developing person, but in which events occur that affect, or are affected by, what happens in the setting containing the developing person. These structures can include major institutions (e.g., agencies of state or federal government), neighbourhood, mass media etc.

The macrosystem refers to the overarching institutional patterns of culture and subculture (e.g., economic, legal, educational, and political systems) that are made up of micro-, meso-, and exosystems, and their underlying ideologies and belief systems. For example, within a given society, one hospital looks much like another, as if they were constructed from the same blueprint. These blueprints are the macrosystems, which are sometimes in the form of explicit

laws and regulations, but mostly in the form of implicit ideologies reinforced by custom and everyday practice (Bronfenbrenner 1977: 514-15; Newman and Newman 2012: 51).

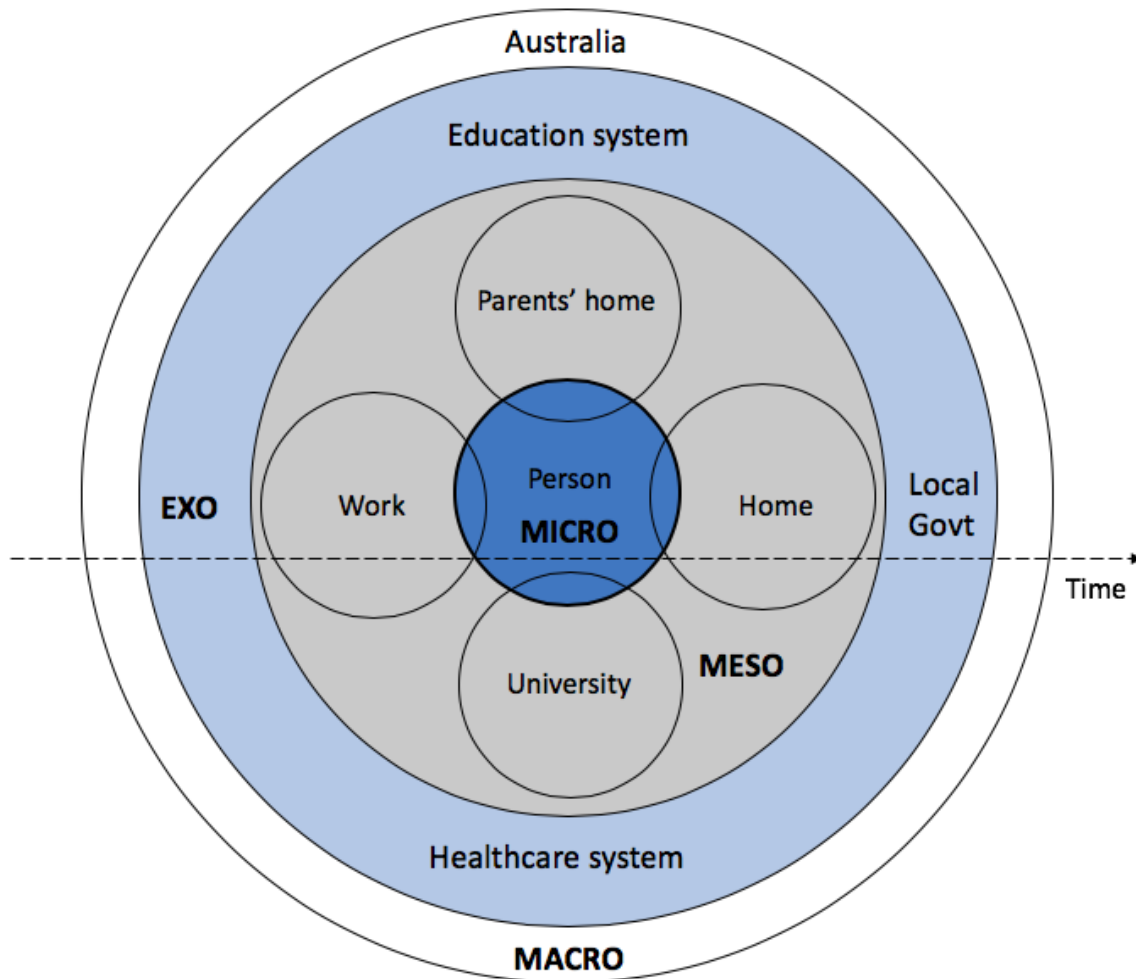


Figure 4. Topography of the relationship between ecological systems.

Abbreviations: Micro, microsystem; meso, mesosystem; exo, exosystem; macro, macrosystem.
Source: Adapted from Newman and Newman (2012: 52).

Bronfenbrenner posited that development was directly shaped by interactions between the developing person and their microsystem (e.g., family and school), and by their broader interactions across the various systems they participate (the mesosystem) (Newman and Newman 2012). Although my analysis does not specifically focus on the ecology of human development, it is framed by Bronfenbrenner's foundational work and acknowledges the critical importance of viewing the young people in this study as undergoing development in a social context; it is the young person in their setting that is the focus of analysis.

3.3.3 Family system genetic illness model

Keeping the developing young person in a social context, it is important to recognise that inherited diseases, like LFS, transpire within families. To achieve this, I used the Family System Genetic Illness (FSGI) model help to understand the psychosocial challenges of genetic conditions for individuals and their families (Rolland and Williams 2005; Rolland and Werner-Lin 2006). The FSGI model is an extension of Family Systems-Illness (FSI) model, which describes the psychosocial typology of chronic illnesses (Rolland 1987). Importantly, both models are built upon a cornerstone of genetic counselling practice, Family Systems Theory, which conceptualises individuals as interdependent members of a family unit: if one family member is affected (e.g., by serious illness), then the family system is also affected, not just the individual in isolation. The family system either accommodates the change to find a new balance, or rejects the change to revert to the old balance (Newman and Newman 2012).

The FSGI model extends Family Systems Theory to a clinical context by providing a guiding template for the psychosocial implications and progression of inherited illness over time. The psychosocial typology outlines a way to understand genetic conditions in psychosocial terms. For this reason, it was particularly suited to this project because it could sketch out likely psychosocial issues for young people based on the clinical characteristics of LFS. The psychosocial typology consists of:

- Likelihood of developing the condition based on genetic mutations (high penetrance=high likelihood, variable penetrance=variable likelihood; complex or low penetrance=low likelihood);
- Overall clinical severity (expected disease burden for individual and family: high or low);
- Timing of clinical onset in the life cycle (childhood-adolescence [0-20 years]; early-middle adulthood/child rearing years [20-60 years]; later life [60+ years]; and
- Prevention and treatment (availability of effective treatment or prevention: available or unavailable) (Rolland and Williams 2005: 8-10).

Rolland (2005) posits that each genetic condition has a pattern of psychosocial demand based on the variables in this typology, which are outlined for LFS in Table 5 (p. 61).

Table 5. Psychosocial typology of LFS based on the Family System Genetic Illness model

Typology	Characteristic
Penetrance	High
Clinical severity: expected level of disease burden ^a	High
Onset	Childhood - Adulthood
Effective intervention	Risk reduction: breast cancer only Risk management: research-based whole-body surveillance (if available)

^aThe clinical severity of a condition within the FSGI model corresponds to the FSI typology used to describe chronic illness after clinical onset. Refer to Table 6 below for the clinical severity of LFS according to the FSI.

The second element of the FSGI model concerns the dimension of time and identifies phases of illness before and after clinical onset (Rolland 1987). To incorporate the genetic component of illness, the timeline extends backwards to include pre-symptomatic time phases of genetic conditions where individuals live with genetic risk before clinical onset. The key time phases are:

- Awareness phase (some knowledge of genetic risk but no active consideration or availability of genetic testing)
- Crisis phase I: pre-testing (active consideration of genetic testing and its implications for self and family)
- Crisis phase II: testing/post-testing (irrespective of result, this is a period of re-evaluation and integration of genetic information into one's personal and family)
- Long-term adaptation phase (the period, short or long, between post-testing and clinical onset, includes adapting to life with known genetic risk and maximising autonomy and intimacy in the face of possible or inevitable loss) (Rolland and Williams 2005: 11-15).

This timeline was particularly useful for situating the young people in this study along a trajectory describing their psychosocial challenges relating to genetic disease, both as an individual and as a member of their family unit. It also provided a clear distinction between asymptomatic young people who undergo predictive genetic testing and young people who have developed cancer and have undergone diagnostic genetic testing (Figure 5, p. 63).

Importantly, after clinical onset in the context of LFS, i.e., a cancer diagnosis, the course of illness is takes on an episodic or relapsing typology, potentially for several family

members across generations at the same time. Not only do individuals with an LFS-related cancer live with risk of recurrence, they also live with high risk of developing multiple primary cancers over their lifetime. The episodic or relapsing course of illness is distinguished by the alternation of stable, asymptomatic periods with periods of flare-up, remission or new diagnosis.

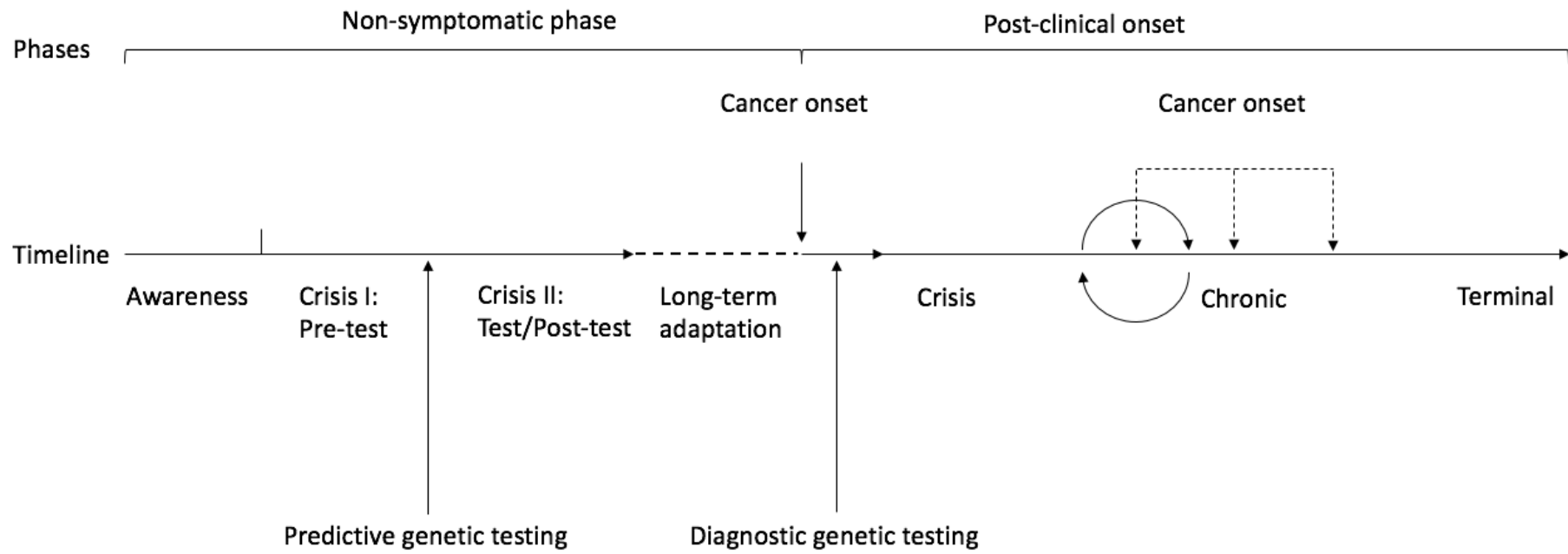


Figure 5. Time phases of genetic disease

Source: Adapted from Rolland and Williams (2005: 17).

Individuals and families ‘are strained both by the frequency of transitions between crisis and non-crisis and by the ongoing uncertainty of when another recurrence will occur’ (Rolland 2005: 2586). The wide discrepancy between periods of normalcy versus flare-up can be particularly burdensome over extended periods. The typology for LFS outlined in Table 6 (p.64) is based on the Family Systems-Illness model described by Rolland (1987) and corresponds to the ‘clinical severity’ typology nested within the FSGI model.

Table 6. Post-clinical onset typology of LFS based on the Family Systems-Illness (FSI) model

Typology	Characteristic
Onset (acute or gradual)	Acute
Course (progressive, relapsing, or constant)	Relapsing
Outcome (fatal, potentially fatal/shortened life span, or non-fatal)	Potentially fatal
Incapacitation	Non-incapacitating

While the FSGI model is designed for clinical application, previous genetic counselling research has also used the FSGI model to varying degrees. Work by Hamilton, Williams, Skirton, et al. (2009) and Sparbel et al. (2008) has established the FSGI model as a useful explanatory tool to help visualise the complexities of life for young people cast as the ‘worried well’; i.e., who are living in the long-term adaptation phase of their genetic illness before clinical onset. Seminal work by Werner-Lin (2007) applied the FSGI model to bring the worlds of genetic counsellors and family clinicians together. Her series of studies showed that by taking a family systems approach to understanding how asymptomatic young women experience their *BRCA1/2*-related cancer risk, a clinician could anticipate time points along family and illness development that may require of additional support, especially at the intersection of reproductive and risk management decision-making (Werner-Lin, Ersig, et al. 2018; Werner-Lin 2010, 2008b, 2008a, 2007). These studies provide a strong rationale for use of the FSGI model in this project, but they also illustrate that research to date has predominantly focussed on the long-term adaptation phase (i.e., the worried-well). We currently lack research that addresses young people’s experiences of inherited illness across the entire illness trajectory, which I plan to address in this thesis.

3.3.4 Psychosocial theory of human development

While the systems theories outlined so far provide a social context for the developing young person, the actual process of human development—and how it may be impacted by LFS—is of key interest to this project and requires a brief description.

There is a panoply of grand theorists who have attempted to account for how humans mature and grow over the lifespan (e.g., Freud, Erikson, Piaget, Vygotsky, Havighurst, and Kohlberg). Using Erikson's (1963) psychosocial theory, Newman and Newman's (2012) life work has been to integrate the array of grand theories into an organising framework for the modern study of human development. In this section I discuss Newman and Newman's (2012) interpretation of Erikson's and other theorists' writings, and how it applies to this project. Although their enterprising work spans the life course, I focus on the adolescent, emerging adult and young adult years (15-39 years) because of their relevance to this thesis.

3.3.4.1 Core concepts

Erikson's (1963) psychosocial theory posits that human development is the product of interactions between the individual and their social environment, which is consistent with my overarching ecological systems structure. There are four core concepts of psychosocial developmental theory that are relevant to this project:

1. Stages of development (Erikson 1963)
2. Ages are proxies for development
3. Developmental tasks (Havighurst 1972)
4. Psychosocial crises (Erikson 1963)

3.3.4.1.1 *Developmental stages*

Developmental stages are universal periods of life characterised by a specific underlying organisation (Newman and Newman 2012). As individuals grow and mature, they progress through these stages in a fixed direction: forwards. Each stage is unique from the preceding and succeeding stage, and accomplishments of previous stages provide skills and resources for mastering new stage-specific challenges: i.e., accomplishments are cumulative (Erikson 1984). At each stage, biological, societal, and psychological systems converge around a set of distinctive challenges, or tasks (see 'Developmental tasks' below). Progression through stages requires a new view of the self in society and a new way of relating to others (Whitbourne, Sneed, and Sayer 2009). Throughout development one can review and reinterpret previous stages in light of new experiences or knowledge, and themes of earlier stages may re-emerge at

any point (Erikson 1963). Challenges of each developmental stage are experienced across the lifespan, but their intensity at certain times marks their importance in the definition of a developmental stage (Newman and Newman 2012; Erikson 1984).

The underlying organisation of three life stages are relevant to this project: adolescence (12-18 years), emerging adulthood (18-29 years), and young adulthood (29-39 years; Table 7, p. 69). These life stages are of particular interest because they represent a formative and transitional period of life, which uniquely impact, and are impacted by serious illness (e.g., cancer).

3.3.4.1.2 *Ages are proxies for development*

Although it is common convention to use age ranges to bracket developmental stages, Erikson (1963) rarely used ranges in his theory. This highlights a key feature of developmental stage theories in general: ages are proxies for developmental stage, and are a guide only: 'each person has a uniquely personal timetable for growth' (Newman and Newman 2012: 67). What can be misleading about age ranges is that they suggest there is an absolute cut-off for development based on the end of one age range and the beginning of the next. As mentioned above, the progression through developmental stages is principally mediated by a change in self-concept to address new developmental tasks. Consequently, age cut-offs are arbitrary and cannot conceptually account for changes in identity. In an attempt to overcome this, I have borrowed a key concept from Levinson's (1986) conception of adult development: cross-era transitions. For simplicity, consider an era to be a life stage. Levinson (1986) describes that as one stage draws to a close, the next gets underway; these transitional periods are therefore part of both stages, but not fully a part of either. Therefore, the age ranges for adolescence (15-18 years), emerging adulthood (18-29 years), and young adulthood (29-39 years) overlap, each range sharing one year of the previous range. This is to help consider young people approaching the upper limits of one stage being already on the path to the next stage.

3.3.4.1.3 *Developmental tasks*

At each developmental stage, one faces new developmental tasks that contribute to increased mastery of one's environment. Developmental tasks are based on the general principle that people develop by attempting to learn tasks expected of them by society (Havighurst 1972). These tasks change with age because each society has age-graded expectations for behaviour. At each stage of life, a small number of major psychosocial challenges dominate a person's problem-solving efforts and learning (Newman and Newman 2012). The whole adolescent and young adulthood period is bookended by the process of puberty and peer acceptance at one

end during adolescence, and social role transitions into long-term relationships, parenthood, and employment at the other during young adulthood. For the stage in between, emerging adulthood, the task of identity exploration is of prime importance. As many young people in Western societies delay marriage and parenthood, they are afforded unprecedented freedom to explore different kinds of love, work and worldviews (Arnett 2000). I have integrated Arnett's (2000) theory of emerging adulthood to describe the life stage of 18-29-year-olds, as it has superseded conventional explanations of development from adolescence to adulthood. The specific developmental tasks for adolescents, emerging adults, and young adults are outlined in Table 7 (p. 69).

3.3.4.1.4 *Psychosocial crises*

Psychosocial crises are internal states of tension between a person's capacities at the beginning of a life stage and society's expectations for behaviour at that life stage (Erikson 1963). Erikson (1963) cast his crises as universal conflicts between the self and society, and viewed them as polarities (e.g., intimacy vs. isolation): positive poles represent normative developmental goals, whereas negative poles offer insight into basic human vulnerabilities. Theoretically, this opposing nature provides the underlying pathway for resolving each psychosocial crisis, and most people experience both ends of the spectrum while figuring it out (Erikson 1963).

A key limitation to Erikson's (1963) psychosocial crises is that they create binary developmental outcomes (normative vs. maladaptive), which may not accurately reflect the variety of pathways one may take during development. Especially pathways that do not subscribe to the male dominant, heteronormative, Eurocentric slant to Erikson's work (Gilligan 1982). Moreover, his crises posit a 'normative' path for development that is entirely theoretical and immeasurable, and predominated by themes of individuality and achievement, instead of interdependence and growth. If and how young people 'resolve' psychosocial crises is not the focus of this project, and for this reason I am using psychosocial crises for two very specific applications. First, they provide an overarching developmental theme for each life stage, and guide my inquiry towards core developmental challenges at each life stage. Second, they highlight potential extreme experiences for young people during development, which may be shaped by coming from a family with LFS.

The psychosocial crisis, or developmental theme, of adolescence relates to the process of peer acceptance. The continuum of experience here spans from achieving a sense of group identity based on shared experiences with peers (i.e., being a part of sports team, or the

‘popular group’ at school), or feelings of alienation and isolation based looking or feeling different to peers (e.g., experiencing the death of a close family member when most peers have complete family units, or developing cancer that may affect one’s outward appearance) (Erikson 1963; Newman and Newman 2012). For emerging adulthood, the developmental theme relates to identity exploration. This theme is more fluid and relates to establishing individual identity at one end (i.e., having the opportunity to explore different ways of living, different forms of work and education, and varied friendship circles and relationships outside of family), and identity confusion at the other (i.e., experiencing serious illness that slows or inhibits the launching of a young person from the family unit and therefore delaying their adoption or understanding of individual identity as an independent adult) (Erikson 1963; Arnett 2000). For young adulthood, the developmental theme relates to developing and maintaining intimacy. This continuum of experience relates to forming intimate relationships at one end (i.e., forming long-term relationships and potentially beginning child rearing) and experiencing isolation at the other end (i.e., feeling unable to form intimacy with another person based on a range of previous experiences, or being unable to undergo normative family formation due to fertility issues) (Erikson 1963; Newman and Newman 2012).

Table 7. Major tasks and crises of psychosocial development during adolescence, emerging adulthood, and young adulthood

Life stage (approx. age range)	Developmental tasks	Psychosocial crisis
Adolescence (12-18 yrs.)	Puberty - Emotional development - Physical maturation - Formal operational thought/cognitive development Conflicts with parents Membership in the peer group Romantic and sexual relationships	Group identity vs. alienation
Emerging adulthood (18-29 yrs.)	Identity exploration (work, love and worldviews) Autonomy from/within family Exploring intimate relationships Career choice The 'Big 3': - Accepting responsibility for oneself - Financial independence - Making independent decisions	Individual identity vs. identity confusion
Young adulthood (29-39 yrs.)	Childbearing Work Lifestyle Nurturing intimate relationships	Intimacy vs. isolation

Source: Adapted from Newman and Newman (2012) and Arnett (2000).

3.4 Summary

This chapter outlined my philosophical stance to research, making it clear that I have adopted critical realism to avoid the incompatibility thesis associated with purist approaches to research (i.e., positivism and constructivism). In this way, my ontological position is a welcome partner to my adopted methodology, pragmatism, which argues for a pluralistic approach to research with an inherent metaphysical flexibility. This chapter also critically appraised the four main theories that inform this research and outlined their key components relevant to the current enquiry, namely: risk society in the context of late modernity; ecological systems theory; the family systems genetic illness model; and, psychosocial theory of human development. This chapter has established the scaffolding for the mixed-method approach to be described in the following chapter.

4 Research design

4.1 Overview

The previous chapter introduced the philosophical and theoretical framework for this research. A key component of my adopted framework is the use of a pragmatic approach to enable the mixing of different methods to achieve the research aims. This chapter outlines and justifies the two-phase multi-method design for this project. The first section addresses Phase 1, the qualitative phase, and outlines the design for Studies 1 and 2 of the thesis: a systematic review and thematic synthesis of young people's experiences with inherited disease generally, and an interpretive description of young people's experiences with LFS. The second section addresses Phase 2, the quantitative phase, which describes the design for Study 3, a descriptive survey Australasian health professional practice for young people from families with LFS.

4.2 A two-phase multi-method research design

This project uses an inductively driven, sequential, multi-method approach with integration at the interpretation stage (Creswell et al. 2003) (Figure 6, p. 72). I used a multi-method approach over two phases for this project to investigate the overarching aim from two different angles: first, from the perspectives of young people from families with LFS; second, from the perspectives of the health professionals who care for them. Using two perspectives enabled me to develop a more comprehensive and nuanced understanding of the research problem than using one perspective alone.

The project as a whole was exploratory; its main thrust was to explore, understand and explain (Morse 2003). I chose a sequential design so that each of the three studies I conducted could be informed by its predecessor. This allowed for the exploratory aspects of the project to build on one another towards a more holistic understanding. The stage of integration was at the interpretation stage such that each study within the project was analysed and completed discretely before findings were compared in the discussion chapter for convergence (Creswell et al. 2003).

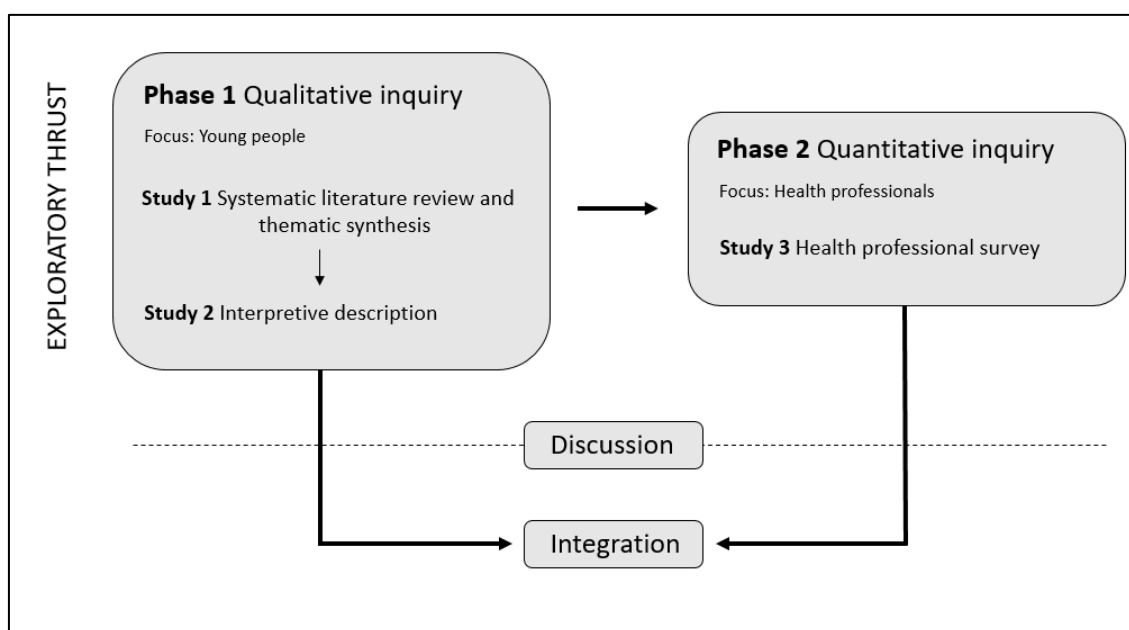


Figure 6. Overarching multi-method research design

4.3 Phase 1: Qualitative inquiry

The first phase of this project was a qualitative inquiry addressing Aim 1, and consisted of Study 1 and Study 2 (Figure 7, p. 73). The design for each study, and how Study 1 informed Study 2, are explained in turn below.

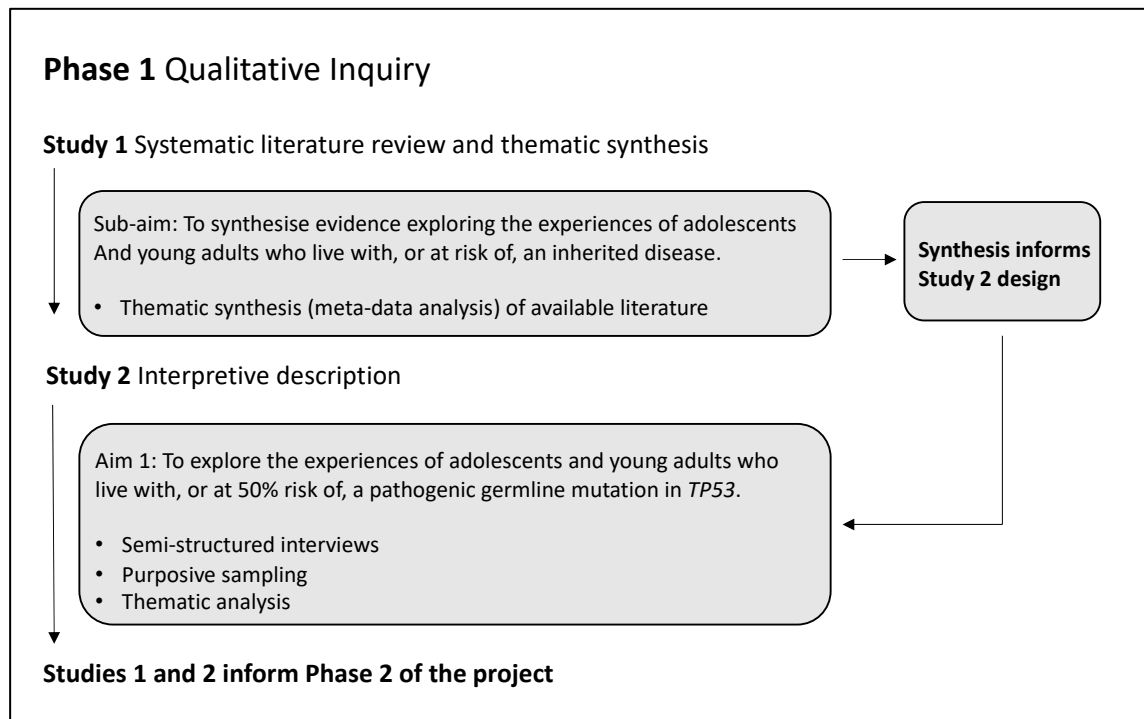


Figure 7. Phase 1 study flow

4.3.1 Study 1 design: systematic literature review and thematic synthesis

Study 1 was a systematic literature review of current evidence elucidating how young people live with inherited disease. The purpose of Study 1 was to inform Studies 2 and 3 in different ways. At the inception of this project, I was cognisant of there being very little primary research addressing the experiences of individuals and families with LFS, especially with a focus on development during the adolescent and young adult years. For this reason, I cast a wide net to better understand how young people experienced inherited disease with similar psychosocial implications to LFS in order to make inferences relevant for Study 2 of the project. Study 1 findings also helped to design Study 3 as they highlighted scenarios in which a young person's experience of inherited disease intersected with genetics and oncology practice. This aided the identification of potential questions to pose to health professionals about their practice with young people with LFS.

In terms of design, my systematic review is distinct from conventional approaches because of its focus on qualitative literature. Despite using systematic search criteria to identify and select relevant primary research for the study aims, I did not conduct a meta-analysis and attempt to aggregate quantitative data like in a conventional review (i.e., Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] statement, Moher et al. 2009). Rather, to best capture and appreciate

the wealth of qualitative evidence describing young people's experiences of inherited disease, my review had a deliberately qualitative stance (Forbes Shepherd et al. 2018). A more detailed account of the meta-data analysis method and how I used it for Study 1 is described in Chapter 5; the research questions, study selection, appraisal of research, and analysis are described in Chapter 6 as part of the author-accepted manuscript.

4.3.2 Study 2 design: interpretive description

Study 2, the principal study of this project, was a qualitative study exploring how young Australians experience Li-Fraumeni syndrome. The methodology I used for this qualitative study was interpretive description (Thorne 2016; Thorne, Jensen, et al. 2004; Thorne, Kirkham, and MacDonald-Emes 1997). Founded in nursing research, interpretive description (ID) was developed by Sally Thorne, Kirkham, and MacDonald-Emes (1997) for 'qualitative inquiry into human health and illness experiences for the purpose of developing nursing knowledge' (173). Consistent with her more recent conceptualisation of ID—i.e., that it is broadly applicable to any applied health discipline (Thorne 2016)—I contend that it is equally suitable for the development of genetic counselling knowledge. In July 2018, I had the opportunity to attend a 3-day workshop with Sally Thorne at the 15th Annual Qualitative Research Summer Intensive in North Carolina, USA. At the intensive I was able to gain in-depth tutelage about how to apply ID to my research from its creator, which has proven instrumental in carrying out this project.

Broadly, ID is a non-categorical, 'inductive analytic approach designed to create ways of understanding clinical phenomena' that yield implications for applied disciplines (Thorne, Kirkham, and O'Flynn-Magee 2004: 11). ID is non-categorical because it is not shackled by the complex procedural rules from conventional approaches to qualitative inquiry (e.g., grounded theory from sociology, ethnography from anthropology, and phenomenology from psychology and other fields). Instead, ID allows the maintenance of methodological integrity while borrowing particular elements from conventional approaches and reconfiguring them to distinct applied research needs (Thorne 2016). While promoting flexibility, ID has strong roots within the interpretive/constructivist camp of qualitative inquiry, and advocates for researchers to be actively engaged in interpreting data through the lens of their own social and cultural memberships, theoretical influences, ideological commitments and scholarly positions (Braun et al. 2019).

The aim of ID is to produce a coherent conceptual description of human experience in a clinical context. The description must canvas common thematic patterns

of experience while simultaneously accounting for the inevitable variation among them. The process of ID necessarily involves disciplinary interpretation that moves the research product from 'mere' description into the 'so what?' domain that drives applied/clinical disciplines (Thorne 2016). Ideally, the research product is clinically applicable, such that a clinician (e.g., a genetic health professional) may make sense of it and extend their available insights for clinical reasoning and decision-making, thereby creating a 'sense-making' structure for the eccentricities of daily practice in the health disciplines (Thorne, Kirkham, and O'Flynn-Magee 2004).

In this way, ID is not a new methodology of qualitative research, it is a 'conceptual label' signposting the kind of research that is intended to be undertaken based on three elements: 1) a 'real-world' research question (i.e., not theoretically-based); 2) an appreciation for current knowledge on the basis of empirical evidence; and 3) an appreciation for the position of the intended audience in terms of receiving the final research product (Thorne 2016).

Having said this, ID is a relatively new conceptual label for qualitative research, and until recently, finding adequate resources and contemporary examples for guidance was challenging (Hunt 2009). ID has now gained traction in nursing fields and applied disciplines, with a growing body of high-quality research assessing a broad range of experiential phenomena in clinical settings. Sally Thorne and colleagues (2003; 2004; 2008) set a strong precedent with seminal interpretive descriptions of everyday decision-making for individuals with chronic illness (Thorne, Paterson, and Russell 2003), and of how healthcare is communicated and impacts patient outcomes in both cancer and multiple sclerosis settings (Thorne, Con, et al. 2004; Thorne et al. 2008). Although an increasingly common methodology in cancer nursing (Bakitas 2007), ID is now also used in broader applied health disciplines: e.g., for exploring how clinicians influence patient beliefs and attitudes towards low back pain (Darlow et al. 2013); for developing applied knowledge to better understand barriers and enablers for regular exercise among middle-aged women (McArthur et al. 2014); and for understanding perceived benefits and barriers to sport participation among children and parents from low-income families (Holt et al. 2011).

Pertinent to this study, ID has also found success in highly sensitive areas of experiential research: e.g., the disclosure processes of male survivors of child sex abuse (Gagnier and Collin-Vézina 2016). It has also been successfully applied to research with younger participants: e.g., to explore how children and adolescents think and feel about

their cancer symptoms (Woodgate 2008), and to explore the impact of severe osteogenesis imperfecta (brittle bone disease) on young patients and their parents (Dogba et al. 2013). In the field of psychosocial genetics, there have been a small collection high-quality ID studies exploring the experiences of young women with a *BRCA1/2* germline mutation, which constitute foundational work for this project (Werner-Lin et al. 2012; Young et al. 2017; Hoskins, Werner-Lin, and Greene 2014; Young et al. 2018). Moreover, this body of work demonstrates that ID is applicable, appropriate and capable of producing in-depth findings for this project. The core elements of ID are outlined in Table 8 (p. 77).

4.3.2.1 Interpretive description is pragmatic

The flexibility and applied focus of ID resonates strongly with my pragmatic approach for this project. Philosophically, my pragmatic-critical realist stance and ID share a constructivist epistemology and conceptualise knowledge as subjective: pragmatism labelling knowledge generated from research as a collection of ‘warranted assertions’ and ID labelling them as ‘tentative truth claims’ (Biesta 2010; Thorne, Kirkham, and O’Flynn-Magee 2004). Importantly, ID and my pragmatic-critical realist stance are also rooted in the ‘real world’: my critical realist approach being embedded in the ‘real world’ in an ontological sense, and ID deliberately placing one foot in the ‘real clinical world’ to render the research product applicable in applied settings. For example, a researcher using ID would accept that pain exists and also recognise the powerful ‘social nature within which it is felt, understood, and expressed’ (Thorne 2016: 56). In this way, despite ID upholding a constructivist ontology, it remains consistent with my pragmatic-critical realist stance as they both appeal to the interpretive/subjective nature of ID as a methodology.

Moreover, the focus on ‘what works’ for studies in ID —instead of adhering to procedural roles of conventional approaches—strongly appeals to pragmatism. The practical slant of pragmatism and ID means they intentionally straddle tensions between theoretical integrity and real-world utility. This makes them appropriate partners for my project (Thorne 2016). The flexibility in approach afforded to researchers who use ID, however, does not excuse ‘methodological slurring’ or the stripping away of important theoretical underpinnings of borrowed approaches (Caelli, Ray, and Mill 2003; Thorne 2016). To clearly signpost borrowed elements from other approaches for my project, I will outline my ID methodology below.

Table 8. Principles of interpretive description

Principle	Description
Philosophical underpinnings	• Constructivist ontology: there is no objective world out there, our reality is subjective. • Constructivist epistemology: there is no separation between the knower and the known, all knowledge is subjective. • Inductive knowledge production is required to understand our socially constructed world.
Analytic framework	• Current knowledge, whether from formal research or (anecdotal) clinical experience, is a critical fore-structure to new enquiry.
Sample selection	• The principles of theoretical sampling, common to Grounded Theory, should be followed or at least recognised. This promotes concurrent data collection and analysis to tailor ongoing recruitment.
Data sources	• Purposeful selection of people who have lived with certain experiences is best. • Do not overemphasise one data source (e.g., interview data); seek multiple data sources to enrich interpretation from different angles.
Data analysis	• Inductive approaches are promoted with repeated immersion in data prior to formal coding or data reduction. A focus on the interpretive versus the technical when it comes to data reduction (e.g., coding).
Rigour	• Attention to rigour is critical. Attention to bias, both personal and disciplinary, must be explicitly documented; eliminating all bias is naïve. Promotion of auditable trail of evidence (e.g., reflective journal and/or personal/analytical memoing) to support analytical insights and abstractions.

Source: Adapted from Thorne, Kirkham, and O'Flynn-Magee (2004).

4.3.2.2 Analytical framework

Analytical frameworks bring together different strands of one's research design, making explicit how the position of the researcher, their chosen paradigm and methodology

come to bear during data collection and analysis. In ID, outlining one's analytical framework is important as it avoids slurring of different methodologies and allows one to be transparent about their research design. To this end, I outline three facets of the analytical framework I used for my ID: 1) experiential orientation, 2) appreciating current knowledge, and 3) theoretical foregrounding.

First, this study has an 'experiential' orientation; that is, it focuses 'on what participants think, feel and do, and [is] underpinned by the theoretical assumption that language reflects reality' (Terry et al. 2017: 4). Therefore, during analysis there was a focus on participant-expressed meaning. This laid the foundation for becoming more interpretive later in analysis to map underlying stories and patterns of meaning (Terry et al. 2017). Second, unlike some qualitative methodologies that ask the researcher to bracket (i.e., identify and set aside) preconceptions (Ray, 1994), ID presumes that there will be some theoretical knowledge, clinical observation, and scientific basis from which all studies of human health and illness are generated (Thorne, Kirkham, and O'Flynn-Magee 2004). For this reason, Study 1 represented a critical basis for the preliminary analytic framework and aided with sampling, design, and early analytic decisions. Further, in terms of providing genetic counselling and clinical genetics knowledge for the design of the project, two members of my supervisor team (L. E. Forrest and M.B. Delatycki) and my mentor (M-A. Young), provided important perspectives based on their clinical training and experience.

Third, this study is foregrounded by the core theoretical constructs outlined in Chapter 3; namely, ecological and family systems theory, and psychosocial human development theory. Although using a deductive theoretical framework within an inductive analytic approach (i.e., interpretive description) might seem at odds, being entirely inductive or deductive is not the aim in pragmatic approaches to research (Morgan 2007). Finding a balance between purist positions (e.g., inductive vs. deductive reasoning) is key to pragmatic research, and for my inductive qualitative study it was necessary to broadly frame the enquiry with an appraisal of current knowledge, which included theory. In so doing, I also met one of the principles of interpretive description: current knowledge, whether from formal research or clinical experience, is a critical fore-structure to new enquiry (Table 8, p. 77) (Thorne, Kirkham, and O'Flynn-Magee 2004).

4.4 Phase 2: Quantitative inquiry

Phase 2 of this project consisted of a quantitative inquiry that was complemented and informed by the qualitative inquiry in Phase 1 (Figure 8, p. 79). Phase 1 identified and explored aspects of young people's experiences with inherited cancer that intersect with key areas of genetic and oncology practice. These areas of practice (e.g., providing genetic testing) were explored from the perspective of health professionals in a health professional survey in Phase 2.

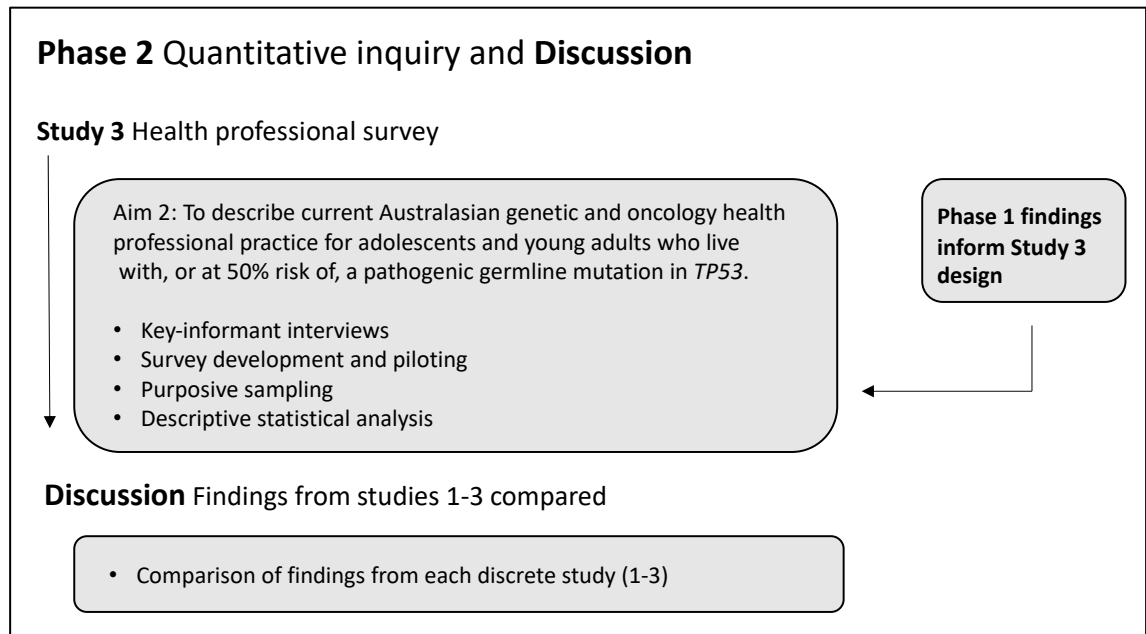


Figure 8. Phase 2 and discussion study flow

4.4.1 Study 3 design: Health professional survey

Study 3 of this project aimed to describe current practice among Australasian genetic and oncology health professionals who provide care to young people with, or at risk of, LFS. Due to the small population of health professionals who care for young people with LFS in Australasia, the survey was deliberately designed to be descriptive and not powered for logistical regression. The survey was developed using key informant interviews with six health professionals experienced in the care of families with LFS, expert input from my supervisor team and in consultation with the Department of Cancer Experiences Research at the Peter MacCallum Cancer Centre, which specialises in survey design. Based on this process and the thematic findings from Studies 1 and 2 that were relevant to genetic and oncology practice, the survey was organised into four parts: 1) participant demographics; 2) genetic testing practices; 3) risk management; 4) psychosocial support. The entire survey consisted of 113 items, survey logic guided respondents to relevant sections based on their clinical experiences with young people

with LFS. Close-ended and open-ended free-text questions were included. The latter allowed respondents to expand on their close-ended answers.

4.5 Summary

This chapter described and justified the mixed-method approach adopted for this thesis. The project consists of two sequential phases: a qualitative and a quantitative phase. The principal component of this thesis is the qualitative phase, which implements interpretive description (ID) as the guiding methodology. The main goal of ID is to produce a coherent conceptual description of human experience in a clinical context. Originally designed to inform nursing practice, I contended in this chapter that interpretive description is equally applicable to develop genetic counselling knowledge. The first step in any ID study is to use existing research and clinical knowledge to establish an analytical framework. For this reason, Phase 1 begins with a large systematic review and thematic synthesis of young people's experience with inherited disease to identify key areas for exploration with young people from families with LFS. Phase 1 also identified aspects of young people's experiences with inherited cancer that intersect with key areas of genetic and oncology practice. The quantitative phase directly builds on the qualitative phase by exploring these areas of practice from the perspective of health professionals in a descriptive survey.

5 Research methods

5.1 Overview

The previous chapter outlined the mixed-method research design for this thesis. This chapter focusses specifically on the research methods used for Studies 1-3 and provides a justification for their use.

5.2 Study 1 methods: meta-data analysis and thematic synthesis explained

Study 1 was a systematic review of primarily qualitative research exploring young people's experience of inherited disease. Synthesising primary qualitative research requires an entirely different approach to the common meta-analytical approach (e.g., for randomised clinical trials), where the main purpose is to aggregate data. The purpose of any synthesis of qualitative research is not aggregative, but interpretive: differences in research findings are retained and their complexity enlightened to achieve a common, rich understanding of a phenomenon (Thorne, Jensen, et al. 2004). The gold standard for synthesising qualitative research is the process of qualitative meta-synthesis: 'a family of methodological approaches to developing new knowledge based on rigorous analysis of existing qualitative research findings' (Thorne, Jensen, et al. 2004: 1343). This family of approaches consists of three analytical components: meta-data analysis, meta-method, and meta-theory. Conducting a full qualitative meta-synthesis was beyond the scope of this project. Instead, I conducted a meta-data analysis of relevant primary qualitative research identified using systematic search criteria.

Meta-data analysis is the study of research findings across a specific collection of primary research studies. It is best thought of as an ‘analysis of analyses’, and there are five main steps to consider (Paterson et al. 2001: 8-9).:

1. Identifying the analytic strategy;
2. Developing a filing and coding system;
3. Categorising data;
4. Obtaining inter-coder consensus; and
5. Discussing and interpreting findings as they relate to the research questions.

For a recent example of a high-quality meta-data analysis refer to Veilleux, Bouffard, and Bourque Bouliane (2019), whose work addresses the needs and preferences of patients and healthcare providers in understanding genomic testing.

5.2.1 Data analytic strategy

For my data analytic strategy, I used thematic synthesis (Thomas and Harden 2008). Thematic synthesis is an adaptation of thematic analysis (TA), a collection of approaches commonly used in primary qualitative research (Braun and Clarke 2006, 2019a). In thematic synthesis, TA is conceptualised as an analytical process that identifies themes across a collection of primary research. The specific form of TA I used was ‘codebook TA’ (Braun and Clarke 2019a; Braun et al. 2019), which sits between more positivist forms of TA (i.e., coding reliability TA) and constructivist forms of TA (i.e., reflexive TA) (Braun et al. 2019). Using codebook TA was consistent with my pragmatic approach as it provided a structured approach to coding that could complement the systematic identification of relevant literature, while also being broadly consistent with the underlying philosophy of qualitative inquiry (i.e., promoting inductive analysis and embracing the subjectivity of interpretive methods) (Braun et al. 2019).

5.2.2 Filing and coding system

The filing and coding system I used for my thematic synthesis began with qualitative data extraction, which consisted of: 1) electronically copying all text under the ‘results’ and ‘conclusion’ sections (or equivalent) from the published manuscripts identified for review; and, 2) uploading them into QSR NVivo (qualitative data management software). With NVivo, I was then able to begin systematically coding data with my co-author, A. Lewis (AL).

5.2.3 Categorising data and inter-coder consensus

Once data were in NVivo, AL and I categorised and developed them into themes (Thomas and Harden 2008). Of the 39 studies that met the inclusion criteria, six were selected for inductive qualitative coding. These first six studies were selected for diversity such that each focussed on a different inherited condition. This ensured initial analysis was not dominated by one set of primary findings and helped to make a sufficiently broad preliminary codebook that could later be pruned.

Next, AL and I independently coded each line of extracted data from the first six studies; extracted data included both participant quotes and author interpretations. Coding consisted of assessing each line of data for content and meaning and tagging them into broad descriptive themes. Each theme had a name, definition and an example excerpt, and from this process, AL and I independently developed preliminary theme lists. Coding was deliberately inductive to ensure we appreciated the possible breadth of findings that were relatable (or not) to young people with LFS and helped to begin translating specific concepts from one study to another.

AL and I then compared similarities and differences between our theme lists from the first six studies. By comparing theme names, definitions, and excerpts, we began grouping, combining, and separating them into a hierarchical structure of themes based on content and meaning. Descriptive theme definitions remained close to the original findings and were primarily semantic readings (i.e., focussed on explicit or surface meaning) of content in original studies. The combined, hierarchical theme list from the first six studies was then worked into preliminary coding framework, which was presented to the full authorship group for discussion. After all authors agreed and any modifications were applied to the coding frame, AL and I then independently coded a further six studies using the coding framework to assess its accuracy and generate new, or modify, existing codes to accommodate new data.

We did not formally assess inter-coder reliability and produce an agreement (Kappa) score. This approach is inconsistent with my critical realist stance, as it reliability measures assume there is a single reality or truth within the reported findings that can be accurately mined by a researcher (Braun and Clarke 2019a). Instead, to increase rigour in our findings, we discussed coding developments at regular coding meetings (once a fortnight) until consensus was reached on parameters for each code (noting our inherent biases and varied training that influenced our views). I then coded

the remaining studies using the stabilised codebook, tagging extracted data with codes developed from the first 12 studies.

5.2.4 Interpreting findings

After I had coded the full dataset, I began the process of developing interpretive insights. I did this by using the specific research questions for the review to frame reinterpretation of each code and its associated data. For each code, I asked: 'what do these data have in common with LFS? How are they similar/different psychosocially and physically? How would these grouped experiences of young people with other inherited disease likely compare to the experiences of young people with LFS?' At the mechanical level I made inferences of the descriptive themes with feedback and input from my supervisors in a cyclical process. I used a 'writing as analysis' process, where small chunks of interpretive and cyclical writing help make sense of data (Richards 2009), to make increasingly more nuanced interpretations.

At this point, researchers using qualitative meta-data analysis 'go beyond' the content of the original primary research (Thomas and Harden 2008), making the final research product a synthesis that generates new perspectives. I went 'beyond' the primary research in this analysis as only one study in the review explored the experiences of AYAs with LFS; yet, the findings of the review as a whole are geared towards implications for LFS., requiring an interpretive leap from the primary data.

A limitation of qualitative meta-data analysis is that it inevitably de-contextualises findings from the original research (Thomas and Harden 2008). The process of translating primary data into descriptive and analytical themes necessarily removes the original context of studies to find commonalities and patterns across the data collectively. Throughout my meta-data analysis, I attempted to preserve context by reporting findings specifically based on gender, gene status and disease type where possible. I chose these specific characteristics because, 1) they were commonly reported among the primary research included in the review, making it easier to consistently extract this information across studies; 2) in the context of living with a genetic predisposition to disease, genetic status and disease type (i.e., disease severity, symptoms, prevention/treatment options, and age of onset) are key factors in predicting likely psychosocial implications, as is gender depending on the type of disease (e.g., inherited breast cancer). These characteristics directly mapped onto the FSGI model (p. 60), allowing me to easily compare the psychosocial typology of each condition to LFS.

In sum, the findings from Study 1 constituted a critical review of current knowledge about how young people live with inherited disease and formed the basis of the preliminary analytical framework for Study 2: namely the sampling strategy, interview guide design, and early analytical decisions. As analysis progressed, this frame was superseded by a more accommodative structure to encompass the richness of data.

5.3 Study 2 methods: operationalising interpretive description

Study 2 was an interpretive description of young people's experiences of LFS in Australia. This section addresses how I used the interpretive description methodology described in chapter 4 and consists of three main parts: setting, population, sampling and recruitment; data collection using semi-structured interviews; and data analysis using reflective thematic analysis.

5.3.1 Setting, population, sampling, and recruitment

A key part of any qualitative research design is to identify and define who is of interest to the study, where the study is set and how participants will be recruited and consented. This section describes each component in turn.

5.3.1.1 Setting

The primary site for my ID study was a multidisciplinary environment including both genetic health professionals and researchers: the Parkville Familial Cancer Centre (PFCC) at the Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Victoria, Australia. Clinical genetics services like the PFCC provide individuals and families at risk of inherited disease with clinical genetics and genetic counselling services with no out-of-pocket costs within the Australian public healthcare system. Those who meet eligibility criteria are able to access genetic counselling, testing, and risk management services financially subsidised by the federal government under the Medicare Benefits Schedule (MBS).

As the largest clinical cancer genetics service in Australia providing care to families with LFS, the PFCC setting allowed for maximum exposure to the population of interest. Importantly, at the time of the study, the PFCC was the only site in Australia to offer research-based whole-body risk management (including MRI) for individuals over 18 with, or at risk of, a germline pathogenic mutation in *TP53*. Consequently, as part of the Surveillance study in Multi-Organ Cancer-Prone Syndromes (SMOC+;

HREC/12/PMCC/17), individuals in Victoria from families with LFS had unprecedented access to cutting edge cancer surveillance.

Being embedded within a clinical department with clinical genetic counsellors, clinical geneticists, and medical oncologists also provided unparalleled opportunity to discuss and recruit potential participants in a sensitive manner to maximise enrolment. Moreover, being in a clinical department meant the ID, with its applied slant, was grounded in current practices and practice issues well-known within the department.

Although the PFCC was the primary site, I also coordinated the study across several other sites in Australia: the Victorian Clinical Genetics Service (VCGS), Victoria; the King Edward Memorial Hospital (KEMH), Western Australia; and, the Royal Brisbane and Women's Hospital (RBWH), Queensland. Sites in Western Australia and Queensland were established to ensure the sample included participants without formalised access to whole-body risk management of LFS, which at the time was limited to Victoria. This approach ensured maximum variation in the sample as participants without access to whole-body risk management for LFS were likely to have very different experiences to those who did.

The VCGS site, which specialises in paediatric genetics, was established to help recruit young people under the age of 18 years, as the PFCC was an adult service. The VCGS also offered whole-body risk management for children, which was coordinated outside of a formalised program by a medical oncologist, Dr Kanika Bhatia. At the time of the study, this was the only paediatric risk management protocol for LFS in Australia. The multi-site ethics application was approved and overseen by the Peter MacCallum Cancer Centre Human Research Ethics Committee (HREC/16/PMCC/196; Appendices 3A-3I).

5.3.1.2 Population

The population for my study included individuals who met the following criteria:

- 1) Adolescents and young adults aged 15-39 years; and,
- 2) Who have, or are at 50% risk of, a *TP53* pathogenic germline mutation.

The eligibility criteria were broad because LFS is a rare condition and focussing on AYAs, further restricted the eligible pool of participants. To estimate the number of AYAs who have a *TP53* pathogenic mutation at each genetic service in Australia, I queried the Inherited Cancer Connect (ICCon) database, a collaboration connecting all Australian Familial Cancer Centres. From the query, the main population of eligible participants

was in Victoria, with smaller numbers at other sites. Assessing the willingness of AYAs to participate in an interview prior to recruitment was not feasible and potential drop out could not be anticipated, so the eligibility criteria was not further defined by cancer status to maximise the number of potential participants and increase the sample size.

5.3.1.3 Purposive sampling and sample size

The population of interest was very specific and its true size was difficult to estimate. Therefore, I used purposive sampling to identify participants who, based on the criteria above, had experienced being from a family with LFS (Denzin and Lincoln 2005). Using purposive sampling enabled me to deliberately select 'information rich' cases who were able to respond to the research questions (Patton 2002).

In statistical research, using probabilistic sampling means a power calculation can determine the requisite sample size to achieve study aims. Conversely, the number of participants required to achieve aims in a qualitative interview study mainly relies on precedent (i.e., published samples sizes from studies with similar methods) and operationalising the concept of 'data saturation'. The widely accepted definition of saturation conceives it as a form of 'information redundancy', or the point at which no new substantive themes or codes can be acquired from data (Miles and Huberman 1994; Braun and Clarke 2019b).

Saturation is widely used as a simple and useful heuristic to understand rigour in qualitative research and provide credibility to sample size decisions. It even features as a criteria for quality in 'quality checklists', such as the 32-item Consolidated Criteria for Reporting Qualitative Research (COREQ), among others (Tong, Sainsbury, and Craig 2007). In practice though, saturation is difficult to operationalise, and there is a dearth of published guidelines on how to assess, report and justify data saturation (Francis et al. 2010; Guest, Bunce, and Johnson 2006; Hennink, Kaiser, and Marconi 2016; Weller et al. 2018; Morse 1995). As a result, 'saturation is the most frequently touted guarantee of qualitative rigour offered by authors to reviewers and readers, yet it is the one we know least about' (Morse 2015: 587).

Furthermore, thinking of saturation as information redundancy is problematic for interpretive types of qualitative research as it suggests a 'completeness of understanding and a determinable, fixed point for stopping data collection' (Braun and Clarke 2019b: 22). Its relevance as a requisite for rigorous qualitative research is contentious among those who practice reflexive and constructivist forms of qualitative

research and take issue with researchers who posit ‘the truth’ is findable within a dataset (Braun and Clarke 2019b, 2019a). Indeed, information redundancy in qualitative analysis has been described as ‘a logical fallacy, as there are always new theoretical insights to be made as long as data continues to be collected and analysed’ (Low 2019: 131).

I concur with such a critique, and because my analytical framework is interpretive and based on the tenets of critical realism, data saturation is incompatible with my chosen paradigm. As an alternative to data saturation, I used the straightforward concept of ‘information power’ to estimate my sample size: i.e., the more relevant information a sample holds, based on participant experiences, the fewer participants are needed to answer the research questions (Malterud, Siersma, and Guassora 2016). Information power is affected by five key dimensions: aims of the study, specificity of the sampling criteria, use of established theory to ground and extend empirical interview data, strength of interview dialogue, and the use of case (few cases, but in depth) or cross-case (many cases, less depth) analysis (Malterud, Siersma, and Guassora 2016). The combination of these factors helps to determine to approximate sample size needed to answer one’s research questions.

Three factors suggested my sample would need to be large (i.e., >30 participants): the exploratory research questions, broad sampling criteria,² and cross-case analysis strategy. Two factors, however, limited the need for a large sample: my theoretically informed approach and the dataset being based on a strong interview dialogue. Overall, this meant I would likely require a medium to large-sized sample (15-30 participants) to answer my research questions (Terry et al. 2017) and I set out to recruit up to 30 participants. This estimate was supported by similar qualitative interview studies conducted by my supervisors, who included 20-40 participants and used similar analytical approaches (e.g., thematic analysis). Using previous work as a guide is consistent with sample size estimation being a pragmatic exercise, contingent upon disciplinary norms, available resources, researcher experience, and many other factors related to design and method (Braun and Clarke 2019b).

² Despite participants being from families with the same type of rare genetic mutation, they varied in terms of developmental stage, gene status, previous cancer diagnoses, gender, and family structure.

5.3.1.4 Recruitment

To identify participants, data managers or lead clinical staff at each site queried their respective clinical databases for individuals who met inclusion criteria, producing a potential participant list for each site. Where possible, this list also included individuals older than 39 years of age who had children so that I could identify AYAs at 50% risk of a *TP53* pathogenic mutation using pedigree data. Potential participants were approached with two different methods of recruitment.

1. They were mailed a site-specific invite letter with information about the study and instructions to either accept or decline the invitation. For potential participants under the age of 18 years, their parent/guardian was mailed an invite letter, which included a plain language information statement designed for adolescents. I followed-up non-responders by phone and/or text four weeks after the invite was sent.
2. Or, if feasible, potential participants with an upcoming appointment were approached by their treating clinician (e.g., genetic counsellor or clinical geneticist) and provided with study information. If I was present at the clinic, and the potential participant agreed, I would meet them in person to discuss the study, or I would follow-up by phone or text.

For potential participants at 50% risk of *TP53* pathogenic mutation, most had no previous contact with clinical services and there was limited available contact information. I therefore relied on snowball sampling from first-degree relatives who had contact with the clinic. Where feasible, first-degree relatives with an upcoming appointment were approached by their treating clinician (e.g., genetic counsellor or clinical geneticist) and provided with study information to pass on to the potential participant. If I was present at the clinic, and the relative agreed, I would meet them in person to discuss the study and provide them with contact details. If the potential participant expressed interest in the study by contacting me, I would follow-up by phone or text to organise an interview.

I supplemented the genetic service-focussed recruitment strategy by 1) setting up a study website available to the public (www.petermac.org/LFS_research); and, 2) circulating study information on the private Facebook page of the Li-Fraumeni syndrome Association (LFSA) support group. I gained approval and assistance from the moderators of the LFSA support group for this step.

All participants who agreed to participate indicated their informed consent by signing a site-specific consent form. Participants under 18 years of age provided their assent in concert with their parent/guardian consent by signing a minor-specific consent form.

5.3.2 Data collection: semi-structured interviews

I collected and analysed data concurrently so each process could inform the other iteratively (Bryant and Charmaz 2007). This allowed me to tailor the interview guide to pursue new leads with each successive interview. Data collection consisted of semi-structured interviews either by telephone or in person using an interview guide developed collaboratively with my supervisor team and based on findings from Study 1. There were three interview guides to accommodate the varied experiences among groups of potential participants (i.e., minors aged under 18 years, those with a *TP53* pathogenic germline mutation, and those not yet tested; all three have been combined for presentation in Appendix 4). Main topics of each interview guide included: experiences with genetic testing and risk management; risk perception; identity; social, romantic, and family relationships; family formation; and emotional, practical and formal supports. Interviews were audio-recorded and I transcribed them verbatim. All interview transcripts were de-identified and pseudonyms are used throughout this thesis.

Participant age, gene and cancer status are provided in parentheses to provide context for interview excerpts. The term ‘unaffected’ is used to describe participants with, or at 50% risk of, a *TP53* mutation, who did not have a personal history of cancer at the time of the study. I am using ‘unaffected’ as a strictly physical descriptor and note that while a participant may be physically unaffected by cancer, they may be considerably affected by cancer in a familial and relational sense. Those with a personal history of cancer, either at the time of study or previously, have an added descriptor for their cancer type (e.g., ‘breast cancer’ or ‘multiple cancers’).

All participants were made aware that they could choose to not answer any particular question, could terminate the interview at any time, and could choose to withdraw their consent (and data) at any time prior to the finalisation of data processing. A distress protocol was established for participants who experienced any psychological discomfort/distress during an interview. My supervisors also established a debriefing process for me after conducting interviews to ensure I had psychosocial support throughout the data collection phase.

5.3.3 Data analysis: reflexive thematic analysis

I used reflexive TA to develop my interpretive description of how young people experience LFS. Braun et al. (2019), major advocates for reflexive TA, describe the essence of their approach as:

The aim of coding and theme development in reflexive TA is not to 'accurately' summarise the data, nor to minimise the influence of researcher subjectivity on the analytic process, because neither is seen as possible nor indeed desirable. The aim is to provide a coherent and compelling interpretation of the data, grounded in the data (Braun et al. 2019: 848).

In this way, using coding reliability measures and a rigid, pre-determined codebook for analysis are incompatible with a reflexive approach to TA (Morse 1997), which consists of six key steps: 1) data familiarisation; 2) generating codes; 3) constructing themes; 4 & 5) reviewing and defining themes; and, 6) writing 'the report' (in this case thesis chapters) (Terry et al. 2017; Braun and Clarke 2019b). I supplemented this approach by collating the codes generated from analysis into a codebook. This allowed me to track coding decisions and help organise the analysis. Importantly, the codebook *supplemented* the reflexive process of TA and did not act as a pre-determined framework for analysis like in codebook TA, as described in Study 1.

5.3.3.1 Familiarisation

Consistent with interpretive description, the first phase of my reflexive TA was familiarisation with the data (Terry et al. 2017; Braun and Clarke 2019b). During data collection, I recorded reflective/analytical memos immediately after interviews; transcribed interviews and checked them against the audio for quality control; read transcripts in full (in some cases repeatedly); and, using hardcopies of transcripts, I made preliminary jottings and notes in the margins about tentative ideas for codes, topics, and noticeable patterns or themes before attempting formal coding (Saldana 2013). I engaged in the process of immersion for an extended period to avoid coding with premature precision and to accommodate broader patterns of experience that could later be re-examined for a range of alternatives (Thorne, Kirkham, and O'Flynn-Magee 2004).

5.3.3.2 Generating codes

After familiarisation, I began the process of coding: reducing and organising interview data into meaningful units of analysis by tagging phrases and passages with a short label or 'pithy' phrase that captures their relevance to the research questions (Terry et al.

2017). The exploratory, interpretive nature of this study meant the main body of codes were intentionally inductive. Inductive codes emerge directly from the raw data and mirror language used by participants. This gives participants' voice primacy and ensures findings remain grounded in their experiences and narratives. As I adopted a critical realist stance, my inductive coding was mainly focussed on the immediately apparent, participant-expressed meaning of data (i.e., semantic coding). Initially, coding closely matched the interview guide, but later coding decisions were made with the knowledge of, and in consideration of, all previously coded interviews (Morse 2018). My coding process was therefore highly interpretive, and where applicable, I coded for deeper, more implicit and conceptual meaning of data (i.e., latent coding) (Braun et al. 2019).

To engage with the data systematically, and to be consistent with interpretive description, I used a core set of analytical questions that I could ask of the data in iterative cycles (Thorne 2016):

- What are people doing? What are they trying to accomplish?
- How, exactly, do they do this? What specific means and/or strategies do they use?
- How does the participant talk about, characterise, and understand what is going on?
- What is going on here?
- What assumptions are people making here? (Saldana 2013: 21-22).

I also used a small collection of deductive codes. These were developed prior to data collection and represented pre-conceived ideas relevant to the research questions, namely related to developmental and family systems theory.

To increase rigour in the coding process, my supervisors (LEF and AWL) and I engaged in familiarisation concurrently for the first six transcripts and met to discuss impressions of the data and our preliminary jottings in detail. Appreciating that we would look at data through our own personal lenses, and make different interpretive choices, we aimed to develop a diverse range of codes to discuss and refine, rather than trying to reach a consensus (Braun et al. 2019). This process helped to gain greater initial insight through sharing each other's perspective on the data and culminated in a preliminary code list. I then continued to generate codes and add to this list alone, meeting regularly with my supervisors to discuss my coding decisions.

5.3.3.3 Using a codebook to track coding decisions

As part of my reflexive TA, I used a codebook to track my coding and help organise my analysis (MacQueen et al. 1998; DeCuir-Gunby, Marshall, and McCulloch 2010). Having a codebook also provided my supervisors with a coherent document to provide feedback and stay up-to-date with my progress. The initial organising structure of the codebook closely matched the topics in the interview guide (e.g., risk perception, relationships, risk management, family formation etc.), and each code definition had three parts: a label, an extensive definition, and an example (DeCuir-Gunby, Marshall, and McCulloch 2010). Throughout my reflexive analysis, the codebook evolved as I organised and re-organised codes into a more hierarchical structure to better represent the relationship between coded data. Codes were split, integrated with others, or dropped all together as analysis continued, and excerpts were continuously reviewed for fit under their code (DeCuir-Gunby, Marshall, and McCulloch 2010). The process of codebook development kept me abreast of relevant data and helped to eliminate overlap in coding. This robust basis also provided a reference point for more abstract interpretations of data in the form of themes. I used QSR NVivo (Version 11.4.3) to assist with data management.

5.3.3.4 Constructing themes

In reflexive TA, themes are generated from the intersection of data, researcher experience and subjectivity, and research questions (Braun et al. 2019). Built from smaller units of meaning (i.e., codes), themes ‘capture the essence and spread of meaning; they unite data that might otherwise appear disparate, or meaning that occurs in multiple and varied contexts; they (often) explain large portions of a dataset; they are often abstract entities or ideas, capturing implicit ideas “beneath the surface” of the data, but can also capture more explicit and concrete meaning’ (Braun et al. 2019: 845).

I constructed candidate themes by collating codes and their associated data into bigger clusters of meaning that could tell a story about aspects of the dataset. I used the research questions as a guide for this process to determine what was or was not a relevant pattern of meaning. For most clusters, I identified a central organising concept that could draw different codes together and underpin the new theme (Terry et al. 2017). Candidate themes were reviewed with my supervisory team to assess their fit across the dataset.

Using principally inductive reasoning inevitably created a form of intellectual chaos during analysis (Thorne, Kirkham, and O'Flynn-Magee 2004). To try and bridge the gap between one's preliminary analytic framework, the complexity that results from

inductive analysis, and the final interpretive research product, Thorne, Kirkham, et al. (2004) contend that researchers must exercise a form of 'disciplined reflexivity'.

Reflexivity is 'a researcher's scrutiny of his or her research experience, decisions, and interpretations in ways that bring the researcher into the process and allow readers to assess how and to what extent their interests, positions, and assumptions influenced the research. A reflexive stance informs how the researcher conducts his or her research, relates to the research participants, and represents them in written reports' (Bryant and Charmaz 2007: 609).

To exercise my reflexivity throughout data analysis, I used the core reflexive mantra described by Richards (2009): when noting that data are striking or interesting, one must ask themselves, 'why is this interesting to me?' (Richards 2009: 145). The following set of questions developed by Sunstein and Chiseri-Strater (2007) helped to operationalise this mantra and fulfil the iterative questioning process of interpretive description (Thorne, Kirkham, and O'Flynn-Magee 2004):

- What surprised me? (to track assumptions)
- What intrigued me? (to track positionality)
- What disturbed me? (to track tensions)

I also maintained a log of analytical memos throughout the study to document my thoughts, concerns, tensions, insights, and musings about the data and the research process. I used these to shape my narrative and explain the data. A critical aspect of memoing is that writing about data itself, in any way that is relevant, is a form of analysis. The practice of writing forces one to crystallise their thoughts, and iterative cycles of writing helped me to explore and distil my analytical interpretations (Richards 2009). Therefore, memoing was not only be a key reflexive tool for my study, but a key analytical tool that acted as an audit trail of key research decisions.

Below is a series of linked memos about my experiences of interviewing participants throughout the study. It documents my reflexive process and the kinds of influence I had on data collection, and vice versa.

The task of interviewing young people was challenging in many respects. As a young person myself, I shared many experiences, language and perspectives with the young people I interviewed. We shared a common identity as a 'young person' and it was easy for me to relate to them and vice versa, especially in use of language. What this meant, however, was that for the first few interviews I busied myself trying to befriend participants, which muddled the purpose of the interview and detracted

from asking difficult questions. After this point, I made a conscious effort to separate the process of rapport building with participants and maintaining my position as researcher, being prepared to be 'un-liked' in the pursuit of richer data.

Despite both participants and I identifying as young people, I did not share with them a 'sick identity' or an 'at-risk identity'. This was an obvious point of difference, especially with participants who had developed cancer, but also for those with a strong family history of cancer. I chose not to disclose that my mother had a sporadic breast cancer when I was finishing high school because I felt it was outside the scope of what many of these young people had experienced regarding cancer in their family. I did, however, use my familial experience to frame for how young people may experience something similar (or different) with LFS; in this way, it made it easier to empathise with their experiences, but also harder remain analytical because it struck a chord with me emotionally thinking of my own mother and her experiences.

Being a young male also influenced data collection. I felt that it was easier for young men in the sample to relate to me and develop rapport as we shared many of the same attitudes and 'laid-back' Australian male chat. I think it was also easier for me to recognise when young men were holding back or finding a line of questioning distressing because I could see myself in their position doing the same thing. Or perhaps I was just more comfortable calling them out if their answers seemed superficial or not well thought out because we shared a frank-speaking male identity. In general though, I found interviewing young men more intensive as I had less time to formulate the next line of questioning due to them having shorter answers and demonstrating less in depth thought on many issues. That is not to say developing rapport with young women in the sample was any harder, but it did mean the majority of the sample were interviewed about personal topics by someone of the opposite sex of a similar age. Talking about mastectomy or femininity in general may have been different or difficult for young women in the sample.

A critical component of my reflexivity was debriefing with my supervisors (mainly LEF) after interviews and throughout analysis. The process of debriefing was important for me to disclose any distressing experiences I had during the interview, or as I found out later, during analysis. Having to explore the distressing experiences of young people in great depth during analysis was surprisingly difficult, constantly thinking and reworking analysis about loss, grief, death and existentialism was exhausting at times, and making use of my support network was critical.

I found there to be no substantive differences between conducting phone and in-person interviews. Phone interviews were easier in some respects because they

allowed a physical distance between me the questioner and they the responder, which I felt help me seem less intrusive, enabling participants to share more personal experiences. Some in-person interviews were challenging, mainly due to location (being at a participant's home or favourite café); large parts of the interviews were taken up by rapport building and chit chat more commonly associated with speaking to someone who doesn't know you at these venues.

5.3.3.5 Reviewing and defining themes

The penultimate step of reflexive TA is reviewing and defining themes. This entails (re)shaping, clarifying and rejecting some themes, similar to a quality control exercise assessing how well themes work in relation to each other, codes, the data, and the research questions (Terry et al. 2017). The main task is to assess whether all coded data strongly relate to the central organising concept of their theme and reflect the diversity of meaning around that concept. Each theme must be distinctive and so making choices about the 'best and sharpest' boundaries between themes is an important task (Terry et al. 2017: 21). The next step was defining and naming themes, which ensured clarity, cohesion, precision and quality of my interpretive description (Terry et al. 2017: 22). Theme definitions are short summaries of the meaning of each theme, similar to a mini-abstract for each theme. The process of writing definitions and names helped to establish whether there was enough depth and detail for each theme to stand alone as a key chapter in the analytic story (Terry et al. 2017).

5.3.3.6 Writing up the report

The final phase was writing up the analysis. In reflexive TA, report writing is a distinct final step of focus and refinement that determines how well themes hang together, tell a compelling story, and link to other literature. In terms of how I treated coded data, I chose to present participant quotes both analytically and illustratively. Analytical presentations focussed on particular excerpts with specific features that formed the basis of my analytical claims. Illustrative presentations consisted of excerpts as examples of my analytical narrative: i.e., evidence from the data that illustrated key elements of the story (Terry et al. 2017). Because different parts of my analysis were written up for different audiences (e.g., Chapter 7 for publication), the writing style is noticeably more expansive for the thesis chapters, allowing the narrative to spill out in more detail.

5.4 Study 3 methods: a descriptive health professional survey

Study 3 was a descriptive health professional survey aimed at identifying trends in current practice for young people from families with LFS. Study 3 has been published (Forbes Shepherd et al. 2019) and the study design and analysis are described in Chapter 11 as part of the author-accepted manuscript; here I provide a brief account of each stage and justification for my approach. This study was approved by the Peter MacCallum Cancer Centre Human Research Ethics Committee (LNR/17/PMCC/281; Appendices 3H-3I).

An anonymous, self-administered online survey was distributed among eligible genetic and oncology health professionals in Australia and New Zealand via email. I used an online platform for the survey (REDCap) so that I could create a highly tailored questionnaire with in-built logic and distribute the survey across Australia and New Zealand with minimal cost and administrative load. I used descriptive statistics to summarise quantitative data relating to categorical variables and demographics. I used Chi-square and Fisher's Exact testing to assess associations between variables. IBM Statistical Package for the Social Sciences (SPSS, version 25) was used for all statistical analyses. A p value of <0.05 was considered statistically significant. For open-text responses, I used inductive content analysis to systematically identify and group responses into content-related categories (Elo and Kyngäs 2008). I chose to use content analysis because it is a simple research method for producing concise descriptions of content in the form categories. It therefore lent itself to rapid descriptive analysis of short open-text responses.

5.5 Summary

This chapter described and justified the methods of Studies 1-3 of this project. Studies 1 and 2 used qualitative methods. Study 1 used conventional systematic review methods to identify relevant primary research for review. Meta-data analysis was used to synthesise qualitative findings across a large sample of research; the guiding analytic framework was thematic synthesis. Study 2 purposively sampled young people (aged 15-39 years) with, or at 50% risk of, a *TP53* mutation from Familial Cancer Centres across Australia. Participants took part in semi-structured interviews about their experiences with LFS over the phone or in person. Interview guides were informed by key themes from Study 1. Reflexive thematic analysis was used to develop findings for Study 2, which is consistent with the pragmatic-critical realist stance adopted for this project. Study 3 used

conventional descriptive and comparative statistics for quantitative data and inductive context analysis for open text responses from the survey. The next chapter presents the first study of this project: a systematic review of young people's experiences with inherited disease.

6 A systematic literature review of how young people live with inherited disease: What can we learn for Li-Fraumeni syndrome?

6.1 Overview

The previous chapter outlined the research methods for each study separately. This chapter begins the main body of the thesis and presents the first study of the project in its entirety: a systematic review and thematic synthesis of how young people live with inherited disease. Due to the dearth of previous research on young people with LFS, it was necessary to first establish a guiding analytic framework based on research for conditions with similar psychosocial implications. To do this, I set out to synthesise psychosocial research with young people from families with inherited disease to make possible links for young people affected by LFS. In this way, this chapter serves to contextualise the main interpretive description study (Chapters 7-10) and project as a whole. As mentioned in the preface, this chapter was published in the *Journal of Adolescent and Young Adult Oncology* (Forbes Shepherd et al. 2018), and is presented here as the author-accepted manuscript.³ Note that this chapter uses terminology suited

³ The published version has better readability (DOI: 10.1089/jayao.2018.0028).

for publication and has slightly different wording for key concepts compared to other chapters

6.2 Abstract

Purpose: Li-Fraumeni syndrome (LFS), a multi-organ cancer predisposition caused by germline *TP53* mutations, confers significant cancer risks for young people (15-39 years). Yet evidence of how individuals experience this condition and the psychosocial implications are lacking. Therefore, this systematic review assessed the psychosocial implications of living with, or are at risk of, an autosomal dominant condition as a young person, to draw evidence that may be analogous for young people with LFS.

Methods: We conducted a systematic search for studies published in peer-reviewed journals using Medline, CINAHL, PsycINFO and Embase databases. Findings were synthesised and are reported thematically.

Results: We screened 352 articles and identified 39 studies, representing the perspectives of 765 young people. Most studies addressed hereditary breast and ovarian cancer (n=22) and used qualitative methodologies (n=35). Only one LFS study was identified, highlighting the distinct lack of psychosocial research describing experiences of young people with LFS. Translatable evidence showed that familial factors strongly influenced young people's experiences of genetic testing and their mutation status. Major adverse reactions to genetic test results were rare, although young people with a gene mutation experienced various psychosocial concerns at key developmental milestones: including family planning, developing romantic relationships and making risk management decisions.

Conclusion: Young people undergoing genetic testing for inherited disease require individualised support and recognition of previous lived experiences. We recommend that longitudinal care be made available to young people with inherited disease as they reach developmental milestones that intersect with risk management, risk perception, and family formation.

Key words: Li-Fraumeni syndrome; young people; inherited condition; psychosocial; systematic review.

6.3 Introduction

The psychosocial implications of living with complex multi-organ syndromes with limited prevention options, such as Li-Fraumeni syndrome (LFS), remain understudied. In particular, the needs of adolescents and young adults aged 15-39 years ('young people' hereafter) remain inadequately understood and often unmet (Zebrack et al. 2013; Bibby et al. 2016; AYA Oncology Progress Review Group 2006). Young people with a genetic predisposition to LFS must simultaneously manage the expectations and demands faced by their peers within a possibly shortened lifespan due to a high risk of multi-organ tumourigenesis. In the absence of targeted psychosocial research, we seek evidence of how young people are impacted by other inherited diseases to guide genetic health professionals who provide supportive care.

6.3.1 Li-Fraumeni syndrome

LFS, a rare cancer predisposition syndrome caused by heterozygous germline mutations in the *TP53* gene, is predominantly characterised by the increased incidence of premenopausal breast cancer, soft tissue sarcoma, osteosarcoma, adrenocortical carcinoma, central nervous system tumours and haematological malignancies from childhood (Kratz et al. 2017). In contrast to other inherited cancer syndromes, LFS confers considerable multi-organ cancer risk for young people: females by age 31 years and males by age 46 years have a cumulative cancer incidence of 50% (Mai et al. 2016). Although, less penetrant *TP53* variants have also been reported (de Andrade et al. 2018). Using whole-body MRI as part of a multimodal approach to screening has recently been demonstrated as an effective strategy to manage the diverse LFS cancer spectrum among *TP53* mutation carriers (both children and adults) (Mai et al. 2017; Kratz et al. 2017; Villani et al. 2016; Ballinger et al. 2017). For the first time, these screening strategies may offer a sense of cancer control to families with LFS (Ross et al. 2017; McBride et al. 2017; Lammens, Bleiker, Aaronson, et al. 2010). While evidence is still emerging regarding the medical benefits of multimodal screening among children, predictive genetic testing for minors is controversial (Kesserwan et al. 2016). Moreover, cancer risk-reducing options remain limited and participating in screening represents only one of many psychosocially significant aspects of living with LFS.

Previous psychosocial research on adults with LFS gives some insight into the potentially devastating nature of the condition. Families with LFS who have faced multiple cancers may be psychologically vulnerable due to persistent exposure to

experiences of grief and threats to personal and familial wellbeing (Oppenheim et al. 2001; Peterson et al. 2008). Some adults also show clinically significant levels of distress when making predictive *TP53* genetic testing decisions (Lammens, Aaronson, et al. 2010). In contrast, other research suggests that individuals from families with LFS make use of diverse support networks with friends and family and are resilient to psychological distress (Peters et al. 2016). At present, however, it is unclear whether this evidence can apply to young people with LFS considering their life stage, and there is lack of scholarship elucidating the lived experiences of young people with LFS.

6.3.2 Young people and Li-Fraumeni syndrome

For this review, we defined young people as aged 15-39 years (AYA Oncology Progress Review Group 2006). Young people with a *TP53* mutation live through the majority of their cancer risk during this age range (Mai et al. 2016). Furthermore, during this critical life stage young people transition through consecutive stages of development (late adolescence, emerging adulthood and young adulthood) characterised by complex psychosocial tasks (Arnett 2000; Sawyer et al. 2012). Experiencing these transitional life stages with LFS presents distinct psychosocial challenges. Concurrently managing significantly increased multi-organ cancer risks; potentially experiencing family members being affected by cancer; knowing there is a 50% chance of passing the mutation to current or future children; possibly engaging with novel research-based screening protocols; having limited cancer prevention options; experiencing cancer diagnoses and treatment and for some, mortality, are likely to create a complex and unique set of psychosocial needs.

Genetic health professionals play a critical role in addressing these psychosocial needs as they offer young people genetic counselling and testing, and post-test counselling for those who receive a positive genetic test result. Nonetheless, no models of care in genetic counselling practice specifically address the needs of young people with genetic conditions (Duncan and Young 2013), especially those with multi-organ inherited cancer syndromes, such as LFS. Two recent reviews assessed the psychosocial impact of cancer genetic testing among adolescents (10-19 years) (Vetsch et al. 2018) and predictive genetic testing generally among young adults (14-30 years) (Godino et al. 2016). Both reviews were small, assessing 9 and 11 studies respectively, and a broader synthesis of applicable evidence is currently lacking to guide genetic counselling practice for young people with LFS. Given the likely burdensome psychosocial implications experienced by young people with, or at risk of, a *TP53* mutation, a comprehensive

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understanding of other conditions with high penetrance and limited prevention options that infer intergenerational psychosocial sequelae is required (Table 9, p. 104).

Table 9. Key features of the inherited conditions included for review

Condition (associated gene)	Age of onset	Penetrance	De-novo mutation rate	PGT for minors	Phenotype	Risk management strategies
LFS (TP53)	Childhood - adulthood	High	7-14%	No	Soft-tissue sarcoma	No international consensus
					Osteosarcoma	Clinical protocols
					Brain tumours	Screening (adults):
					Breast cancer (early onset)	Breast MRI (annual from age 20)
					Adrenocortical carcinoma	Colonoscopy and endoscopy (2-5 yearly from age 25)
					Leukaemia	Comprehensive physical review incl. dermatological exam (annual; for children incl. neurological exam)
					Bronchoalveolar cancer	
					Colorectal cancer	
					Among others	Risk-reduction:
						BPM (under age 50)
						Risk-reducing medication (e.g., tamoxifen)
						Avoid unnecessary radiation exposure (incl. children)
						Research protocols
						Additional to above screening for children and adults:
						Whole-body and brain MRI (annual)
						US of abdomen/pelvis (3-4 monthly)
						Blood tests/biochemical tests (3-4 monthly)

FAP (APC)	Childhood - adolescence	High	11-25%	Yes	Colorectal cancer	International consensus
					Duodenal/perampullary cancer	Clinical protocols
					Desmoid tumour	Screening:
					Duodenal adenomas	Flexible sigmoidoscopy or colonoscopy until polyps detected (annual from age 10-12)
					Gastric fundic gland polyps	Colonoscopy (annual until colectomy completed)
						Surveillance of residual rectum or ileal pouch (annual post-colectomy)
						Upper GI endoscopy (from 25 years)
						Risk-reduction:
						Prophylactic colectomy (late adolescence)
						Prophylactic duodenectomy
VHL (VHL)	Childhood - adolescence	High	~20%	Yes	Retinal angioma	International consensus
					Renal cell carcinoma	Clinical protocols
					CNS hemangioblastoma	Screening:
					Pheochromocytoma	Brain/spinal MRI (triennial from age 12; biennial from age 18)
					Endolymphatic sac tumour	Renal imaging (annual from age 12-20)
					Epididymal cystadenomas	Abdominal MRI/US (triennial from age 12; biennial from age 20)
						Physical exam with BP (annual from age 2)
						Ophthalmologic review (annual from age 2)
						Baseline audiometry (at school entry)
						Nil risk reduction

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NF1 (<i>NF1</i>)	Childhood - adolescence	High	~50%	Yes	Tumours Neurofibromas Optic pathway glioma Brain/spinal cord glioma Paraganglioma Breast cancer GIST Other Learning, cognitive and social deficits	International consensus Clinical protocols Screening: Ophthalmic review (6 monthly from infancy; annual from 4-16; 3-5 yearly from 16) Breast mammography (annual from age 40; biennial from age 50) BP measurement (annual from age 10) Nil risk reduction
MEN1 (<i>MEN1</i>)	Adolescence - adulthood	High	~10%	Yes	Endocrine tumours Gastroenteropancreatic NET Thymic NET Bronchopulmonary NET Parathyroid adenoma Pituitary adenoma Non-endocrine tumours Lipomas Cutaneous collagenomas Facial angiofibromas Adrenal cortical tumour	No international consensus Clinical protocols Screening: Biochemical screening: plasma or serum (annual from age 10) Pancreatic and duodenum MRI or endoscopy (biennial from age 20) Chest and renal MRI (biennial from age 20) Brain MRI (triennial from age 10) Physical exam with attention to visual fields (annual from age 10) Nil risk reduction

HBOC (<i>BRCA1/2</i>)	Adulthood	High	Negligible	No	Breast cancer Ovarian/fallopian tube/primary peritoneal cancer	International consensus Clinical protocols Screening: Breast MRI + MMG +/- US (annual from age 30-50) Breast MMG +/- US (from age 50) Risk reduction: Risk-reducing medication (e.g., tamoxifen) BPM (under aged 40) BSO (around age 40)
HD (<i>HTT</i>)	Adulthood	High	n/a	No	Irreversible neurodegeneration of the brain	None

Note that all clinical protocols are based on Australian eviQ guidelines (Cancer Institute New South Wales, 2018). All ages are in years. NF2 and MEN2 were also included in the literature search, but no studies were found that met eligibility criteria; they are not included here.

Abbreviations: PGT, predictive genetic testing; LFS, Li-Fraumeni syndrome; FAP, familial adenomatous polyposis; VHL, von Hippel-Lindau Syndrome; NF1, neurofibromatosis 1; MEN1, multiple endocrine neoplasia 1; HD, Huntington disease; HBOC, hereditary breast and ovarian cancer; NET, neuroendocrine tumour; MRI, magnetic resonance imaging; MMG, mammogram; US, ultrasound; BPM, bilateral prophylactic mastectomy; BSO, bilateral prophylactic salpingo-oophorectomy; GI, gastrointestinal; GIST, gastrointestinal stromal tumour.

Sources: Villani et al. (2011); Gonzalez, Buzin, et al. (2009); Hampel et al. (2014); Renaux-Petel et al. (2018); Aretz et al. (2003); Rasmussen et al. (2010); Gutmann et al. (2017); Ferner and Gutmann (2013); Thakker et al. (2012).

6.3.3 Objectives

This systematic review synthesised evidence from inherited disease literatures to identify significant psychosocial domains for the young population with LFS. Based on LFS-specific literature and other inherited conditions, this review sought to answer:

1. What are the psychosocial experiences of young people who live with, or are at risk of, an inherited disease?
2. What are the likely implications of these psychosocial experiences for young people who live with, or are at risk of, an inherited disease?
3. How might the findings from 1) and 2) apply to those who live with, or are at risk of, a *TP53* mutation?

6.4 Methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2009) and the Enhancing Transparency in Reporting the Synthesis of Qualitative Research (ENTREQ) framework (Tong et al. 2012) to guide this review.

6.4.1 Search strategy

Between March and August 2017, we searched PsycINFO, Embase, CINAHL and Medline using combinations of search terms (Table 11, p. 110). Searches were run and combined using EndNote X8 (Thomson Reuters, New York City, NY). Studies were included for review based on inclusion-exclusion criteria (Table 10, p. 109). Inherited conditions were included in the search if they inferred similar psychosocial sequelae to LFS based on their clinical characteristics (Table 9, p. 104): autosomal dominant inheritance, high penetrance, limited prevention options, availability of clinical/research screening protocols and severe phenotype.

Table 10. Systematic review inclusion and exclusion criteria

Inclusion criteria

- Original, peer-reviewed research article, and;
- Published in English between 2007 and 2017, and;
- Study sample reported on the experiences of young people living with, or at risk of, at least one autosomal dominant condition selected as the focus for this review, and;
- Included young people aged 15-39 years at recruitment,^a and;
- Reported on psychosocial factors or an element of supportive care.

Exclusion criteria

- Results not reported such that they could be directly applicable to young people (i.e., results averaged across groups and young people perspectives could not be distinguished), or;
- Findings not stratified by participant age, or;
- Findings not stratified by mutation status.

^aFor studies that included participants that were aged <15 years or over 39 years at recruitment, findings had to be clearly stratified by age.

Table 11. Systematic review search terms and search combination

Psychosocial terms		Genetic terms		Age-related terms		Inherited conditions^a
Psychosocial OR psycho* impact OR decision making OR decision-making OR risk management or risk perception OR family planning or experience*	AND	Genetic testing OR predictive genetic testing	AND	Adolescent* OR young adult* OR young people or young wom#n OR youth OR teen	AND	Li-Fraumeni syndrome OR LFS OR TP53 OR Huntington disease OR hereditary breast and ovarian cancer OR HBOC OR BRCA OR BRCA1/2 OR BRCA1 OR BRCA2 OR familial adenomatous polyposis OR FAP OR von Hippel-Lindau or VHL OR neurofibromatosis OR NF1 OR NF2 OR multiple endocrine neoplasia OR MEN1 OR MEN2

^aAutosomal recessive conditions have significantly different implications for heterozygous carriers and were therefore excluded.

6.4.2 Data extraction

We identified 352 articles that met search criteria after excluding duplicates (Figure 9, p. 113). Two authors (RFS and LEF) independently screened titles and abstracts; any disagreements were discussed until consensus was reached. Of the 104 full-text studies included for review, 34 studies met our eligibility criteria. An additional five studies were included for review by manually searching reference lists. In total, 39 studies were included in the final review (Table 12, p. 115).

6.4.3 Quality appraisal

Studies were critically appraised using the Standards for Reporting Qualitative Research (SRQR) for qualitative studies (O'Brien et al. 2014) and the Mixed Methods Appraisal Tool (MMAT) for quantitative and mixed-method studies (National Collaborating Centre for Methods and Tools 2015). A novel scoring system was developed for qualitative studies using the SRQR checklist (for a summary of this process see Table 30S, p. 312; Appendix 1), this allowed for more detailed appraisal of qualitative studies specifically for synthesising study findings and evaluating consistency in reporting (O'Brien et al. 2014). Two authors (RFS and LEF) independently appraised studies; any disagreements were discussed until consensus was reached. All criteria were equally weighted and studies were not excluded based on a quality threshold; methodological considerations are detailed in the results.

6.4.4 Thematic synthesis

We used thematic synthesis to guide data extraction and analysis (Thomas and Harden 2008). This approach enabled inductive identification of key concepts from published studies and comparisons across findings to develop novel interpretations beyond any single study (Thomas and Harden 2008). RFS electronically extracted all text under the headings 'results and conclusions'. RFS and AL independently read extracted text from the first six studies included for review to coalesce descriptive themes relevant to the psychosocial implications of LFS. All authors agreed on themes and developed a coding framework to summarise and communicate findings. A further six studies were then independently coded by RFS and AL using the coding framework to establish good inter-coder reliability. Coding disagreements were discussed at coding meetings (RFS, AL and LEF) until consensus was reached on parameters of each code. RFS then coded the remaining studies using the coding framework to develop the final analytical themes for reporting the findings.

6.5 Results

A total of 39 studies were reviewed, representing the perspectives of 765 young people (647 female and 118 male). Half of the young people had genetic testing: 325 were gene mutation positive and 54 were gene mutation negative. Nearly a fifth ($n=143$) were clinically affected, 43 of whom were also gene mutation positive. A third ($n=251$) were at increased risk (i.e., family history of disease, or at 25% or 50% genetic risk) and 43 were at general population-level risk.

Twenty-three studies were from the United States, eight from Australia/New Zealand, seven from the United Kingdom, four from Canada, and one from Norway (Table 12, p. 115; four studies had samples with more than one country of origin). The studies focussed on a range of clinically variable inherited conditions: LFS (Alderfer et al. 2017), familial adenomatous polyposis (FAP) (Andrews et al. 2007; Duncan et al. 2008, 2010; Mireskandari et al. 2009; Durno et al. 2012), hereditary breast and ovarian cancer (HBOC) (Bradbury et al. 2012; Bradbury et al. 2009; Bradbury et al. 2016; Brunstrom, Murray, and McAllister 2016; Glassey et al. 2018; Hamilton 2012; Hamilton and Hurley 2010; Hamilton, Williams, Bowers, et al. 2009; Hoskins and Greene 2012; Hoskins et al. 2008; Hoskins, Roy, and Greene 2012; Hoskins and Werner-Lin 2013; Hoskins, Werner-Lin, and Greene 2014; Patenaude et al. 2013; Werner-Lin 2007, 2008b, 2008a, 2010; Werner-Lin et al. 2012; Young et al. 2017; Mand et al. 2013; MacLeod et al. 2014; Evans et al. 2016; Ormondroyd et al. 2012), Huntington disease (HD) (Duncan et al. 2007, 2008; Forrest Keenan, McKee, and Miedzybrodzka 2015; Forrest Keenan et al. 2007; Forrest Keenan et al. 2009; Gong et al. 2016; Kavanaugh, Noh, and Studer 2015; Mand et al. 2015; MacLeod et al. 2014), and neurofibromatosis 1 (NF1) (Hummelvoll and Antonsen 2013; Draucker et al. 2017). Two studies had diverse samples: one included familial cardiomyopathy (FCM) (MacLeod et al. 2014), another included cases of autosomal dominant cerebellar ataxia, hereditary diffuse gastric cancer and Lynch syndrome (Mand et al. 2013). Samples sizes ranged from 3-320 (Hoskins and Werner-Lin 2013; Bradbury et al. 2016), and participants ranged in age from 9-50 years (Forrest Keenan et al. 2007; Durno et al. 2012). Over half of the studies emanated from the USA and focussed on young women with a *BRCA1/2* mutation, many with overlapping study samples; 22 HBOC-specific studies reported on 12 separate samples. Only one study included young people from families with LFS and findings did not reach thematic saturation (Alderfer et al. 2017). No studies focussed on von Hippel-Lindau syndrome (VHL) or multiple endocrine neoplasia (MEN).

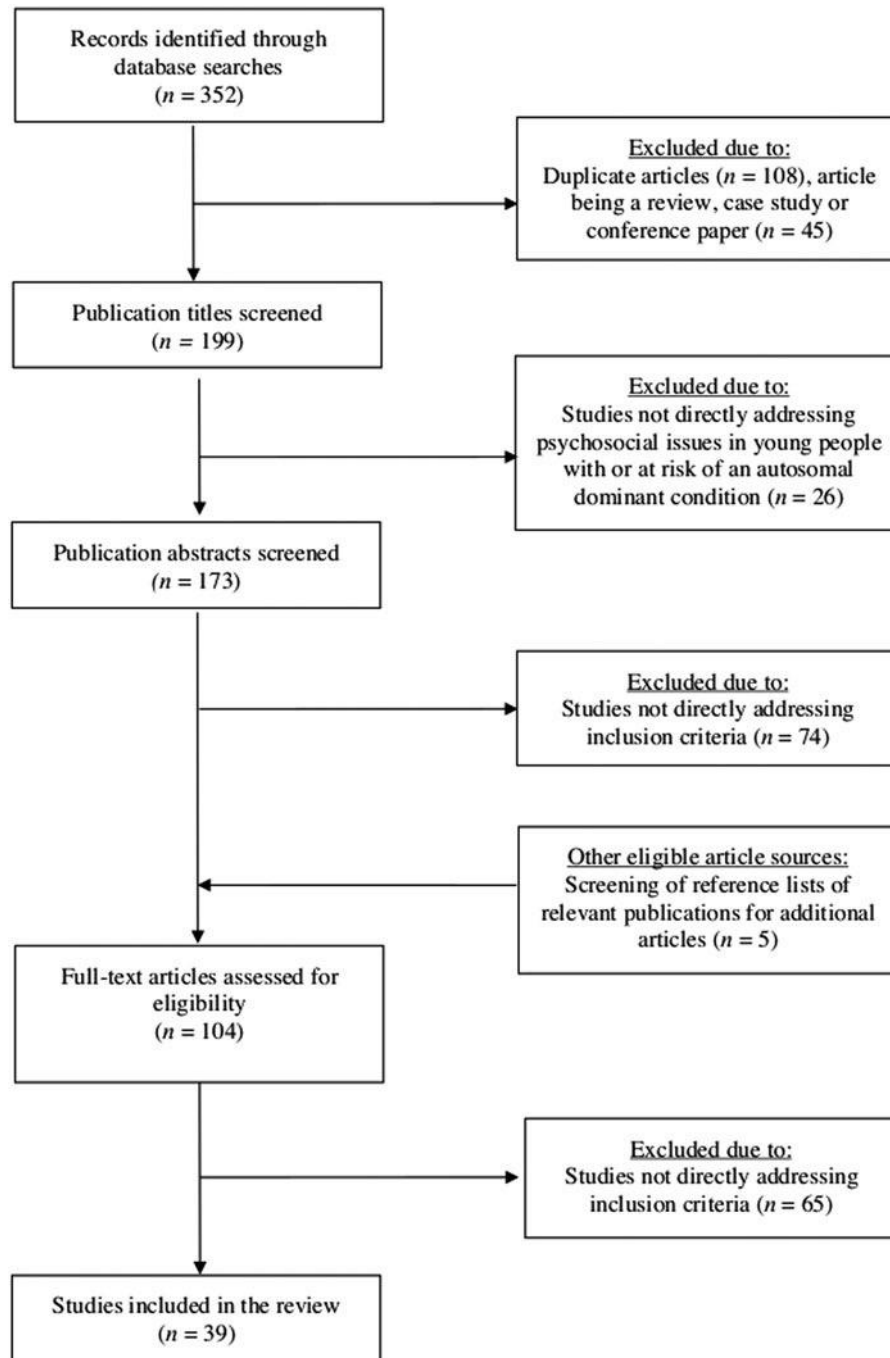


Figure 9. The preferred reporting items for systematic reviews and meta-analyses flow diagram indicating how studies were included and excluded in this review

6.5.1 Quality appraisal

Thirty-five studies (90%) used qualitative approaches, three used quantitative survey approaches, and one used a mixed-method approach (Table 13, p. 126). Qualitative studies mostly described study aims (89%), qualitative approach (74%), data collection (89%) and analysis (89%), trustworthiness (80%) and limitations (89%). Conflicts of interest (60%), researcher characteristics and reflexivity (23%), sampling strategies (43%) and study context (63%) were inconsistently described. Quantitative and mixed-method studies scored highly, with a mean score of 87.5%, but were limited by non-representative samples.

Table 12. Summary of reviewed articles addressing the psychosocial impact of inherited conditions in young people

Author (yr., country)	Study aim(s)	Condition(s)	Design and analysis	N (sample characteristics)	Age range (yrs.) at study (mean)	Age range (yrs.) at testing (mean)	Appra- isal score
Li-Fraumeni syndrome (LFS)							
Alderfer et al. (2017, USA)	To explore the general perspectives and experiences of genetic testing for young people from families with LFS	LFS	Cross-sectional, qualitative interviews Content analysis and thematic analysis	12 (3-ve, 1 AR, 7+ve, 1 assumed +ve) M:F=4:8	12-25 (17.8)	3-20 (11.4)	74%
Mixed samples							
Duncan et al. (2008, AUS)	To explore the harms and benefits of predictive genetic testing among young adults with FAP or HD	FAP, HD	Cross-sectional, qualitative interviews Grounded theory: content and thematic analysis	18 HD=8 (6-ve, 2+ve) FAP=10 (5-ve, 5+ve) ^a M:F=8:18	14-26 (21.8) 20-26 (24) 14-25 (20.1)	10-25 (17) 17-25 (20.7) 10-17 (14)	86%
Mand et al. (2013, AUS)	To report on the process and impact of predictive genetic testing for adult-onset conditions among young people	ADCA HBOC HD HDGC LS	Cross-sectional, qualitative interviews Thematic analysis	9 ADCA=1+ve; HBOC=2+ve; HD=2+ve; 1-ve; HDGC=1+ve; LS=2+ve M:F=2:9	17-21 (18.8)	16-17 (16.2)	69%

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MacLeod et al. (2014, UK)	To explore motivations and experiences of genetic testing for adult-onset conditions among young people	FCM HBOC HD	Cross-sectional, qualitative interviews Interpretive phenomenological analysis	36 FCM=10 (5-ve, 5+ve) HBOC=16 (7-ve, 9+ve) HD=10 (4-ve, 6+ve) M:F=9:27	15-31 (median 25)	15-25 19-25 18-24 15-24	98%
Familial adenomatous polyposis (FAP)							
Andrews et al. (2007, AUS)	To assess quality of life and psychological adjustment among young people with or at risk of FAP	FAP	Cross-sectional, self-report questionnaire (IES; QoL and Life Impact of FAP scales) Descriptive statistics	88 (15 AR, 2+ve, 71 CA) M:F=25:63	18-35 (28)	n/a	84% ^b
Mireskandari et al. (2009, AUS)	To explore the psychosocial impact of having or being at risk of FAP as a young person	FAP	Cross-sectional, qualitative interviews Multi-phase iterative approach	11 (3 AR, 8+ve): 7/11 CA ^c M:F=5:6	19-34 (26)	n/a	83%
Duncan et al. (2010, AUS)	To evaluate key ethical concerns for predictive genetic testing for FAP in young people	FAP	Cross-sectional, qualitative interviews Content and thematic analysis	10 (5-ve, 5+ve) ^a M:F=4:6	14-25 (20.1)	10-17 (14)	88%
Durno et al. (2012, CAN)	To assess functional outcomes and quality of life among patients with FAP who had undergone surgery ≤14 years.	FAP	Cross-sectional, self-report questionnaire (IES, SF-12, RSES, BES, FAP-specific cancer-related worry) Descriptive statistics	28 (28 CA) M:F=18:10	14-50 (24)		100% ^b

Table 12 cont.

Author (year, country)	Study aim(s)	Condition(s)	Design and analysis	N (sample characteristics)	Age range at study (mean)	Age range at testing (mean)	Appraisal score
Huntington disease (HD)							
Duncan et al. (2007, AUS)	To explore the experiences and impact of predictive genetic testing for HD among young people	HD	Cross-sectional, qualitative interviews Thematic analysis	8 (6-ve, 2+ve) ^a M:F=4:4	20-26 (24)	17-25 (20.7)	81%
Forrest Keenan et al. (2007, UK)	To describe the experiences of young people from families with HD	HD	Cross-sectional, qualitative interviews Modified grounded theory	33 (5-ve, 26 AR, 1+ve, 1 CA) ^d M:F=12:21	9-28 (20.5)	n/a	95%
Forrest Keenan et al. (2009, UK)	To explore young people's experiences of finding out about their family history of HD	HD	Cross-sectional, qualitative interviews Modified grounded theory	33 (5-ve, 26 AR, 1+ve, 1 CA) ^d M:F=12:21	9-28 (20.5)	n/a	90%
Forrest Keenan et al. (2015, UK)	To explore the experiences and impact of predictive genetic testing for HD among young people	HD	Cross-sectional, qualitative interviews Thematic analysis	12 (9 AR at first interview, 3 unreported HD status) 7 completed interviews before and after testing, 2 before testing, 3 after testing All female participants	17-26 (21)	n/a	81%
Kavanaugh et al. (2015, USA)	To explore the support needs of teenagers providing care to family members with HD	HD	Cross-sectional, qualitative interviews Inductive content analysis	40 (40 AR) M:F=9:31	12-20 (17)	n/a	86%

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Mand et al. (2015, AUS)	To explore the psychosocial context of young people from families with HD	HD	Cross-sectional, qualitative interviews Thematic analysis	10 (10 AR) M:F=4:6	15-20 (15)	n/a	93%
Gong et al. (2016, USA/UK)	To explore the developmental impact of testing positive for HD as a young person	HD	Cross-sectional, qualitative interviews Grounded theory: thematic analysis	14 (14+ve) M:F=2:12	20-33 (median 29)	n/a	86%
Hereditary breast and ovarian cancer (HBOC)							
Werner-Lin (2007, USA)	To explore how family histories with cancer influence beliefs about cancer risk in young women with a <i>BRCA1/2</i> mutation	HBOC	Cross-sectional, qualitative interviews, medical family genograms Narrative methodology, listening guide	22 (22+ve) ^f	21-35	n/a	81%
Werner-Lin (2008a, USA)	To explore how cancer risk perception and family histories with cancer intersect with family planning for young women with a <i>BRCA1/2</i> mutation	HBOC	Cross-sectional, qualitative interviews, medical family genograms Narrative methodology, listening guide	23 (23+ve) ^f	22-35	n/a	83%
Werner-Lin (2008b, USA)	To explore formal and informal support needs of young women with a <i>BRCA1/2</i> mutation	HBOC	Cross-sectional, qualitative interviews, medical family genograms Narrative methodology, listening guide	23 (23+ve) ^f	22-36	n/a	90%

Table 12 cont.

Author (year, country)	Study aim(s)	Condition(s)	Design and analysis	N (sample characteristics)	Age range at study (mean)	Age range at testing (mean)	Appraisal score
Werner-Lin (2010, USA)	To identify how family histories of cancer and genetic testing influence parenting, reproductive choices and family planning among young women with a <i>BRCA1/2</i> mutation	HBOC	Cross-sectional, qualitative interviews, medical family genograms Narrative methodology, listening guide	23 (23+ve) ^f	21-35	n/a	98%
Bradbury et al. (2009, USA)	To examine the experiences and impact of family communication of HBOC as a young person	HBOC	Cross-sectional qualitative interviews, structured and open-ended questioning Self-regulation Theory of Health Behavior Thematic analysis Descriptive statistics	22 (4-ve, 15 AR, 3+ve) M:F=10:12	18-33 (median 26)	n/a	79%
Hamilton et al. (2009, USA/CAN)	To describe the decision-making processes of young women with a <i>BRCA1/2</i> mutation for predictive genetic testing and risk management	HBOC	Cross-sectional, qualitative interviews (email and phone) Grounded theory method, symbolic interactionism	44 (44+ve): 21/44 CA ^g	18-39	n/a	88%

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Hamilton and Hurley (2010, USA/CAN)	To explore the experiences of young single women with a <i>BRCA1/2</i> mutation	HBOC	Cross-sectional, qualitative interviews (email and phone) Grounded theory method, symbolic interactionism	11 (11+ve): 4/11 CA ^g	18-35	n/a	90%
Hamilton (2012, USA/CAN)	To explore the experiences of marriage, childbearing and being diagnosed with breast cancer among young women with a <i>BRCA1/2</i> mutation	HBOC	Cross-sectional, qualitative interviews Grounded theory method, symbolic interactionism	44 (44+ve): 21/44 CA ^g	18-39	n/a	60%
Hoskins et al. (2008, USA)	To investigate the challenges of forming intimate relationships as a young woman with a <i>BRCA1/2</i> mutation during early adulthood	HBOC	Cross-sectional qualitative interviews, Grounded theory, Attachment theory, Thematic analysis	11 (11+ve) ^h	26-35 (30)	21-33 (25)	98%
Hoskins et al. (2012, USA)	To explore cancer risk perception of young women with a <i>BRCA1/2</i> mutation	HBOC	Cross-sectional, qualitative interviews Grounded theory method	60 (60+ve) ^h	21-36 (29.6)	18-35 (24.5)	93%
Hoskins and Greene (2012, USA)	To explore the decision-making process of young women with a <i>BRCA1/2</i> mutation to undergo BPM	HBOC	Cross-sectional, qualitative interviews Grounded theory method	60 (60+ve) ^h	21-36 (29.6)	18-35 (24.5)	93%

Table 12 cont.

Author (year, country)	Study aim(s)	Condition(s)	Design and analysis	N (sample characteristics)	Age range at study (mean)	Age range at testing (mean)	Appraisal score
Young et al. (2017, USA)	To explore the decision-making process of young women with a <i>BRCA1/2</i> mutation regarding family formation, fertility, breastfeeding and cancer risk-reducing surgery	HBOC	Cross sectional, qualitative interviews Combined analysis of previous baseline interviews (Hoskins, Roy, and Greene 2012) and novel data set of follow-up interviews ~3 years afterwards. Grounded theory and interpretive description	12 (12+ve) ^h	23-37 (30)	n/a	93%
Werner-Lin et al. (2012, USA)	To explore the experiences of predictive genetic testing and risk management for young women with a <i>BRCA1/2</i> mutation	HBOC	Cross-sectional, qualitative interviews, focus group discussions (novel sample: n=6) Combined 2 ^o retrospective analysis with two other qualitative data sets (n=26) (Werner-Lin 2007) Grounded theory and interpretive description	32 (32+ve) ⁱ	21-27 (23)	≤ 25	95%

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Hoskins and Werner-Lin (2013, USA)	To explore the experiences of predictive genetic testing and risk management for young women with a <i>BRCA1/2</i> mutation	HBOC	Retrospective analysis, multi case study, qualitative interviews Grounded theory	3 (3+ve) ⁱ	22-25	~18-21	88%
Hoskins, Werner-Lin and Greene (2014, USA)	To explore the experiences of cancer risk management among young women with a <i>BRCA1/2</i> mutation tested before age 25 years	HBOC	Cross-sectional, qualitative interviews, focus group discussions Grounded theory methods	32 (32+ve) ⁱ	21-27 (23)	≤ 25	90%
Bradbury et al. (2012, USA)	To explore how adolescent girls at high risk or population risk of breast cancer understand and respond to breast cancer risk	HBOC	Cross-sectional qualitative interviews, structured and open-ended questioning Self-regulation Theory of Health Behavior Framework/thematic analysis Descriptive statistics	54 High risk=35 (6 AR, 6 with family history and/or mother with breast cancer, 23 with 1 or more SDRs with breast cancer) Population risk=19 n=15/54 eligible age	11-19	n/a	93%
Ormondroyd et al. (2012, UK)	To explore reproductive decision-making and knowledge of/attitudes towards reproductive genetic testing among young women with a <i>BRCA1/2</i> mutation	HBOC	Cross sectional qualitative interviews, inductive thematic analysis	25 (25+ve) n=20/25 eligible age	26-45	n/a	93%

Table 12 cont.

Author (year, country)	Study aim(s)	Condition(s)	Design and analysis	N (sample characteristics)	Age range at study (mean)	Age range at testing (mean)	Appraisal score
Patenaude et al (2013, USA)	To determine the impact of a mother's positive <i>BRCA1/2</i> result on their daughter's risk perception, distress and future plans	HBOC	Cross sectional, mixed-method approach Qualitative interviews; self-report questionnaire (BSI-18; GSI; IES; BCKQ) Thematic analysis	40 (7-ve, 32 AR,1+ve)	18-24 (median 21)	n/a	75% ^b
Bradbury et al. (2016, USA)	To evaluate the impact of breast cancer history and maternal positive <i>BRCA1/2</i> status on adolescent girls' psychosocial adjustment and perceived cancer risk	HBOC	Cross-sectional, case-control, psychosocial self-report questionnaire (BASC-2; CRIES; FADS; HADS; IES-R; single item measures), Self Regulation Theory of Health Behavior/Developmental Theory	320 Cases=208 BCFH+ve Controls=112 BCFH-ve n=113/320 eligible age	11-19 (15.4) (15.1)	n/a	98% ^b
Brunstorm et al. (2016, UK)	To explore the experiences of predictive genetic testing for young women with a <i>BRCA1/2</i> mutation below the minimum age for screening in the UK (30 years)	HBOC	Cross-sectional, qualitative interviews Thematic analysis	7 (7+ve)	24-30 (27)	22-28 (25.1)	81%

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Evans et al. (2016, USA)	To explore critical domains of care for young women with a <i>BRCA1/2</i> mutation	HBOC	Cross sectional, qualitative interviews Grounded theory method Descriptive statistics	12 (4+ve, 8 at 25% or 50% risk) Interviews with genetic counsellors (n=12) excluded from analysis	19-28 (23)	n/a	86%
Glasse et al. (2017, AUS/NZ)	To explore the factors influencing perceived breast cancer risk in young women with or at risk of a <i>BRCA1/2</i> mutation who have undergone/planning to undergo BPM	HBOC	Cross-sectional, qualitative interviews Interpretive phenomenological analysis	46 (7AR, 3 BCFH+ve, 36+ve) Undergone BPM=26 Planning BPM=20	23-38 (30)	n/a	100%
Neurofibromatosis 1 (NF1)							
Hummelvoll and Antonsen (2013, NOR)	To describe the psychosocial experiences and concerns of young people with living with NF1	NF1	Cross-sectional, qualitative interviews Hybrid thematic analysis	15 (15+ve): 15/15 CA/ M:F=7:8	18-37 (median 26)	n/a	76%
Draucker et al. (2017, USA)	To describe the health-related quality of life of children, adolescents and young adults with NF1 and their families	NF1	Cross-sectional, qualitative interviews Content analysis	23 (23+ve) (n=5/23 of eligible age; M:F=3:2) Parent interviews (n=18) excluded from analysis	5-25	n/a	90%

Abbreviations: n/a, not available; M:F, male : female participants; LFS, Li-Fraumeni syndrome; FAP, familial adenomatous polyposis; HD, Huntington disease; ADCA, autosomal dominant cerebellar ataxia; HBOC, hereditary breast and ovarian cancer; HDGC, hereditary diffuse gastric cancer; LS, Lynch syndrome; FCM, familial (hypertrophic or dilated) cardiomyopathy; NF1, neurofibromatosis 1; BPM, bilateral prophylactic mastectomy; +ve, tested positive; -ve, tested negative; AR, at 50% risk; CA, clinically affected; SDR, second-degree relative; IES, impact of events scale; QoL, quality of life; SF-12, Health-related quality of life SF-12; RSES, Rosenberg self-esteem scale; BES, Body esteem scale; BSI-18, brief symptom inventory-18; GSI, global severity index; BCKQ, breast cancer genetic counselling knowledge questionnaire;

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BASC-2; behavioural assessment system for children; CRIES, child revised impact of events scale; FADS, McMaster family assessment device; HADS, hospital anxiety and depression scale; IES-R, revised impact of events scale; BCFH, breast cancer family history, where +ve means one or more first-degree relatives with breast cancer or a mother with a *BRCA1/2* mutation.

Note: unless otherwise stated, articles were scored with the SRQR checklist and HBOC samples consisted of exclusively female participants. Median age of participants was provided in cases where a mean age was not available.

^{a,d,e,f,g,h,i} Articles share the same or have overlapping samples; ^b Articles appraised with MMAT guidelines; ^c n=3 had a *de novo* mutation; ^j n=8 had a *de novo* mutation.

Table 13. Critical appraisal criteria: % of studies meeting assessment criteria

SRQR (n=35)	n met criteria (%)		MMAT (n=4)	n met criteria (%)	
	Qualitative studies (n=35)			Mixed-methods studies (n=1)	Quantitative studies (n=3)
Title	35 (100)	Quantitative component			
Abstract	28 (80)	Relevant sampling strategy	1 (100)		3 (100)
Problem formulation	31 (89)	Representative sample	0 (0)		2 (67)
Purpose or research question	32 (91)	Appropriate measurements	1 (100)		3 (100)
Qualitative approach and research paradigm	26 (74)	Response rate above 60%	1 (100)		3 (100)
Researcher characteristics and reflexivity	8 (23)	Qualitative component			
Context	22 (63)	Relevant qualitative data	1 (100)		n/a
Sampling strategy	15 (43)	Relevant qualitative data analysis	1 (100)		n/a
Ethical issues pertaining to human subjects	24 (69)	Appropriate consideration of context	1 (100)		n/a
Data collection methods	31 (89)	Appropriate consideration of researcher's influence	0 (0)		n/a
Data collection instruments and technologies	26 (74)	Mixed-methods component			
Units of study	30 (86)	Relevant mixed methods research design	1 (100)		n/a

Table 13 cont.

Data processing	29 (83)	Integration of qualitative and quantitative data	1 (100)	n/a
Data analysis	31 (89)	Limitations associated with integration	0 (0)	n/a
Techniques to enhance trustworthiness	28 (80)			
Synthesis and interpretation	28 (80)			
Links to empirical data	34 (97)			
Integration with prior work	33 (94)			
Limitations	31 (89)			
Declared no conflicts of interest	21 (60)			
Funding	29 (83)			
Mean total score (%) ^a	86.8		75	92
Range of total score (%)	59.5 - 100		-	75 - 100

Abbreviations: SRQR, standards of reporting qualitative research; MMAT, mixed methods appraisal tool.

^aRefer to Table 30S (p. 312, Appendix 1) for a summary of how total scores were calculated.

6.5.2 Genetic testing for young people

Three analytical themes were pertinent to genetic testing of young people living with, or at risk of, a *TP53* mutation: family narratives of illness, decision-making for genetic testing, and the immediate harms and benefits of genetic testing.

6.5.2.1 Family narratives of illness

Family narratives of illness are the stories people tell about how their families are impacted by, and adapt to, a condition over multiple generations. These stories help attribute meaning to the disease, shape expectations regarding disease expression, delineate expected roles and communication patterns, and provide guidance for coping (Werner-Lin and Gardner 2009). These narratives played a pivotal role in shaping risk perceptions before genetic testing, willingness to pursue testing, and coping for young people at risk of a range of adult onset conditions (FCM, HBOC, HD and Lynch syndrome) (Mand et al. 2013; Forrest Keenan et al. 2007; Duncan et al. 2007; MacLeod et al. 2014; Bradbury et al. 2009; Ormondroyd et al. 2012; Evans et al. 2016).

One study of young women with a *BRCA1/2* mutation suggested cumulative and intergenerational experiences of cancer contribute to strong family narratives of illness (Hamilton, Williams, Bowers, et al. 2009). In fact, narratives were so strong that 40/43 young people tested for HBOC, HD or Lynch syndrome assumed a mutation positive status before genetic testing, believing they would share the fate of affected or deceased relatives (Duncan et al. 2007; MacLeod et al. 2014; Mand et al. 2013; Evans et al. 2016). This belief outweighed their understanding of the 50% chance of inheriting the mutation, and for some, served as a protective strategy in anticipation of a possible mutation positive result (Duncan et al. 2007; Mand et al. 2013; MacLeod et al. 2014).

Two studies showed that how and when relatives disclose aspects of the family history of disease resulted in a staged understanding of familial illness (Forrest Keenan et al. 2009; Bradbury et al. 2009). Young people with a genetic predisposition to adult onset conditions (e.g., HBOC, HD and Lynch syndrome) felt that growing up with knowledge of their condition (i.e., being told at younger ages) helped them consider predictive genetic testing and adapt to results (Mand et al. 2013; Forrest Keenan et al. 2007; Bradbury et al. 2009). Similarly, individuals who had experienced the familial implications of inherited disease at a young age (e.g., family members' reduced lifespan, cognitive, behavioural and personality disturbances because of HD), possessed the necessary maturity to make informed decisions for predictive genetic testing (Mand et al.

2013). Three studies, however, suggested familial experiences of HD could be distressing and isolating for young people (Forrest Keenan et al. 2007; Mand et al. 2015; Kavanaugh, Noh, and Studer 2015), especially if they adopted caring roles and adult responsibilities with insufficient resources and practical support (Kavanaugh, Noh, and Studer 2015; Mand et al. 2015).

6.5.2.2 Decision-making for genetic testing

Young people predominantly described the decision to undergo genetic testing as uncomplicated (MacLeod et al. 2014; Duncan et al. 2007; Mand et al. 2013). Motivations were similar for conditions with and without associated risk management, including relief from uncertainty or distress (MacLeod et al. 2014; Duncan et al. 2007; Forrest Keenan, McKee, and Miedzybrodzka 2015; Duncan et al. 2008; Mand et al. 2013, 2015; Brunstrom, Murray, and McAllister 2016), perceiving genetic information as useful for health and reproductive planning (Alderfer et al. 2017; Forrest Keenan, McKee, and Miedzybrodzka 2015; MacLeod et al. 2014; Mand et al. 2013, 2015; Evans et al. 2016; Ormondroyd et al. 2012), and to benefit current or future children (Forrest Keenan, McKee, and Miedzybrodzka 2015; MacLeod et al. 2014; Brunstrom, Murray, and McAllister 2016). For conditions with risk management options, the possibility to take action to alter disease progression was an added motivator (MacLeod et al. 2014; Hamilton, Williams, Bowers, et al. 2009; Alderfer et al. 2017; Brunstrom, Murray, and McAllister 2016; Mand et al. 2013; Evans et al. 2016; Ormondroyd et al. 2012), although some harboured concerns about receiving a positive result (Patenaude et al. 2013). When testing was used to determine treatment following a diagnosis, young people at risk of a *TP53* or *BRCA1/2* mutation perceived testing as a secondary priority (Hamilton, Williams, Bowers, et al. 2009; Alderfer et al. 2017). Little was known about young people who declined to undergo genetic testing.

A young person's autonomous decision-making capabilities may be complicated by the implications of genetic information for other family members, their reliance on family for emotional and pragmatic support, parental attitudes, and family dynamics (Hallowell et al. 2003; Werner-Lin et al. 2012; MacLeod et al. 2014; Werner-Lin et al. 2016; Evans et al. 2016). These factors varied by disease group, although three studies with young people at risk of a *BRCA1/2* or *APC* (cause of FAP) mutation showed that some young people rely on immediate family members for emotional support and value their active participation with genetic testing decisions (Werner-Lin et al. 2012; Duncan et al. 2010; Hamilton, Williams, Bowers, et al. 2009). While others felt bound by parental

expectations (Werner-Lin et al. 2012; Duncan et al. 2010; Hamilton, Williams, Bowers, et al. 2009), and experienced family participation as coercion (Hoskins and Werner-Lin 2013). For conditions with childhood onset and effective prevention methods (e.g., FAP), parental involvement was common and welcomed in the genetic testing decisions of young people when under the age of majority (Duncan et al. 2010). Data, though limited, suggested that 12/12 young people from families with LFS also felt genetic testing should be offered as an option for children, despite limited prevention options, and should actively involve parents in decision-making (Alderfer et al. 2017).

6.5.2.3 Immediate harms and benefits of genetic testing outcomes

Major adverse emotional responses to genetic test results for the full range of inherited conditions examined for this review were rare, although LFS-specific data are lacking (Forrest Keenan, McKee, and Miedzybrodzka 2015; MacLeod et al. 2014; Mand et al. 2013; Duncan et al. 2010, 2008). Despite this, documented harms for young people with mutation positive results included disruption to relationships (intimate, peer and familial); feelings of isolation; disruption of schooling; employment concerns; knowledge of future illness; the possibility of passing on a mutation to future children; experiencing a range of negative emotions; remaining uncertainty and fear of disease progression (Duncan et al. 2008; Mand et al. 2013; Brunstrom, Murray, and McAllister 2016; Forrest Keenan, McKee, and Miedzybrodzka 2015; Gong et al. 2016; Hummelvoll and Antonsen 2013; Evans et al. 2016).

Predictive genetic testing also induced distress for young people at risk of HD and FAP when the process was inadequately managed or failed to respect their concerns and autonomy (Forrest Keenan, McKee, and Miedzybrodzka 2015; MacLeod et al. 2014; Mand et al. 2013; Duncan et al. 2010, 2008). Two studies showed that some young people at risk of HD accessed testing by deliberately presenting as well-adapted (MacLeod et al. 2014; Forrest Keenan, McKee, and Miedzybrodzka 2015), underlining their perceived lack of control over the testing process and disease course, and the potential for young people to hide their emotional needs (Forrest Keenan, McKee, and Miedzybrodzka 2015; Duncan et al. 2008; Mand et al. 2013). Harms from testing negative included unexpected survivor guilt; worry about implications for siblings; and feeling distanced from family members with a mutation (Duncan et al. 2008, 2007; Mand et al. 2015). One case of LFS reported similar harms (Alderfer et al. 2017).

Benefits for young people with mutation positive results included experiencing a sense of solidarity with other affected family members; relief from uncertainty; and

feeling a sense of control about managing their condition (for conditions with risk management options) (Duncan et al. 2008, 2007; Alderfer et al. 2017; Hummelvoll and Antonsen 2013). Benefits from testing negative included feeling relief from uncertainty and that the condition will not develop; witnessing relief in parents; and being able to move on in life (Duncan et al. 2008, 2007; Mand et al. 2013). Irrespective of outcome, no young people (86/86) across six separate studies reported any decisional regret for undergoing genetic testing for their family's inherited condition, including LFS (MacLeod et al. 2014; Duncan et al. 2007; Mand et al. 2013; Alderfer et al. 2017; Brunstrom, Murray, and McAllister 2016; Gong et al. 2016).

6.5.3 Young people with a genetic predisposition

Three analytical themes emerged from the literature examining the lived experiences of young people with a genetic predisposition, which may support hypothesis generation for the study of young people living with, or at risk of, a *TP53* mutation: evolving risk perceptions, risk management, and planning for relationships and reproduction.

6.5.3.1 Evolving risk perceptions

Family illness narratives critically shaped young people's perceived cancer risks. Young women with a *BRCA1/2* mutation perceived dramatic increases in cancer risk as they approach ages, or 'danger zones', when relatives were diagnosed or died from cancer (Hoskins et al. 2008; Werner-Lin 2007; Hoskins, Roy, and Greene 2012; Hamilton, Williams, Bowers, et al. 2009; Patenaude et al. 2013; Werner-Lin 2010; Evans et al. 2016; Ormondroyd et al. 2012). Older adolescent girls (aged 17-19 years) from families with a *BRCA1/2* mutation or families with a breast cancer history experienced heightened perceived breast cancer risk and greater breast cancer-specific distress compared to their population-risk peers (Bradbury et al. 2012; Bradbury et al. 2016). Moreover, young women with a *BRCA1/2* mutation with a family history of breast cancer had a heightened sense of breast cancer risk than their risk of ovarian cancer, and vice versa (Werner-Lin 2010).

For young people with *NF1* especially, the unpredictability of the condition in terms of phenotype, age of onset and severity meant family illness narratives were critical to anticipating one's personal risk of developing symptoms (Hummelvoll and Antonsen 2013). Conversely, some young people with a *BRCA1/2* or *NF1* mutation did not have a readily identifiable family illness narrative: e.g., one young woman with a *BRCA1/2* mutation inherited it from her asymptomatic father and eight young people had a *de*

de novo NF1 mutation. In these cases, young people lacked a family history indicative of their condition to help them navigate their expectations of disease, which made them feel especially vulnerable to a diagnosis (Hoskins, Roy, and Greene 2012; Hummelvoll and Antonsen 2013). Another study suggested that three young people with a *de novo APC* variant felt isolated from family members due to a lack of shared understanding, and that they may have unique support and informational needs to be addressed after genetic testing (Mireskandari et al. 2009).

Information provided by health professionals and a young person's level of genetic and health literacy also shaped understanding of disease and cancer risk perceptions. Genetic and health literacy levels vary widely among young women with or at risk of a *BRCA1/2* mutation (Hoskins, Werner-Lin, and Greene 2014; Werner-Lin et al. 2012; Patenaude et al. 2013; Ormondroyd et al. 2012), and some voiced a need for clear and direct explanations of their HBOC risk from health professionals (Evans et al. 2016). Young women with still developing health literacy overestimated their cancer risk, focusing on their lifetime relative risk of developing cancer versus short-term absolute risk (Hoskins, Werner-Lin, and Greene 2014), a belief supported by frequent visits to health professionals compared to peers (Hoskins, Roy, and Greene 2012). Whereas young women with a *BRCA1/2* mutation who had an accurate understanding of personal cancer risk were encouraged by interactions with health providers (Hoskins, Roy, and Greene 2012; Glassey et al. 2018). Overestimating cancer risks was linked to uptake of risk-reducing surgery (e.g., bilateral prophylactic mastectomy: BPM) at younger ages (Hoskins, Roy, and Greene 2012; Glassey et al. 2018; Werner-Lin et al. 2012; Hoskins and Greene 2012).

6.5.3.2 Risk management

There were limited data on young people's experiences of engaging in comprehensive, multi-organ cancer screening. One study showed that three out of seven young people who had tested positive for LFS found it difficult to conceptualise undergoing comprehensive, regular surveillance at the time of testing (Alderfer et al. 2017). Another study showed that young people with NF1 expressed frustration with limited treatment options for their condition, having to rely on screening for risk management (Draucker et al. 2017). For conditions with risk-reducing options (i.e., HBOC and FAP), young people's experiences were noticeably different.

For FAP, young people (<18 years) who had undergone prophylactic colectomy experienced poorer quality of life and psychological functioning compared to older

adults, and they continued to worry about developing intestinal cancer after their surgery (Durno et al. 2012). Whereas, seven separate studies reported on the complex decision-making young women with a *BRCA1/2* mutation experienced when considering breast cancer risk management and the intersection with family planning (Werner-Lin et al. 2012; Hoskins, Werner-Lin, and Greene 2014; Glassey et al. 2018; Young et al. 2017; Hoskins and Greene 2012; Hoskins, Roy, and Greene 2012; Werner-Lin 2010; Hoskins and Werner-Lin 2013; Brunstrom, Murray, and McAllister 2016; Hamilton, Williams, Bowers, et al. 2009; Evans et al. 2016). Immediately following genetic testing, many young women elected to manage their breast cancer risk with screening; the duration of this approach was related to tolerance for ambiguity and screening fatigue (sustained distress, tiredness and anxiety when attending regular screening and awaiting results) (Werner-Lin et al. 2012; Glassey et al. 2018; Hoskins, Roy, and Greene 2012; Hoskins and Greene 2012). Some young women pursued BPM to obviate such fatigue, or to manage fear and anxiety (Glassey et al. 2018; Hoskins, Roy, and Greene 2012; Hoskins and Greene 2012). Others continued breast screening and delayed BPM to breastfeed (Hoskins and Greene 2012; Hoskins, Roy, and Greene 2012; Hoskins and Werner-Lin 2013). Young women with a *BRCA1/2* mutation commonly pursued risk-reducing surgery to alter the cancer narrative shared by affected family members (Glassey et al. 2018; Young et al. 2017; Hamilton, Williams, Bowers, et al. 2009), especially if their mother was affected by, or died from, cancer (Hamilton, Williams, Bowers, et al. 2009). One study indicated that some young women completed BPM before conceiving because they doubted the efficacy of screening during pregnancy or to minimise fear of developing cancer during the pregnancy rather than focus on the health of their baby (Hoskins and Greene 2012).

Young women with a *BRCA1/2* mutation and who have children were often concerned about the impact of a cancer diagnosis, and cancer mortality, on their children and partner (Werner-Lin 2010; Hamilton 2012). To mitigate personal cancer risk and family burden they pursued screening and/or risk-reducing surgery with increased vigour compared to same age peers (Werner-Lin 2008a; Young et al. 2017; Werner-Lin 2010; Hamilton 2012). Women who received conflicting risk management advice from health professionals involved in their care were often frustrated and uncertain about how to navigate family planning and risk management during the reproductive years (Werner-Lin et al. 2012; Hoskins, Werner-Lin, and Greene 2014; Brunstrom, Murray, and McAllister 2016; Evans et al. 2016).

6.5.3.3 Planning for relationships and reproduction

Inherited cancer risk and visually noticeable differences added complexity to developing romantic intimacy or peer networks (Hoskins et al. 2008; Mireskandari et al. 2009; Hummelvoll and Antonsen 2013; Draucker et al. 2017). This was especially pronounced when planning or following risk-reducing surgery, which for some affected self-esteem, sexual functioning, and body image (Mireskandari et al. 2009; Hamilton and Hurley 2010; Andrews et al. 2007; Hummelvoll and Antonsen 2013; Durno et al. 2012). Five studies reported that young people with a genetic predisposition to FAP, HBOC, HD or NF1 were sometimes unsure of how and when to inform partners of their risk or condition, and experienced distress (Hoskins et al. 2008; Hamilton 2012; Mireskandari et al. 2009; Hummelvoll and Antonsen 2013; Draucker et al. 2017).

Three studies showed that subsequent to learning their mutation status, some young people with a genetic predisposition to FAP or HBOC perceived an abbreviated timeline to identify a life partner and start family planning (Werner-Lin 2008b, 2008a; Mireskandari et al. 2009). Similarly, seven studies strongly suggested that young women with a *BRCA1/2* mutation experienced a sense of urgency to complete family planning before reaching recommended ages to undergo breast/ovarian cancer risk-reducing surgery (Hamilton and Hurley 2010; Werner-Lin 2008a; Hamilton 2012; Hoskins, Werner-Lin, and Greene 2014; Hoskins and Greene 2012; Werner-Lin 2010; Brunstrom, Murray, and McAllister 2016). This urgency was compounded for young women who were not partnered (Werner-Lin 2008a; Hamilton 2012; Werner-Lin et al. 2012; Hoskins and Greene 2012), and left them feeling anxious and distressed (Werner-Lin 2008a; Hamilton and Hurley 2010; Brunstrom, Murray, and McAllister 2016). In the context of HD and HBOC, young people often reprioritised qualities they sought in a partner to include increased desire for compassion, nurturing, and resilience (Werner-Lin 2008b, 2008a; Gong et al. 2016). Yet, the presence of any partner seemed to mitigate psychological distress: unpartnered young people with a genetic predisposition to FAP were more likely to experience distress than those who were partnered (Andrews et al. 2007).

Young people with a genetic predisposition to HD, HBOC, Lynch syndrome or FAP were often aware of reproductive options to avoid passing on their mutation to their children (Mireskandari et al. 2009; Mand et al. 2015; Hoskins and Werner-Lin 2013; Gong et al. 2016; Hamilton 2012; Mand et al. 2013; Ormondroyd et al. 2012). Six studies indicated that young people learnt of, and considered, the availability of pre-

implantation genetic diagnosis (PGD) to conceive children who do not have the familial mutation (Hoskins and Werner-Lin 2013; Mand et al. 2015; Mireskandari et al. 2009; Gong et al. 2016; Mand et al. 2013; Ormondroyd et al. 2012). A minority of young people with a genetic predisposition to HBOC, HD or FAP also considered prenatal diagnosis (PND) and pregnancy termination to avoid passing on the mutation to their children (Mand et al. 2015; Gong et al. 2016; Mireskandari et al. 2009; Ormondroyd et al. 2012).

Two studies, however, suggested some young women with a *BRCA1/2* mutation did not fully appreciate the complexities of decision-making for PGD or PND and pregnancy termination, and grappled with the morality of using reproductive technologies (Hoskins and Werner-Lin 2013; Ormondroyd et al. 2012). There were no data on how young people experience prenatal diagnosis of an inherited condition, and how they approach decisions regarding pregnancy termination. One study showed that young women with a *BRCA1/2* mutation considered adoption and gamete donation as less appealing than PGD (Werner-Lin et al. 2012). Five studies demonstrated that it was common for young people with a genetic predisposition to HBOC, HD or NF1 to have actively decided not to have children (or more children) (Werner-Lin 2008a; Hamilton 2012; Mand et al. 2015; Hummelvoll and Antonsen 2013; Ormondroyd et al. 2012). Conversely, three studies showed that for some young people with a genetic predisposition to FAP or HBOC, the desire to have biological children negated concerns about the risk of passing on the mutation, believing that future technological advances in prevention and early detection would help their children stay healthy (Werner-Lin 2010; Mireskandari et al. 2009; Ormondroyd et al. 2012).

6.6 Discussion

This is the largest systematic review to comprehensively evaluate the psychosocial experiences of young people who live with, or are at risk of, an autosomal dominant condition and the possible implications of this experience. Our aim was to draw together relevant evidence for young people living with LFS. The 39 reviewed studies represent six countries and focussed on four clinically variable inherited conditions (HBOC, HD, FAP and NF1) that share psychosocial features with LFS. Yet, only one article addressed LFS, clearly indicating LFS-specific psychosocial research is in its infancy.

There were no studies from the search that focussed on VHL or *MEN1/2*, comparable conditions to LFS with high tumour burden, early onset and intensive surveillance (Table 9, p. 104). Similar to research on adults with LFS, adults with VHL or

MEN_{1/2} may experience clinically significant levels of distress (Rodrigues et al. 2017; Goswami et al. 2017; Lammens, Bleiker, Verhoef, et al. 2010). Psychological distress is more likely among adults who experienced the death of a family member as a result of VHL during adolescence (Lammens, Bleiker, Verhoef, et al. 2010), and is likely chronic among adults with MEN₂ (Rodrigues et al. 2017). Some adults with VHL or MEN₁ can also become socially isolated due to the medical burden of their condition, frustrated with life-long screening commitments and have difficulties accessing appropriate psychosocial or clinical care (Kasparian et al. 2015; Goswami et al. 2017). Without research specific to young people with VHL or MEN_{1/2}, this evidence base is currently difficult to apply to young people with LFS.

Studies across inherited conditions consistently reported familial factors, including illness narratives, history of disease, and the roles and influence of family members affect young people's experiences and perceptions of genetic testing and risk management. Comparable evidence from young people undergoing genetic testing for HD and HBOC showed that family narratives of illness, and the timing of family communication of disease can strongly influence a young person's understanding of the personal and familial implications of a genetic diagnosis. Due to the familial nature of LFS, familial factors are highly likely to play a similar role for young people from families with LFS.

Compared to adults, young people had similar motivations for, and experienced similar harms and benefits from genetic testing (Meiser 2005). Especially for undergoing genetic testing to reduce their uncertainty and pursue risk management. The role of family in the decision-making for genetic testing, however, was more complex for young people. Especially for adolescents who are under the age of majority (aged 15-17 years), where family dynamics and promoting a young person's autonomy can be difficult to negotiate for genetic counsellors (Tse et al. 2013; Werner-Lin et al. 2015). Familial factors were also critical in shaping young people's risk perception. For young people from families with LFS, the concept of 'danger zones' could manifest at earlier ages or represent concern for future children, and cancer-specific awareness could be more widespread. In contrast, for young people with a *de novo* mutation predisposing to NF₁ or FAP, the lack of shared understanding of their condition produced feelings of isolation from family and uncertainty about disease progression. Young people with a *de novo* TP₅₃ mutation may have similar experiences and possess different cancer risk perceptions due to the experience of cancer diagnosis and treatment. This could

manifest in more concern for recurrence risk rather than risk of another primary malignancy.

In combination with how health professionals communicate cancer risk and risk management options, genetic and health literacy was highlighted as an important factor that influences evolving cancer risk perception among young people. Currently we have a limited understanding of health literacy among young people generally (Sansom-Daly et al. 2016), and their understanding of genetics is variable and mostly dependent on their family experience of disease (McGill, Wakefield, Vetsch, Barlow-Stewart, et al. 2019). Multi-organ cancer risks for LFS could be challenging to communicate for health professionals and difficult to understand for young people, leading to inaccurate cancer risk perceptions that have implications for risk management decision-making and distress levels. Little is known about how individuals with, or at risk of, a *TP53* mutation understand the distinct risk estimates for multiple tumour types, and the ways these perceptions coalesce, or do not, into an overall perception of short-term or long-range cancer risk. We hypothesise that given this heightened complexity, young people with LFS may rely heavily on family heuristics to interpret multi-organ cancer risk.

The majority of studies included in this analysis addressed HBOC and focussed exclusively on women with a *BRCA1/2* mutation. Risk management decisions of young women with a *BRCA1/2* mutation were closely linked with family planning. Due to LFS and HBOC both predisposing to breast cancer, young women with a *TP53* mutation may be confronted with similar issues regarding breast cancer risk management as their peers with a *BRCA1/2* mutation. *BRCA1/2* mutations are, however, highly publicised and well known, which could be a point of difference among young people with a *TP53* mutation. Notably, breast cancer risk increases at earlier ages for LFS compared with HBOC and is one of the only cancer risks associated with LFS that can be prophylactically managed with risk-reducing surgery (Mai et al. 2016). Which may impact breast cancer risk perception, engagement with breast cancer screening, and/or completion of BPM.

Moreover, there were no translatable data from other inherited conditions that addressed young people's experiences of multi-organ comprehensive cancer screening. The prospect of lifelong, intensive, multimodal screening merits further empirical attention. A focus on young people should form part of ongoing investigations into the psychological impact of screening for LFS, VHL, and *MEN1/2* generally (McBride et al. 2017; Ross et al. 2017). Presently, comprehensive screening for LFS is only offered by a

small number of centralised and predominantly research-based services, which poses logistical concerns for young people and adults alike. Limitations to accessing screening due the cessation of research trials, geographical mobility, financial disadvantage, transitions between paediatric and adult services all remain potentially considerable barriers for multi-organ conditions.

This review highlighted that for conditions with noticeable physical differences (NF1), or with high likelihood of prophylactic or treatment-related surgery (FAP or HBOC), body image and self-esteem were concerns for young people. How and when to tell partners of their condition was also a common concern across all conditions, and young people expressed range of views concerning PGD, PND and passing on the mutation to future children. Some young women with a *BRCA1/2* mutation experienced an abbreviated timeline to complete childbearing and rearing due to recommendations to undergo breast/ovarian cancer risk-reducing surgery before 40 years. This may not be the case for young men and women with a *TP53* mutation as they are at risk of a broader constellation of cancers in organs that are not essential for reproduction.

Lastly, this review also highlights a general lack of perspective from young men: 118/765 participants were male. In the context of inherited cancer, it remains unclear how young men experience the suite of psychosocial themes described in this review or whether, and in what ways, their support needs compared to young women are unique. For LFS, sex-specific cancer risks may also contribute to salient gender differences in healthcare experiences and support needs.

6.6.1 Practice implications

This review underlines the need for health professionals to identify young people's interpretation of genetic testing through the lens of their family history. Providers may identify pre-existing maturity with respect to decision-making for predictive genetic testing from young people's stories as caregivers, of coping, and bereavement during pre-test counselling. This process may reduce distress, empower the young person to make informed healthcare decisions, and increase the articulation of support needs. Health professionals should be mindful of young people's motivations for testing, the role family plays in medical decision-making, and whether these roles compromise the young person's agency and autonomy. Individualised and age-appropriate pre-test genetic counselling can personalise and bring meaning to testing. Since families often present together for testing, providers should facilitate private consultation with each family member to assess understanding, motivation, and coercion. For LFS more specifically,

consistent, coordinated recommendations from the range of health professionals caring for young people with LFS is also required to avoid frustration and uncertainty about how to manage their multi-organ cancer risks. Providing absolute short-term cancer risks to young people with LFS could help to mitigate heightened cancer risk perceptions.

Longitudinal care after genetic testing must be available as a safety net to catch young people with LFS at critical stages when considering or undertaking normative developmental tasks associated with adolescence and young adulthood. LFS-related risk management decisions, understanding and preparedness for risk-reducing surgery, conversations about forming relationships, family planning and assisted reproductive technologies will manifest in diverse ways over the course of the patient-provider relationship, and over an extended period after testing. In the context of diagnostic testing for LFS, follow-up care may be necessary to support young people as they come to terms with having a mutation after primarily focusing on their cancer treatment, or to facilitate understanding and anticipation of disease burden for young people with a *de novo* *TP53* mutation. Longitudinal care can also serve to identify and support young people in families with LFS who provide caring roles for affected relatives. Therefore, sustained clinical contact provided by a genetically oriented multidisciplinary team, with mental health integration, is necessary to meet the ongoing needs of clients and their families (Hoskins, Werner-Lin, and Greene 2014). Longitudinal psychosocial care is a critical aspect of optimal clinical management for LFS. The ideal organisation and delivery of such care requires institutional and policy research.

6.6.2 Limitations

Due to the underrepresentation of studies investigating LFS, we drew inferences from research addressing other inherited conditions with variable, yet shared clinical characteristics, management, and prognoses. Like all systematic reviews, the captured studies represent those that fulfil the criteria of the search strategy, meaning some relevant studies may have been missed. The reviewed studies emanated from only a small selection of Western, English-speaking countries, which may limit generalisation beyond Western cultures and health systems. This review predominantly focussed on qualitative literature, and reported findings are context-specific and reflect purposive samples. Findings reflect the experiences of those who participated in research, which may be substantially different to those who declined to participate. The majority of

included studies were of high quality, although there is a small risk of selective reporting. Lastly, the selected age range for this review was broad, which could affect interpretations about developmental stages.

6.6.3 Conclusion

This review identified a distinct lack of psychosocial research addressing the experiences of young people living with or at risk of a *TP53* mutation. Research is urgently required to explore how LFS-related familial factors influence young people's cancer risk perceptions, willingness and decision-making to undergo genetic testing, and ability to adapt to their results. Also, in the absence of familial factors, the support needs and experiences of young people with *de novo* variants need to be clearly elucidated. Research addressing how young people experience predictive genetic testing for LFS may establish age-appropriate genetic counselling recommendations for supportive care either side of the genetic testing episode.

The advances in multimodal LFS screening have allowed for a discourse of optimism in terms of the clinical management of multi-organ cancer risk. Ultimately, however, psychosocial research of comparative weight and significance is lacking for the LFS population, especially within the context of normative developmental tasks of adolescence and early adulthood. This review is the first step to understanding the psychosocial impact of LFS on young people and hypothesis-driven research is desperately needed to develop evidence-based guidelines for the provision of longitudinal and age-appropriate care.

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6.6.3.1.2 *Author disclosure statement*

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6.7 Summary

This chapter critically reviewed 39 studies addressing the psychosocial needs of young people with inherited disease. It outlined that familial factors (e.g., family history of disease and the stories associated with those histories) are critical in shaping how young people approach genetic testing, adapt to their gene status, and make decisions about

risk management. It also identified that young people's relationship formation and reproductive decision-making intersect with the implications of their gene status. Importantly, it outlined key gaps in the current literature, especially for early onset multi-organ conditions like LFS; namely, experiences of being at high risk of disease from a young age; experiences of engaging with whole-body, intensive cancer surveillance; and, experiences with diagnostic genetic testing, especially for young people without a family history suggestive of an inherited condition (i.e., potentially *de novo*). These key findings formed the basis of the analytical framework for the interpretive description of young people's experiences of LFS.

The chapters to come (7-10) present four salient themes developed from the interview data collected for Study 2. While several other candidate themes were developed from the vast amount of interview data, only the most novel and impactful themes that were consistent with the findings from Study 1 were developed in chapters. Data relating to experiences of genetic testing, making sense of LFS as a young person, experiences of risk management and reproductive decision-making were therefore developed into chapters as they clearly related and built upon key themes from Study 1. The next chapter is the first of four findings chapters derived from Study 2 and focusses specifically on young people's experiences of undergoing and considering *TP53* genetic testing.

7 ‘I need to know if I’m going to die young’: Adolescent and young adult experiences of genetic testing for Li-Fraumeni syndrome

7.1 Overview

The previous chapter presented a systematic review that described and critiqued a substantial amount of literature addressing the experiences of young people with inherited disease. It outlined that genetic testing, making sense of inherited disease as a young person, risk management, and reproductive decision-making were key areas for investigation among young people with LFS, which will be explored over the next four chapters based on interview data from Study 2. Presenting the first major theme developed for Study 2, this chapter aims to describe how young people experience a specific and critical aspect of clinical genetics: the genetic counselling process and genetic testing. Genetic counselling is one of the first interactions with a clinical genetics service, and it is therefore important to understand how this interaction is impacted by a young person’s developmental stage. In this way, this chapter adds a fundamental piece of evidence that can inform developmentally appropriate genetic counselling for young people at risk of LFS. As mentioned in the preface, this chapter was published online first in the *Journal of Psychosocial Oncology* (Forbes Shepherd et al. 2020),

and is presented here as the author-accepted manuscript.⁴ Note that this chapter uses terminology suited for publication and may have slightly different wording for key concepts compared to the preceding chapters (e.g., using 'asymptomatic' instead of 'unaffected' to describe participants with a germline *TP53* mutation who have not developed cancer).

7.2 Abstract

Purpose: This study explored the genetic testing experiences of adolescents and young adults (AYAs; aged 15-39 years) with, or at 50% risk of, an early onset cancer predisposition syndrome: Li-Fraumeni syndrome (LFS).

Design: We used interpretive description and conducted semi-structured interviews with 30 AYAs (mean age 25.5 years): 26 with LFS and four at 50% risk. Findings were developed using team-based, inductive thematic analysis.

Findings: Participants reported genetic testing uptake to reduce uncertainty about their gene status and to access cancer risk management. Learning their gene status, however, introduced a new uncertainty about living with high multi-organ cancer risk. Participants preoccupied with surviving cancer during diagnostic testing underestimated the implications of LFS. Reliance on family at this life stage complicated decision-making for genetic testing, especially among adolescents.

Conclusion: AYAs undergoing genetic testing for LFS have unique support needs based on their life stage and require developmentally appropriate psychosocial care.

Keywords: Li-Fraumeni syndrome; *TP53*; adolescent and young adult; psychosocial; genetic testing; qualitative.

⁴ The published version has better readability (DOI: 10.1080/07347332.2020.1768199).

7.3 Introduction

Adolescents and young adults (AYAs; aged 15-39 years) represent a unique population in oncology (Zebrack 2011). AYAs with cancer and survivors experience challenges that are dissimilar to both paediatric and older patients because AYAs occupy a transitional and formative life stage characterised by complex psychosocial tasks (Table 14, p. 147) (Arnett 2000; Patton and Temmerman 2016). Common challenges include cancer affecting physical and cognitive maturation, identity exploration, growing independence from family, social role transitions, forming long-term partnerships, and reproductive decision-making (Zebrack and Isaacson 2012; Zebrack et al. 2013; Kent et al. 2012). While these challenges have been well-documented, AYAs who live with, or at risk of, elevated cancer risk due to an inherited genetic mutation have received less attention. AYAs with a genetic predisposition to cancer are psychosocially unique as they live with exceptionally high lifetime cancer risk compared to their peers and complex family systems that may have been affected by multigenerational legacies of cancer.

Li-Fraumeni syndrome (LFS; OMIM #151623) is a rare cancer predisposition syndrome caused by heterozygous germline mutations in *TP53*. LFS is characterised by increased incidence of a wide spectrum of cancers from childhood, including soft-tissue sarcoma and osteosarcoma, central nervous systems tumours, haematological malignancies, and premenopausal breast cancer, among others (Mai et al. 2016). While LFS confers nearly 100% cancer risk by age 70 (Mai et al. 2016), the potential for early onset profoundly affects AYAs. Estimates suggest females by age 31 and males by age 46 with LFS have a 50% chance of developing cancer (Mai et al. 2016), with a mean age at first tumour diagnosis of 25 years (Bougeard et al. 2015). In addition to the risk of recurrence, nearly half of individuals with LFS develop a second primary malignancy (Mai et al. 2016).

To manage LFS-associated cancer risks, multimodal surveillance protocols using whole-body Magnetic Resonance Imaging (MRI) are under trial internationally. Early evidence suggests they enable early-stage detection and improved survival (Ballinger et al. 2017; Villani et al. 2016), but they are not yet widely accessible in routine clinical practice. Importantly, only high-risk individuals (i.e., with a confirmed *TP53* germline mutation) are eligible to enrol in these protocols; consequently, genetic counselling and testing play a critical role in accessing appropriate care. High-risk individuals may be asymptomatic and eligible for predictive genetic testing based on a known familial mutation and/or family history of cancer, or have a personal history of cancer that is consistent with LFS and are eligible for diagnostic genetic

testing (Bougeard et al. 2015). In the Australian public health system, high-risk individuals do not incur out-of-pocket costs for genetic testing as it is covered by the Medicare Benefits Schedule.

Early research with families with LFS suggests that approximately a quarter of adults undergoing predictive genetic testing for LFS experience clinically significant levels of distress, which was associated with a lack of social support (Lammens, Aaronson, et al. 2010) and a strong family history of cancer (i.e., >2 first-degree relatives died of cancer) (Peterson et al. 2008). Nearly 10 years later, the perceived manageability of LFS has shifted, and genetic testing is believed to offer tangible medical and psychological benefits by enabling access to whole-body surveillance (Ross et al. 2017; McBride et al. 2017; Bancroft, Saya, Brown, et al. 2019). Consequently, parents in North America have become more accepting of predictive *TP53* testing for their children (Valdez et al. 2018; Alderfer et al. 2015). Nonetheless, while previous research has focussed on how adults and parents perceive genetic testing for LFS, we have limited understanding of AYA genetic testing experiences, which could have implications for engaging them in testing, post-test cancer screening, and supportive care.

Psychosocial development during the AYA years complicates the process and implications of genetic testing for inherited cancer (Table 14, p. 147) (Godino et al. 2018; McGill, Wakefield, Vetsch, Barlow-Stewart, et al. 2019; Forbes Shepherd et al. 2018; Godino et al. 2019). AYAs undergoing genetic testing must contend with successively more complicated developmental tasks, while also grappling with complex genetic information and trying to make meaning of their condition. For those still developing legal or cognitive decision-making capacity, genetic testing raises important issues for informed consent, a core ethical principle of genetic testing (Botkin et al. 2015; Alderfer et al. 2015). One study suggested AYAs from families with LFS are accepting of predictive genetic testing and have varied levels of involvement in genetic testing decisions with parents (Alderfer et al. 2017). Furthermore, none regretted undergoing predictive genetic testing and mutation positive results had reportedly limited impact on participants' future career plans, reproductive choices and intimate relationships (Alderfer et al. 2017).

However, the sample was small (n=12), did not reach data saturation, and a major limitation was that not all participants were aware of their mutation status or family history of LFS (Alderfer et al. 2017). Moreover, AYAs who undergo diagnostic genetic testing, and who may not have a family history of cancer (i.e., individuals with a *de novo* mutation), have rarely been included in previous research (Forbes Shepherd et al. 2018). Due to the early age of onset

and the ~14% *de novo* *TP53* mutation rate (Renaux-Petel et al. 2018), this subgroup remains an important yet underrepresented LFS population in research.

At present, little is known about how AYAs consider and experience *TP53* genetic testing for themselves and how this may impact, or be impacted by, their adolescent and young adult development (Forbes Shepherd et al. 2018; Alderfer et al. 2017; Schultz et al. 2018). In this study, we sought to explore AYA experiences of predictive and diagnostic genetic testing for LFS.

Table 14. Core tasks and crises of psychosocial development over adolescence, emerging adulthood, and young adulthood

Life stage ^a	Late adolescence (15-18 yrs.)	Emerging adulthood (18-29 yrs.)	Young adulthood (29-39 yrs.)
Core developmental tasks	Emotional development	Identity exploration (work, love and worldviews)	Childbearing
	Physical maturation	Autonomy from/with family	Managing a career
	Formal operational thought/cognitive development	Accepting responsibility for oneself	Nurturing intimate relationships
	Membership in the peer group	Financial independence	Managing the household
	Romantic and sexual relationships	Making independent decisions	
Core psychosocial crises^b	Group identity vs. alienation	Individual identity vs. identity confusion	Intimacy vs. isolation
Intersection with cancer risk, diagnosis and treatment	Time away from school		Time away from work/financial strain
	Potential cognitive delay	Sexuality and intimacy	Fertility concerns from cancer/treatment
	Fertility concerns	Launching from family	Reproductive decision-making
	Feeling and looking different among peers	Body image/self-esteem	Cancer risk to children
	Familial bereavement	Identity as cancer survivor/patient, or 'at-risk' of cancer	Adapting to modified parental role

^aAges are proxies for development and cannot be used as the sole criteria for ascertaining developmental stage.

^bCore psychosocial crises are states of tension between a person's capacities at the beginning of a life stage and society's expectations for behaviour at that life stage.

Source: Adapted from Arnett (2000), Erikson (1963), Havighurst (1972), and Zebrack (2011).

7.4 Methods

We adopted a critical realist stance for this research (Maxwell 2012) and used interpretive description to guide research design, the aim of which is to produce a coherent conceptual description of human experience in a clinical context to yield implications for practice (Thorne, Kirkham, and O'Flynn-Magee 2004). This multisite study was approved by the Human Research Ethics Committees of the Peter MacCallum Cancer Centre (PMCC; HREC/16/PMCC/196), the Victorian Clinical Genetics Service (VCGS; RCH/HREC/370574), Genetic Services of Western Australia (GSWA; PRN:RGS1002), and Genetic Health Queensland (GHQ; HREC/16/PMCC/196).

7.4.1 Participants

We purposively sampled participants using clinical databases from four Australian clinical genetic services: PMCC, VCGS, GSWA, and GHQ. Participants were eligible if they were: (1) aged 15-39 years; and, (2) diagnosed with, or at 50% risk of having, a pathogenic germline mutation in *TP53*. Participants were eligible regardless of when they were tested or if they had previously developed cancer. Based on the likely information power of the intended sample (i.e., the more relevant information a sample holds, based on participant experiences, the fewer participants are required) we needed a medium-large sample to answer the research questions; therefore, we aimed to recruit up to 30 participants for this study (Malterud, Siersma, and Guassora 2016). Recruitment consisted of first inviting eligible participants by mail. Non-responders were followed up after four weeks by text/phone call. Second, where feasible, potential participants with upcoming clinical appointments were approached by their treating clinician and provided with study information. Those who expressed interest were then followed-up by RFS. Third, family members who had contact with a genetics service assisted in circulating study information to their eligible family members to facilitate snowball recruitment. Written consent was obtained for all participants; participants under the age of 18 provided written assent in tandem with written consent from their parents/guardians.

7.4.2 Data collection

One-on-one, semi-structured interviews were conducted by RFS (a male doctoral candidate within the AYA age range with qualitative research experience in genetic counselling) by telephone or in person between May 2017 and January 2019. In-person interviews were conducted at a place of the participant's choosing (e.g., at their home, local café, in clinic etc.). Participants were recruited as part of a larger project exploring how AYAs experience LFS in

their day-to-day life. The interview guide was developed based on previous research (Forbes Shepherd et al. 2018) with an expert multidisciplinary team of researchers and clinicians (Appendix 4), and was piloted before use. Interviews were audio-recorded and transcribed verbatim; all transcripts were de-identified. Participants under 18 years of age could elect to have a parent/guardian present. All participants could choose to review their transcript.

7.4.3 Data analysis

We used codebook thematic analysis to generate findings (Braun et al. 2019) and inductively developed a coding frame from a sample of six transcripts, selected for maximum variation, which RFS, AWL and LEF open coded independently (MacQueen et al. 1998). Initial codes and categories from this sample were grouped, and variation discussed among co-coders. RFS, AWL and LEF then independently re-coded all six transcripts, reviewing each other's coding decisions for confirmation using the preliminary coding frame (MacQueen et al. 1998). The full multidisciplinary team then met to review coding categories and to delineate rules for applying codes before RFS coded the remaining body of data. The codebook was updated and coding decisions were discussed at regular team meetings throughout analysis (MacQueen et al. 1998). We ceased recruitment after reaching our target of 30 participants. QSR NVivo v11.4.3 supported data management.

7.5 Findings

A total of 51 AYAs were approached for this study: 11 did not respond or were uncontactable, and ten declined. The final sample consisted of 30 AYAs (mean age 25.5, range 17-38 years): 26 had a pathogenic germline mutation in *TP53* and four were untested and at 50% risk (Table 15, p. 151). There were three discrete groups across the sample (Figure 10, p. 154). The first group included four participants at 50% risk of a germline *TP53* mutation based on family history, but who had not completed predictive genetic testing. The second group included fifteen participants who had completed predictive genetic testing and were *TP53*+ve. Collectively, these 19 participants had a family history of LFS but were asymptomatic. The third group included 11 symptomatic participants who had completed diagnostic genetic testing after developing cancer. Of this latter group, all were *TP53*+ve and the majority (n=9/11) were the first in their family to develop cancer.

Participants who had undergone genetic testing (n=26) received their results on average 3.2 years (range 4 months - 16 years) prior to the interview and had completed genetic counselling. Three participants were tested under the age of 15 years and learnt of their

mutation status during early adolescence from their parents (n=1) or with their parents and a genetic counsellor (n=2); the remainder (n=23/26) underwent genetic testing aged 15-39 years (Table 15, p. 151). Eighteen participants completed interviews over the telephone and 12 in person (mean duration 84 mins, range 48-140); type of interview did not substantively affect interview dialogue. Twelve participants requested a copy of their transcript, but none were returned after review.

Table 15. Participant demographic and clinical characteristics

Characteristic (n=30)		
Demographic characteristics		
<i>Age at interview (years)</i>		
Mean (SD)	25.5 (6.3)	
Range	17-38	
<i>Age distribution</i>	n	%
Aged 15-17	3	10.0
Aged 18-29	20	66.7
Aged 30-39	7	23.3
<i>Gender</i>		
Female	20	66.6
Mean age (SD)	26.8 (6.8)	
Range	17-38	
Male	10	33.3
Mean age (SD)	22.8 (4.0)	
Range	17-29	
<i>Ethnicity</i>		
Caucasian	26	86.7
Asian	4	13.3
<i>Highest attained level of education</i>		
High school	15	50.0
Other non-school qualifications	3	10.0
Certificate/Diploma	3	10.0
Bachelor Degree and above	9	30.0
<i>Place of residence</i>		
At family home	10	33.3
Independent	20	66.6
<i>Current residence</i>		
Victoria	20	66.7
Western Australia	6	20.0
Queensland	2	6.7
New South Wales	1	3.3
New Zealand	1	3.3

Table 15 cont.

Characteristic (n=30)	n	%
Clinical characteristics		
Gene status		
TP53+ve	26 (2 <i>de novo</i>)	86.7
50% risk	4	13.3
Genetic testing		
	n=26	
Predictive genetic testing	15	50.0
Diagnostic genetic testing	11	36.7
Age at genetic testing (years)		
Mean (SD)	22.4 (7.1)	
Range	5-35	
Age distribution (at testing)		
Aged <15	3	11.6
Aged 15-17	4	15.4
Aged 18-29	14	53.8
Aged 30-39	5	19.2
Time since genetic testing at interview (years)		
Mean (SD)	3.2 (3.8)	
Range	0.3-16	
Cancer history		
Personal cancer diagnosis	11	
Multiple cancer diagnoses	4	36.7
Age at first cancer diagnosis (years)		
	n=11	13.3
Mean (SD)	22.3 (9.4)	
Range	5-34	
Risk management		
Research-based whole-body screening ^a	15	50.0
Tailored whole-body screening incl. WBMRI	5	16.7
Tailored whole-body screening not incl. WBMRI	2	6.7
BC and CRC screening, skin and physical exam	3	10.0
BC screening only	2	6.7
None ^b	3	10.0

Abbreviations: WBMRI, whole-body MRI; BC, breast cancer; CRC, colorectal cancer.

^a Australian equivalent of the Toronto protocol incl. whole-body MRI (i.e., SMOC+).

^b All AYAs who were not enrolled in risk management were untested and at 50% risk of a TP53 germline mutation.

Our analysis identified three distinct themes describing AYA experiences of genetic testing for LFS: motivations for genetic testing; balancing knowledge of mutation status with uncertainty of cancer development; and, AYA autonomy and interdependence with families of origin when making genetic testing decisions. Each theme is explained below and illustrated with quotes in text and in Table 16-Table 18. Pseudonyms are used throughout with age, gene mutation status (i.e., +ve, *de novo*, or 50% risk) and cancer status (i.e., asymptomatic or type of cancer) provided for each participant.

7.5.1 Motivations for genetic testing

Participants delineated three core motivations for genetic testing: 1) to reduce uncertainty and plan for the future; 2) to find a cause for their cancer; and 3) to protect family across generations.

7.5.1.1 Reducing uncertainty and planning for the future

Over 75% of participants (n=23/30) stated their primary motivation to undergo genetic testing was to reduce uncertainty about their mutation status and plan for their future. Uncertainty for asymptomatic participants with a family history of LFS was primarily about if they might develop cancers similar to their symptomatic or deceased family members (quote 1, Table 16). Reducing uncertainty about mutation status went hand in hand with preparing for the future, which for many meant availing themselves of risk management if they were found to be *TP53*+ve. Clarifying their mutation status with genetic testing, therefore, represented the first step of instrumental action participants could take to begin managing their cancer risk with surveillance.

It makes me feel better that I know as much as I can't control getting cancer, I can't control whether I live or die, I can control that if I do get [cancer], it will be caught early because I've had the [genetic] testing and I'm getting routine MRIs. (Tasha, 24, +ve, asymptomatic)

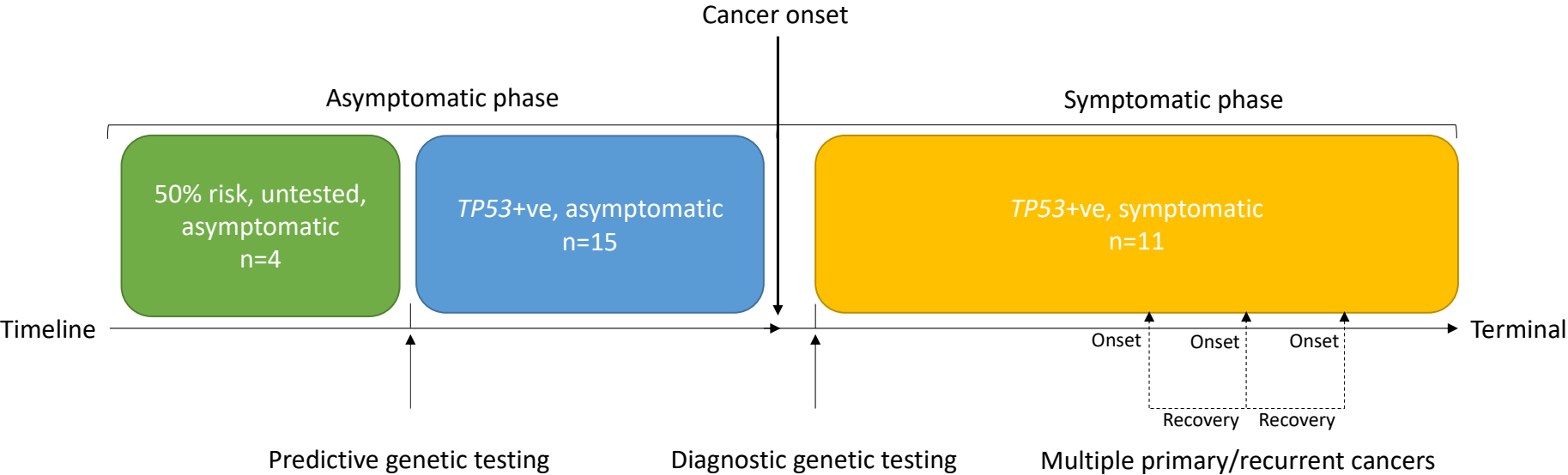


Figure 10. Participant characteristics plotted against the phases of Li-Fraumeni syndrome (n=30)

7.5.1.2 Finding a cause for cancer

In contrast, for the 11 participants who underwent diagnostic genetic testing during or after cancer treatment, uncertainty was primarily about why they had developed cancer (quote 2, Table 16). Since the majority (n=9/11) were the first in their family to develop cancer, their motivation for testing was to find 'an answer or reason to the chaos' of their unexpected diagnosis (Rachel, 37, +ve, breast cancer). Irrespective of age, while being treated for cancer most described going along with their doctors' recommendations or family's wishes to undergo genetic testing, 'I just did whatever was sort of suggested to be honest' (Lara, 34, +ve, breast cancer).

7.5.1.3 Protecting family across generations

A minority of participants were motivated for testing to protect their family members. Although all parents (n=9) were universally alarmed for their children after learning of the pediatric cancer risk associated with LFS, only three described being motivated to test themselves as a mechanism to clarify their children's risk and to seek out testing and risk management if needed (quote 3, Table 16). One parent had undergone diagnostic testing, and two had undergone predictive testing. Importantly, all three had access to paediatric testing and surveillance for LFS because they lived near a tertiary children's hospital that offered paediatric whole-body surveillance for LFS, which is not ubiquitous across Australia. In contrast, Tasha (24, +ve, asymptomatic), whose father died due to LFS-related cancer when she was six years old, described undergoing testing to protect her mother from blaming herself if Tasha developed cancer (quote 4, Table 16).

Table 16. Quotes illustrating motivations for *TP53* genetic testing

Quote #	Participant	Quote
1	Adam, 29, 50% risk, asymptomatic	The reason why I'm getting genetic testing is obviously I need to know if I'm going to die young [laugh], if I have a shorter [life] expectancy I kind of want to know that.
2	Sadie, 22, +ve, breast cancer	I'd rather know than not know and spend my whole life wondering why these things keep happening to me.
3	Harriet, 25, +ve, asymptomatic	[I got testing] for my kids. I wanted to make sure that if I had it, then I would get them tested and then we could be on top of it.
4	Tasha, 24, +ve, asymptomatic	... [mum] was my motivation for getting the testing done because I thought, at least if she knows that I'm doing everything that I possibly can to get an early diagnosis or early treatment for when I do get sick, maybe she won't blame herself.

7.5.2 Balancing knowledge of genetic status with uncertainty of cancer risk

While most participants underwent testing to reduce their uncertainty, learning of their positive mutation status confirmed a different kind of uncertainty: a future pervaded by high, unpreventable multi-organ cancer risk.

I wouldn't have been settled not knowing. But also, knowing is obviously not settling [...] now I will spend the rest of my life worrying that I might get cancer. (Catherine, 24, +ve, asymptomatic)

Asymptomatic participants with inherited mutations and a family history used their family stories of cancer as a guiding frame to understand the implications of their mutation status. The early ages at which family members developed and died from myriad types of LFS-related cancer meant that many felt having a *TP53* gene mutation conferred a bleak future (quote 1, Table 4). In comparison, participants who underwent diagnostic testing during cancer treatment were preoccupied with tasks of survival, masking the full implications and additional uncertainties associated with an LFS diagnosis (quote 2, Table 17). In some cases, this resulted in later confusion and surprise at their *TP53* diagnosis: 'I didn't realise it was so serious, the gene... I just thought it was new technology... I didn't realise that it could cause so many cancers' (Kylie, 29, +ve, breast cancer). This was especially pronounced for Tom (age 17), who underestimated the implications of his *de novo* mutation (quote 3, Table 17).

Whether based on family or personal history of cancer, nearly all participants with a confirmed *TP53* mutation were resigned to developing cancer, potentially multiple times, over their lifetime (quote 4, Table 17): 'I guess with my family history, I just feel like [cancer] is sort of inevitable' (Georgia, 22, +ve, asymptomatic). Learning of their mutation status therefore signalled a fruitless waiting game characterised by unpreventable multi-organ cancer risk. Uncertainty in this context was not about if they would develop cancer, but about when and what type of cancer it would be (quote 5, Table 17).

7.5.2.1 The utility of genetic information with LFS

Navigating the tension between learning one's mutation status and living with the uncertainty of high cancer risk was a complex balancing act. Exemplifying this tension, Olivia (23, +ve, asymptomatic) regretted genetic testing because it added to her pre-existing cancer worry for herself and her children:

...now that I know that I have the gene, I wish I didn't get the testing so I didn't stress so much, because already having anxiety and depression it just made it worse knowing [I had] the gene... I wish I could take it back because then I wouldn't have to stress about my kids.

(Olivia, 23, +ve, asymptomatic)

Immediately following the comment above, Olivia continued:

But I'm glad I've had [genetic testing] done because I can take both the breasts off and always be looked at and make sure I'm okay, or if something does pop up that we could hopefully get it early. (Olivia, 23, +ve, asymptomatic)

Olivia's cognitive dissonance surrounding her mutation status suggests her decisional regret for testing was not static, but in a state of flux with her perceived utility of results because it enabled access to risk management. Irrespective of age and illness phase, participants commonly reconciled the uncertainty surrounding their cancer risk by appealing to the utility of their genetic information. Those enrolled in whole-body risk management (n=20/26) felt their genetic information provided them with the agency to make informed life decisions (quote 6, Table 17). In contrast, for the six participants without access to whole-body risk management, reconciling the utility of their genetic information was more challenging. With limited means to address their multi-organ cancer risk, some questioned the benefit of knowing their mutation status at all (quote 7, Table 17).

Table 17. Quotes illustrating how AYAs balance knowledge of genetic status and uncertainty of cancer risk associated with LFS

Quote #	Participant	Quote
1	Adam, 29, 50% risk, asymptomatic	[Having LFS means] you're going to have a shorter life, so you're going to die young and that's just the reality of it. That's definitely been the reality in my family, if you're not going to die young, you're going to deteriorate and be weakened younger.
2	Emily, 36, +ve, breast cancer	I didn't want to get [testing] done at first, because I'm just, like, just fix [my breast cancer] and then we'll keep trying to be healthy and not get sick again [...] then to find out that you've got what I've got, it makes you feel a little bit like, 'oh, that's pretty full on.' Not that I fully grasp the whole concept of it, but when they talk about [LFS], it's really serious.
3	Tom, 17, <i>de novo</i> , Burkitt's lymphoma	...when I got told I was like 'aw yeah, that's all right'. Then, I think maybe two months [later], because I wasn't at [the hospital] I had time to think a lot and then that's when I kind of realised, 'oh shit, this is going on'.
4	Anna, 17, +ve, colon cancer	[Having LFS] just means that I will have cancer multiple times throughout my life.
5	Melissa, 20, +ve, asymptomatic	...they don't know what type of cancer I'm going to get. [Dad] got brain cancer but his sister got breast, so there is no indicator that will tell us what sort of cancer it will be.
6	Carolyn, 34, +ve, asymptomatic	I feel like it was the right decision [to get testing] ... This now puts me in a more medicalised situation for the rest of my life, but at least I'm aware of it, [which] means I can make informed decisions about my life.
7	Emily, 36, +ve, breast cancer	Well I don't really understand, like, they give me all the different cancers that you can get, like, brain cancer, and breast cancer, and [...] leukaemia... Bone cancer. [...] But then [after] giving you all the percentages of it, like, nothing happens [...] nothing is happening with it anyway, so, what's the point of knowing you have the gene mutation if they're not checking it regularly?

7.5.3 Autonomy and interdependence with family of origin

Seven participants had undergone genetic testing under the age of 18, and one was at 50% risk and eligible for predictive testing aged 17. For this subgroup (n=8), where growing independence from the family unit is a key developmental task (see Table 14, p. 147), family involvement in genetic testing was especially complex. Adolescent participants who did not have a personal cancer diagnosis, and therefore underwent predictive testing, had witnessed a parent develop or die from LFS-related cancer at young ages. Though they were involved in genetic testing, being a part of a family unit under stress, the process was mainly driven by their parent(s). Similarly, adolescents with a cancer diagnosis advised to complete diagnostic testing had limited involvement in the testing process because they were undergoing cancer treatment.

7.5.3.1 Complex family involvement: predictive testing under the age of 18

Four participants completed predictive genetic testing under the age of 18. Sarah (age 20 at interview) sought out predictive testing with encouragement from her parents at the age of 16, but experienced barriers to testing from health professionals, who were reportedly reticent to order testing due to her age. Consequently, pre-test counselling was angled towards assessing her maturity to handle her results (quote 1, Table 18).

Felix and Melissa, both age 20 at the time of the study, underwent predictive testing at age 16 with their respective siblings. Both recalled receiving their results individually before meeting as a family, and each appreciated the process of separate disclosure and then joint family debriefing (quote 2, Table 18). Having lost one parent to LFS-related cancer, both underwent testing at the behest of their surviving parents. Parental instigation and drive were critical to participants undergoing testing in this context (quote 3, Table 18), demonstrating that AYAs may struggle to distinguish parental support from coercion or undue influence. In comparison, Georgia (age 22), the only participant to be tested predictively as an infant, did not participate in her parents' decision-making for testing; however, she empathised with their decision, stating it was in her best interests to access risk management from an early age: 'I think it was something that they just felt they just had to do [to keep me safe]' (Georgia, 22, +ve, asymptomatic).

Sean (age 17 at interview, untested) was yet to contemplate LFS in depth and explained that genetic testing was 'probably something I will consider in the future... I don't know if I would trust myself to do the testing now'. He was heavily reliant on his family for guidance in decision-making for genetic testing; his mother attended the interview with him and shared

her disapproval of testing for the first time, possibly due to his age (quote 4, Table 18). Sean's older brother, Justin (age 22, untested), was hesitant to go against his mother's wishes. Despite legally being able to pursue predictive testing of his own accord, his growing autonomy remained in tension with wanting to support and respect his mother, especially after his father's death to LFS-related cancer. His disappointment at not sharing the same view of genetic testing with his mother was difficult to navigate (quote 5, Table 18).

7.5.3.2 Limited autonomy: diagnostic testing under the age of 18

Three participants with cancer underwent diagnostic testing under the age of 18. Because of their age and cognitive development during late adolescence, they experienced limited autonomy in decision-making for testing, and in combination with a cancer diagnosis, there was a clear power differential relative to their parents and health professionals (quote 6, Table 18). Tom (age 17 at interview) described a lack of agency and perceived control over the diagnostic testing process when he was 16. He did not recall being tested during cancer treatment, and felt his opinion was overlooked because of his age. Without the maturity and self-confidence to question what was happening, he was vulnerable.

I don't remember taking a test. [...] a lot of the things I didn't have a say in because I was underage still. I would have agreed to [genetic testing]. I'm not one to say no to a doctor that wants to test for something [laughs]. (Tom, 17, *de novo*, Burkitt's lymphoma)

Table 18. Quotes illustrating autonomy and interdependence among AYAs undergoing *TP53* genetic testing

Quote #	Participant	Quote
1	Sarah, 20, +ve, asymptomatic Tested at 16	I think mostly I told my parents I was interested in getting the testing. So they went to the correct people and got that all set up and [genetic health professionals] tried to discourage me because I was younger than they generally prefer, but I ignored them.
2	Felix, 20, +ve, asymptomatic Tested at 16	I think it's probably good to go individually first, just like maybe one of us didn't have it and then two of us would have felt like 'oh, you're a fuckhead, [I] hate you.' I don't know, I reckon it was good to get it individually first and then kind of break it to each other I guess and then we know what we're in for, or I don't know, we know we're all in it or whatever.
3	Felix, 20, +ve, asymptomatic Tested at 16	...myself, [brother 1] and [brother 2] wouldn't have done it without [dad] bringing it up... Yeah, he's always been like 'it's our decision'. But he was pushing for it a lot, like he really wanted us to do it.
4	Sean, 17, 50% risk, asymptomatic	Interviewer: What does your mum think about testing? Sean: I think she approves of it definitely... No, you don't think I should do testing [addressing mum]? Mother: I don't think you need to do it. Sean: Oh ok, I didn't realise that.
5	Justin, 22, 50% risk, asymptomatic	...[mum] does factor in quite heavily with my decision-making because I do respect her opinion and take it on board. [But] it makes it harder because... in a sense I don't want to disappoint her I guess. It's difficult because I thought she would agree with me [to have testing].
6	Anna, 17, +ve, colon cancer Tested at 14	I was only 14, so my parents just kind of told me what to do [laughs]... They made the ultimate decision [to get testing] because I didn't really understand what it all was, but they did talk to me about the process and why I was doing it and stuff like that.

7.6 Discussion

This is the largest study to explore AYAs experiences of genetic testing for LFS. Findings suggest that respecting and promoting the autonomy of AYAs may help to engage them in the genetic counselling process; that clinicians must be clear about the limitations and burdens of engaging in whole-body risk management for LFS during pre-test counselling; and that longitudinal supportive care is required for AYAs as they come to terms with their mutation status over time and as the implications of their cancer risk intersect with key developmental milestones.

Motivations for testing complement previous findings which suggest AYAs view genetic testing for LFS as a means to reduce uncertainty about mutation status and access cancer risk management (Alderfer et al. 2017). These motivations are similar to those reported among AYAs and adults at risk of other inherited disease risk (Meiser 2005; Forbes Shepherd et al. 2018). While genetic testing reduced uncertainty about mutation status in this sample, similar to previous research, it also introduced a pervading uncertainty regarding future development of disease (Brunstrom, Murray, and McAllister 2016; Mand et al. 2013). Uncertainty is common for AYAs living with adult onset inherited cancer risk (Godino et al. 2018; Godino et al. 2019), but it is uniquely exacerbated for AYAs with LFS because of the variability, magnitude and unpreventable nature of their cancer risk from birth. Genetic testing is therefore only one point on a much longer trajectory of uncertainty when living with LFS, and thinking of decisional regret about testing as a static, cross-sectional measure, cannot appreciate the complexity of tensions AYAs may experience after learning their mutation status. How AYAs navigate the implications of LFS beyond genetic testing and as it intersects with their development warrants further investigation.

Access to whole-body risk management and the potential for early detection were powerful motivators for genetic testing in this study. Considering that some AYAs do not fully grasp the implications of LFS until they begin risk management (Alderfer et al. 2017), providers need to be clear about the experimental nature of whole-body surveillance at present and the potential for screening fatigue. Recent research suggests whole-body surveillance for LFS has limited medium-term (<1 year) adverse psychosocial effects (Bancroft, Saya, Brown, et al. 2019), and that it offers a sense of control to individuals and families with LFS (McBride et al. 2017; Ross et al. 2017). The long-term psychosocial implications, especially for those engaged potentially from childhood

remain unknown. This will be important to address during pre-test genetic counselling for providers in regions where practice is changing (e.g., Australia) to incorporate new recommendations for whole-body surveillance (Cancer Institute New South Wales 2019).

This study provides important insight into diagnostic genetic testing experiences of AYAs with cancer, an underrepresented group in previous research (Alderfer et al. 2017). Our findings support that a primary motivator for symptomatic individuals to undergo genetic testing is to understand why they had developed cancer (Hallowell et al. 2004). For AYAs who were the first in their family to be diagnosed with LFS, the implications of their genetic diagnosis sometimes came as a shock and were difficult to interpret without a family history. This mirrors similar research with AYAs affected by familial adenomatous polyposis (FAP), where individuals with a *de novo* mutation found it difficult to come to terms with and understand their diagnosis without being able to relate to a family history (Mireskandari et al. 2009). Unlike previous work with adult onset conditions (i.e., *BRCA1/2* research), only one participant in this study reported undergoing diagnostic testing to generate genetic information to benefit family members (her children), and enable them to undergo predictive testing (Hallowell et al. 2003; Hallowell et al. 2004). This may be because LFS is early onset, and most participants were yet to begin family formation and child-rearing; therefore, genetic testing may have been viewed as having the greatest immediate impact for themselves.

Participants who considered or underwent predictive testing had considerable family histories of LFS. As a result, they possessed experiential frames of reference that helped to anticipate the implications of being mutation positive, which is similar to AYAs from families with Huntington disease (HD) (Mand et al. 2015). The differences between experiences of predictive and diagnostic testing illustrates the importance of distinguishing between AYAs with and without a family history of cancer (McGill, Wakefield, Vetsch, Lim, et al. 2019; Hamilton, Williams, Bowers, et al. 2009; Alderfer et al. 2017). Respecting and asking AYAs about their familial experiences of LFS could act to promote autonomy and reduce barriers to genetic testing (Forrest Keenan, McKee, and Miedzybrodzka 2015; MacLeod et al. 2014; Mand et al. 2013; Duncan et al. 2010).

This study also adds to research focusing on how AYA development affects family decisions about genetic testing for LFS (Schultz et al. 2018). These findings support previous work showing that individuals under the age of 18 have varied involvement in decision-making for *TP53* genetic testing (Alderfer et al. 2017). Indeed, it was clear that fostering respect for autonomy and ensuring informed consent for genetic testing for LFS

was especially complex around the age of majority. Consistent with previous research, participants' autonomous decision-making capabilities for genetic testing were complicated by their families' investment in the outcome of testing and their reliance on family for emotional and financial support (Werner-Lin et al. 2012; MacLeod et al. 2014; Werner-Lin et al. 2016; Duncan et al. 2010; Hamilton, Williams, Bowers, et al. 2009). This means providers of genetic testing for LFS must appreciate the complexity of a family system under strain as its members consider the pros and cons of genetic testing. Critically, providers must advocate for time alone with AYA patients to ensure they have the space away from family to share their views on genetic testing (Duncan and Young 2013; Young et al. 2019).

7.7 Limitations and future directions

Although the potential for recall bias in the current study was considerably lower compared to previous research (Alderfer et al. 2017), it still may have affected responses from participants who were tested some years before their interview. The final sample was heterogeneous because participants were at different points along the genetic testing pathway and at different life stages. Future research could focus on specific clinical and/or demographic characteristics to develop more targeted and detailed findings on less common experiences (e.g., testing under the age 18). Prospective research, targeting participants before and soon after genetic testing, may further develop our understanding of the factors influencing AYA genetic counselling experiences. The sample was also predominantly white (n=26/30) and aged 18-29 years (n=20/30), therefore Western culture norms and developmental tasks of emerging adulthood (Arnett 2000) were dominant in analysis and findings. Future research efforts could include culturally diverse samples (e.g., the Brazilian LFS population with its distinctive founder *TP53* mutation). Similarly, despite recruiting 10 males, male voices were under-represented in our sample, which is a perennial issue in psychosocial oncology research (Wakefield et al. 2017). Lastly, important perspectives critical to optimal care may have been provided from those who declined an interview, or those who tested negative.

7.8 Implications for psychosocial oncology

- AYAs with inherited cancer require longitudinal psychosocial care that can provide ongoing support as they reach new developmental milestones and illness

phases. Initiating psychosocial check-ups at key transitional life and illness stages could help to facilitate this process.

- Assessing an AYA's prior experiences with cancer, either personal or family history, is an important psychosocial tool to understand how they may anticipate and make meaning of outcomes from genetic testing for inherited cancer.
- Psychosocial care for AYAs with inherited cancer should be mediated by a multidisciplinary team that integrates youth-friendly genetic counselling, family practice, and mental health providers.

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7.9 Summary

This chapter described the experiences of young people undergoing genetic testing for Li-Fraumeni syndrome. It illustrated that young people's experiences differed between predictive and diagnostic genetic testing. While most participants were motivated to undergo testing to reduce uncertainty about their mutation status and access risk management, probands who underwent diagnostic testing were sometimes surprised by the implications of being diagnosed with LFS. Young people under the age of 18 described complex family dynamics and limited autonomy when making genetic testing decisions, highlighting the difficulties in facilitating genetic testing for adolescents while they are still developing autonomous decision-making capacity. The main finding described that confirmation of mutation status introduced a new uncertainty of living with high multi-organ cancer risk, emphasising that genetic testing is only one clinical episode on a much longer trajectory of uncertainty while living with LFS as a young person. The next chapter addresses the second major theme developed for Study, how young people make sense of this uncertainty based on their personal and familial experiences of cancer, and how they appraise their cancer risk and options for risk-reduction.

8 Making sense of Li-Fraumeni syndrome: perceptions of cancer risk and control

8.1 Overview

The preceding chapter described young people's experiences with a specific clinical episode: genetic testing for LFS. While genetic testing is a critical juncture on a young person's trajectory with LFS, their psychosocial history leading up to genetic testing and their life after learning their gene status have implications for developmentally appropriate care in this context. The second major theme developed from Study 2 interview data is presented in this chapter, which aims to move from the episodic focus on genetic testing and begin to address how young people make sense of LFS as an illness. To achieve this aim, the current chapter consists of three sections. The first section addresses how young people with a family history of cancer understand the implications of their gene status. The second section addresses how young people with a personal history of cancer, and in most cases with no family history (i.e., they are the proband), make sense of LFS. The third section addresses how participants construct cancer risk and appraise their options for cancer control, especially focussing on young women and their approaches to reducing breast cancer risk. The chapter finishes with discussion of the main findings in the context of relevant theory and previous research.

8.2 Findings

As mentioned in the previous chapter, a total of 51 young people were approached for this study: 11 did not respond or were uncontactable, and ten declined. Table 19 (p. 168) provides information on the breakdown of recruitment per site. The final sample consisted of 30 young people, the majority of which were white (87%, $n=26/30$), emerging adults aged 18-29 years (67%, $n=20/30$), female (67%, $n=20/30$) and from Victoria (67%, $n=20/30$) (Table 15, p. 151).

Table 19. Recruitment tracking

Study site	Invited	Declined	Uncontactable	Recruited
PMCC	29	6	4	19
VCGS	3	1	1	1
GHQ	3	1	0	2
GSWA	16	2	6	8
Total	51	10	11	30
Response rate	30/51=59%			

Abbreviations: PMCC, Peter MacCallum Cancer Centre (Vic); VCGS, Victorian Clinical Genetics Service (Vic); GHQ, Genetic Health Queensland (QLD); GSWA, Genetic Services Western Australia (WA).

Half of the sample was enrolled in the SMOC+ research program offering whole-body cancer risk management using WBMRI ($n=15/30$). A further five (17%) were enrolled in tailored whole-body risk management using WBMRI organised privately, meaning a total of 20 (67%) had access to WBMRI (Table 15, p. 151). Nine participants had children and two were pregnant at the time of their interview (Table 20, p. 169). The living arrangements and education status of participants reflected their life stage. One third ($n=10$) were living at their family home, and 50% reported that high school was their highest attained level of education, with tertiary education under progress for many (Table 15, p. 151).

Table 20. Additional participant demographic and clinical characteristics

Characteristic (n=30)	n	%
Clinical characteristics		
<i>Risk-reducing surgery</i>		
<i>Bilateral prophylactic mastectomy</i>		
Planned	3	10.0
Completed	3	10.0
<i>Contralateral prophylactic mastectomy</i>		
Planned	3	10.0
Completed	3	10.0
<i>Bilateral salpingo-oophorectomy + hysterectomy</i>		
Planned	1	3.3
Completed	2	6.7
<i>Partial colectomy^a</i>		
Completed	2	6.7
Sociodemographic characteristics		
<i>Remoteness of residence^b</i>		
Major city	19	63.3
Inner regional	11	36.7
<i>Relationship status</i>		
Partnered	20	66.6
Single	10	33.3
<i>Reproductive history</i>		
Participants with children	9	30.0
Participants pregnant at interview	2	6.7
Mean number of children (range)	2.4 (2-4)	
Attempted PGD	1	3.3
Completed PND (+/- TOP)	2	6.7
<i>Religious affiliation</i>		
Christian	2	6.7
None stated	28	93.3

Abbreviations: PGD, pre-implantation genetic diagnosis; PND, prenatal diagnosis; TOP, termination of pregnancy

^aAs per the Accessibility/Remoteness Index of Australia (ARIA), 2011.

^bOne participant had undergone a partial colectomy prophylactically, and one during excision of a colorectal tumour.

Findings for this chapter are organised into three sections (Table 21 provides a thematic breakdown of this chapter and which participant subgroups themes were drawn from, p. 171). The first two sections explore how participants make sense of LFS based on familial and personal experiences with cancer. These two themes refer to two distinct groups within the sample. The first group consists of participants who were either considering or had undergone predictive genetic testing. Participants in this group had not developed cancer and predominantly made sense of LFS based on familial experiences and knowledge of cancer (n=19) (Table 21, p. 171). These experiences are outlined in the 'Familial knowing' section below. The second group consists of participants who developed cancer at least once (n=11) and undergone diagnostic genetic testing. The majority of this group were the first in their family to develop cancer (i.e., probands; n=9/11), and they predominantly made sense of LFS based on their personal experiences and knowledge of cancer. Their experiences are outlined in the 'Personal knowing' section below. The third section addresses how the sample as a whole understood and constructed cancer risk based on the numerical probabilities provided in genetic counselling. It also explores the intersection between young people's embodiment of their cancer risk and use of risk-reducing surgery to remove at-risk organs.

Table 21. Making sense of LFS: thematic and participant breakdown

Theme	Sub-theme	Relevant participant subgroup
Familial knowing	Proximal knowing	Unaffected young people with a <i>TP53</i> mutation and with close relatives affected by cancer (n=17)
	Distant knowing	Unaffected young people with a <i>TP53</i> mutation and with distant relatives affected by cancer (n=2)
Personal knowing	Cancer diagnoses provide meaning to at-risk status	Affected young people with a <i>TP53</i> mutation (n=11)
	Proband experiences: the importance of membership to shared stories of cancer	Affected young people with a <i>TP53</i> mutation and the first in their family to develop cancer (n=7)
	Multiple cancer diagnoses and the material body	Affected young people with a <i>TP53</i> mutation who had developed cancer more than once (n=2)
Constructing risk and control	Subjective risk	All participants who had completed genetic testing at the time of their interview (n=26)
	Embodied risk and self-surveillance	
	Young women's perceptions of control: the role of risk-reducing surgery	All young women with a <i>TP53</i> mutation (n=20)
	Young men's risk perceptions and coping without cancer control	All young men with a <i>TP53</i> mutation (n=6)

N refers to the size of the participant subgroup each sub-theme was developed from but does not correlate with the importance or rigour of theme development. 'Familial and personal knowing' are mutually exclusive themes, whereas 'constructing risk and control' is not.

8.2.1 Familial knowing

Because unaffected participants had either undergone, or were on the pathway to, predictive genetic testing, they necessarily had a family history of cancer (n=19). This group of the sample derived a familial knowing of LFS based on social and biological ties with family who had developed cancer and empathy towards their experiences. They gained meaning from others around them with cancer by watching, learning, and caregiving from young ages. Familial knowing was further broken down into proximal and distant knowing. Many of these 19 participants had experienced a first-degree relative develop or die from cancer; consequently, their familial knowing of LFS was proximal to them, both socially and biologically. In contrast, the small number of participants with distant biological or social relations to family members with cancer (i.e., estranged relatives or second- to third-degree relatives) had a distant familial knowing of LFS (n=2).

8.2.1.1 Proximal knowing

Without a personal diagnosis of cancer, unaffected young people with a *TP53* mutation relied heavily on proximal knowledge and experiences of cancer to provide meaning to their at-risk status. Because unaffected young people comprised nearly two thirds of the sample (n=19), proximal knowing was the most common way for participants to make sense of LFS.

Georgia's (age 22) excerpt below typifies the kind of proximal knowledge young people gained from a family history of cancer. Having her younger sister, father, two uncles, and grandmother develop cancer reflects the sheer number of affected relatives across generations in some families with LFS. Further, her sister and father had developed cancer multiple times, highlighting the relentlessness of the disease trajectory for each family member. In this context, Georgia described her family history as an endless 'cycle' of illness:

There's been so much cancer [in my family] sometimes you feel like, 'oh no, not again' sort of thing. At the start, when dad first got diagnosed, it felt like my world was going to end, and I remember just being so depressed about it and it was just horrible. Then it just keeps on happening, the cycle keeps on happening.

(Georgia, 22, +ve, unaffected)

Seeing family members around them develop different types of cancer, across a range of ages, provided participants with a set of tangible experiences to make sense of being at an increased risk of cancer.

Certainly seeing [cancer] happen around me has... I don't want to say it's been a wake-up call, because the severity has always been made clear, but it lends weight to what everyone's saying when they say, 'you have an increased chance of getting cancer'. (Sam, 28, +ve, unaffected)

For most unaffected young people, their membership to the family story based on their gene status meant they believed they would develop cancer in the future: 'I guess with my family history, I just feel like [cancer] is sort of inevitable' (Georgia, 22, +ve, unaffected). Constructing their cancer risk as a certainty (or near certainty) was a way of considering risk.

It's really a 'more likely than not' kind of situation. Obviously, you hope that won't get [cancer] but I think everyone is aware that it's on the table and it's fairly likely. There's no real point pretending it's not going to happen, I guess. Either it will or it won't and I think it's maybe just a way of not living in denial, I guess.

(Sarah, 20, +ve, unaffected)

Many young people described the age at which family members either developed or died from cancer as high-risk periods for their health. High-risk periods represented ages at which participants' perceived risk of cancer dramatically increased even in the face of knowing their absolute risk had not.

...when I hear the age 34, straightaway I think of death, and I think of sickness and of my father and missing him. And I know it's ridiculous because I know that not everybody has the same life and most people make it past 34! But yeah, I think that year, or that couple of years where [my dad] was going through treatment, I think that will be hard for me. (Tasha, 24, +ve, unaffected)

In contrast, young people with families where several family members developed cancer across a range of ages described a more uncertain frame of reference. Perceived high-risk periods were spread across different life stages and it was difficult to ascribe meaning to any one age over others:

Well, like, I had a dad who at least lived to his 50s and his brother who didn't get cancer until his 70s, and his other brother who made it to 70 before getting cancer [as well]. But, at the same time I had dad who was 51, which is not ideal but halfway to 100, and a cousin who was 26 [when they died]. I don't know, it's never something

that keeps me awake at night but it's also, I just sort of don't know what to think.

There's never certainty in terms of feelings. (Sam, 28, +ve, unaffected)

Because of the varied phenotypes many young people observed among their family, looking to affected family members for guidance on what cancer they may develop was unhelpful.

...they don't know what type of cancer I'm going to get. [Dad] got brain cancer but his sister got breast, so there was no indicator that would tell us what sort of cancer it will be. (Melissa, 20, +ve, unaffected)

Unlike family stories of organ-specific inherited cancer syndromes (e.g., HBOC and Lynch syndrome) young people with LFS described a multi-organ cancer risk: 'It's a lucky draw kind of thing but I know there are certain cancers I'm a lot more at risk of' (Sarah, +ve, 20, unaffected).

Participants who underwent or were considering predictive genetic testing (n=19) based on their family history learnt from a young age that cancer in their family had a genetic cause. LFS and *TP53* were concepts that they had always grown up with: 'LFS has kind of always been there ever since I finished school, whenever I've kind of had to think about the future I've known about this' (Ben, 23, +ve, unaffected). Core family stories of cancer were undergirded by *TP53*, and although understanding of *TP53* and genetics varied, for many, learning of their family mutation came as no surprise.

It already ran in the family, like cancer. So, I wasn't really surprised that there was a gene for it or anything. I kind of just figured that that was already the case. (Will, 24, +ve, unaffected)

8.2.1.1.1 *Loss and bereavement*

Because of the early age of cancer onset associated with LFS, over half of the sample (53%, n=16/30) had lost a parent to cancer, mostly when participants were young, and one participant had lost her brother (Table 22, p. 175). Participants described that losing close family members to cancer strongly influenced their understanding of how LFS manifests as an illness. Kylie (age 29), who lost her mother to breast cancer when she was eight years-old, perceived cancer as lethal: 'The experience that I had with my mum is that when you have cancer, you just die' (Kylie, 29, +ve, breast cancer). For many, the most obvious and readily available constant of their family story was that cancer onset was early and that cancer was lethal. This provided young people with a frame of reference for their own future characterised by a predictable and likely ending: an early death due to cancer.

[Having LFS means] you're going to have a shorter life, so you're going to die young and that's just the reality of it. And it's definitely the reality in my family, if you're not going to die young, you're going to deteriorate and be weakened younger.

(Adam, 29, 50% risk, unaffected)

Experiencing a parent die from cancer had a lasting impact on participants. Adam's (age 29) mother died during his early 20s due to breast cancer, and at the time of the interview he was awaiting his genetic test results. Compared to witnessing his mother's death to cancer, he described the implications of his pending results as insignificant: 'literally dust'. He was resolved to approach his genetic information in the knowledge that he had already faced and overcome the 'darkest' experience of his life, losing his mother.

I loved her more than me, she was more than me, she was my whole existence. So, when she left [pause] that was the darkest. I won't be as dark now with this gene, this gene is literally dust compared to what I went through with mum.

(Adam, 29, 50% risk, unaffected)

Table 22. Participants who lost a parent or sibling by life stage (n=16)

Life stage participant experienced bereavement	Participants	Total
Childhood (<13 years)	Sadie, Tasha, Michelle ^a , Kylie ^a , Harriet, Emma, Melissa	7
Adolescence (13-18 years)	Sean ^b , Felix ^c , Ben ^c , Sophie ^d	4
Emerging adulthood (18-29 years)	Justin ^b , Adam, Olivia, Sam	4
Young adulthood (29-39 years)	Kirsty	1

^{a, b, c} Denotes sibling pairs; ^d Sophie's brother died from LFS-related cancer, the remainder had a parent who died from LFS-related cancer.

Adam also described that experiencing the death of his mother meant he lost a part of his identity that he would never regain. This prompted him to undergo reconstruction of his sense of self without her during his early 20s, a critical time for identity exploration.

What I've realised over time, which hurts me more, is that you never heal. So, when she passed away there was definitely a chunk of me that's gone with her. And it was a very, very big chunk of my personality. And it was a happiness that I could never get anywhere else... (Adam, 29, 50% risk, unaffected)

Importantly, 11 young people had a parent who died during childhood or adolescence, meaning they were aware of cancer and their own mortality from young age

(Table 22, p. 175). Tasha (age 24), whose father died from cancer when she was six years-old, described being afraid of death for long periods when she was teenager, which she felt was the direct result of experiencing bereavement as a child.

My father died so young... I have memories of walking through the kitchen and basically just, you know, at the age of seven or eight just breaking down into tears and going 'I'm going to die mum, I'm going to die.' And she didn't quite understand where I was coming from, because I was that age [where] I couldn't communicate to her exactly how I was feeling, all I could do was keep saying 'I'm going to die.' I think because dad died so young and me being young as well, I wasn't able to process that properly. (Tasha, 24, +ve, unaffected)

After the death of a family member, some young people described a shift in their family system; the death of one, often key family member, meant the whole family system was affected. Adam (age 29) described his family going through a process of healing and reorganisation after the death of his mother, until, seemingly inevitably, another family member developed cancer, plunging them back into crisis. This brought back memories and feelings of loss for some, which were difficult to navigate and highlights the cyclical nature of illness, loss and readjustment for young people from families with LFS.

Mum passed away [and] obviously she was the corner of our life, so it was very devastating, she was my best friend, so our family just disintegrated into a shambles. And then slowly, slowly we started rebuilding and we started healing and we were all on different journeys, and then my brother got cancer.

(Adam, 29, 50% risk, unaffected)

A subset of participants described strong bonds with their siblings who had developed or died from cancer. Unaffected participants described significant feelings of empathy for their affected siblings. Although they shared the same gene mutation, being constantly reminded of their own healthy status in the face of their sibling experiencing cancer was distressing and seemed unfair: '[my sister] normally tries to smile for us, but then sometimes she's in a lot of pain... It makes me really sad that she tries to put a brave face when she can just talk to us... you just see that she was always in pain and it just made me really sad' (Emma, 20, +ve, unaffected). For Georgia (age 22), the only member of her family to have a gene mutation but remain unaffected, witnessing her sister develop cancer multiple times manifested as intense feelings of survivor guilt: 'I've got my own sort of demons with the guilt, the fact that my sister has had cancer three times... How have I not had anything yet?' (Georgia, 22, +ve, unaffected).

Four participants had influential experiences of close family members surviving cancer: ‘not everyone dies from it... I don’t think [LFS] is a death sentence at all. My sister and my dad, they just show that...’ (Georgia, 22, +ve, unaffected). Seeing family members around them survive cancer meant knowing LFS was not always lethal. Overall, however, exposure to positive role models who survived cancer were less common among those with a family history of LFS.

8.2.1.2 Distant knowing

Only two participants described a distant familial knowing of LFS, i.e., had distant biological or social relations to family members with cancer (n=2). Catherine’s (age 24) unaffected grandfather had sought out predictive testing because her extended family had a history of cancer consistent with LFS. Her immediate family, however, had no experience with cancer; consequently, her familial knowledge of LFS was primarily obtained through stories and discussions of distant relatives.

...so my grandfather, he has Li-Fraumeni and so he is the one who has sort of passed the gene down and my mum is one of five and I have, you know, I have several cousins and nobody in my family has ever had cancer. So, for this to all kind of come out of the woodwork, was a little bit, a little bit surprising for me. But also, a little bit difficult to interpret because [...] it hasn’t actually infiltrated my family as such. But it’s more my mum’s aunties and uncles and my mum’s cousins who have been affected. (Catherine, 24, +ve, unaffected)

Never having possessed close emotional ties with someone with LFS-related cancer, she felt removed from the familial cancer experience. She described the risk estimates provided in pre-test genetic counselling as ‘difficult to interpret’: ‘it was difficult to read facts like that and sort of know what to make of them’ (Catherine, age 24, +ve, unaffected). As a result, Catherine’s uncertainty about her future was high and the implications of her gene status were less tangible.

Melissa (age 20), whose estranged father died of LFS-related cancer, described an interesting, and varied familial reaction to his death at the funeral:

At his funeral [my younger sister] didn’t cry and it was because he was a stranger to her; she didn’t have any memories of him at all... [My older sister] and I were bawling our eyes out and so was mum. And to my sister we were just like... ‘Why didn’t you cry?’ She was like ‘I didn’t know him’. (Melissa, 20, +ve, unaffected)

Being older, Melissa possessed clearer memories and a more developed relationship with her father that helped her to understand the implications of LFS. The description of her

younger sister's reaction to their father's death, however, suggests that her sister may have been too young when he estranged himself to have established a strong emotional tie to him. Consequently, in the absence of this parental relationship, and a close tie with a family member who developed and died from LFS-related cancer, knowledge of LFS for Melissa's younger sister may be based on second-hand stories of a close, but long since estranged and now deceased relative.

In sum, participants' familial knowing of LFS was predominantly shaped by their experiences of close family members developing and dying from cancer. Family stories of cancer provided them with frames of reference, which helped to anticipate whether and how they might develop cancer themselves. The associated grief and bereavement with the death of a first-degree relative meant young people were acutely aware of the implications of their at-risk status despite being unaffected by cancer. Few participants described a distant familial knowing of LFS, and their stories highlighted how risk estimates bear little meaning without being rooted in close familial experiences of cancer. This suggests that lived experiences of disease bear much stronger meaning for those at-risk of inherited disease risk than numerical estimates, which I explore in the 'Constructing risk and control' section below.

8.2.2 Personal knowing

Eleven young people in the sample had developed cancer at least once (Table 15, p. 151), nine of whom were probands (i.e., the first in their family to be diagnosed with a *TP53* germline mutation). Nearly all probands had no family history of cancer (n=7), meaning they represented a family first on two counts; they were the first to develop cancer and the first to be diagnosed with a germline mutation in *TP53*. In the absence of familial experiences of cancer, these probands described drawing on their personal experiences to make sense of their gene status. Consequently, their knowledge of LFS was impacted by the type and extent of their cancer (presence of metastases, recurrences and new primary cancers), the effects of treatment on their bodies and sense of identity, and the age at which they were diagnosed.

8.2.2.1 Cancer diagnoses provide meaning to at-risk status

Unlike unaffected young people, who could make use of their family story as a roadmap to anticipate their future trajectory of disease, affected young people primarily made sense of their cancer risk based on personal experiences of cancer. One participant, Rachel (age 37), felt her personal cancer risk was difficult to interpret based on her previous cancer experience.

...pretty much everyone with LFS will get cancer under the age of 50. But then you kind of think, well I've already had it, so am I going to get it again? [...] I suppose most of me doesn't really think that I will get another one, you just don't think that you will be that unlucky twice. (Rachel, 37, +ve, breast cancer)

The predominant perception, however, was that given their 'track record' of cancer, most young people felt they were likely to develop cancer again in their lifetime (Kirsty, 38, +ve, multiple cancers), either a recurrence or another primary cancer.

I don't want [cancer] to be my life, but I think with the gene mutation and with having such a strong cancer, with having the spots on my ribs and sternum, and in my lymph nodes, I think, I do think, I hate, you know, I think it's going to happen again. (Emily, 36, +ve, breast cancer)

[Having LFS] just means that I will have cancer multiple times throughout my life. (Anna, 17, +ve, colon cancer).

Paired with knowledge of their gene mutation, participants' personal experiences of cancer meant they constructed their cancer as a persistent and tangible health threat, not an abstract numerical probability for which they had to rely of family heuristics or social discourse to make sense of. This differentiated them from cancer survivors in the general public.

Just say I had [a sporadic form] breast cancer, I would probably say I'm in remission, now I'm fine, but this gene... the mutation is there, you don't know, anytime you can mutate again and then, you know... (Kylie, 29, +ve, breast cancer)

Having developed cancer previously, their risk was already manifest and they possessed an understanding of what cancer felt like. Now their attention turned to the possibility of developing cancer again.

8.2.2.2 Proband experiences: the importance of membership to shared stories of cancer

Probands' experiences of cancer highlighted the importance of shared stories of cancer among family. Without a family history suggestive of LFS it was difficult for probands (n=7) to find meaning in developing cancer at such a young age, and the majority (n=6/7) pursued genetic testing to find a cause for their cancer (Chapter 6). Many, like Ashley (age 34), were initially unable to make sense of their initial cancer diagnosis. Having no previous experiences with cancer, personally or within their family, probands were not primed to suspect their physical symptoms were anything to be concerned about.

[With my] breast, all the way down I felt something there but I never thought it was anything. Because our family, I never have met anyone in my family who has ever had cancer, so I just didn't know anything. (Ashley, 34, +ve, breast cancer)

Two probands had confirmed *de novo* mutations: i.e., they were confirmed to be the only carriers of a germline *TP53* mutation in their family. Although many other probands had family histories suggestive of a *de novo* mutation, incomplete cascade testing among family precluded gaining confirmatory results, especially in cases where the parent likely to have the mutation was deceased. One proband with a *de novo* mutation, Tom (age 17), described that learning he had LFS came as a complete surprise. Jamie (age 25), also *de novo*, however, had lived with cancer since childhood and was tested at the age of 20. As a result of surviving several cancers, learning that he had a pathogenic *TP53 de novo* mutation 'didn't come as much of a surprise': 'I kind of expected it given [my history] ... When I heard about what the mutation was, I was just like, 'oh yeah, that makes sense.' [...] Three cancers at 20 kind of suggests something is amiss' (Jamie, 25, *de novo*, multiple cancers).

In comparison, for the three probands who had experienced a close family member develop cancer, their shared cancer experiences with family served to connect them more intensely to their family story. These connections could be positive, like Anna (age 17, +ve, colon cancer), who described: '[Mum's] had breast cancer as well, so I think that meant when I got sick, that actually helped me so much. Because I felt like I had someone in the family that I could relate to.' Or these connections could trigger powerful feelings of empathy for deceased relatives based on a shared narrative, like Kylie (age 29), who felt her experience of developing breast cancer was strikingly similar to her mother's, and described the likeness as 'haunting'.

[There's] just a lot of similarities between her and me [crying], because... I'm almost 30 [crying] and she lost her life at 30 [crying], and then when she had the surgery, she had to leave us behind in Mauritius, and I had to leave my children behind [in Mauritius] for about six months while I had the chemo and everything... it's just the same journey. It's not the same outcome, but it just kind of, it's there, kind of haunting me. (Kyle, 29, +ve, breast cancer)

Sophie (age 19) was a unique proband in that her cancer narrative was a shared experience with her brother. Sophie described being especially close to her younger brother: having both developed cancer in quick succession at the age of 12, they developed a strong caring relationship for one another: 'he was always there for me, even when through my treatment, he always acted like a big brother even though he was the

little one' (Sophie, 19, +ve, orbital osteosarcoma). After Sophie had recovered from her cancer, she was admitted back into hospital for urgent surgery on a brain bleed related to her treatment. At the same time, her brother was admitted into palliative care as his condition deteriorated.

I came out of surgery to find that [my brother had died]. But he took his last breath once he knew that I was alright. Mum told him, 'Sophie's out of her operation, it's all fine.' And that's what I think probably was consoling for him, in that he always looked out for me even in the worst times. (Sophie, 19, +ve, orbital osteosarcoma)

Sophie's story exemplifies how distressing experiences of LFS can be for young people at an age when they are still developing emotional intelligence and capacity. Her story highlights the powerful sense of loss and trauma LFS can inflict on a family system where several members of one generation can develop life threatening disease at a young age, and the connection from shared experiences of cancer risk.

8.2.2.3 Multiple cancer diagnoses and the material body

Due to the high risk of multiple primary cancers associated with LFS, another, small subgroup consisted of young people who had developed cancer more than once (n=2). Jamie (age 25) had an extensive personal history of cancer, most notably having his arm amputated above the elbow at the age of seven. He explained that his sustained experiences of cancer had pushed him to a point of 'running out of [healthy] body parts'. By using terms like 'the body' and 'spare parts' he implicitly disconnected his sense of self from his physical body.

Well at this point everything's been different, a different type of tumour in a different part of the body. So, I don't know, if it keeps going this way I'm kinda' running out of body parts. I don't have many spare parts left.

(Jamie, 25, *de novo*, multiple cancers)

His body's deterioration under the burden of cancer meant adapting to constant changes and threats to his health and sense of self. He had experienced so many bodily losses to cancer that the habitual use of his primary senses (i.e., sight and hearing) and his cognitive abilities were treasured. Losing these, he described, after persevering through all of his bodily afflictions, including late effects from treatment, would be 'disastrous'.

I can keep [getting cancer], as long as it stays out of my head. That would be... I'd almost say disastrous... because as far as things go, my brain is the only thing that works properly, or hasn't been affected. I can deal with the one arm, I can deal with

the limp from this hip surgery, I mean shit, I can even deal with my heart condition from one of the chemo drugs, which basically cut salt out of my diet, which was my favourite flavour! But I can deal with that, you know, it's just a lifestyle change. But if something happens because, like something in my brain or I lose an eye or something, or I lose my hearing, that's probably a bit too much. That changes too much. (Jamie, 25, *de novo*, multiple cancers)

Altering the materiality of his body through the removal of body parts, multiple rounds of cancer treatment, and myriad late effects, incurred losses to his sense of self. Consequently, with a body that was 'running out of spare parts', Jamie's sense of identity was resolutely housed in his cognitive abilities. By the age of 25 he had completed a Bachelor's and Master's degree, and was enrolled in a Ph.D. focussing on a project with personal meaning, making a new prosthetic arm. He pushed himself academically, where he still had strength, to make up for his physical limitations.

Young people who developed multiple cancers, described being 'in tune' with their body and being able to 'feel when something is not right' (Kirsty, 38, +ve, multiple cancers). Their personal knowledge of cancer meant they were able to discern what it felt like to be healthy versus being sick. It also led them to perceive their healthy self as in flux with their sick self, and being healthy was seen as temporary: 'I'm healthy *at the moment*, so I'm in a good place' (Kirsty, 38, +ve, multiple cancers). They cycled between chronic and crisis phases of illness, being acutely aware that they may fall into a crisis phase in the near future. When the fall did inevitably come, they spoke of going 'through the motions' of diagnosis and new treatment plans. Having experienced cancer so many times, diagnosis had become a normalised experience: 'when something comes up, like when the brain tumour comes up, you just go through the motions, you go get it checked, go and get it scanned, and wait for the plan I guess' (Kirsty, 38, +ve, multiple cancers).

To summarise, unaffected young people with a family history of cancer made sense of their gene status based on their familial knowledge and experiences with cancer. Proximal family stories of cancer provided them with important and tangible frames of reference, which helped to anticipate whether and how they might develop cancer themselves in the future. In the absence of a family history, however, probands primarily made sense of their gene status and cancer risk based on their personal experiences of cancer. Their personal knowing of LFS was impacted by the type and extent of their cancer, and the age at which they were diagnosed. Most believed they would develop cancer again in the future, and those already with multiple cancer diagnoses described a

split between their habitual body and sense of self under the burden of cancer. Both personal and familial ways of knowing LFS had a strong influence on how young people perceived their cancer risk and their options for controlling it. The next section addresses this more closely, exploring how participants constructed cancer risk and control with LFS as an entire group and then by gender.

8.2.3 Constructing risk and control

How individuals construct and understand their genetic risk of disease has significant implications for how they consider genetic testing, risk management, prevention, treatment, family communication and adaptation to their risk. Perceptions of cancer risk and control were relevant for the entire sample (n=30) and are described here as one construct because participants described risk in term of control, and vice versa throughout their interviews.

8.2.3.1 Subjective risk

Many unaffected young people found it difficult to interpret the cancer risk estimates provided during pre-test genetic counselling: 'I've been told all of this stuff but most of it just goes straight over my head' (Felix, 20, +ve, unaffected). Indeed, a small number of participants, namely young men, simplified the complex risk estimates conveyed to them by reducing their cancer risk to a binary outcome. Compared to understanding abstract numerical probabilities, it was easier to relate to the physicality of cancer, which remained fixed in the concrete world: one is either diagnosed with cancer or they are healthy. By dichotomising their cancer risk based on outcome, it made it easier to live with LFS with on a day-to-day basis: 'having the mutated gene I am a 50-50 of getting cancer in my life [...] but I'm not too worried... I'm sort of content with it. If it happens, it happens. If it doesn't, then that's great' (Will, 24, +ve, unaffected). As the majority of individuals with a *TP53* mutation almost certainly develop cancer in their lifetime, Will underestimated his risk, illustrating how the complexity of risk information can lead to mistaken risk perceptions, or perhaps that he minimised his risk as a coping strategy.

Exemplifying the difficulty in understanding cancer risk beyond a binary outcome, Ben (age 23) explained: 'I mean basically to me [my cancer risk] is still just kind of 50-50, but increased 50-50?' (Ben, 23, +ve, unaffected). Throughout his interview Ben described being avoidant of seeking information about LFS and generally not thinking about his gene status unless he had to (i.e., when interacting with health professionals). It was clear that Ben *felt* as though his risk was higher than 50-50, but perhaps quantifying how much higher was worrisome or not important for him. Ben's account

highlights how uncomfortable and unfamiliar some young men were with constructing their risk in terms of numerical probability. Grasping the general gist of their risk was a way to construct and live with the complex multi-organ cancer risk associated with LFS.

Young women demonstrated better recall of their cancer risk estimates compared to young men in the sample. However, better recall did not necessarily translate to constructions of risk that were concordant with risk estimates provided by health professionals. For example, Tasha (age 24) overestimated her risk of death from LFS-related cancer, feeling as though she was almost guaranteed an early death.

The facts basically say you have a 50% of getting cancer before the age of 30. I think that was the scary part, it was the words before the age of 30. And even if you get rid of it, even if you find it straightaway and you treat it, there's a 40% chance of it coming back. So, to me, I know this is not necessarily what it translates into, but to me there is a 90% chance that I'm going to die quite young.

(Tasha, 24, +ve, unaffected)

Notably, Tasha's father died in his early 30s from LFS-related cancer; consequently, her proximal knowing of LFS was coloured by loss and grief, and to her, cancer was evidently lethal at young ages. Despite having a high-level understanding of her age-specific cancer risk and risk of multiple primary cancers/recurrences, she still conflated her risk of death with her risk of developing cancer.

Interviewer: Do you believe you will develop cancer in your lifetime?

Tasha: Yes! Yes, definitely. Unless I get hit by a bus first. (Tasha, 24, +ve, unaffected)

This points to the powerful influence of familial knowledge in constructions of risk. Even when participants could accurately recall their risk in terms of numerical probability, for some, thinking mathematically was not a useful way to make sense of their risk in practice.

Importantly constructions of risk were not static. Melissa (age 20) described that based on her frame of mind and positivity day-to-day while living with LFS, she would feel more or less vulnerable to developing cancer and her construction of risk fluctuated.

[My cancer risk] sort of varies... sometimes it's 80% and other times it's lower. And so, I think it also depends on my state of mind. Like, right now, I'm feeling okay about it. I don't really think that I'm going to [get cancer]. But if I'm in a bad, like, a worse state of mind, I think it would be 'oh, I'm going to get cancer'.

(Melissa, 20, +ve, unaffected)

There was a key divergence in how she constructed her cancer risk associated with LFS. Melissa recognised that in a rational sense she was 'absolutely healthy' and her immediate cancer risk was low. This rational way of thinking was supported by technological and medical appraisals of her cancer risk, which suggested she was in good physical health. However, she would feel increasingly vulnerable to cancer if she found herself in a 'bad headspace', emphasising the ultimate subjectivity of risk perceptions, even when health professionals 'logically and practically' provide concrete information, in this case from whole-body MRI, which suggests otherwise.

...based on my actual biological and physical tests I'm fine. There is no apparent risk at the moment, I'm absolutely healthy. So, I think that realistically and logically and practically, all of that sort of left-brain stuff, I know that I'm relatively safe at the moment and that the likelihood of me getting cancer in my current state of my health is very low. But when I sort of think about it a bit more and get into a bad headspace, I do think I sort of go down that path and think that I will [get cancer].

(Melissa, 20, +ve, unaffected)

This pitching between perceived vulnerable and healthy states highlights the kind of patterned risk construction young people may experience based on mood and frame of mind while living with LFS. This kind of pattern may persist for their whole life and influence different life decisions. Importantly, without preventive clinical action that can help structure these thought processes, the pattern may manifest in constant rumination and anxiety if vulnerable states predominate one's thinking.

Young men had noticeably poorer recall and understanding of their cancer risk. They broadly understood they had an increased risk of cancer, but not necessarily where in their body it could manifest. Although the accounts of young men who had developed cancer (Tom, age 17 and Jamie, age 25) illustrated their vigilance to any new bodily symptoms, most of the remainder showed little or no knowledge of their general or organ-specific cancer risk.

Interviewer: do you know what kinds of cancer you're at increased risk of?

Will: I'm not sure exactly. I think breast cancer maybe, but obviously being a male it's a lot harder for me to get breast cancer. But I'm not too sure exactly.

(Will, 24, +ve, unaffected)

For the four untested young men, this may have been because they were yet to benefit from information provided during pre-testing genetic counselling. Adam (age 29) was

the exception to this common narrative, vividly recalling the cancer risk estimates presented to him after his mother was diagnosed with LFS.

...we were given a spreadsheet, a printed spreadsheet. It was pretty crazy, I remember we were all sitting there as a family going over them crying... it was basically just like two-year intervals, 18, 20, 22, 24, 26, 28 and as each age increased, so did the percentage of you getting cancer. And then each category was the different cancers. So, you know, to put it into perspective, at 29, you would have an 80% chance of getting sarcoma. You would have a 70% chance of getting breast. And you would have a 92% chance of getting brain. So, you know, it's almost like: 'wow, cool, I'm going to get all of these cancers, how exciting.' And the percentages are very shocking because obviously there were very, very high... (Adam, 29, 50% risk, unaffected)

To summarise, interpreting cancer risk estimates in numerical terms was foreign to many participants. Instead, how participants talked about, explained and constructed their risk was influenced by other relational and social factors, namely family history and gender. Young men mostly underestimated their lifetime cancer risk, *feeling* it was a 50% chance with poor recall of the numerical estimates provided by health professionals, whereas participants with strong family histories would over-estimate their risk of death from cancer even with accurate recall. Importantly, these subjective appraisals of cancer risk took primacy over numerical estimates, and could fluctuate depending on mood and frame of mind. This suggests risk is not a static construct for young people with LFS and is likely to vary throughout one's life depending on perceived vulnerability to cancer.

8.2.3.2 Embodied risk and self-surveillance

The previous section described that when young people talked about their cancer risk, subjective appraisals of risk were more salient than the numerical estimates provided by health professionals. These subjective appraisals served to translate abstract probabilities into more meaningful mental representations of risk. In a similar fashion, participants also made their cancer risk more meaningful by giving it a concrete physicality. Once young people had undergone genetic testing (n=26), confirmation of their gene status resulted in a new awareness of their material body. Their body was now manifest as a repository of risk. Living 'at-risk' meant cancer was a persistent threat to their body and their self; consequently, many had a preoccupation with pending illness and made a habit of checking for bodily symptoms. Because of the phenotypic variability of LFS, constructions of how cancer may develop physically were fluid, uncertain and ambiguous. Any and all bodily symptoms suddenly became omens for cancer, and young

people with LFS embodied their multi-organ risk: 'Findings out that I had the gene, every little thing [about my body] worries me now. Where it didn't before' (Olivia, 23, +ve, unaffected).

As an example, many participants had a pre-occupation with headaches as symptoms of brain cancer: 'with the migraines I'm like, 100%, cut my head off, it's a brain tumour' (Carolyn, 34, +ve, unaffected). Living in fear of a pan-cancer risk meant that not only were previous sites of cancer seen as hot spots for recurrence, but daily aches and pains in other parts of their body were cause for alarm, especially the head.

Sometimes I get a bit worried that I will [get cancer again]. Like every little pain scares me. Even though it's nothing compared to the pain that I felt when I was sick. Just even little headaches scare the shit out of me.

(Tom, 17, *de novo*, Burkitt's lymphoma)

Despite being highly vigilant, discerning the difference between day-to-day aches and pains, and possible cancer was difficult to negotiate for some participants. The same bodily symptom, e.g., a headache, masked different levels of sickness: is it just a headache or is it a brain tumour?

If I wake up and I've got a headache, it's like, 'oh shit, I'm dying' [laugh]. But then you just soldier on and get over it, take a couple of Panadols and you feel fine. [But] there's a point where you're going: 'oh, you've got a headache, take a couple of Panadols.' [But] if a headache has gone on for too long, [it's like]: 'do I have a headache or am I sick?' (Emily, 36, +ve, breast cancer)

Many used their bodily symptoms as a warning sign for cancer and promptly sought out further investigation from their doctor(s). Getting the 'doctor's approval' that 'everything is all right' was important for some young people to reduce their cancer worry (Sophie, 19, +ve, orbital osteosarcoma). Many participants, however, described a tension between being aware of their bodily risk and seeking out help when needed, and being over vigilant and anxious about any and all bodily symptoms.

I try not to think about it too much... if I was thinking about it all the time I would drive myself nuts. But sometimes I'll get a random pain somewhere and I'll be like, 'Oh God, is it back?' (Sadie, 22, +ve, breast cancer)

For some, like Sophie (age 19), having survived cancer meant they now had a 'responsibility' to not 'blow' their 'second chance at life', and monitoring bodily

symptoms became a moral exercise, one which they were obliged to carry out to stay healthy (Sophie, 19, +ve, orbital osteosarcoma).

I try to look out for [cancer] a lot more than I did back [when I was a kid]. It's kind of my responsibility now... It's like, 'you've already had your second chance', so you kind of don't want to blow it. Like, you go through [cancer] and some people don't make it, and some people do. So, it's kind of your second chance at life, so don't screw it up basically. (Sophie, 19, +ve, orbital osteosarcoma).

In addition to young people's embodiment of their multi-organ cancer risk, which they regularly monitored, young women also described discriminating risk by organ, especially breast cancer risk.

I'm really focussed on my breasts and my underarms... if something feels wrong or if there is a tenderness or something like that, it would make me immediately jump to cancer. (Melissa, 20, +ve, unaffected)

Being acutely aware of their reportedly high breast cancer risk, young women viewed their breasts as dangerous body parts, as vessels of risk to their self.

...having my breasts, it [cancer] could happen at any time. So, I just think we'll just go with the surgery [BPM]. (Harriet, 25, +ve, unaffected)

Knowing that it's such a high chance for me to get breast cancer now... I thought it was only a matter of time [so I'm planning for a BPM] (Olivia, 23, +ve, unaffected)

When I went in for my first surgical appointment [for breast cancer], I said, just take both of them [my breasts] ... But [my doctor] was just like, no, 'we're only working on your cancer and later on you can worry about the other one.' Which didn't make sense to me at the time, because I just thought, you know, if one is broken, why is the other one not broken? [...] I just don't want to be sick again. I want to do everything I can so that I can obviously live for as long as possible. (Emily, 36, +ve, breast cancer)

The excerpts above all tell of young women wanting to remove their breasts to improve their longevity. They also tell of how embodiments of LFS-related cancer risk can be gendered. Having no at-risk organs associated with gender (e.g., testes), young men did not embody their cancer risks in the same way as young women, and the next two sections address how these gendered differences intersect with cancer risk perceptions and control.

8.2.3.3 Young women's perceptions of control: the role of risk-reducing surgery

Young women's accounts of their breast cancer risk had an interesting intersection with their perceived control (n=20). They were all acutely aware of their 'obscenely' high breast cancer risk (Catherine, 24, +ve, unaffected); yet, they were least worried about breast cancer because of the control afforded to them in terms of effective breast cancer surveillance, potential risk-reducing surgery, and the many women around them who had survived breast cancer, either from family or in the media, who acted as positive role models for survivorship.

Yeah [breast cancer] stuck in my mind, but it's also the one that I feel least threatened by. I know that some [breast cancers] are still difficult to cure, but it is still the one that I feel less threatened by... I'm much more afraid of getting glioblastoma or sarcoma. (Catherine, 24, +ve, unaffected)

I think the [cancer] I'm probably the least worried about is breast cancer, because I know I can do something about that. There is some level of control that you have, although it is not great, it's still a choice. (Carolyn, 34, +ve, unaffected)

I think the fact that mum has had [breast cancer] twice, of all the cancers, breast cancer seems the least scary, because if she's got through it twice, I don't know, it just seems as though it's not so scary. Whereas other cancers, like, I know people that have died from, they're a lot more scary, even though breast cancer is a high risk. (Anna, 17, +ve, colon cancer)

Other, harder to prevent and detect cancers associated with LFS prompted increased worry because they represented an uncontrollable risk. Indeed, Sarah (age 20), split her level of focus based on the controllability of the cancers associated with LFS. Cancer risk that could be effectively controlled (i.e., breast cancer risk) were a cause for concern and required action. Cancer risks that could not be controlled, however, were not worth focussing on beyond being aware they were a possibility.

I sort of break it down into the 'these are the ones I can constantly try to avoid and these are the ones I don't have a lot of control over.' Obviously, breast cancer is the big one and I can do something to minimise that risk as much as I can, which I'm doing. As far as I know brain cancer is not really one you can avoid if it's going to happen. So, some of them are more at the forefront of you know how to avoid these ones and what to do about them. And some of them are things I need to be aware of but ultimately can't control. (Sarah, 20, +ve, unaffected)

The principal and most effective means for young women to take control of their risk was risk-reducing surgery. Indeed, for participants like Kirsty (age 38), who had

developed several different cancers, the removal of dangerous body parts was routine: 'I get anything cut off that I don't need' (Kirsty, 37, +ve, multiple cancers). Across the sample, however, experiences of risk-reducing surgery were more specific to mastectomy.

8.2.3.3.1 *Breast cancer and mastectomy*

Breasts embodied such a high risk to health that over half of young women in the sample (n=12/20) seriously considered or had completed a bilateral prophylactic mastectomy (BPM), or contralateral mastectomy if they had already developed breast cancer from as young as 22 years of age (Table 20, p. 169): 'I mean with a risk that high, it's like: I'd rather be alive with fake boobs then have cancer but still have real ones' (Sarah, 20, +ve, unaffected). Olivia (age 23) explained that developing cancer or completing a BPM would have the same outcome: the removal of her breasts. With BPM, however, she would avoid cancer treatment, which to her was a better option.

If I was to get breast cancer, I would take the boobs off anyway, so why not do it before? I don't want to have to go through the surgery and also the chemo and the radiation, I'd rather just have to go through only surgery. (Olivia, 23, +ve, unaffected)

Prophylactic mastectomy enabled young women to evade the anticipated biography, or future, they perceived as being written in their genes: that of a cancer patient.

For women who had one breast completely or partially removed due to cancer, their remaining breast tissue was perceived as a continued threat to their health and longevity. Kylie (age 29) described an urgency to have her remaining breast removed.

I mean, for me, when you have cancer you just want to get it out of your body [...] so I was always pestering oncologists, like, 'When am I going to do the other side!?', you know, it was a bit of an urgency for me. (Kylie, 29, +ve, breast cancer)

For Sadie (age 22), who had a lumpectomy, the decision to undergo a contralateral mastectomy and remove healthy tissue was initially counterintuitive. By constructing risk-reducing surgery as a benefit to her future self though, she was able to reconcile the inherent loss of self that the procedure entailed.

Obviously, you don't want to get rid of your body while it is still in good health, you know, you don't want to get something cut off when you know it's fine 'or the moment. So, in a way, it was hard to sort of wrap my head around that, 'oh well, you'll be doing it for the future you, not the right now you.'

(Sadie, 22, +ve, breast cancer)

Emily (age 36) was in a similar position having one breast removed due to cancer. However, she felt that even if her 'risky' breast was removed, there remained a sustained and uncontrollable risk to herself in other body parts.

[My doctors] know that I've got LFS, and that's what's encouraged them to take off this other breast, which is great. But then what about my bones? I said to them: 'why don't we test my bones again?' (Emily, 36, +ve, breast cancer)

Young women were aware that although they could significantly reduce their risk of breast cancer with prophylactic mastectomy, they would still be at risk of the many other cancers associated with LFS. They were unable to exercise the same removal of risk for other implicated body parts and their physical risk remained because those parts could not be 'cut off'. Referring to BPM, Carolyn (age 34) described 'I feel cutting something off means that it's gone. Whereas I'm not sure what else I could cut off for the other cancers' (Carolyn, 34, +ve, unaffected).

Not all participants shared a positive view towards mastectomy. Despite her mother developing breast cancer twice, Anna (age 17) did not perceive her mother's experiences with cancer as a premonition for her own cancer risk. Nor did she perceive her breasts as embodiments of her cancer risk. She felt that removing healthy body parts was a slippery slope when living with multi-organ cancer risk. If she viewed her breasts as risky and removed them prophylactically, she would logically have to remove all body parts that harboured risk, which in the case of LFS implicated all body parts.

I would only [have breast surgery] if I got cancer. But I don't know, precaution stuff, I wouldn't really worry about... because I know that I could get any type of cancer... say you get like a kidney cancer or whatever, I wouldn't go and lose my kidneys, so why would I have a mastectomy kind of thing? And lose that?

(Anna, 17, +ve, colon cancer)

Catherine (age 24) felt that undergoing BPM would be a 'radical' approach considering she did not have a family history of breast cancer and her mother had not completed a BPM.

For me, I don't think that I will consider [a BPM]. If mum got breast cancer, I think that would change things for me. I probably would consider it a lot more seriously. But given that I don't have a family history, to do something that's so radical, I'm just not going to. (Catherine, 24, +ve, unaffected)

Despite her seemingly clear position, Catherine also described a considerable ambivalence about the timing of BPM and the implications for breast feeding, and the ‘guts’ necessary to go ahead with such a physically demanding surgical procedure that could drastically change one’s sense of self and body image.

It’s [BPM] a weird thing to even think about [laughs]. Like just in terms of when I’m thinking about having a double mastectomy, what that makes me think of first is not being able to breastfeed. And so, it would more be something maybe I would consider after I’ve had kids, but even still, I don’t know if push came to shove, to make the first step to have something like that done would take a fair bit of guts and I don’t know if I have that. (Catherine, 24, +ve, unaffected)

Likewise, Michelle (age 27) initially shared a similar ambivalence towards BPM based on its physical toll and implications for family formation and breast feeding. Without a BPM though, Michelle felt she would knowingly be ‘putting [her]self in danger’, and therefore completed the procedure because it was the ‘best option’ to stay healthy.

Michelle: I was really bummed out about [the BPM] because I didn’t want to do the surgery, but after thinking about it for a while, I thought it was the best option to take [...] the pros kind of outweighed the cons because it will reduce the risk of getting cancer by a lot, so yeah, I just decided to do it.

Interviewer: and you were saying there were some cons as well, what kinds of cons did you consider?

Michelle: there weren’t many cons it was just me, like, my emotional side, like not having breasts and like, if I want to have a baby I can’t breastfeed and all that. Yeah but the pros outweigh the cons because I could be putting myself in danger like getting cancer and then I might not even be able to have a kid...

(Michelle, 27, +ve, unaffected)

Catherine and Michelle’s perspectives show that despite the surgical endpoint being divergent, i.e., Michelle underwent BPM and the Catherine did not, their ambivalence about mastectomy was similar.

Endpoint assessments of prophylactic mastectomy uptake can mask the uncertainty around the *process* of decision-making for surgery among young women both unaffected and previously diagnosed with breast cancer in the context of LFS. On the road to arriving at a concrete decision about whether to remove healthy breast tissue to preserve longevity, young women may hold ambivalent feelings about the pros and

cons of such a procedure while contending with the complex implications for self and for some, family formation. Indeed, five participants, all unaffected, made no mention of considering BPM during their interview. From their accounts, they had prioritised other risk management strategies (e.g., losing weight or committing to breast cancer screening in the first instance) perhaps because of a lack of knowledge about surgical options or a tentativeness to consider drastic risk-reduction when only recently learning of their gene status (e.g., under six months ago for Emma, age 20). Collectively, this suggests that even though young women with LFS may be recommended to consider mastectomy, they may not be at the stage to contemplate it actively or openly for a range of reasons that require careful exploration during genetic counselling.

8.2.3.3.2 *Ovarian cancer and oophorectomy*

Some female participants described looking for other at-risk body parts that could also be removed, namely their ovaries and the uterus (n=4). Even though ovarian and uterine cancer are not strongly associated with *TP53* germline mutations, and risk-reducing bilateral salpingo-oophorectomy (BSO) and hysterectomy not being recommended for LFS risk management, four women considered these procedures as commonplace measures to reduce their cancer risk, two of whom completed hysterectomies with BSO prophylactically. Completing this drastic procedure underscores the severe health threat that LFS posed, where the removal of any and every body part, even if not 'at-risk', was perceived as a viable approach for risk-reduction. It also suggests that health professionals operated outside of risk management guidelines for LFS.

Interviewer: For your surgery, your risk-reducing surgery for your ovaries, uterus and fallopian tubes, did the doctor recommend that? How did you know about that?

Ashley: We knew straight away, because we did quite a bit of research and my husband knew that. And my oncologist, before I said something, he already recommended that. So, we kind of like: 'we have the same idea, so let's go ahead.'

(Ashley, 34, +ve, breast cancer)

Referring to the lack of effective surveillance and easily identifiable bodily symptoms for ovarian cancer, both women who had BSO justified their surgery by adopting common perceptions of ovarian cancer being 'a silent killer' (Kirsty, 38, +ve, multiple cancers). While they both spoke of their ovarian cancer risk in some detail, it was unclear from their accounts why the uterus was implicated in their pursuit of risk-reduction. For Ashley (age 34), it seemed as though a hysterectomy was simply another opportunity to reduce her perceived cancer risk in addition to her contralateral mastectomy after breast cancer.

I have my left side mastectomy for the cancer and all of my nodes in my armpit are all gone. And then I chose to have the right side [removed] and then I also chose to have a hysterectomy with all my ovaries and tubes and everything out. Because I can reduce four cancers right there. If I still had them... you never know. I've reduced four, I'll take that chance. (Ashley, 34, +ve, breast cancer)

Ashley acknowledged a sense of loss having removed organs which embodied her femininity; however, she felt it was worthwhile due to her now reduced overall cancer risk: '...sometimes, only sometimes, I feel like I've lost something as a woman. But then I'm like, 'Ha! Who cares!' If I can reduce four of five cancers that I'll never have, I'll take that' (Ashley, 34, +ve, breast cancer).

Importantly, both women had completed family formation. Whereas for Olivia, who was considering a BSO at the age of 23, removing her ovaries meant being unable to have any more children at a time when her plans for family were unclear: 'I have thought about removing my ovaries but it's not something that is on the cards just yet, because obviously I'm not sure if I'm done having kids' (Olivia, 23, +ve, unaffected).

Kirsty and Olivia described that the example set by their mothers was to undergo risk-reducing surgery for ovarian and/or uterine cancer risk. Interestingly, neither of their mothers had developed ovarian cancer, illustrating that family stories of treatment and prevention are equally as powerful as family stories of illness when young people consider their risk management options for LFS.

That's what mum did [a BSO], that was the first thing she did. When she got the boobs removed she got her ovaries taken out straight away as a preventative thing. (Olivia, 23, +ve, unaffected)

My mum had a hysterectomy [and BSO] when she had finished having kids. So, I was happy with what information she told me, you know, it didn't worry her, she was fine and she was glad that she got it done. (Kirsty, 38, +ve, multiple cancers)

8.2.3.4 Young men's risk perception and coping without cancer control

Importantly, risk-reducing surgery as a means of cancer control was only available for breast cancer among the broad spectrum of cancers associated with LFS. Consequently, risk-reduction was only available to women in the sample and young men had no means to reduce their multi-organ cancer risk. Their only source of cancer control resided in engaging in surveillance to enable early detection of cancer (refer to Chapter 8).

For this reason, and perhaps from other, yet unexplored sociocultural factors, young men approached their cancer risk in a very different way to young women in the

sample. While most young women engaged with risk-reducing options to avoid an anticipated future as a cancer patient, many unaffected young men resisted relating or considering a future self that was defined in any way by having cancer.

I'm not 'the cancer guy', it doesn't define my life or anything so there is no point, in my eyes, worrying about the future where I get cancer and get sick and have trouble with that. I might as well look forward to a normal, healthy life and then if I do get sick, I can deal with that. (Ben, 23, +ve, unaffected)

Although young men understood that they were at increased risk of cancer to some degree, they actively forced LFS out of visions for their future self. The point where cancer risk manifested physically would be the signal to face it.

Will (age 24) anticipated that he would 'miss out on stuff in life' if he focussed on developing cancer one day. Making life decisions based on LFS would mean letting it control his future.

I don't want to make decisions based on [LFS]. Like, I don't want to miss out on stuff in life or not do stuff because I might get cancer one day. I don't want to let that control my life. (Will, 24, +ve, unaffected)

In an act of rebellion against LFS, Will continued to engage in risk-taking behaviour in the form of cigarette smoking. Despite being aware of the lung cancer risk it entailed, smoking symbolised the last vestige of his normal identity before being diagnosed with LFS, and it was something he was not yet willing to part with.

I smoke and I know I shouldn't because I carry the gene, but it is something that I like doing: having a cigarette, you know, with a beer or something and I feel like [...] just because I'm a carrier of the gene that I should give up something that I like doing. I don't want it to control me. (Will, 24, +ve unaffected)

The last two sections explored the differences in constructing cancer risk and options for control based on gender. Due to the cancer spectrum of LFS, young men did not embody their risk like young women, and without any options to reduce their multi-organ cancer risk, most avoided thinking about a future with cancer as a form of coping. In contrast, young women possessed at-risk organs directly associated with their femininity, namely their breasts, which were embodiments of LFS. Importantly, young women were able to engage in problem-focussed coping and pursue risk-reducing surgery. Having the option to control and reduce their risk meant that although breast cancer risk was the greatest health threat to young women with LFS, it was also the one they were least worried about. This highlights the critical emotional buffering risk-

reducing options can confer to young women with LFS, and underscores perhaps how difficult it may be for young men with LFS to cope with their cancer risk without an equivalent option for medical intervention.

8.3 Discussion

These findings cover a wide range of young people's experiences with LFS. They clearly document that making sense of the complexities associated with LFS, both in a medical sense and in a relational sense, is a challenging prospect for young people. Their experiences are broadly consistent with, and bring novel aspects to, two streams of literature. The first is the idea of risk being a sociocultural construct that is heavily shaped by familial and personal frames of reference. The second idea is that the embodiment of cancer risk can lead to efforts of control that submit the body to drastic modification.

8.3.1 Making sense of cancer risk

Because of the uncertainty and variability associated with LFS in terms of penetrance and phenotype, cancer risk estimates were difficult for young people to interpret. In the face of this complexity, young people referred to their familial or personal knowing of cancer to understand LFS as an illness and their risk of developing cancer and their options for control. These findings are consistent with a collection of work which has established that individuals understand inherited illness using family experiences and heuristics as a guiding framework (d'Agincourt-Canning 2005; Kelly et al. 2005; Kenen, Ardern-Jones, and Eeles 2003; McAllister 2003; Walter and Emery 2006; Hallowell, Statham, and Murton 1998; Werner-Lin 2007; Werner-Lin and Gardner 2009).

The interconnections between experiences of cancer and making sense of inherited cancer risk is not a novel concept among families with inherited disease. The findings from this chapter were informed by, and therefore consistent with, a previously described concept among families with adult onset conditions (i.e., HBOC, HD and Lynch syndrome), termed experiential knowledge; specifically, 'empathetic' (familial) and 'embodied' (personal) knowledge (d'Agincourt-Canning 2005; Abel and Browner 1997; Mand et al. 2013). For the first time, however, the phenomenon of experiential knowledge has been extended to young people with an early onset condition. The high penetrance of *TP53* mutations and the early age of onset meant the vast majority of young people's knowledge of LFS was derived from either personally developing cancer at a young age (i.e., personal knowing of LFS), or from relatives who had developed or

died from cancer (i.e., familial knowing of LFS). Familial knowing was further broken down into proximal and distant forms based on the closeness of relatives, either biologically or socially, to the young person, with distant forms being much less common (n=2).

These findings are also consistent with research among families with Lynch syndrome, where McAllister (2003) developed a theory of engagement to explain how family history of cancer influenced risk perception. Engagement refers to the 'the degree of cognitive and emotional involvements with one's increased risk of developing cancer as a result of one's family history of cancer' (McAllister 2003: 180). Although engagement may be partial (i.e., at the cognitive level only) or intense (at cognitive and emotional levels), each level necessarily involves knowledge and interpretation of family history (McAllister 2002), which was clearly evident among the accounts of young people who had a strong family history of LFS.

Similar to unaffected young women with a *BRCA1/2* mutation, termed by some authors as 'pre-vivors', unaffected young people with a *TP53* mutation made use of family narratives and knowledge of LFS to guide their perceptions of developing cancer and the progression of disease (Hoskins, Roy, and Greene 2012; Werner-Lin 2007; Werner-Lin and Gardner 2009). Family narratives for those with a family history of LFS were replete with a seemingly endless cycle of disease for several family members, sometimes across generations simultaneously. For many young people, bearing membership to their family legacy of cancer lead them to believe they would also develop cancer in the future, and for some, this meant they would most likely die at a young age. Indeed, a substantial portion (37%, n=11/30) of young people had lost a parent or close family member under the age of 18, which for most, directly impacted their views of the severity of LFS. To them, LFS as an illness was lethal.

These rates of early-life bereavement are comparable to previous research reporting that 26% (n=24/92) of participants from a cohort of families with LFS had experienced the death of at least once first-degree relative by the age of 21 (Peterson et al. 2008). In this cohort, cancer-specific distress was highest among those who had lost more than two first-degree relatives to cancer (Peterson et al. 2008). While the current analysis did not measure psychological distress, it is reasonable to suggest young people who had experienced bereavement at a young age may also have high levels of cancer-related distress which shaped their risk perceptions. Moreover, experiencing bereavement and loss at such an emotionally labile age has broad implications for

psychosocial development (Tennant 1988). Exactly how these implications manifest over time for young people with LFS merits further investigation.

It could be argued that due to the intergenerational impact of LFS, like that seen in adult onset conditions (e.g., HD) (Kavanaugh, Noh, and Studer 2015; Mand et al. 2015), that young people from families with LFS are likely to adopt caring roles for affected family members at young ages. Although many participants in the current analysis reported many close family members being affected by cancer, only two described taking on additional roles of responsibility to care for their affected relatives. This may be due to the early age of onset associated with LFS, meaning most family members developed cancer at younger ages when participants themselves were too young at the time to adopt additional roles of support. Whereas for adult onset conditions, young people have the opportunity to reach an age where they can adopt these roles as their affected relative may not become symptomatic until late in their life. Alternatively, because over one-third of the sample had no family history and/or were probands, there were in fact the ones receiving care from other family members, and had unwittingly started a new familial legacy.

Unlike pre-vivors with a *BRCA1/2* mutation, who can refer to a family history predominated by two cancer types (breast and ovarian), the phenotypic variability associated with LFS meant the family histories of cancer for young people in this sample were more complex. Some young people found that this complexity, based on the varied age of onset and types of cancer among their family, provided little guidance as to when and what cancer they themselves might develop. Living with this level of uncertainty differentiates unaffected young people with LFS from pre-vivors with HBOC in an important way. The young LFS pre-vivor is at high risk *now* of a multitude of cancers with varying lethality, whereas the young HBOC pre-vivor may not yet be at high risk of organ-specific, largely preventable cancer.

For probands and participants with a *de novo TP53* mutation, making sense of their cancer in the context of a sparse family history was difficult. In the absence of readily available family narratives young people constructed their risk based on their personal experiences of cancer. Almost all that had experienced cancer previously felt they would, based on their 'track record', develop cancer again in the future. This is consistent with previous research showing that women with a *BRCA1/2* mutation who had developed cancer understood their cancer risk in the context of their previous cancer experiences, and adopted a fatalistic attitude to their risk of developing cancer

again in the future (Hallowell et al. 2004). Hallowell et al. (2004) also demonstrated that former cancer patients do not necessarily perceive their genetic risks of developing additional cancers as anxiety provoking. This was also evident in the current analysis in two cases where young people were unsurprised and unfazed to learn of their gene status based on their extensive personal history of cancer.

Evident among the accounts of young men was a general lack of interest in learning and understanding their cancer risks. This may be explained by the use of mental processes similar to those defined in Fuzzy Trace Theory to make sense of their cancer risk. Fuzzy Trace is a decision-making theory centred on two mental process: gist and verbatim (Reyna 2008). Gist traces are fuzzy representations of an event (i.e., its bottom-line meaning: high or low risk), whereas verbatim traces are detailed representations (e.g., recalling specific cancer risk estimates from genetic counselling) (Biesecker, Austin, and Caleshu 2017). In the face of their complex cancer risks, young men predominantly used gist traces to understand LFS as an illness. The gist meaning of their cancer risk was that it was high, and therefore they enrolled in surveillance, but understanding the extent of their cancer risk was seemingly unimportant. Indeed, most dichotomised their cancer risk based on outcome (i.e., having cancer or not). Perhaps simplifying their cancer risk was an avoidant coping strategy for young men in the sample. Without any risk-reducing options for their cancer risk, it remained uncontainable. The current limitations of screening protocols for LFS meant learning of their gene status meant waiting for a cancer diagnosis. Therefore, learning about the specifics of their cancer risk may have provoked feelings of cancer worry and distress that were better left ignored than contemplated in any depth.

8.3.2 Embodied risk and control

The intersection between young women's perceived cancer risk with LFS and their attitudes towards risk-reducing surgery yielded interesting and novel findings. Broadly, young women's accounts of embodied cancer risk were consistent with the experiences of women with a *BRCA1/2* mutation, who feel their breasts and ovaries are embodiments of their *BRCA1/2*-related cancer risk (Hallowell and Lawton 2002; Hallowell, Statham, and Murton 1998). Young women with LFS also felt their breasts were embodiments of their *TP53*-related cancer risk. Because the risk of breast cancer dramatically increases from the age of 20 for women with LFS, most young women in the sample were near certain they would develop breast cancer in the future, if they had not already. This meant the majority seriously considered, planned and completed risk-reducing surgery

for their breast cancer risk at very young ages, the earliest being 22 years. The elimination of at-risk body parts provided young women with the means to eradicate breast cancer risk and regain control of their futures (Hallowell and Lawton 2002).

This points to another interesting comparison to young women with a *BRCA1/2* mutation. Glassey et al. (2018) showed that young Australian women with a *BRCA1/2* mutation who underwent BPM (n=26, mean age 31) overestimated their risk of developing breast cancer risk at young ages, and underwent BPM because they were highly anxious. Similarly, Hoskins and Greene (2012) found that young women's tolerance for uncertainty (i.e., being uncertain about the efficacy of breast screening and uncertain of results before and after screening appointments) would steadily diminish over time in favour for drastic, direct action to remove their breast cancer risk (i.e., BPM). For young women in this sample, they correctly understood that among the broad spectrum of cancers they were at risk of, breast cancer was the highest and most immediate threat to their health. Yet, counterintuitively, it was the one they were least worried about. From their accounts, it was clear that they were least anxious about breast cancer because they could effectively reduce their breast cancer risk with risk-reducing mastectomy. In comparison to their other, potentially more lethal cancers they were at risk of, breast cancer was the only manageable one, and therefore the least worrisome. That is, perceptions of breast cancer risk and associated distress were relative to what they knew about LFS. To summarise, young women with LFS were least worried about breast cancer because they could reduce their risk with BPM, whereas young women with a *BRCA1/2* mutation who pursue BPM are most worried about breast cancer *despite* being able to reduce their risk.

Interestingly, while *BRCA1/2* mutations confer similarly high risk of breast cancer to *TP53* mutations up to age 70, the onset is generally later in life, and BPM is recommended before the age 40 (Kurian, Sigal, and Plevritis 2010). In contrast, consideration of BPM among young women with LFS is recommended from age 20 (Cancer Institute New South Wales 2019). For a young woman with *BRCA1/2* mutation to pursue BPM in her 20s or 30s is perceived as drastic, whereas the same practice for young women with LFS is acceptable, if not expected. This makes sense when thinking about risk as a biomedical construct: i.e., statistical risk estimates show that breast cancer risks are higher and have an early onset in the context of LFS, therefore reducing risks by the best means possible (i.e., BPM), as early as possible, is a rational decision. Yet, this biomedical rationale masks the moral and social aspects of risk that permeate the clinical genetics service as an arm of our risk society. Further, it demonstrates that the same

discourse of control promoted by the clinical genetics service—i.e., the removal of at-risk body parts—manifests in different ways depending on how risks are presented and embodied by individuals.

The core premise of the risk society is that managing one's risks is a personal responsibility. Risk-reducing surgery, although couched in the rhetoric of personal choice, is in fact constructed as a moral act (Lupton 1993). Individuals who do not take action to reduce their bodily risk of disease are irresponsible because when they become sick, they are removing themselves from a useful, productive role in society (Lupton 1993). Or in more immediate circles, they become a burden on their family who must care for them. Therefore, the presumption of risk-reducing surgery is that if you *can* remove at-risk organs, you *should* remove them to maintain a useful role to society. An interesting quirk to this argument in the context of LFS is that breast cancer risk is the *only* cancer risk that can be reduced with surgical intervention, so some women with LFS feel as though they *should* undergo surgery to increase their chances of survival. This reinforces that genetic information constructs individuals as personally responsible for controlling and managing their bodies to avoid exposing the body to health risks (Hallowell and Lawton 2002).

Striving to achieve a risk-free body with risk-reducing surgery, however, could only get so far with multi-organ cancer risk. This makes LFS different to other inherited cancer conditions (e.g., HBOC, Lynch syndrome and familial adenomatous polyposis) where the implicated at-risk organs are readily removable and the control offered by risk-reducing surgery covers the full spectrum of physical risk. In this way, the control over one's body offered by the removal of at-risk body parts is incomplete in the context of LFS; multi-organ cancer risk remains omnipresent and ambiguous. Perceptions of multi-organ risk were so all-consuming that two women underwent BSO with hysterectomy, and two considered these procedures, despite not being recommended for LFS risk management (Cancer Institute New South Wales 2019). One possible explanation is that these women and their health professionals conflated HBOC and LFS due to them sharing breast cancer risk; i.e., effective risk management for one syndrome would be effective for the other. The implicated health professionals may have been misinformed about appropriate risk management for LFS, or it may be that they acted on more complex medical and/or psychosocial circumstances that were not addressed in the interview.

Importantly for LFS, accounts of embodied risk and the intersection with risk-reducing surgery were gendered. Due to the spectrum of cancer associated with LFS, young men had no at-risk organs that could be suitably removed with surgery, yet they still lived with high multi-organ cancer risk. Unlike young women, who could act to avoid their anticipated biography of breast cancer, young men had no means to evade their anticipated biography of being a cancer patient (Bury 1982; Hallowell and Lawton 2002; Williams 2000). They had no means for biographical reappraisal and their accounts suggested they engaged in avoidant coping to skirt having to integrate an anticipated biography of cancer. These findings suggest that coping strategies among young men with LFS is worth exploring further. At this stage it is unclear whether their avoidant style is a gendered approach or whether it is due to their cancer risk profile.

A novel finding from this analysis was that for those who had developed several cancers, LFS represented a constant and insidious threat to their health. The incessant loss of body parts to cancer and late effects from treatment had lasting impacts on identity development at a life stage where it is a key developmental task. Altering the materiality of the body through the removal of body parts and multiples rounds of cancer treatment, with myriad late effects, incurred losses to self-identity; 'a situation brought about the inherent contradictory experience of both having a body and simultaneously being an embodied self' (Hallowell and Lawton 2002: 438; Merleau-Ponty 1962). The separation of the habitual, material body and one's sense of self suggests young people with LFS who develop multiple cancers over their life time may need additional support to navigate and integrate divergent senses of self.

8.4 Summary

This chapter showed that young people make sense of LFS as an illness primarily by drawing on their familial and personal experiences of cancer. Based on these experiences most felt they would inevitably develop cancer in the future. It also illustrated an interesting intersection between young women's embodiment of their breast cancer risk and how they considered risk-reducing mastectomy. While breast cancer represented the greatest risk to their health, it was also the cancer risk they were least worried about because of the control available to them in the form of mastectomy and effective breast cancer screening. Perceptions of breast cancer risk were necessarily gendered, and how young men construct their cancer risk requires further investigation. To this end, the next chapter goes some way to addressing this by exploring experiences of risk management across the sample more generally.

9 Burden and utility of cancer surveillance for Li-Fraumeni syndrome among young people

9.1 Overview

The previous chapter illustrated how young people make sense of LFS as an illness, and how they perceived and acted on their cancer risk. While Chapter 8 addressed risk-reducing surgery as an option for cancer control, especially for young women, it would be remiss to leave out a critical aspect of cancer control for young people more generally with LFS: risk management in the form of screening and surveillance. This chapter is the third major theme developed for Study 2 and aims to describe young people's experiences with engaging in either whole-body or organ-specific cancer surveillance. To achieve this aim, this chapter describes the three main subgroups within the sample who were enrolled in risk management. Subgroups one and two consist of young people with access to whole-body risk management using whole-body MRI, but who differ based on being personally diagnosed with or unaffected by cancer. Subgroup three consists of young people, both diagnosed and unaffected by cancer, with access to organ-specific surveillance only. This chapter is divided into three main sections. The first section describes participants' perceived utility of engaging in cancer surveillance. The second section describes participant experiences of distress leading up to screening/surveillance appointments and waiting for results. The third section describes the logistical burdens of regular, intensive surveillance and their intersection with life goals associated with adolescence and young adulthood.

9.2 Findings

Universally across the sample, risk management strategies offered by clinical genetics services were perceived by participants as a fundamental means to gain control over their cancer risk. Indeed, accessing risk management was a primary motivation to undergo genetic testing (Chapter 7), and in combination, genetic testing and risk management represented instrumental actions of control that young people could take to begin mitigating their risk of cancer. Critically, young people described that having the option to ‘do’ something about their risk empowered them to be active agents in reducing their cancer-related morbidity and mortality.

Many felt that the only way to regain control over LFS was to ‘do the right thing’ and commit to intensive cancer surveillance if available (Kirsty, 38, +ve, multiple cancers). Yet, the control offered by risk management manifested in subtly different ways for young people across the sample, and universally exposed a tension between knowing one’s risk and managing one’s risk.

[Risk management] makes me feel like I’m doing the right thing for my body. It does also make me very aware of how fragile I am... (Tasha, 24, +ve, unaffected)

This chapter describes participants’ experiences of risk management as separate from their experiences and attitudes towards risk-reducing surgery (refer to Chapter 7). Participants’ engagement with risk management were split across three different subgroups (Table 23, p. 204; n=27); three participants were excluded from this analysis because they were untested and not enrolled in risk management.

Table 23. Risk management across the study sample (n=27)

Risk management access	Subgroup	
Access to whole-body surveillance with WBMRI (n=20)	Subgroup 1	Unaffected young people with a <i>TP53</i> mutation (n=12)
	Subgroup 2	Affected young people with a <i>TP53</i> mutation (n=8)
Access to organ-specific screening and surveillance only (n=7)	Subgroup 3	Affected and unaffected young people with, or at-risk of, a <i>TP53</i> mutation (n=7)

Abbreviations: WBMRI, whole-body MRI.

Across all three subgroups, participants described a core tension with their engagement in risk management, either with or without whole-body MRI. There was a balance to be

struck between the perceived utility of detecting cancers at an early stage and the psychosocial burden of partaking in regular intensive cancer surveillance.

9.2.1 Perceived utility of cancer surveillance

Participants described that cancer surveillance and screening offered the only means to detect cancers at an early stage and therefore increase the likelihood of a better prognosis and longevity. Ben's (age 23) views on screening were reflective of the perceived utility of whole-body surveillance among participants in subgroups one and two. He explained that he and his two brothers, also diagnosed with LFS, felt that screening provided peace of mind:

...we're getting this observation, so if it does happen, if we do get cancer, it will be caught out pretty early. So, peace of mind I guess helps. (Ben, 23, +ve, unaffected)

Justin (age 22), although not tested, was able to participate in research-based screening. His approach to surveillance and frame of mind highlighted the comfort young people found in there being a process available to them if something was identified from surveillance.

[My cancer risk] doesn't worry me because I know there are things in place that can help. So, I don't get in a fluster, it doesn't cause anxiety or anything because I believe I've got a pretty rational way of thinking [about it], and I know that if this happens then A, B and C will happen as well. (Justin, 22, 50% risk, unaffected)

In this way, engaging in cancer surveillance constituted a critical safety net for young people with LFS and served to allay most participants' cancer worry.

For subgroup two (i.e., affected participants with access to WBMRI), surveillance provided peace of mind that any recurrences would be detected early and they would avoid any delayed diagnoses. For those who had faced repeated primary diagnoses and were cycling between chronic and crisis phases of illness, receiving a negative scan meant they had some 'breathing room' and freedom to live a normal life for a short time.

It gives me peace of mind to know that if the scan comes back clear... it gives me some breathing room. (Jamie, 25, +ve, multiple cancers)

Participants across all three subgroups were aware that surveillance was limited to diagnosing cancers at early stages and that it did not reduce of their cancer risk. In the knowledge of its inability to reduce their cancer risk, many avoided thinking beyond the task of 'doing screening' as a form of coping.

Aside from me doing my screening, that's all that I can do... so to keep thinking of hypotheticals of what might happen, I feel that it's not, it wouldn't be very good for my mental health to keep thinking about this more regularly than I needed to, so I try not to. (Catherine, 24, +ve, unaffected)

Tasha's (age 24) account below reflects the sense of control provided by accessing genetic testing and surveillance that many across the sample experienced. Being fully aware that surveillance did not reduce her risk, she placed her faith in being able to gain a better prognosis from attending regular whole-body MRIs. She described it as 'the only solace' available, and she took it without hesitation.

It makes me feel better that I know as much as I can't control getting cancer, can't control whether I live or die, I can control that if I do get it, it will be caught early because I've had the [genetic] testing and I'm getting routine MRIs. And it's the only solace you can take in that, so it's small, but you gotta take what you can get.

(Tasha, 24, +ve, unaffected)

In a similar vein, Carolyn (age 34) also described surveillance as her 'best shot' to stay healthy. In contrast though, the act of engaging in surveillance meant that while she had gained control over her body to some degree, she had lost control of her future. She constructed surveillance as a false empowerment because the ultimatum for no surveillance was a potentially early death, meaning her options were limited in a way she was unaccustomed to.

I hate [surveillance], I really hate it. It makes me feel like I've lost control over myself in a way that I am really, it really doesn't sit well with me. But I also understand that this is my best shot right now, so... I'm used to negotiating things, like I'm used to having options, I guess? And here... This is kind of the first-time where it's like, you know, you do this or you're fucked, so... (Carolyn, 34, +ve, unaffected)

With two young children she felt that partaking in surveillance was a moral exercise. She was obliged to stay healthy for her family and fulfil her role as a responsible parent: '...if I was single and I didn't have any kids, I'm not sure that I would be sitting here going through the [surveillance] study' (Carolyn, 34, +ve, unaffected). In this way, surveillance provided the means to secure a viable social self.

For subgroup three, participants with access to organ-specific screening or surveillance (both affected and unaffected; n=7), the perceived utility of their genetic testing was questionable. Without the means to control their whole-body cancer risk, the entire discourse of control offered by the clinical genetics service seemed false.

Well I don't really understand, like, they give me all the different cancers that you can get, like, brain cancer, and breast cancer, and [...] leukaemia... Bone cancer. [...] But then [after] giving you all the percentages of it, like, nothing happens [...] nothing is happening with it anyway, so, what's the point of knowing you have the gene mutation if they're not checking it regularly? (Emily, 36, +ve, breast cancer)

Interestingly, this was not the case for all those in subgroup three. Despite only having access to breast and colon cancer-specific risk management, Olivia (age 23) still felt learning her gene status afforded her a degree of control over her cancer risk.

I'm glad I had [genetic testing] done because I can take both the breasts off and [have] some of this cancer surgery and always be looked at and make sure I'm okay, or if something does pop up that we could hopefully get it early.

(Olivia, 23, +ve, unaffected)

Unaware of the option for whole-body MRI, Olivia trusted her health professionals and did not hypothesise there was a better or more comprehensive way to manage her cancer risk. Focussing on high-risk organs was sufficient for her to feel in control.

9.2.2 Cancer surveillance is an emotional burden

For subgroups one and two, engaging in regular whole-body cancer surveillance to detect possibly untreatable cancers was a logistically challenging and emotionally stressful endeavour.

[Surveillance] is a lot of time... it's time, it's money, it's all of these things for something that even if they find [cancer], the chances, my odds of survival probably still aren't that good. (Catherine, 24, +ve, unaffected)

Most participants described the lead up and the process of whole-body MRI scans as a distressing time. Ruminating on the possible outcomes of their scan and the implications of a finding made them feel vulnerable. Coming up to appointments and wondering 'is today going to be the day?' was a common experience among those who attended surveillance (Tasha, 24, +ve, unaffected). In this way, surveillance appointments represented a trigger for cancer worry for both affected and unaffected participants, and was the core burden of engaging in screening.

...in the MRI machine, I'm there for three hours and it's just sort of going through my head, like: 'oh, what if they find something? Oh, what are you going to do if they find something? What are going to be your immediate actions and how are you going to, like, deal with this? What are going to do with your study, like, how is it going...

what if you get really sick, like, what happens? It's sort of like a downward spiral of those thoughts. (Melissa, 20, +ve, unaffected)

In contrast, Anna (age 17) described a process of adapting to distress about her scans. The turning point for her was realising that worrying about her scan results would not change the outcome, and therefore there was no point on pre-empting the result. In so doing, she demonstrated a form of mindfulness. She would stay in the present as a form of coping with any distress from surveillance and not let her mind stray into the exhausting process of thinking about her future self with cancer.

...after the first few times of worrying about the scan and how it will go, you start to realise that whether you worry about it or not, you can't change how that scan looks. So, then you just can't be bothered worrying, because there is no point, because it's not going to change anything. (Anna, 17, +ve, colon cancer)

An important aspect to engaging in whole-body risk management for LFS was that it was a lifetime commitment: 'in terms of screening, it's going to be a forever thing. It will just be a case of how streamlined it will get over my lifetime' (Catherine, 24, +ve, unaffected). Living with the emotional burden of surveillance for the course of their life was a daunting prospect, especially for participants diagnosed at a young age, who potentially could be engaged in surveillance for decades.

I got diagnosed or told at 15, and you're like, 'I have 70 years to think about it.' Like, I have scans every three months and you just get worried every three months, and to know that could go on for 70 years is just really scary.

(Anna, 17, +ve, colon cancer)

Many described there being no real alternative to engaging in surveillance if they wished to stay alive, and were resigned to regular appointments being the norm of their life into the future. Some participants described a level of acceptance with their new norm: '[screening] is just something that I have to do... it's like paying the bills or something, you just have to do it. It's just another part of life for me having this gene' (Felix, 20, +ve, unaffected).

Only one participant, however, had been engaged in whole-body risk management for an extended period of time (more than three years). Kirsty's (age 38) experiences of long-term engagement suggested it became part of everyday life where 'going through the motions' and not dwelling on the build-up or outcomes were

important aspects of normalising her screening experiences. She did, however, describe a process of adjustment:

...it's hard because at first all I seemed to do was go and see doctors and tests and the annual testing is, as good as it is to keep monitoring you and stuff, it does... It's a lot [...] it does [laugh] muck around with your time schedules with work and kids.
(Kirsty, 37, +ve, multiple cancers)

Importantly, like Carolyn above, Kirsty's engagement in surveillance was constructed as a moral action: 'I just try and *do the right thing* and keep myself going for as long as I can' (Kirsty, 37, +ve, multiple cancers), and with three young children, this meant sustaining her roles of responsibility as a parent. Moreover, Kirsty's experience suggests there may be a trajectory in becoming accustomed to the regularity of whole-body risk management. At the beginning, intensive screening may seem daunting, especially in the context of being newly diagnosed with LFS, but after a period, out of necessity (either for their own health or to support their family) screening becomes a normal part of life.

9.2.2.1 Introducing a new relationship between body and self

Despite the perceived power of MRI to monitor the body for disease, it could only provide temporary proof that one's body was healthy before the cycle would have to begin again. Always dredging one's body for 'secrets' was an exhausting proposition, and underscores the cyclical nature of emotional burden associated with surveillance for LFS (Carolyn, 34, +ve, unaffected).

For Carolyn (age 34), her nervousness about beginning whole-body surveillance was based on realising it heralded a new relationship with her body. The diagnostic power of whole-body MRI meant her material body could no longer hide any 'secrets' from her, and introduced a dissociation of body from self that she had not considered.

I'm a little nervous, not just about... Not really about the procedures and things, more like the realisation that my body is not going to have any secrets from me anymore, which is kind of a weird thing to think about.

(Carolyn, 34, +ve, unaffected)

Harriet (age 25) shared this kind trepidation for her first MRI scan: 'Because this is the first [scan], it's a bit scary thinking what could be happening in my body' (Harriet, 25, +ve, unaffected).

This new relationship between one's material body and one's self underscores an interesting intersection. The discomfort at being repeatedly subjected to a powerful form of technological knowing (MRI) that supersedes human knowing was clear to see for participants like Carolyn. Only MRI could effectively monitor and know their material body, moving the locus of control away from their self and into the hands of technology. Their body was now separate to their self, and was manifest as an agent of deceit, potentially harbouring 'secrets' (i.e., cancer) and that had to be managed by constant surveillance. The act of using MRI drove a wedge between mind and body and introduced the mind-body dualism for some participants in an unprecedented fashion.

Although nearly all participants viewed the diagnostic power of MRI as the best option to ensure good health into the future, their sense of agency in this context was constrained as the alternatives were limited. Carolyn was one of the only participants to demonstrate a willingness to cease surveillance and exercise her agency against the discourse of control promoted by the genetics clinic. Exercising her agency, however, meant accepting the possibility of an early death.

I might decide in five years that this is bullshit and I don't want to do any of this and I will just wait for it to come. (Carolyn, 34, +ve, unaffected)

9.2.3 Logistics and life goals

Participants' attitudes and perceptions of engaging in surveillance highlighted a key intersection between the logistics of surveillance and their developmental tasks. For some, young men especially, the logistics of surveillance were not perceived as burdensome: 'It's only two or three days out of every year, so it's not like a burden on my life or anything' (Ben, 23, +ve, unaffected). Sam (age 28) spoke of the benefits of being enrolled in a research-based surveillance protocol and having a research coordinator organise his screening appointments, greatly reducing his logistical burden.

I can be slightly disorganised, so basically just having someone manage my cancer screening for one and paying for it for two, and yeah, it was just yeah, one of the easiest decisions of my whole life. (Sam, 28, +ve, unaffected)

Many others in the sample, however, found it difficult to fit their appointments into a busy schedule at university or work. For example, Catherine (age 24) was a medical student and knew that in her upcoming intern year she would be randomly placed at a hospital in her home state. This posed an issue for her staying within an

accessible range to benefit from the centralised whole-body surveillance on offer in her state capital.

I'm not sure where I'm going to be living in the future and even with where I get a job next year. In [my home state] you get randomly allocated within quite a big system, so if I'm working quite far away then that's also going to be quite a problem.
(Catherine, 24, +ve, unaffected)

Carolyn (age 34) described having to juggle her upcoming surveillance appointments, and their associated distress, while trying to perform to her usually high standard at work. This was especially stressful because her job was on the line while her unit underwent a restructure.

...there's a restructure that's going to happen [at work] and while they're making all of these decisions about who needs to go where and their value and things like that... I'm walking into literally the most intense psychological head fuck, not to mention I'm going to have to miss a fair amount of work [for my screening appointments].
(Carolyn, 34, +ve, unaffected)

The anticipated logistical and emotional burden of whole-body cancer surveillance and possible cancer diagnoses meant readjusting career and study aspirations for many participants. At a time when career planning was a key developmental task, this readjustment was especially pronounced for emerging adults with ambitious goals. Adam (age 29), yet to learn his gene status, hoped to be an active member in the LGBTQI community offering legal services in a pro bono capacity. He described that if he learnt that he was *TP53*+ve he would enrol in whole-body risk management, but felt the weight of his health management would prevent pursuing his career goals: 'I just won't have time for pro bono if I'm going to be dealing with my health that's going to be really turbulent' (Adam, 29, 50% risk, unaffected).

From these accounts it was clear that balancing the logistical and emotional burdens of surveillance were difficult for some. Yet, despite reported emotional burdens and logistical juggling, all participants engaged in surveillance because the perceived utility outweighed the perceived burdens. The tension was worth navigating to increase their longevity and reduce their distress.

9.3 Discussion

These findings are the first to describe the experiences of young people with risk management for LFS. The mean age of this sample is considerably younger (25.5 years,

range 17-38) compared to previous qualitative work on the psychosocial implications of screening for LFS by McBride et al. (2017), mean age 43.3 years (range 21-65), and Ross et al. (2017) mean age 39.1 years (range 18-61), respectively. Young people's experiences with surveillance for LFS were similar to these earlier works, as I will outline below, but had important differences regarding the prospect of long-term engagement from a young age, and a previously undescribed dissociation between body and self by the use of whole-body MRI in this population.

9.3.1 Risk society and risk management

The general perceptions of young people towards risk management support that individuals with a genetic predisposition construct themselves as responsible for controlling and managing their bodies to avoid exposing themselves to health risks (Hallowell and Lawton 2002). In this way, risk management for inherited cancer risk is marketed as empowering for individuals, and many studies support that individuals feel empowered by their genetic information because it enables them to take control of their cancer risk with surveillance and potential risk-reducing strategies (d'Agincourt-Canning 2006a, 2006b; Hallowell et al. 2003; Hallowell and Lawton 2002). Young people in this study also felt that genetic testing and risk management for LFS empowered them to act as moral agents and 'do the right thing' for their body and stay healthy. Indeed, in the face of high, multi-organ cancer risk where cancer and death seemed certain, risk management was as critical form of active or problem-focussed coping: young people could actively 'do' something about their cancer risk.

Yet, engaging in intensive cancer risk management involves a degree of self-sacrifice: sacrificing one's body to constant monitoring for peace of mind, and sacrificing one's mental state for a healthy body and longevity. In the context of LFS, the disciplined, healthy body, was subjected to intensive regular surveillance for potentially poor outcomes (i.e., diagnosis of incurable cancer). Undergoing a whole-body MRI meant continually dredging one's body for 'secrets' and physical manifestations of their cancer risk. The cyclical process of getting the all clear before putting one's body under the microscope again was distressing for many in the sample, and reflects a similar concept reported in previous research among individuals undergoing whole-body surveillance for LFS, termed 'scan-xiety' (Ross et al. 2017). Surveillance therefore offered some control over their body but no control over their future. Participants with access to organ-specific surveillance only (subgroup three) were equally distressed, but for the

opposite reason. Without the means to monitor their whole-body cancer risk, they felt a lack of control over their body, LFS and their future.

The concept of self-sacrifice when engaging in risk management extends far beyond the phenomenon of ‘scan-anxiety’ in an interesting way, and echoes research highlighting the intersection of medical imaging technology and embodied experience (Griffiths et al. 2010). In the context of surveillance for disease using medical imaging, the technological knowing of the body is given more credence than the patient’s experiences, creating a fragmented sense of body and self (Gunderman 2005; Green, Thompson, and Griffiths 2002). Previously this fragmentation has been restricted to the visualisation of the certain body parts (e.g., the breast) (Griffiths et al. 2010), but the introduction of whole-body MRI heralds a new type of fragmentation. The entire body becomes an object to be scrutinised in great detail by experts (Reventlow, Hvas, and Malterud 2006), and one’s sense of autonomy in relation to their own health may decline. The locus of control for one’s health moves away from the individual and into the hands of technology. The impact of medical visualisation of the body’s interior on individuals embodied experiences of their multi-organ cancer risk merits further investigation.

For participants who engaged in surveillance from a young age (i.e., from adolescence), the prospect of having to navigate screening distress and the medicalisation of their body for the duration of their life was daunting, and highlights the potential for screening fatigue, similar to young women with a *BRCA1/2* mutation (Hoskins and Greene 2012). Indeed, the high false positive rate of baseline whole-body MRI surveillance for LFS at present (42.5%) suggests the tension between the burden and utility of risk management may tip to being more burdensome over time (Ballinger et al. 2017). Although young people’s adaptation to intensive cancer surveillance over time is unclear from this sample, and likely highly variable based on sociocultural and contextual factors, general approaches could include the following. Young people may begin surveillance at an early age and have a better opportunity to normalise screening experiences, therefore improving their adherence in the long-term. Or, having begun intensive surveillance at such a young age, they may experience screening fatigue earlier in life and drop out of screening programs, and live with unmonitored risk for longer periods.

Similar to Ross et al. (2017) and McBride et al. (2017), these findings suggest that despite the distress associated with screening for LFS, young people felt the benefits of

screening heavily outweighed the logistical and emotional burdens. A limitation to this analysis is that the current sample drew on a similar demographic group as the McBride et al. (2017) study, and there could be considerable overlap that accounts for the similarity in findings. A novel aspect was that young men in particular seemed unfazed by screening appointments. In combination with their avoidant approach to learning of their cancer risks in any depth, as outlined the previous chapter, this makes for an interesting finding. Perhaps engaging in screening buffered having to contemplate their risk, in that learning any more about their cancer risk would make no difference to their best available course of action to manage it, screening, which they were already engaged in.

Unlike previous research, however, the logistical issues of screening described by young people in this sample did not include worry about insurance cover (Ross et al. 2017) or, bar one participant, worry about the cessation of the SMOC+ research program and therefore their access to whole-body risk management (McBride et al. 2017). This is likely because the universal healthcare system in Australia obviates the need for extensive insurance, and the extension of the SMOC+ program at the time of the study, which participants were likely aware of. These findings also add to preliminary data suggesting some young people change career plans to accommodate living with LFS (Alderfer et al. 2017). Three participants in the current sample reported considering the impact of intensive screening on their career aspirations and the time commitment it required, with one abandoning plans for extensive pro bono work in the legal sector.

I contend that by moving beyond an individual's assessment of the pros and cons of 'doing screening', it is clear that young people may be accepting of surveillance for LFS because they feel obliged to take responsibility for their body and perform their role as a responsible citizen of the risk society. To avoid being labelled and stigmatised as irresponsible for their health by family and health professionals, they engage in surveillance as moral agents. In this way, the body is a project that could and should be regulated to conform to socially viable identities (Hallowell and Lawton 2002). This kind of adherence was evident among young parents, who focussed on establishing and maintaining their identity as 'good parents' by enrolling in surveillance and availing themselves of risk-reducing surgery to increase longevity and care for their children (Wilson 2007). A young person's participation in screening programs for LFS may therefore represent more than their concern for the early detection of cancer if participation comes to be based more on familial, medical, and societal expectation and less on the basis of personal choice (Armstrong and Eborall 2012).

An alternative viewpoint is that young people were primed to accept that screening was ‘inherently good’ because of the social discourse surrounding cancer surveillance in the general public. A prime example is the highly publicised ‘Angelina Jolie effect’ for women with a *BRCA1/2* mutation (Juthe, Zaharchuk, and Wang 2015; Tetteh 2019). The intense media exposure of her experiences with risk-reducing surgery has normalised breast and ovarian cancer risk management, and made it an exemplar for the effectiveness of cancer risk management more generally. Young people, especially young women, may therefore be primed to surmise risk management for LFS is equally effective.

Another key aspect to young people’s acceptance of surveillance is that the screening process for cancer has no inbuilt mechanism that can counter the strong effects of positive reinforcement, leading many to erroneously conclude it provides benefit (Ransohoff, McNaughton Collins, and Fowler 2002). As Ransohoff, McNaughton Collins, and Fowler (2002) explain about prostate cancer screening: ‘the screening process is one without negative feedback. A negative test provides reassurance. A positive one is accompanied by gratitude that disease was caught early. And a false positive test, regardless of the distress it may cause, is nevertheless followed by relief that no cancer was ultimately found’ (665). In the same way, whole-body cancer surveillance for LFS is also without a negative feedback loop, and the opportunity for young people to fully reflect on their adherence is constrained by the positive social discourse that surrounds them regarding cancer surveillance in general, and the risk society they bear membership to.

9.4 Summary

This chapter described how young people experience a tension between the burden and utility of risk management for LFS. On one hand it enables the early detection of cancer and the potential for improved survival. On the other hand, it was emotionally and logistically burdensome for some. Yet, despite this tension, all those with access reported being compliant with whole-body surveillance, and their decision-making highlights their role as citizens of a risk society, where their bodies become projects to be managed and kept risk-free. A novel finding was that whole-body MRI fragmented the body from the self, which points to the power and intrusiveness of technological knowing compared to human knowing. While this chapter focussed exclusively on personal experiences of risk management and attempts to monitor one’s body for cancer, an equally important facet of inherited cancer risk is the risk to future generations. To this end, the next

chapter describes the fourth and final theme developed for Study 2: reproductive agency among young people with LFS, and complexities associated with reproductive decision-making during a period of life when it may not yet be a core developmental task.

10 Reproductive decision-making for young people with Li-Fraumeni syndrome

10.1 Overview

The previous chapter described young people's experiences of engaging in intensive risk management for LFS. One of the core themes of this analysis was that young people perceived 'doing screening' as a moral act; they felt morally obliged 'do the right thing' for their body and engage in screening to stay healthy. Similarly, a central feature of this fourth major theme developed for Study 2 is the sense of moral responsibility young people felt when making reproductive decisions with LFS. More specifically, this chapter aims to synthesise the varied approaches young people with LFS considered, planned for, and carried out in terms of reproductive decision-making. To achieve this aim, this chapter explores the experiences of participants who learned of LFS before or after having children; the tensions between aspiring to conceive naturally and taking 'responsible' but more complex routes to have a family and prevent passing LFS on to future generations; participant experiences of considering and using reproductive technology; and lastly, gendered approaches to reproductive decision-making.

10.2 Findings

Across the sample, the core narrative surrounding having children was one of prevention. Reproductive decision-making—the decision to have children, or not, in ways that prevented passing the family mutation onto the next generation—therefore represented a critical form of individual agency for young people in the context of LFS. In deciding how to go about starting a family, if at all, they had the power to act to reduce or eradicate the burden of LFS on future generations.

Reproductive decision-making was influenced by previous experiences with cancer, life stage, gender, and the timing of learning their gene status (i.e., before or after having children): Table 24 provides a thematic breakdown of this chapter and which participant subgroups themes were drawn from (p. 219). For most young people, exercising their reproductive agency meant using or contemplating the use of reproductive technology; i.e., pre-implantation genetic diagnosis (PGD) or prenatal diagnosis (PND) with the option of pregnancy termination when they reached a stage in their life where starting a family was a core focus. In terms of reproductive history, nine participants had children and two were pregnant at the time of their interview (Table 20, p. 169).

Only one participant reported using pre-implantation genetic diagnosis (PGD) in an attempt to conceive a child without a *TP53* mutation, but was unable to complete a successful implantation of an embryo. Two participants reported using prenatal diagnosis (PND) to determine if their foetus was *TP53*+ve, and one terminated a pregnancy based the gene status of the foetus (Table 20, p. 169). Some considered adoption or surrogacy (n=2), or forgoing plans to have more children if they learned of LFS as a parent (n=5). A small number of participants described being opposed to PGD and/or PND for various reasons, and their experiences are described separately below.

Table 24. Reproductive decision-making: thematic and participant breakdown

Theme	Relevant participant subgroup
Reproductive agency	Young people without children (n=19)
	Young people who were pregnant at their interview (n=2)
Learning of LFS as a parent	Young people who were parents (n=9)
Considering the use of reproductive technology	Young people without children (n=19)
	Young people who were pregnant at their interview (n=2)
	Young people who were parents (n=9)
Gendered approaches to reproductive decision-making	Young people planning to have their first child or more children (n=22)

N refers to the size of the participant subgroup(s) each theme was developed from but does not correlate with the importance or rigour of theme development.

10.2.1 Reproductive agency for young people without children

The majority of the sample (n=19) occupied the early stages of emerging adulthood (mean age 22.5 years, range 18-29 years) and were yet to begin making plans to have children (Table 25, p. 220). Although this group were not yet making active choices about becoming or not becoming a parent, they were clearly already engaged with decisions about how they might theoretically go about having children in the future. A key aspect to their future plans was having to reconsider their reproductive agency—i.e., the power to act in accordance with their reproductive priorities and wishes (Bandura 2006)—and the choices they could reasonably make to avoid passing on their mutation in the context of LFS.

Nearly all participants in this group shared in the common narrative of wanting to prevent passing their mutation on to future children, and participants who had developed cancer held especially strong convictions (n=5). To them, knowingly having children at risk of LFS meant asking them to share in their experiences of cancer.

Knowing that I have LFS and then passing it on, like, that's asking my kid to go through what I went through. (Anna, 17, +ve, colon cancer)

There is no way in hell that I'm passing on this gene to anyone. I will do everything in my power to make sure that does not happen. So, you know, IVF and testing on the embryo before. That's my final decision at this point. (Jamie, 25, *de novo*, multiple cancers)

I wouldn't want to pass this on at all, if it starts with me I want it to end with me, definitely. (Sadie, 22, +ve, breast cancer)

Table 25. Reproductive history of participants organised by cancer status (n=30)

Characteristic	n	%	M	F	Mean age (range)
No children	19	63	9	10	22.5 (17-32)
Unaffected	14	47	7	7	23.4 (17-32)
Affected	5	17	2	3	20.0 (17-25)
Have children	9	30	1	8	31.0 (23-38)
Unaffected	4	13	1	3	26.2 (23-34)
Affected	5	17	0	5	34.8 (29-38)
Pregnant					
Unaffected	2	7	-	2	29.0 (24-34)

Abbreviations: M, male; F, female. Ages are in years.

Despite having strong beliefs about not passing on their mutation, participants recognised that deciding to have children who were not at risk of LFS meant forgoing the potential for normative child bearing. Many discussed their reproductive agency in terms of losing a future where they could simply 'just have kids' (Anna, 17, +ve, colon cancer), and having to consider alternative pathways for having children while being diagnosed with LFS.

It really worries me, like, with the future... my partner and I would love to have kids one day and not have to go through the whole IVF road or genetic testing, and just be able to have a baby normally. (Georgia, 22, +ve, unaffected)

As a group yet to begin their child bearing, there was core tension between aspiring to have children and the risk of dying young. Having children in the knowledge that they themselves might die young was considered irresponsible. Starting a family with high cancer risk therefore raised several existential issues for participants regarding their own life and the lives of their children. For Catherine (age 24), who was considering the use reproductive technology to start a family, the process of PGD seemed a futile exercise if she might not even survive long enough to have children; or if she did, she

may die when her children were still young, leaving the parental responsibilities to her surviving partner.

I thought to myself, 'the main reason that I would do [PGD] is in case I get sick and that I can't ovulate so I can't have children', but then I was like, 'if I get sick I'm going to die.' And even if I get better I will probably get sick again and have young children and then die. (Catherine, 24, +ve unaffected)

Georgia (age 22) also described a worry not only for her future children developing cancer, but also wanted to avoid her children growing up without her being there as a parent, thus repeating her family history:

I would love to have kids one day... and not have to worry that they could have cancer, or even that I could have cancer, like, I don't want my kids to grow up and not have a mum around, that's what happened with dad. (Georgia, 22, +ve, unaffected)

Melissa (age 20) described pregnancy itself as a risk to her own health. Thinking of ways to avoid increasing her breast cancer risk due to pregnancy, she considered alternatives like adoption and surrogacy to form her own family with her present as a parent.

I've also got to consider the risk to me because I know that breast [cancer] risk also goes up with pregnancy. So then obviously I would have to look at whether I want a surrogate or adopt or something like that. (Melissa, 20, +ve, unaffected)

The accounts above illustrate that a primary source of tension was weighing up aspirations for having children against potentially dying from cancer at a nascent stage of the family life cycle, thereby leaving their children with only one parent.

Although many participants were clearly engaged in thinking about having a family in the future, some felt major decision-making was thrust upon them before they were developmentally prepared. Exercising their reproductive agency seemed a way off in their future plans as having a family was not a core focus. Will (age 24), who was single at the time of his interview, described his reproductive decision-making as:

It's more of a thing that I might be worried about when I'm a bit older. Not at this age... Maybe when I'm starting to think about having a family and whatnot then I might start to think, like I don't want my kids to carry the gene or be at higher risk, so I'd probably start to think about it more then. (Will, 24, +ve, unaffected)

Sadie (age 22), who was in a long-term relationship at the time of her interview, spoke of waiting to have a child until she was financially and emotionally ready. Growing

up without a father due to LFS meant she was acutely aware of how sole parenting impacted family life. It was important for her to break the family cycle of not only LFS, but of poverty.

Sadie: Growing up without money I'm very money conscious. So, I would want to be prepared for anything, like, it's going to cost me, like, it's a lifelong thing having a kid... so I would wait until I am in a better position than I am in now, not paying off a house and not about to go through Uni [laugh].

Interviewer: and is that regardless of their gene status?

Sadie: yeah, regardless yeah. That is what I would have thought beforehand. I just don't want to bring up a kid that's not going to be in the most ideal situation. I don't want it to get brought up like I was and not have the money and have everything second-hand... I want to be in the best situation possible before I think about having kids. (Sadie, 22, +ve, breast cancer)

These two accounts indicate that irrespective of relationship status and cancer status, some participants in the early stages of emerging adulthood deferred reproductive decision-making to when they felt ready. This suggests that reproductive decisions, and the complexities that surround them in the context of LFS, may resurface at a future point in a young person's developmental trajectory.

10.2.1.1 Limited reproductive agency for participants with compromised fertility
Reproductive decision-making with LFS differed for those who developed cancer (n=5/19) and compared to those who were unaffected (n=14/19; Table 25, p. 220). While those unaffected by cancer possessed the agency to choose different pathways for starting a family (e.g., conceive naturally or use reproductive technology), participants with compromised fertility from cancer treatment spoke of a limited reproductive agency: 'I did have chemo in the middle of puberty, so that's probably not helping [with my fertility]' (Jamie, 25, *de novo*, multiple cancers). A striking example from the sample was Anna (age 17), who had her ovaries surgically removed after her colon cancer had metastasised at the age of 14. She was acutely aware of her inability to conceive her own biological children in the future and felt cancer had precluded her from a future that she had not yet even considered due to her age. Her personal knowledge of cancer was that it had dire implications for her reproductive agency.

I have a breakdown probably every two months [about it]. I was only 14 [when they removed my ovaries], it just kind of shut doors at 14 that I hadn't even opened. Like,

it just kind of said, 'you'll never have your own kids.' And at 14 you're not even thinking about kids... (Anna, 17, +ve, colon cancer)

In reference to her more complex and costly pathway to having her own children using reproductive technology, she described: 'I didn't choose to lose my ovaries, but then I have to pay to make up for it... that frustrates me. Just because I'm not normal, why do I have to pay extra? Normal people get their own [children] for free!' (Anna, 17, +ve, colon cancer). Despite her disappointment at being different to 'normal people' who could conceive naturally, she also described being 'thankful' at not having to grapple with the ethical complexities of conceiving naturally with LFS and risk giving birth to a child with her mutation.

I'm kind of thankful in a way that the decision [to conceive naturally] is gone from me, like I don't have to decide to take the risk and possibly give it to my kid, it just stops at me, it doesn't go on. (Anna, 17, +ve, colon cancer)

Being 'thankful' that the decision was taken from her was in direct tension with the sense of unfairness around her reproductive choices compared to her peers, which reveals a cognitive dissonance about reproductive decision-making well before she may even be at the life stage to seriously consider starting a family.

Similarly, Sophie (age 19) was also aware of her potentially compromised fertility due to her cancer treatment. She described that while starting a family was a future concern, adoption was her preferred option: 'I haven't really thought about [having children] because I'm not really there yet or anything. But I've always wanted to adopt so I've never... I don't know. I've always wanted to help other young kids that aren't able to be [cared for]' (Sophie, 19, +ve, orbital osteosarcoma). While it is unclear whether Sophie preferred adoption because of LFS—i.e., in order to prevent the passage of her *TP53* mutation, or that it was potentially her most viable option for starting a family in the face of limited fertility—her reproductive decision-making illustrates that young people find different ways to navigate these difficulties depending on a range of social factors, personal values, and life experiences.

10.2.2 Learning of LFS as a parent

In contrast to participants who were yet to have children, there were eight parents in the sample who learned of LFS after having children. Specifically, there were four parents who learned of their mutations status after undergoing diagnostic testing to determine the cause of their cancer; three unaffected parents who had a *TP53* mutation; and, one

unaffected parent who was at 50% risk and planning to undergo predictive testing. For these eight participants, learning of LFS had serious and immediate implications for their young children. It signalled a change in their knowing of LFS as cancer was no longer a risk to their own health, it was a risk to their children and current way of life.

When I had cancer, it was about me. But when you find out about Li-Fraumeni, it was about the children [...] The stress that we actually experienced in our family... we couldn't really talk much. Even my husband and I, we were both just terrified. Literally terrified. (Ashley, 34, +ve, breast cancer)

All parents expressed regret at not knowing their gene status before they had children. If they had known, they stated they would have gone about starting their family differently.

I might not have had two kids if I had known that information. They wouldn't be here. I would have been scared shitless the whole time, I most likely would have had IVF instead of getting pregnant naturally (Carolyn, 34, +ve, unaffected)

Josh (age 23), unaffected and untested at the time of his interview, found it difficult to contemplate potentially being mutation positive and what this meant for his two young daughters. Despite being uncertain of his own gene status, the guilt of potentially implicating his young family was a self-destroying: '...it would [pause] full destroy ya if your kid got cancer and you knew you had a part of it' (Josh, 23, 50% risk, unaffected).

Realising that it was too late to prevent passing on their mutation, the seven parents who were mutation positive were universally concerned for their children and placed their efforts for risk management in predictive testing and accessing paediatric screening for LFS (if available). Four parents had tested their children at the time of the interview, all of whom were found to be negative. All described experiences of pure elation when learning of their children's negative gene status, underscoring the extreme stress parents experienced once learning of the implications of their gene status for family.

When I got the phone call, I screamed [laugh], I was crying, I was screaming and my mum was there and I just said 'they don't have it!', and she started crying and the kids were like, 'what's going on?' [laugh], so it was the best news I've ever heard. Best day. (Harriet, 25, +ve, unaffected)

For most parents, the distress of learning about their gene status and the implications for their young children was reason enough to avoid having more children entirely. After learning of her children's negative gene status, Ashley (age 34) was not 'going to push [her] luck' with having any more children naturally because it would be

testing fate. Knowingly conceiving more children at risk of LFS was considered irresponsible and 'selfish'.

I'm lucky enough to have two negative children, I'm not really going to push that luck, I think that's enough. Because in order for me to have another child at that point, I would have to have it genetically selected. I wouldn't go through a natural pregnancy because I wouldn't risk that for the children, it's not fair with them. If you don't know [about your gene status] it's different, but if you do know, and you still move forward... in my opinion, I don't accept that. I think it's selfish for the parents. (Ashley, 34, +ve, breast cancer)

[Having more children] would be stupid. I don't even understand why people who have had cancer before would have children again. Like, I don't understand that, I really don't. I think that's stupid [...] I think it's selfish. I think I'm lucky with who I've got now and that's enough. (Emily, 36, +ve, breast cancer)

Similarly, Carolyn (age 34) described that if she were to have more children, it would require a lot more consideration than her first two pregnancies.

It's not going to be just a natural thing that you do if we do decide to have kids again. You know, it's going to be IVF or... Because for us, there wouldn't be any situation where we would not test for this now that we understand the implications for a child... (Carolyn, 34, +ve, unaffected)

In contrast, Olivia (age 23), the youngest mother in the sample, hoped to have more children. Her aspirations, however, were severely complicated by her gene status: 'I don't want to risk it but I still want more kids [...] I've always wanted heaps of kids and it's just hard, I'm not ready to not have more kids ... but if I have more kids and they had the cancer gene, it's going to be a lot harder' (Olivia, 23, +ve, unaffected). Her role as a responsible parent who ensured the health of her future children was in direct tension with her identity as a future mother of many. She was confronted with the collision of her risky self and her maternal self.

Navigating this tension was difficult for Olivia and a key barrier to actively planning for more children was the outcome of testing for her current children. If they did not both test negative, or she did not test them at all, Olivia was hesitant to use PGD for future pregnancies because it would highlight a difference in how she cared for her family.

...if I was to get [my children] tested and they both came back negative, then I would feel like I could do that IVF where I could get the gene removed [...] but then if I

didn't get the boys tested and I got to remove this kid's cancer gene and I didn't do it for the other two, when I could have found out earlier... it's hard! (Olivia, 23, +ve, unaffected)

Olivia's reproductive agency with LFS was limited to her future children and not her current family. A situation where her children had mixed outcomes with genetic testing was problematic, especially because her plans for having more children were still emerging and uncertain: 'I don't want them to feel like, "why did you care about that kid more than you cared about me?" Even though it's something we might not even do' (Olivia, 23, +ve, unaffected). The mere availability of reproductive technology exerted a pressure on her to do the 'right thing' for her future children and yet highlighted that she did not, or could not, do the 'right thing' for her current children.

10.2.3 Considering the use of reproductive technology

Reproductive decision-making for all participants, either for their first child or for more children, was a complicated endeavour for young people in the context of LFS. Many placed their hopes in using reproductive technology to have their own LFS-free, biological family. Contemplating the use of PGD or PND, however, introduced new kinds of moral responsibility and existential issues around reproductive decision-making that many participants had not previously considered.

Carolyn (age 34), who learned of her gene status after having children, felt that if she were to have any more children, she would use PGD. This, however, forced her to reflect on the potentiality of children with a mutation and the ethics surrounding the selection of embryos based on *TP53* gene status.

But there's a whole lot of other ethical things that come with [selecting embryos] as well. If you go through IVF and you have one [embryo] that has the mutation and one that doesn't, what if the one that doesn't [have it] is a raging asshole or whatever, or is Donald Trump when it grows up? And the other one is actually a really cool person and they figure out some amazing gene therapy that sorts this out in 10 years, like, it makes every decision that you make so much heavier around those big developmental and life things. (Carolyn, 34, +ve, unaffected)

Having to consider the kind of life of future children may have beyond their gene status made reproductive decision-making with LFS a much 'heavier' process compared to having a family with natural conception. This heaviness is centred on making the 'right' reproductive choice and the semblance of control PGD provides in ensuring the health of a child. Having to make a choice at all exposes one to making the wrong choice and

being subject to blame from others, which is not the case with natural conception, as we accept having much less control over the health of a child.

Sam (age 28), whose father, uncles and cousin had developed or died from LFS-related cancer, also grappled with existential issues when thinking of starting a family. Despite his familial knowing of LFS, he found it difficult to ascribe meaning to his own at-risk status and could not justifiably decide against having children because of LFS.

I knew from the start that [LFS] never would affect my attitude towards having kids for the same reason that it's sort of doesn't... that I can't really draw a conclusion about what to think [about LFS], because it is so uncertain how it will pan out in my life and what impact that it has. I don't think it would really be right to say, 'because of this I don't think I want to have children.' (Sam, 28, +ve, unaffected)

The uncertainty surrounding the implications of LFS for himself in terms of penetrance and phenotype meant he resisted LFS being a theme of his own life, and he rejected it as a theme for his future children's lives.

I want [LFS] to be something that I'm aware of but I don't want to be ruled by it when raising a child. I don't want it to be a death sentence for them, I don't want it to be the theme of my children's life, should they have the gene or not. I want them to be aware of it just for the same reason that I want to be aware of my own [gene status]. (Sam, 28, +ve, unaffected)

Another source of tension for family formation with reproductive technology described by participants was negotiating the views of their partners. Many participants in relationships reported that their partners instinctively considered that having a child without a *TP53* mutation was the best option. This prompted a tension for young people who identified with future children based on their gene status. The proposition of discarding affected embryos during the process of PGD struck a chord with Georgia (age 23), who related strongly to once being an affected embryo herself. The act of selecting *TP53*-ve embryos for her own family meant undermining her own identity and sense of self as an individual with a *TP53* mutation. To so willingly discard 'affected' embryos would devalue the life she had lived so far and promote that a life with LFS was a life not worth living. This raised an existential awareness she had not previously considered, and one that she felt her partner did not understand.

[My partner] doesn't want our kids to carry that gene. I think it worries him, it scares him and his opinion is that he just wants to stop it. He doesn't want to have that mutation anymore... But at the same time, like, I've had to explain to him, I am one

of those kids. Mum and dad didn't know that I had the gene, and would you get rid of me sort of thing? (Georgia, 22, +ve, unaffected)

Despite being acutely aware of the implications of LFS, having witnessed close family members develop and die from cancer, Sam and Georgia were clearly hesitant to use reproductive technology to start a family. This starkly contrasts the views of participants who had developed cancer, and were strongly against passing on their mutation because it risked their future children developing cancers like their own, therefore repeating the personal and/or family history. Perhaps Sam and Georgia identified more strongly with being 'at-risk' of cancer versus being a cancer patient. Based on their own cancer-free experiences to date, it was hard to contemplate preventing a life 'like theirs' from coming about. If they felt their own life was worth living, and they identified with future children with LFS, then they could not justifiably select against a future life like their own.

10.2.3.1 Pre-implantation genetic diagnosis

Despite the majority of young people stating that PGD was their preferred approach to start a family, they had limited knowledge of the logistics of PGD in terms of cost and process.

Interviewer: what do you understand of the process of IVF? In terms of the costs and how long it takes and that kind of stuff?

Olivia: I have no idea about it, I just know that there is that option there.

(Olivia, 24, +ve, unaffected)

Interviewer: if you were to go about planning to use IVF and planning a family in the future, what would you do? How would you go about it?

Jamie: I have no idea, I haven't thought that far ahead [chuckle].

(Jamie, 25, *de novo*, multiple cancers)

Catherine (age 24) was one of few participants to have demonstrated not only a willingness to use PGD and an understanding of how it worked, but also an appreciation of the complex logistics it entailed. The excerpts below describe her decision-making process for wanting to use PGD; however, it is important to note that due the perceived burdens of pursuing this option, she never went ahead with IVF or PGD.

After learning of her gene status, Catherine felt that starting a family had suddenly become an immediate concern, and this it was no longer a simple, carefree

process, it had become complicated. Indeed, Catherine recalled being overwhelmed with logistical decisions about starting a family and PGD well before she was thinking of having children with her current partner. Having to decide about how best go about PGD was 'a bit too much' at the current stage of her relationship.

I do think that he would be the person that I stay with and I feel like that's reciprocated but... we're not, like, thinking about getting married, we're not thinking about having children, that's just not something that we've really talked about before, and then all of a sudden, we were trying to make a decision surrounding [PGD] and it was just a bit, I don't know [laugh] a bit much. A bit too much.
(Catherine, 24, +ve, unaffected)

Realising that embryos had a better chance of successful implantation compared to frozen eggs, Catherine and her partner considered freezing embryos for future use. Deciding to freeze embryos as a couple instead of Catherine freezing her eggs alone, however, would mean her partner was inextricably linked to her future plans for having a family at an early stage in their relationship. The logistics of freezing embryos to start a family in the future underscored the temporality of romantic relationships during emerging adulthood. Emerging adulthood is a life stage of exploration and it is commonplace for young people to experiment with different romantic partners. Thinking about destroying embryos if they ended their relationship was a 'pretty heavy' consideration. It would symbolise a complete and utter severance of their togetherness in a way that is uncommon to romantic experimentation in emerging adulthood.

My boyfriend and I were making that decision together because for IVF the rates of successful implementation are much better for an embryo, so that would require his fertilisation of the egg. Which is quite serious, especially because, well it's not something that's going to be happening in the near future, and I think both of us realise that if we were to break up in the future, especially if it was his decision to break up with me, then the embryos would have to be destroyed or whatever, and that would be pretty heavy [laugh]. (Catherine, 24, +ve, unaffected)

If for whatever reason their relationship broke down, having to think about what to do with frozen embryos was an added and unwanted complexity. The joint decision to seek out information for embryo storage underscored the high level of cohesion in their relationship. Despite this, it was unclear what would happen if their goals became divergent in the future. Catherine felt the implications of a break up could be 'devastating' for her on a 'fertility level'. She would either have to start all over again with a new partner, or take control of the frozen embryos for future use on her own. At the

same time, however, she did not want her partner to feel pressured to maintain the relationship if he wanted to leave.

[There's] just a bit too much pressure for him as well, because if in the future he chooses to end the relationship, he would be very cognisant of the fact that it would be really quite devastating for me on a fertility level [laugh]. Aside from obviously, I would be very sad that that was happening [laugh], but it would be much harder for him I think too. I don't know, it would just add an extra level of complexity that I would rather avoid. (Catherine, 24, +ve, unaffected)

The role of young partners, and the perceived pressure on them to forgo typical options to start a family, was also clear in other accounts. LFS not only implicated young people's plans for family, but it necessarily implicated their current partner. Amelia (age 32) described having to talk her partner around to the idea of PGD. While feeling it was unfair on him at times, she was assertive about her decision to consider PGD.

[Thinking about PGD] is not necessarily unfair on me, but I feel like it's unfair on [my partner] sometimes. I don't know, because he did get quite upset about it [...] He's always wanted to just [have children] the natural way but he understands why I want to do it this way. It was hard for him to get his head around it in the beginning, but... [PGD] is the way I want to do it, so I'm not going to budge [laugh].

(Amelia, 32, +ve, unaffected)

The overwhelming logistical considerations of PGD at a fledgling time in Catherine's relationship meant that ultimately, she chose to exercise her reproductive agency by using PND and consider termination of pregnancy. Although she was acutely wary of the anticipated difficulties in going ahead with this approach, she felt it bought her some more time to think about having a family without the stress of planning for PGD.

I'm obviously not going to know how I feel about [pregnancy termination] until I'm in the situation, but I don't have any strong beliefs against termination, so I'm happy to do [use PND] instead. Because IVF has been sort of weighing on my mind a fair bit and it's just a lot of mucking around and if I could get pregnant naturally and then have a baby without the gene first up, then that would be great.

(Catherine, 24, +ve, unaffected)

To realise she had more options than she had originally appreciated in terms of starting a family with LFS was a weight off her mind. Exercising her choices was part of appraising

different options for reproductive agency with LFS, and indicates that navigating these options at a young age is a process, not a one-off decision.

In my mind I was sort of thinking that IVF and preimplantation diagnosis was sort of my only option. But I feel like a lot of people go down the IVF route because they have no other choice since... so maybe I do have another choice. I think, at least at the moment, I feel better about doing the foetal sampling and sort of managing it that way. (Catherine, 24, +ve, unaffected)

Lara (age 34) also tried different reproductive options, and was the only participant to have used PGD in an attempt to have a child without a *TP53* mutation. After three unsuccessful rounds of PGD, however, she decided to try and conceive naturally and test her child predictively as an infant. Pregnant during her interview, she described:

[PGD] didn't work for us, so we've actually ended up having our kid naturally. So, I have a risk that I'll pass it on, I've got a 50% chance that I'll pass it onto the child that I'm carrying. [We will] be considering genetic testing and what we will need to do once the child comes into the world [...] but it's more of a process for me, if the child has [the mutation], then we will be doing routine scans, you know, it becomes part of that life, it triggers what actions need to be taken and precautions and steps.

(Lara, 34, +ve, breast cancer)

The decision-making process for Lara to stop using PGD was spurred on by finding out her fertility had not been affected by her breast cancer treatment. At this point, and after having tried a few cycles of PGD, deciding to go any further with PGD butted up against the now feasible alternative of trying to conceive a child naturally.

[PGD] is a pretty amazing thing, but it just didn't work for us... We had to make that call on how many times we do it and then where do we draw the line? Because you could go forever and some people do, obviously. And when all the testing came in that my fertility hadn't been affected [from my cancer treatment], we were like, 'do we keep going? Or do we stop and try naturally and see how we go?'

(Lara, 34, +ve, breast cancer)

Lara's approach was unlike other women in the sample who conceived naturally (Kirsty, age 38 and Tasha, age 24), who chose to use of PND and possible pregnancy termination to avoid having children at risk of LFS. Lara was content with testing her child predictively after birth and enrolling them in paediatric cancer surveillance if necessary. This was perhaps because she generally perceived LFS to be a manageable

condition, which in her personal experience, it was. Being the first in her family to develop cancer and being ‘pretty lucky’ throughout treatment—with limited time off work and minimal physical side-effects—she experienced LFS as being manageable: ‘I literally would go to chemo on the Friday and then go to the pub afterwards, I didn’t get sick’ (Lara, 34, +ve, breast cancer). Ben (age 23) shared a similar view. Though he was aware that ‘some people might consider it a bit greedy to have kids [naturally] anyway’ (Ben, 23, +ve, unaffected), he was comfortable with the option of predictive testing and paediatric screening, mainly because this was his own experience of LFS and was unaffected to date. Ben and Lara were the only two participants in the sample who chose or planned to conceive a child naturally and risk them having a *TP53* mutation.

Lara’s experience of using PGD and then changing her mind to have a child naturally and rely on paediatric cancer surveillance is similar to Catherine’s experience; i.e., planning to use PGD and then switching to PND. Although they settled on different reproductive decisions, their shifting preferences exemplify the same phenomenon: deciding how to start family with LFS was not a static, set in stone decision for young people. The accounts above illustrate that young people could contemplate and attempt one approach of reproductive action before changing to another, or relinquishing reproductive agency all together in favour of managing LFS with paediatric screening.

10.2.3.2 Prenatal diagnosis and termination of pregnancy

Only two participants in the sample had used PND to determine the *TP53* gene status of their foetus, though they differed in how they considered PND. From the outset, Kirsty (age 38) chose to navigate having a family with LFS by conceiving naturally and using PND to determine if the foetus had her *TP53* mutation. Whereas Tasha (age 24) had an unplanned pregnancy, and while she would have preferred to use PGD, she felt forced to consider the alternative of PND to prevent the birth of a child with her mutation. For both women, using PND necessarily involved considering termination of the pregnancy if the foetus was found to be *TP53*+ve, which eventuated for Kirsty’s second pregnancy: ‘I did have a termination when I was younger because my second pregnancy was positive for Li-Fraumeni’ (Kirsty, 38, +ve, multiple cancers).

Kirsty was the only participant to terminate a pregnancy based on the gene status of her foetus. Having lived through several cancer diagnoses since her early 20s, she was strongly opposed to having children at risk of LFS. Despite being resolved to prenatally test her foetus for her *TP53* mutation, talking about her decision to terminate her second pregnancy was difficult during the interview.

Me and my husband spoke with the counsellors and you know, we spoke with each other, and... It was really hard I can remember. Yeah it was just, my biggest thing was that I just didn't want [LFS] to go any further. I just felt... it was my part [crying] sorry, I'm getting a bit upset about it [crying]. It was my part, I just didn't want to pass it on. I don't think I could live with that, watching my kid go through... you know, even worse than what I've had to deal with. Because there's just so many cancers... that was, yeah, that was our decision in the end for [terminating the pregnancy]. (Kirsty, 38, +ve, multiple cancers)

Having tested all three of her children in utero, Kirsty had experienced the process of amniocentesis many times and described it as 'horrible'. Having to wait until 12 weeks before testing the foetus and then having to wait for the results was especially stressful; however, the alternative, using PGD, was too expensive and inaccessible for Kirsty. Admitting that she had not looked at the option of PGD in depth, she described:

I don't know if they even did [PGD] in [home town] at that particular time, I know they do a lot now, but I think we had to go over to [another state] or somewhere... I didn't fully look into it but it probably came down to the amount of money, it was going to cost [a lot]. (Kirsty, 38, +ve, multiple cancers)

It was important for Kirsty to distance herself from the termination of her second pregnancy: 'I never found out with the second [pregnancy] whether it was a boy or a girl, I yeah... They've got that on record but I didn't want to know' (Kirsty, 38, +ve, multiple cancers). By managing her expectations of grief and choosing not to learn the sex of the foetus, she was able to remain, in a limited way, emotionally detached from an emotionally charged and burdensome experience.

In contrast, Tasha (age 24) became pregnant unexpectedly and had not planned to use PND in the same premediated fashion as Kirsty. She also held strong views about not having a child with LFS:

Why should I turn around and say to my child, 'I brought you into this world because I wanted you here, because I love you, but your health and wellbeing didn't matter enough to me to stop you coming into this world if it was going to be like this [with LFS].' (Tasha, 24, +ve, unaffected)

Because her pregnancy was unexpected, she was faced with the exact situation she vehemently opposed: knowingly bringing a child into the world at risk of LFS. The only form of agency left to her in order to prevent passing on her *TP53* mutation was to use

PND and consider termination of her pregnancy, which was an option she was ready to pursue.

I said to the baby's father when it all, you know, came to pass that I was pregnant, I said, look 'if this baby has the gene, I will terminate.' [...] I didn't want to bring a child into the world that may not even have as much life as I've had already. And that would be just purely my fault, my selfishness that I wanted a child and I brought it into the world knowing that there was something wrong with it.

(Tasha, 24, +ve, unaffected)

Tasha was fully aware that exercising her reproductive agency at this stage would entail pregnancy termination and, similar to Kirsty, for self-protection she described not allowing herself to become emotionally attached to the foetus.

When I found out I was pregnant I made sure I had no connection with the child until I knew that the child was LFS-free [...] I think [my partner] felt more of a connection than I did for a long time because I wouldn't allow myself to feel anything [...] And that's just so that if I did have to terminate then I wouldn't have a... mental.... not mental breakdown, but you know, I wouldn't actually affect myself any more than I already had. (Tasha, 24, +ve, unaffected)

Reflecting on the process of her forced emotional detachment, Tasha described wanting to prevent passing on her mutation as something she had prepared for since learning of her gene status at age 22. Although her pregnancy was unexpected, her choice of using PND and her willingness to terminate was not: 'I know you probably expect someone to say it was hard... But for me, it wasn't. It was something that I'd always knew that I had to do as soon as I got my [genetic] diagnosis. I always knew that [preventing the passage of my mutation] was something that I wanted to do, when I had my own children' (Tasha, 24, +ve, unaffected). It was only when she learned that the foetus was *TP53*-ve that she allowed herself to become emotionally attached and experience motherhood. This event immediately signalled a change in language when referring to the foetus, from 'it' to 'she'; the personification of her foetus heralded the first steps to recognising she would be a mother: 'when they told me that *she* was healthy, that I think that's when all the emotion set in because I allowed myself to feel something' (Tasha, 24, +ve, unaffected).

In comparison to Kirsty and Tasha's views regarding PND and pregnancy termination, some participants described being reticent to consider these options. Amelia (age 32) believed that if she had an unplanned pregnancy, she would be unable to

go through with PND and possible termination of her pregnancy. For this reason, she focussed heavily on PGD to start a family with LFS.

I know in myself that if I got pregnant naturally and then we did the genetic testing, which is possible before the 12 weeks, then I would have to make the decision to keep going or to abort. And I wouldn't be able to do that, mentally, it's not a decision [I could make]. (Amelia, 32, +ve, unaffected)

Sam (age 28) was the only male in the sample to describe his stance on PND and outlined that he had strong convictions against terminating a pregnancy based on the gene status of a foetus.

In terms of terminating a pregnancy, that, I probably would never do. Just purely on the fact that they had the same gene that I have. Because I look at the life that I've had and there's been so much positive stuff, so you can't throw away all that, just for the, you know, a slightly, maybe not slightly, I don't know how severely increased my chances are, I know that I have x amount of chance by a certain age, what chance do other people have? I'm not sure. (Sam, 28, +ve, unaffected)

Importantly, despite having witnessed several family members develop and die from LFS-related cancer, Sam was unaffected. Looking back at his own experiences, he felt that he was living proof that life with LFS was a life worth living, and in that knowledge, he would not consciously terminate a pregnancy based on *TP53* gene status.

The key difference between participants who used PND with termination of pregnancy was the level of uncertainty they ascribed to living with a *TP53* mutation. On one hand, both Kirsty and Tasha were certain that a life with a *TP53* mutation meant developing and dying from cancer at a young age, and for this reason, they were prepared to prevent that kind of future for their children. Amelia held a similar view, but was uncertain whether her convictions to not have a child at risk of LFS would hold under the intensity and burden of considering the termination of a pregnancy. While on the other hand, Sam felt that, based on his own experiences of being unaffected, having a *TP53* mutation did not prescribe a future ridden with cancer. In this way, he was uncertain if his future children would ever develop, let alone die from cancer; therefore, he could not justify termination of pregnancy based on gene status.

10.2.4 Gendered approaches to reproductive decision-making

It was evident that participants across the sample approached reproductive decision-making with LFS differently based on their gender. Young women took on the primary responsibility for reproductive decision-making and considered the implications of LFS

in more depth than young men. Of the 22 participants⁵ who were planning to have children or more children in the sample, 63% (n=14/22) named a preferred pathway for reproduction to have child without LFS. The overwhelming majority of this subgroup were female (86%, n=12/14), and some had either attempted these options or considered them in detail. In contrast, most young men (n=7/9)² were unable to nominate a preferred pathway, and had limited knowledge of reproductive technology and options for having children without a *TP53* mutation (Table 26, p. 237).

Young men's limited understanding of ways to have children without LFS may have been due them being, on average, younger than the female portion of the sample (mean age 22.8 years for males vs. 26.8 years for females). This may mean that as a group, males were less likely to be at the life stage where having children was core focus. For example, Sean (50% risk, unaffected) and Tom (*de novo*, Burkitt's lymphoma), both aged 17, were perhaps unaware of the reproductive options available to them because they were in late adolescence. In contrast, however, despite being the same age, Anna (age 17) had an in-depth knowledge of her reproductive options. Speaking of her inability to have her own children due to the surgical removal of her ovaries at age 14 for cancer treatment, she clearly demonstrated a more advanced understanding of reproductive decision-making compared to Sean and Tom: 'I still have a uterus, so I know that I can do IVF, like, donor eggs, like my sisters' eggs, or like adoption and all that' (Anna, 17, +ve, colon cancer). Another differentiating factor could be that Anna's cancer had direct implications for her fertility, meaning she was primed to think of reproduction at that

⁵ Eight participants were excluded from this analysis because n=5 females had completed their family, n=1 male did not intend to have a family; n=2 females were not explicitly asked about reproduction in their interview.

Table 26. Young men's understanding of reproductive technology (n=9)

Participant	Excerpt
Sean, 17, 50% risk, unaffected	Sean: If I do have [a mutation] I would still probably have kids... Interviewer: Do you think you would look into ways to maybe make sure they don't get the mutation or the gene change? Sean: Um, probably when it comes around, yeah.
Tom, 17, <i>de novo</i> , Burkitt's lymphoma	Interviewer: Are you aware of any ways that you can make sure that [having children with a <i>TP53</i> mutation] doesn't happen? Tom: Nup.
Felix, 20, +ve, unaffected	Interviewer: Are you aware of any ways of not passing on the gene to your children? Felix: Nup.
Ben, 23, +ve, unaffected	Interviewer: are you aware of any ways you can avoid passing on the mutation to your children? Ben: Not as far as I'm aware.
Will, 24, +ve, unaffected	Interviewer: Has anyone told you here at the familial cancer centre what you can do to have children without the gene mutation? Will: Um, na.
Josh, 23, 50% risk, unaffected	Interviewer: Are you aware of any ways to have a child without the gene mutation? Josh: [pause] Nup.
Justin, 22, 50% risk, unaffected	[The genetic counsellor] said that there is also the possibility that if I was positive that something to do with IVF and you can actually take the gene out I think. Is that a thing?
Jamie, 25, 17, <i>de novo</i> , multiple cancers	Interviewer: Do you think you'll have a family in the future, of your own? Jamie: I have thought about that. And at this stage it would have to be through IVF [...] I know that is pretty damn expensive, but my understanding is that it's more than possible to fertilise the egg outside the womb and test [the embryo] without harming it.
Sam, 28, +ve, unaffected	[IVF] gives you a really high chance of having twins, I've heard, or triplets. Disproportionately large chance. And it is not highly successful, at least I know of some people that have gone in for multiple rounds before actually becoming pregnant. And I think what they do is they inseminate a number of eggs and implant them, which is part of why the chances of having twins or multiple pregnancies is much higher.

Note that this table does not include the full male sample (n=9/10). Adam (age 29) shared that because he was gay, he approached family formation differently; his perspectives are shared separately.

age, whereas Tom's cancer had a yet unknown impact on his fertility, and Sean was untested and had not developed cancer.

The male portion of the sample was also more heterogeneous than the female portion. By virtue of the recruitment process, the only participants to have not been genetically tested were all young men (n=4, age range 17-29 years). This raises another point of difference that may have impacted their reproductive decision-making and the three young men who had not accessed pre-test genetic counselling (Sean, age 17; Justin, age 22; and Josh, age 23) clearly possessed information needs regarding reproductive decision-making if they were found to be mutation positive (Table 26, p. 237). Or, if they had been provided any information, perhaps it was presented differently to them compared to young women.

Adam (age 29), the only other participant who was yet to learn his gene status, was awaiting his results at the time of his interview. His perspective on having a family with LFS was entirely different from other participants in the sample because of his sexual orientation: over the course of his interview, he intimated that he was gay. Even before considering his gene status, Adam felt as though he would go through life without children. In this way, being *TP53*+ve did not impinge on his already self-described 'biological' limitations to family formation.

I guess with me, with children, it's just hard because I have considerations like, what does my family look like? Like, I'm obviously not going to have sex with a female [chuckle], that's not what's going to happen. So, I guess the reason why I approach life where I probably just won't have children is because biologically my relationships don't lead that way. (Adam, 29, 50% risk, unaffected)

In contrast to other young men in the sample, Jamie (25, *de novo*, multiple cancers) and Sam (28, +ve, unaffected) demonstrated an in depth understanding of reproductive technology. For Jamie, similar to Anna above, his multiple experiences of cancer meant he was primed to consider his potentially limited fertility due to treatment at a young age. He was therefore acutely aware that PGD was the ideal way for him to have children of his own in the future without LFS. For Sam, one of the oldest males in the sample, and with a long-term partner, his general knowledge of IVF and interest in science meant he understood the complexity of the process (Table 26, p. 237). Yet, like many young men, irrespective of their relationship status, he deferred starting a family until a time when he was ready.

[Having a family] is far from a topic of conversation at this point in time. But we're both fairly on the same page in terms of children, it's like: 'sure, if we stay together for long enough, yep, one day.' But not in the next say five years or so [laugh].

(Sam, 28, +ve, unaffected)

Felix (age 20), single at the time of his interview, spoke of a future 'we' when thinking about the implications of being *TP53*+ve and his reproductive decision-making: 'If I have kids, they'll have a chance of having this, but yeah, it's something that we'll have to talk about and figure out I guess when it comes to that, I don't know' (Felix, 20, +ve, unaffected). In this way, young men did not perceive themselves as the primary, or only, decision-maker regarding their own reproductive agency.

10.3 Discussion

These findings are the first to document reproductive decision-making of young people from families with LFS in-depth. Importantly, they begin to address a need voiced by other authors in the field, who have called for further attention to be focussed on reproductive decision-making among young people in the LFS population (Schultz et al. 2018; Alderfer et al. 2017). This brief discussion focusses on placing these findings in the context of other research on reproductive decision-making for individuals with an inherited predisposition to cancer. It also comments on the developmental readiness of young people to consider and exercise their reproductive agency in the context of LFS.

10.3.1 Sick parents looking after sick children: a shift in the family life cycle

All young people in the sample felt that LFS impacted their reproductive decision-making, either for their first child or for more children; almost all stated they wanted to prevent passing on their *TP53* mutation to the next generation, though a small number grappled with the ethical implications of using reproductive technology. This is similar to previous research with young women (aged 18-45 years) with a *BRCA1/2* mutation, where the perceived severity of HBOC influenced thoughts about passing the mutation to children, and willingness to consider reproductive options to achieve this (Ormondroyd et al. 2012). The tensions and uncertainty around having biological children in the context of LFS are similar to HBOC more generally, and centre on having children with increased cancer risk while also being at increased risk as a parent (Donnelly et al. 2013; Ormondroyd et al. 2012).

A major point of difference for LFS compared to other inherited cancer conditions is the early age of cancer onset. This manifests in many ways across how young people know, understand and perceive LFS, but has profound implications for their family life cycle. The pattern of cancer risk for young people with LFS shifts forward in the family life cycle and simultaneously affects the young person and their child. This means that for a young person with LFS, not only is their future self at high risk of cancer, which is common to adult onset genetic conditions, but their present self is also at high risk of multiple, largely unpreventable cancers at the same time as their current/future children. In comparison, a young parent with HBOC or Lynch syndrome may not yet have reached the age where their largely preventable cancer risk has increased to a level to warrant cancer surveillance (e.g., at 30 years for breast cancer surveillance for HBOC) or prophylactic measures (e.g., a BPM), and their child, even if born with a gene mutation, would not yet be at high risk until adulthood.

Living with high cancer risk from birth makes reproductive decision-making with LFS potentially highly distressing for young people, especially for parents who have been newly diagnosed with an LFS-related cancer. Thoughts and concerns about who will look after children if the young parent dies from cancer, and who will look after sick children while the young parent is sick highlight the simultaneous intergenerational impact of LFS. Many participants avoided, or were not yet at the life stage to think that far into the future, whereas some made plans to use or used reproductive technology to at least spare their children of LFS, while others felt that the variable penetrance of a *TP53* mutation was worth trying to conceive naturally. These thought processes merit specific attention during genetic counselling, as they are intensified in the context of LFS unlike other inherited cancer conditions. All options for reproductive decision-making should be explored and discussed in an age appropriate manner.

10.3.2 Identifying with *TP53*+ve embryos

PGD was the preferred option for the majority of participants, but similar to previous work that showed some young women with a *BRCA1/2* mutation have concerns about selecting embryos (Ormondroyd et al. 2012; Quinn et al. 2012), two participants found it difficult to discard embryos that were *TP53*+ve. The main reason being that *TP53*+ve embryos resembled themselves and their affected family members. Importantly, these participants had not developed cancer, and perhaps the lack of personal experience with cancer meant they identified more strongly with being 'at-risk' versus being a cancer patient. Based on their own cancer-free experiences to date, it was hard to contemplate

preventing a life like theirs from coming about. If they felt their own life was worth living, and they identified with future children with LFS, then they could not justifiably select against a future life like theirs.

10.3.3 Willingness to use PND as a surrogate marker for the severity of LFS

Despite not attempting to quantify the decisions of participants, it is worth noting that the uptake of PND across the current sample is similar to a recent national Dutch audit of PND uptake for inherited cancer syndromes (LFS, VHL, RB, FAP, and HBOC) (Dommering et al. 2017). Out of a total 26 different families with LFS represented in this study, two participants had performed PND (7.7%, $n=2/26$) a total of 5 times combined. Similarly, the Dutch study showed that two couples among 41 families with LFS (4.9%, $n=2/41$) had used PND a total of 5 times (Dommering et al. 2017). More generally, PND uptake for LFS in this sample is also comparable to the proportion PNDs among Dutch families with VHL (6.5%, $n=6/92$) but less than families with retinoblastoma (11.8%, $n=22/187$), suggesting the willingness to use PND may act as a surrogate marker for the severity of disease (Dommering et al. 2017).

Similar to research with young women with a *BRCA1/2* mutation, reproductive decision-making was also impacted by personal/familial experiences of cancer (Donnelly et al. 2013). The two participants who used PND in this sample both had considerable personal and/or family histories of cancer and perceived LFS to be a severe condition. In contrast, the two participants who described wanting to conceive naturally and risk having children with a *TP53* mutation perceived LFS to be manageable based on their personal and family histories of cancer. The intersection with personal and familial experience of cancer and attitudes towards PGD and PND for LFS warrants further investigation in Australia. Ideally this would be supplemented with a systematic audit of clinically available uptake rates for both technologies.

10.3.4 The new genetics and gendered reproductive decision-making

As outlined in the previous chapter, the new genetics movement constructs individuals as not only responsible for their own health but also the health of others (Hallowell 1999). The majority of participants ($n=19/30$) were yet to make any concrete reproductive decisions; consequently, their responsibility to others came in the form of considering appropriate reproductive decisions in the future. They felt personally charged with not passing on their gene mutation to the next generation, and thereby acted as conscientious citizens of a 'risk society'. In this way, reproductive decisions were moral

acts, acts they could do and therefore *should* do. For those like Kirsty (age 38), who used PND four times and terminated a pregnancy based on the *TP53*+ve status of the foetus, bearing a child with LFS was clearly construed as an irresponsible act, and to be avoided at a heavy emotional and physical price. Her steadfast approach to emotionally detaching herself from the foetus and terminating one of her pregnancies strongly indicates that exercising her reproductive agency responsibly was of paramount importance to her identity as a parent with LFS.

Steinberg (1996) argued that women bear the brunt of responsibility when making reproductive decisions. While young men in this study also felt a responsibility to prevent passing on their mutation, young women were the primary reproductive decision-makers and considered their reproductive options in more depth. Young men displayed little knowledge of how to have children without a *TP53* mutation and they commonly deferred reproductive decision-making until they were older, suggesting that gendered roles in family formation hold true in this sample. This may have been due to the male portion of the sample being younger and more heterogeneous (e.g., not all had confirmed their gene status), and therefore less likely to experience the intersection of reproductive decision-making with LFS. The inclusion of more young men in future research would be beneficial, especially those with a confirmed *TP53* mutation and those in young adulthood who are more likely to have experienced reproductive decision-making.

10.3.5 Reproductive decision-making and developmental readiness

Parents in the sample, and those soon to be parents ($n=11$, mean age 30.6 years), were older than those who were yet to engage in reproductive decision-making ($n=19$, mean age 22.5 years). This suggests most participants were not yet at the life stage where starting a family was a core focus, and that LFS prompted thinking about this developmental task sooner than normally anticipated. Illustrating their unreadiness to contemplate starting a family with LFS, many young people stated that PGD would be their preferred option to have children, yet few understood the process, cost and logistics of PGD. It was enough for them to have PGD as a future option, and many deferred any thoughts about having a family until reaching an age where it was a primary concern. For the small number of young people who did begin the process of planning PGD, they were very quickly overwhelmed by the process because it either placed unforeseen pressure on budding romantic relationships during emerging adulthood, or IVF cycles were unsuccessful.

10.4 Summary

This chapter was the fourth and final theme from Study 2 and described the reproductive decision-making of young people from families with LFS. It showed that there were key differences in decision-making based on the variability and intensity of the LFS phenotype of participants, their life stage and gender. Younger participants commonly deferred reproductive decision-making until they felt 'ready', and young women stood out as the primary reproductive decision makers compared to young men. A common theme of this chapter was the sense of moral responsibility participants felt when making decisions about reproduction with LFS: many felt obligated to eradicate the burden of LFS on future generations and nominated or used reproductive technology to have a 'healthy' family. The next chapter shifts to Phase 2 of the project, and moves away from the experiences of young people to focus on the practices of genetic and oncology health professionals who care for young people with LFS in Australasia.

11 Health professionals' practice for young people with, or at risk of, Li-Fraumeni syndrome: An Australasian survey

11.1 Overview

The previous chapter described young people's experiences with reproductive decision-making for LFS and was the final chapter addressing the findings from Phase 1 of the study. So far, this thesis has focussed exclusively on the experiences of young people from families with inherited disease (Chapter 6) and families with LFS (Chapters 7-10), and used qualitative techniques to explore primary and secondary qualitative data. To holistically inform developmentally appropriate genetic counselling for young people with LFS, it is also important to understand health professionals' perspectives. The aim of this chapter is to describe the experiences of Australasian health professionals' who care for young people from families with LFS. To achieve this aim, this chapter focusses on three specific aspects of genetic and oncology health professional practice that were identified as important in the qualitative phase: predictive genetic testing, risk management, and psychosocial support. All three of these practices represent key points in the clinical care of young people with LFS (Chapters 7-10) and are explored in this chapter from the perspective of health professionals using a descriptive survey. As mentioned in the preface, this chapter was published online first in the *Journal of Genetic Counselling* (Forbes Shepherd et al. 2019), and is included here as the author-

accepted manuscript.⁶ Note that this chapter uses terminology suited for publication and has slightly different wording for key concepts compared to the preceding chapters.

11.2 Abstract

Li-Fraumeni syndrome (LFS), a rare cancer syndrome caused by pathogenic germline variants in *TP53*, has serious implications for adolescents and young adults (AYAs; aged 15-39 years). The early onset and multi-organ cancer risk associated with LFS means health professionals must concurrently contend with the developmental needs of individuals who are diagnosed from a young age, and recent changes in practice due to advances in whole-body cancer surveillance.

To help understand how current practice meets the developmental needs of AYAs with, or at risk of, LFS, we conducted a national online survey to explore the experiences of health professionals who care for this population in Australia and New Zealand. Forty-three respondents completed the survey (56% genetic counsellors), one third of whom had facilitated predictive *TP53* testing for minors ($n=14/43$). In hypothetical scenarios describing 15-year-olds eligible for predictive *TP53* testing, respondents were more supportive of testing for emotionally mature compared to immature minors ($p=0.009$); and more supportive of adolescent wishes compared to parental wishes for testing ($p=0.020$) when families held discordant views on testing. Genetic health professionals were more likely than oncology health professionals to address psychological ($p=0.017$) and information needs about reproductive options for LFS during consultations than to refer them on ($p=0.004$). All respondents supported comprehensive risk management for LFS, but noted important medical, logistical, and psychosocial limitations for AYAs.

This study offers valuable insight into developmentally appropriate practices of Australasian health professionals who care for AYAs with, or at risk of, LFS. These findings suggest they may foster the autonomy of minors undergoing predictive *TP53* genetic testing and be supportive of new whole-body risk management guidelines.

Key words: Adolescent and young adult; Li-Fraumeni syndrome; survey; health professionals; practice.

⁶ The published version has better readability (DOI: 10.1002/jgc4.1199).

11.3 Introduction

Adolescents and young adults (AYAs; aged 15-39 years) represent a unique cohort in health settings. The AYA years represent a significant transitional life stage characterised by physical and cognitive maturation, identity exploration, growing independence from family, social role transitions, forming long-term partnerships, and family planning (Arnett 2000; Patton and Temmerman 2016). For genetic health professionals, managing the life stage-related complexities of AYAs with a genetic condition is a documented difficulty (Werner-Lin et al. 2015; Tse et al. 2013; Gaff, Lynch, and Spencer 2006). Yet, youth-friendly models of care in clinical genetics are nascent, and the intersection between AYA development and genetic risk remains challenging to navigate for AYA patients, their families, and health professionals alike (Duncan and Young 2013; Pichini et al. 2016; Godino et al. 2019).

11.3.1 Li-Fraumeni syndrome during the AYA years

Li-Fraumeni syndrome (LFS), a rare cancer predisposition syndrome caused by pathogenic germline variants in *TP53*, has serious implications for AYAs. Beginning from childhood, the cumulative cancer incidence associated with a pathogenic germline *TP53* variant reaches 50% for females by age 31 and males by age 46 (Mai et al. 2016). These individuals are subject to a strikingly variable phenotype, including: breast cancer, osteosarcoma and soft-tissue sarcoma, CNS tumours, and haematological malignancies, among others (Mai et al. 2016). Genetic and oncology health professionals must concurrently contend with the clinical complexity of LFS—with its varied, difficult-to-manage phenotype—and the normative developmental changes that impact how individuals at high risk of cancer live with LFS in family life from a young age. These changes centre on growing capacity for autonomous decision-making regarding genetic testing, with varying levels of family involvement; cognitive capacity to understand the short and long-term implications of genetic testing and risk management; decision-making and engagement with risk management and/or risk reducing strategies; health literacy; how they identify, label and manage emotional responses; existential awareness; and, confidence in navigating the healthcare system (Pichini et al. 2016; Duncan and Young 2013; Forbes Shepherd et al. 2018; Werner-Lin, Zaspel, et al. 2018). Similar clinical and psychosocial challenges are also common for other early onset multi-organ conditions with complex screening protocols; e.g., von Hippel-Lindau syndrome (VHL), multiple endocrine neoplasia 1 (MEN1), neurofibromatosis, constitutional mismatch repair deficiency (CMMRD), and emerging conditions like DICER1 syndrome. How

health professionals meet these challenges in their practice, however, remains relatively undocumented.

11.3.2 Whole-body MRI

Advances in whole-body MRI technology have increased feasibility and clinical utility of enrolling children and AYAs with LFS in experimental surveillance protocols, causing a shift in the recommendations for cancer surveillance to begin at younger ages (Malkin 2014). This is reflected in current recommendations for LFS risk management from the National Comprehensive Cancer Network (2017), and more recently in Australasian guidelines. Recommendations now stipulate that adults and minors with a pathogenic germline variant in *TP53* should enrol in cancer surveillance using whole-body MRI as early detection may reduce mortality (Cancer Institute New South Wales 2019; Ballinger et al. 2017; Kratz et al. 2017). Despite this shift, many health professionals internationally face a discrepancy between recommendations and the clinical availability of screening modalities.

In Australasia, access to subsidised whole-body MRI is currently limited to research-based protocols available at tertiary healthcare centres. As a result, providers may be unable to ensure their patients can access recommended screening. How providers navigate this tension is important to investigate, and taking Australasia as an example of a region in transition, we hope to elucidate salient challenges for other regions internationally who may also be in transition (e.g., areas of the USA where LFS programs are still nascent, most regions in Europe outside of France, Netherlands, and the UK, and regions outside of South-Eastern Brazil) (Mai et al. 2012).

The introduction of whole-body MRI has also dramatically impacted the paediatric genetic testing landscape for complex inherited syndromes (Malkin 2014). Historically, health professionals have been hesitant to offer predictive *TP53* testing to minors because of limited medical benefit (Fresneau et al. 2013; Evans et al. 2010). However, the prospect of effective screening for LFS now provides a strong rationale for predictive *TP53* testing for individuals of all ages, and in the USA, this has resulted in increased provider acceptance of *TP53* testing among children (Alderfer et al. 2015). As evidence of the medical utility of *TP53* testing mounts, health professionals' opinions about ordering testing for minors must be explored, especially focusing on how they manage the developing autonomy of AYAs approaching the legal age of majority with parental expectations about genetic testing (Warby et al. 2019).

Bakhuizen et al. (2018) recently highlighted that some Dutch genetic health professionals (29%, n=17/57) have difficulty providing genetic counselling for diagnostic *TP53* genetic testing among young women (aged <30 years) with breast cancer due to the often-unexpected multi-organ cancer risk associated with LFS and limited options for risk management (Bakhuizen et al. 2018). Despite focusing on the care of young women, the authors did not examine how health professionals considered the provision of developmentally appropriate genetic counselling for LFS.

11.3.3 Study aims

This study aimed to explore experiences of health professionals who care for AYAs with LFS in Australia and New Zealand. Specifically, this study explored attitudes and practices of health professionals in the domains of predictive genetic testing, risk management, and psychosocial support for AYAs from families with LFS. These data provide a snapshot of clinical practice in a region where guidelines for LFS risk management are in transition and frameworks for AYA-specific care are still emerging in genetics.

11.4 Methods

We conducted a cross-sectional online survey among eligible genetic and oncology health professionals in Australia and New Zealand to investigate their current practice for AYAs with, or at risk of, LFS. Survey responses were collected between June 2018 and March 2019. This study had approval from the Peter MacCallum Cancer Centre Human Research Ethics Committee (LNR/17/PMCC/281).

11.4.1 Participants

Because of the complexity and rarity of LFS, it requires specialist cancer genetics care that is provided by Familial Cancer Centres and affiliated health professionals. A recent census of genetic health professionals indicates that approximately 117 clinical genetic counsellors and 29 clinical geneticists see cancer patients in Australia, with approximately 32 genetic counsellors operating solely in cancer genetics (Nisselle et al. 2018). In New Zealand, there are approximately 14 clinical genetic counsellors and 9 clinical geneticists (Nisselle et al. 2018). There are an estimated 139 medical oncologists; 145 oncology nurses; 18 surgeons who are active members of the Clinical Oncology Society of Australia (Clinical Oncology Society of Australia 2018); no estimates were available for oncology health professionals from New Zealand.

From this population of currently practising Australasian health professionals, we used purposive sampling to recruit genetic health professionals (clinical geneticists and genetic counsellors); oncology specialists (surgical and medical oncologists); and oncology nurses who had experience in providing at least one of the following to AYAs (aged 15-39 years) with, or at risk of, a *TP53* pathogenic germline variant (Palinkas et al. 2015):

- Predictive *TP53* genetic counselling/genetic testing; and/or,
- Risk management advice/risk management for LFS; and/or,
- Psychosocial support (defined as psychological, informational, educational/vocational, financial, peer-support, reproductive and fertility advice).

11.4.1.1 Procedures

We recruited eligible respondents using three strategies. First, we asked a senior staff member at each clinical genetics service and familial cancer centre located throughout Australia and New Zealand to disseminate study invitations with the survey link among their staff via email. Second, all members of listservs associated with the Human Genetics Society of Australasia (HGSA), Australasian Society of Genetic Counsellors (ASGC), Australasian Association of Clinical Geneticists (AACG), and the Clinical Oncology Society of Australasia (COSA) received an e-blast advertising the study. Third, we asked respondents to pass on the survey link to their eligible colleagues. We sent email reminders one month after the initial invitation. By completing the survey, respondents indicated consent. Respondents could exit the study at any time, elect to submit an incomplete survey, or discard survey results entirely.

11.4.2 Instrumentation

A multidisciplinary team developed novel survey content using a four-stage process (Middleton et al. 2014). First, we explored current practice trends for LFS in Australasia using key informant interviews with six experienced health professionals specialising in LFS. Australian informants included: two senior genetic counsellors (one metropolitan and one rurally-based); one metropolitan-based paediatric clinical geneticist and two metropolitan-based medical oncologists (one with extensive rural outreach). New Zealand informants included two senior genetic counsellors from different regions.

Secondly, we extracted findings from previous work investigating the psychosocial needs of AYAs with, or at risk of, inherited disease (Forbes Shepherd et al.

2018), which highlighted the following key survey domains: predictive genetic testing for mature minors (aged 14-17 years), risk management practices, and the provision of developmentally appropriate psychosocial support (Werner-Lin et al. 2015). Third, we undertook a process of item drafting and face-validity checking with a multidisciplinary expert panel, and member-checking with potential respondents to refine content. The survey was piloted with five eligible respondents of the target population before being released online, where it was managed using the Research Electronic Data Capture (REDCap) tool hosted at The University of Melbourne (Harris et al. 2009).

11.4.2.1 Survey content

The survey consisted of four sections. The first section collected personal and professional demographic information. The second section, 'Genetic Testing', consisted of vignettes describing AYAs with varying psychosocial characteristics who were eligible for predictive *TP53* genetic testing. Five vignettes described male or female 15-year-olds seeking predictive testing, with varied maturity and parental support. Respondents were then asked whether they would support genetic testing in each case. We chose the age of 15 years because it is commonly considered the point at which young people have decision-making capacity comparable to adults (Santelli et al. 2003); however, because 15-year-olds have not yet reached the legal age for consent, it can be a challenging age to consider. Maturity was captured by the adolescent's ability to understand the potential impact of genetic testing on themselves and their family, and their level of active involvement in decision-making (Duncan et al. 2005). Below are excerpts from vignettes describing: (a) a mature minor and (b) an immature minor who would be eligible for predictive *TP53* testing:

- a) Tim is a mature 15-year-old and understands the impact of the genetic test on himself and his family. He has expressed that he would like to be tested. His parents also think he should be tested.
- b) Jake is an immature 15-year-old and has limited interest and understanding of the potential impact of the genetic test on himself and his family. He seems to be going along with his parents' wishes to get testing and has not engaged with the decision-making process.

The remaining three vignettes described 18-, 25-, and 35-year-old women eligible for predictive testing. For each vignette, respondents were asked to select their most commonly used pre-test genetic counselling strategies from a list of options informed by a youth-friendly framework for genetic counselling (Young et al. 2019). The third section,

'Risk Management', asked respondents about their attitudes, perceptions, and practices for LFS risk management. The fourth section, 'Psychosocial Support' consisted of eight potential psychosocial needs for AYAs from families with LFS derived from a literature review and an ongoing qualitative study on AYAs' experiences of LFS (Forbes Shepherd et al. 2018). Respondents were asked if and how they meet these needs in clinic and if, or where, they refer externally. The final survey contained a maximum of 133 items. Survey logic guided respondents to specific sections based on their clinical experience.

11.4.3 Data analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS, version 25). Descriptive statistics were used to analyse close-ended responses and summarise demographic data. Chi-square and Fisher's exact testing were used to assess associations between categorical variables. A p value of <0.05 was considered statistically significant. Open-ended responses were analysed using inductive content analysis to systematically identify and group responses into content-related categories (Elo and Kyngäs 2008).

11.5 Results

11.5.1 Participant characteristics

In total, 48 health professionals responded to the survey. Of those, four were excluded because their responses were incomplete and one was ineligible. Forty-three surveys were included for analysis (Table 27, p. 252). The majority of respondents were female (88.4%), aged 30-39 years (46.5%), practicing genetic counsellors (55.8%), and had 10+ years professional experience (55.8%). Genetic counsellors were significantly more likely to be aged <40 years compared to physicians ($p<0.001$). The distribution of respondents across different types of care mostly reflected the known responsibilities of each profession (Table 31S, p. 312, Appendix 1). The majority (79.1%, $n=34/43$) of respondents consulted individuals under 18 years in their practice.

Table 27. Participant characteristics (n=43)

	Genetic counsellors n (%)	Physicians ^a n (%)	Oncology nurse n (%)	Total n (%)
Total	24 (55.8)	17 (39.5)	2 (4.6)	43 (100)
Clinical geneticist	-	6 (13.9)	-	-
Medical oncologist	-	8 (18.6)	-	-
Surgical oncologist	-	3 (7.0)	-	-
Psychiatrist	-	1 (2.3)	-	-
Years of experience				
0-5	9 (37.5)	3 (17.6)	0 (0)	12 (27.9)
6-10	5 (20.8)	2 (11.8)	0 (0)	7 (16.3)
10+	10 (41.6)	12 (70.6)	2 (100)	24 (55.8)
Gender				
Female	22 (91.7)	14 (82.4)	2 (100)	38 (88.4)
Male	2 (8.3)	3 (17.6)	0 (0)	5 (11.6)
Age range (years)				
20-29	7 (29.2)	0 (0)	0 (0)	7 (16.3)
30-39	15 (62.5)	5 (29.4)	0 (0)	20 (46.5)
40-49	1 (4.2)	6 (35.3)	0 (0)	7 (16.3)
50-59	1 (4.2)	4 (23.5)	0 (0)	5 (11.6)
60-69+	0 (0)	2 (11.8)	2 (100)	4 (9.3)
Country/region of workplace				
New South Wales	6 (25.0)	2 (11.8)	0 (0)	8 (18.6)
Queensland	0 (0)	3 (17.6)	0 (0)	3 (7.0)
Victoria	13 (54.2)	9 (52.9)	2 (100)	24 (55.8)
Western Australia	3 (12.5)	3 (17.6)	0 (0)	6 (13.9)
New Zealand	2 (8.3)	0 (0)	0 (0)	2 (4.7)

^aOne respondent selected more than one profession, meaning total exceeds 39.5% for physicians.

11.5.2 Facilitating TP53 predictive genetic testing for AYAs

Twenty-eight of 43 respondents reported they had facilitated predictive *TP53* genetic testing for AYAs (aged 15-39 years). Of the 26 who reported the number of times they had facilitated testing, the majority (73%, n=19/26) reported doing so fewer than five times in their practice (Table 32S, p. 313, Appendix 1). Professional and demographic characteristics were not associated with number of times testing was facilitated ($p>0.2$).

11.5.2.1 Predictive TP53 genetic testing practices for minors

Of the 26 respondents who reported the number of times they had facilitated testing for AYAs, 54% ($n=14/26$; 7 GCs and 7 physicians) had also facilitated predictive TP53 genetic testing for minors under the age of 18 years (Table 32S, p. 313, Appendix 1). Ten respondents had facilitated predictive testing for 1-5-year-olds; five facilitated testing for 6-11-year-olds; and seven facilitated testing for 12-17-year-olds. Of those who had not provided testing to minors (46%, $n=12/26$), only one reported they were personally opposed to TP53 predictive testing for minors due to the perceived limited medical benefit and the risk of psychological harm. The remainder ($n=11$) did not see children in their practice.

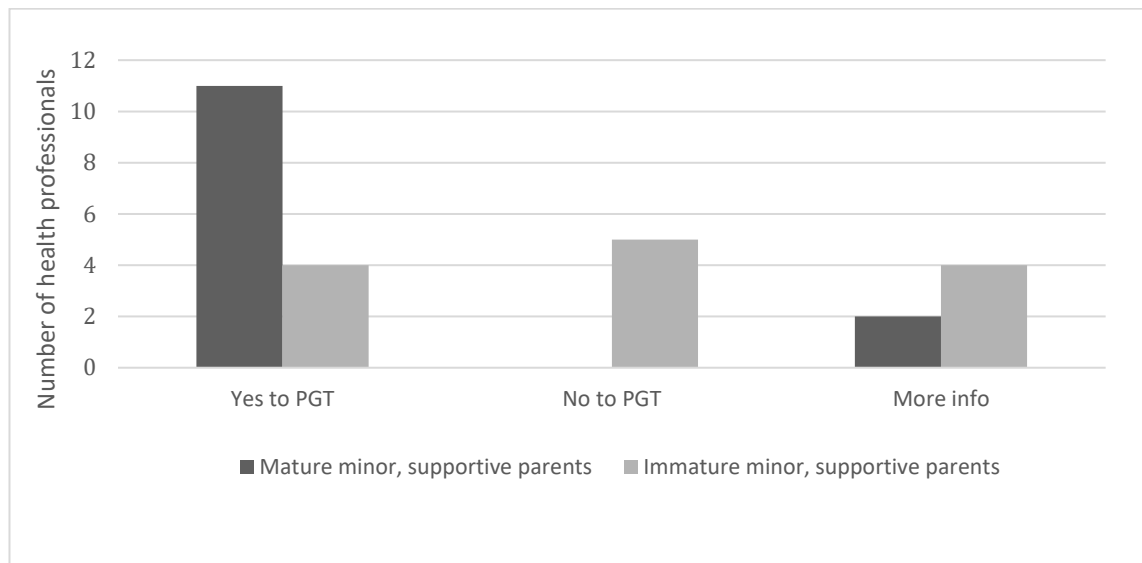
The 14 providers who had facilitated predictive TP53 genetic testing for minors were provided with vignettes describing 15-year-olds eligible for predictive TP53 genetic testing (note that due to drop out, $n=13$ responses were received for the first vignette and $n=12$ for the second vignette). In the first vignette, when parents were in favour of testing their child, respondents were more supportive of testing among mature minors, irrespective of the adolescent's sex, compared to immature minors ($n=11/13$ vs. $4/13$, $p=0.009$, Figure 11A, p. 255). There was no difference between genetic counsellors' and physicians' reported practice for genetic testing among mature and immature minors ($p>0.05$). Irrespective of adolescent maturity, respondents who stated they needed more information to make a recommendation ($n=6/13$) were most interested in family dynamics around decision-making for testing and the adolescent's understanding of the condition. The five respondents who did not support testing for immature minors (Figure 11A) expressed in open text that testing could be deferred until the adolescent became more interested in the testing process, and an interim measure could be to monitor the adolescent for symptoms and offer investigation, as indicated.

In vignettes where adolescents and parents held discordant views on testing (i.e., one party requested testing and the other did not), respondents supported adolescent wishes to pursue testing when their parents did not ($n=6/12$ vs. $1/12$, $p=0.020$, Figure 11B, p. 255). That is, the autonomy of the 15-year-old was prioritised when adolescents and parents disagreed. Only one respondent ($n=1/12$) supported parental wishes to override their child's desire for testing, stating that testing might cause the adolescent and their family psychological harm. There was no difference between genetic counsellors' and physicians' reported practice for genetic testing among adolescents and parents with discordant views on testing ($p>0.05$).

11.5.2.2 Differences in pre-test counselling strategies for 18-, 25- and 35-year-olds at risk of LFS

Twenty-three of 43 respondents reported their most commonly used pre-test genetic counselling strategies for 18-, 25-, and 35-year-olds undergoing predictive *TP53* genetic testing (Table 28, p. 256). The most frequently reported strategies were common to general genetic counselling practice (i.e., contracting and addressing AYA to build rapport). Documented AYA-specific strategies (e.g., planning additional time, planning time alone with the AYA, and conducting a formal psychosocial assessment) were practiced over half the time for 18-year-olds. Over 90% of respondents rejected approaches that undermined the independence of the AYA in pre-test counselling: i.e., following family wishes over those of the AYA, and directing communication to parents and not the AYA during consultations (Table 28, p. 256). This analysis was not sufficiently powered to report differences between professions or vignette age groups.

A



B

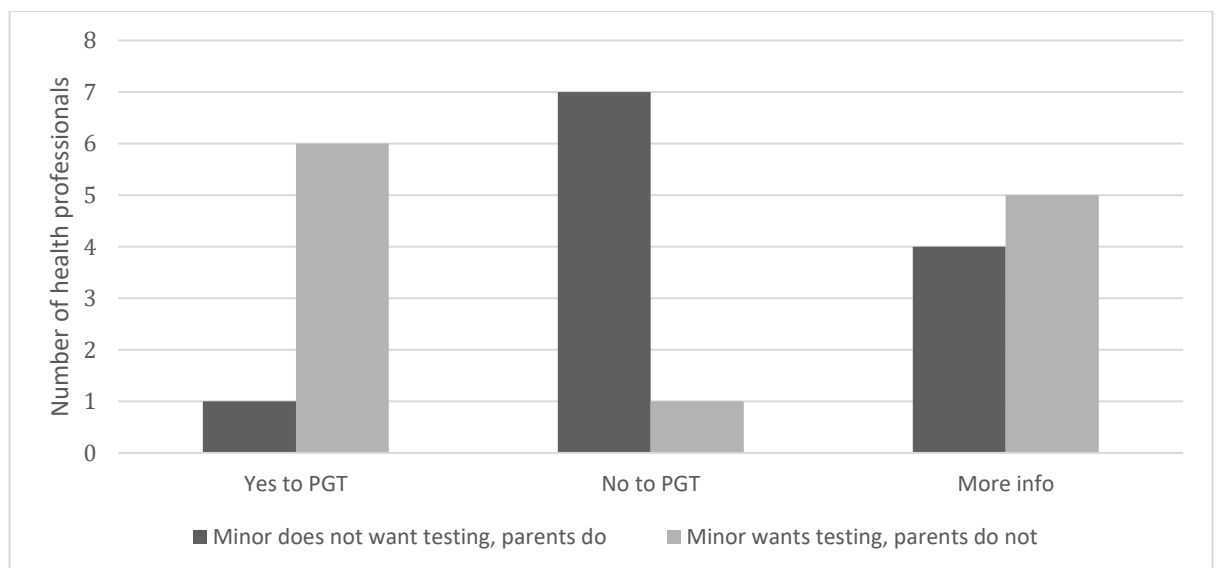


Figure 11. Predictive *TP53* genetic testing practices for 15-year-olds. (A) mature compared to immature 15-year-olds; (B) discordant views on testing between 15-year-olds and their parents

Abbreviations: PGT, predictive genetic testing; 'more info' was an option for providers to select if they needed more information before deciding to offer PGT or not. Their open-ended responses for what kind of information they needed are included in-text.

Table 28. Pre-test genetic counselling strategies for 18-, 25-, and 35-year-olds undergoing predictive *TP53* genetic testing

Strategies	AYA age (yrs.)		
	n=23		
	Aged 18 n (%)	Aged 25 n (%)	Aged 35 n (%)
Set expectations of the genetic testing appointment from the outset	22 (96)	20 (87)	20 (87)
Address AYA directly as much as possible to develop trust and rapport	22 (96)	20 (87)	20 (87)
Organise to spend time alone with AYA	19 (83)	17 (74)	14 (61)
Follow AYA's wishes with respect to testing, irrespective of her family's wishes	17 (74)	16 (70)	17 (74)
Plan additional time for the consultation	14 (61)	9 (39)	8 (35)
Conduct, or refer AYA for, a psychosocial assessment (e.g., HEADSS or PAHC)	12 (52)	7 (30)	5 (22)
Direct communication to AYA's parents at appointments for genetic testing	2 (9)	1 (4)	1 (4)
Follow the family's wishes with respect to testing, irrespective of AYA's wishes	0 (0)	1 (4)	1 (4)

Abbreviations: HEADSS, Home, Education/employment, peer group Activities, Drugs, Sexuality, and Suicide/depression assessment; PAHC, psychosocial aspects of hereditary cancer questionnaire.

11.5.3 Risk management

Twenty-nine of 43 respondents described their attitudes, perceptions, and referral practices LFS risk management. Fifty-two percent (n=15/29) reported adhering to national guidelines, which at the time of the study recommended annual clinical review, annual breast MRI from age 20, and 2-5 yearly colorectal and gastric cancer surveillance (Cancer Institute New South Wales 2010); three respondents recommended breast cancer risk management only. In addition to following national guidelines, most also referred to research-based comprehensive risk management for LFS (72%, n=21/29). Seventeen percent (n=5/29) stated they did not know of any research protocols for comprehensive risk management or that services were not yet established in their area of practice. These providers were mostly from outside of Victoria: one from Queensland, one from New South Wales, and two from Western Australia). No differences were reported for risk management practices based on profession.

In addition to recommending breast MRI surveillance for young women, respondents (86%, n=25/29) also stated they would recommend consideration of

bilateral prophylactic mastectomy (BPM). Seven (24%) stated in open text that they discussed BPM among a range of options to manage breast cancer risk, not as a prescriptive recommendation. Two genetic counsellors did not support recommending BPM, stating that they would refer to an oncologist. From 19 responses, the median recommended age to begin considering BPM was 20 years (range 18-30).

11.5.3.1 Attitudes and perceptions of comprehensive risk management for LFS
Respondents agreed about the major advantages, disadvantages, and barriers to implementing comprehensive risk management (Table 29, p. 258). Genetic counsellors were more likely than physicians ($p=0.044$) to report a lack of evidence to support the medical benefits of screening. Younger (<40 years, $p=0.026$) and less experienced (having <10 years professional experience, $p=0.024$) respondents were more likely to articulate 'hope' as an advantage of comprehensive risk management. Respondents from outside the state of Victoria, Australia were more likely to state that comprehensive risk management was logistically challenging to coordinate ($p=0.023$).

Table 29. Most commonly stated advantages, disadvantages and barriers to comprehensive research-based risk management for LFS

	Genetic counsellors	Physicians	Total
	n (%)	n (%)	n (%)
Total	16 (100)	13 (100)	29 (100)
Advantages			
The early detection of cancers	13 (92.9)	13 (100)	26 (89.7)
Offering a sense of hope	14 (100)	10 (76.9)	24 (82.8)
Emotional containment ^a	12 (85.7)	10 (76.9)	22 (75.9)
Increased survival	10 (71.4)	10 (76.9)	20 (69.0)
Disadvantages			
There is a high false-positive rate for whole-body MRI	12 (75.0)	9 (69.2)	21 (72.4)
Comprehensive screening could cause psychological harm	9 (56.3)	8 (61.5)	17 (58.6)
Comprehensive screening could provide a false sense of hope	10 (62.5)	4 (30.8)	14 (48.3)
There is inequitable access to comprehensive screening	7 (43.8)	6 (46.2)	13 (44.8)
Barriers			
The risk of screening anxiety/fatigue for participants	11 (68.8)	12 (92.3)	23 (79.3)
Geographical distance	13 (81.3)	10 (76.9)	23 (79.3)
Availability at services within tertiary centres only	11 (68.8)	10 (76.9)	21 (72.4)
Logistical coordination of different health professionals	11 (68.8)	9 (69.2)	20 (69.0)

^aEmotional containment refers to providing a sense of control over cancer risk and therefore reducing cancer fear and anxiety.

11.5.4 Psychosocial support

Twenty-seven of 43 respondents answered questions about their practice for likely psychosocial needs of AYAs from families with LFS. There were overall differences between which needs were addressed in clinic and/or referred to external specialists (Figure 12, p. 260). The vast majority (>90%) of respondents referred AYAs with educational, vocational, or financial needs to social work services. Respondents almost always addressed cancer risk information and risk management needs in clinic (96%, n=26/27). Reproductive information regarding risks to future children were predominantly addressed in clinic (85%, n=23/27), but a substantial proportion (63%,

n=17/27) also referred onto IVF clinics for provision of further information and to discuss pre-implantation genetic diagnosis. Genetic health professionals (genetic counsellors and clinical geneticists: GHPs) were more likely to address information needs about reproductive options in clinic compared to oncology health professionals (medical/surgical oncologists and oncology nurses: OHPs) (n=19 GHPs vs. n=4 OHPs, $p=0.004$).

Respondents primarily addressed psychological support needs (for anxiety, depression and emotional stress related to being from a family with LFS) by attending to them in clinic and referring the AYA externally (75%, n=20/27). Genetic health professionals were more likely to address psychological support needs in clinic compared to oncology health professionals (n=18 GHPs vs. n=4 OHPs, $p=0.017$). Steps taken in clinic were centred around ascertaining AYAs' specific needs and then offering counselling within their training before referring to a specialist. Those who provided details of their external referrals (n=19) referred primarily to hospital psychology services (37%, n=7/19) and to the patient's GP to organise a mental healthcare plan (37%, n=7/19). The majority of respondents (59%, 17/29) did not recommend any support groups for AYAs with LFS, mainly because they did not know of any or none were locally available. Of the 12 respondents (41%) who recommended support groups, most provided details of the LFS Association (a patient advocacy group for LFS based in the USA) and/or Youth Cancer Services/CanTeen Australia. There were no differences between respondents who did or did not recommend support groups.

Coming of age with Li-Fraumeni syndrome: perspectives of young people and health professionals

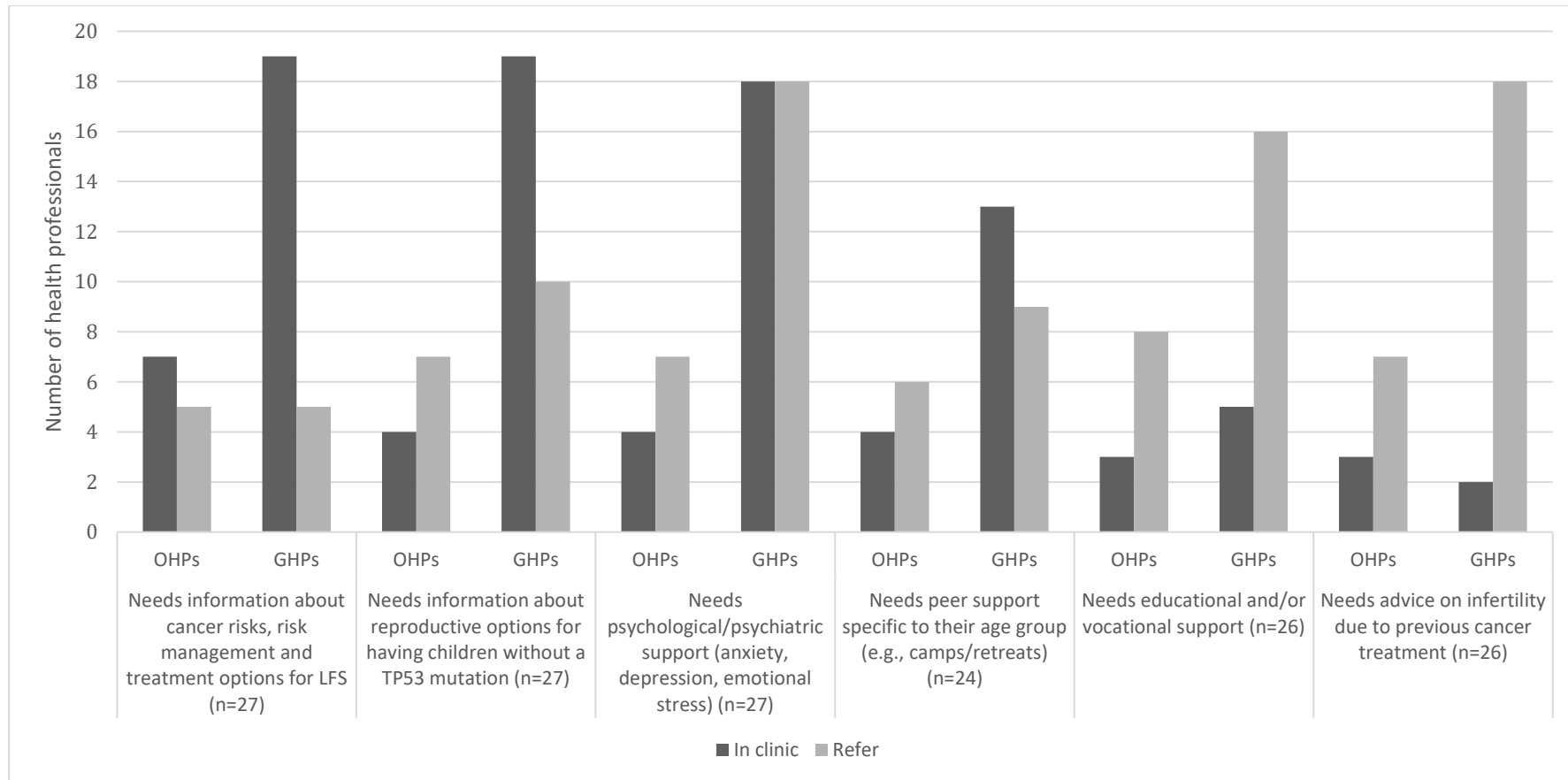


Figure 12. Health professionals who address the psychosocial needs of AYAs with LFS in clinic and/or refer to external specialists

Abbreviations: OHPs, oncology health professionals (medical/surgical oncologists and oncology nurses); GHPs, genetic health professionals (genetic counsellors and clinical geneticists).

11.6 Discussion

This is the first study to document the attitudes, perceptions, and practices of Australasian genetic and oncology health professionals who care for AYAs with, or at risk of, LFS. Respondents supported predictive *TP53* testing for minors and reported fostering autonomous decision-making for genetic testing among mature minors. Respondents mostly used common pre-test genetic counselling strategies for 18-, 25-, and 35-year-olds eligible for predictive *TP53* genetic testing, and some supplemented their approach elements of youth-friendly genetic counselling for 18-year-olds. Genetic health professionals held critical roles in facilitating front line psychological support and reproductive information for AYAs with LFS, more so than oncology health professionals. There was general consensus about the advantages and disadvantages of comprehensive risk management for LFS using whole-body MRI.

This study showed that a substantial proportion ($n=14/26$) of Australasian health professionals had facilitated predictive *TP53* testing to minors in their practice, which is markedly higher than previously reported rates among health professionals from France ($n=3/20$) and the UK ($n=4/26$) (Fresneau et al. 2013; Evans et al. 2010). This mirrors the growing acceptability of *TP53* testing among parents who wish to test their children in the USA (Alderfer et al. 2015), and suggests that the introduction of new risk management guidelines using whole-body MRI has caused a shift in the perceived manageability of LFS. This is also consistent with changes in attitudes to genetic testing for other complex early onset cancer syndromes (e.g., CMMRD), where the introduction of increasingly effective paediatric interventions has brought into question guidelines still hesitant to endorse genetic testing for children (Malkin 2014).

While the enthusiasm surrounding novel surveillance protocols for LFS is justifiable, health professionals should consider guarding against overhyping its benefits, especially in the face of parental requests for testing premised on medical reasons. Multicentre, prospective studies are still assessing the clinical utility of cancer surveillance for individuals with LFS, and the burden of engaging in regular, whole-body surveillance for potentially incurable cancer has unknown psychosocial effects on children, parents, and family systems. Professional guidelines stipulate that the best interests of the child must underpin any decision to test unaffected children for inherited conditions (Ross et al. 2013; Human Genetics Society of Australasia 2020; Botkin et al. 2015). With an emerging evidence base, the best interests of the child with

respect to screening are difficult to determine. Therefore, it is critical that health professionals clearly unpack the risks and benefits of genetic testing and screening with potentially anxious parents who believe that any form of screening is preferable to inaction.

This study suggests some Australasian providers appreciate and address the unique developmental needs of mature minors (aged 15+ years) during predictive testing. These providers prioritised adolescent preferences over parental wishes for testing—promoting adolescent autonomy—and recommended delaying genetic testing if the adolescent was not yet mature enough to understand the implications of testing or to engage in decision-making. Although these findings are based on small numbers and should be interpreted with caution, they are consistent with current Australasian guidelines, which state that care must be taken for early onset conditions when a minor is too young to be involved in decision-making. In these cases, advocating for the young person during the genetic counselling process is critical (Human Genetics Society of Australasia 2020).

While there were no reported differences in predictive testing practices based on sex of the patient, only one vignette alternated the sex of the mature minor in this component of the survey. The vignettes used to examine practice for patients of different ages held sex constant to enable comparison of practice as a patient ages through young adulthood. Therefore, we were unable to compare whether sex influenced practice using these vignettes but it is possible that providers may promote testing at younger ages for females at risk of LFS due to the significant increase in breast cancer risk from the early 20s (Mai et al. 2016).

This study reported that providers use the same genetic counselling strategies when facilitating predictive *TP53* testing for AYAs as for older adults. For 18-year-olds, the majority reported including elements of youth-friendly care, documenting an important aspect of practice for this population and suggesting some providers may use developmentally appropriate genetic counselling approaches that promote AYA autonomy and independence. This may be due to response bias as the majority of respondents (79.1%, $n=34/43$) saw minors in their practice and may be more practiced in delivering youth-friendly care on a day-to-day basis. As increasing numbers of providers become aware of youth-friendly genetic counselling practices, it will be important to document the uptake of developmentally appropriate care for a range of conditions with implications for AYAs.

Australasian health professionals were generally supportive of comprehensive risk management for LFS using whole-body MRI. Within the context of recent updates to Australasian guidelines endorsing a whole-body approach (Cancer Institute New South Wales 2019), this suggests health professionals will likely incorporate new recommendations into their practice. Respondents did, however, identify important limitations and barriers, mainly relating to the risk of screening fatigue and anxiety, and equitable access across Australia and New Zealand. Consequently, some health professionals in remote regions may be unable to offer whole-body risk management. This, in turn, could reduce uptake of predictive testing for LFS due to there being limited medical benefit.

Genetic health professionals are key facilitators of psychological support and reproductive advice for AYAs with LFS, significantly more so than oncology health professionals. Yet, they had little knowledge of LFS-specific support groups able to provide peer support, and options for AYA-specific services were limited for unaffected young people, as many are currently geared towards AYAs affected by cancer. Moreover, youth-friendly models of care are still largely nascent in clinical genetics, and the workforce may need formalised training and resources to help guide them (Werner-Lin et al. 2015; Young et al. 2019).

11.6.1 Study limitations

Our sample was underpowered to compare patterns of practice between different professions and vignettes with high confidence. There was a limited number of respondents from New Zealand, most being from Victoria, Australia. This skewed findings to a resource-rich medical environment but may also reflect that Victoria is a hub for LFS-specific care in Australasia. While we focussed on AYA-specific issues in the context of LFS, providers who care for patients with LFS outside the AYA age range may possess equally important perspectives that warrant further inquiry. Survey questions were non-compulsory and drop out within the survey was difficult to manage. Although we explored hypothetical scenarios of predictive testing among minors, variables were not exhaustive, and additional scenarios may have yielded different results. Last, most respondents who reported facilitating predictive testing for minors (n=12/14) had done so under five times in their practice. Reported attitudes, therefore represent early experiences which may change over time as they become more experienced with genetic testing for the LFS population.

11.6.2 Practice implications

Recent updates to risk management guidelines for LFS will likely increase demand for *TP53* testing to progressively younger individuals. Regions like Australasia which are experiencing a transition in practice for LFS may find this study of benefit as it outlines current practice trends for providers facing a discrepancy between national guidelines and what is clinically available. Despite this discrepancy, our findings demonstrate that health professionals provide AYA-led predictive testing for LFS, and it is reassuring to know that health professionals are likely to be discerning with increased demand for such testing. Genetic health professionals in this study provided more supportive care than their medically-trained colleagues, which is in line with their professional scope of practice. Our data indicate the need for more integration and awareness of LFS-specific support groups, and collaborative networks with AYA-specific cancer support services (e.g., Youth Cancer Services) to establish referral pathways. The roll out of research-based whole-body MRI surveillance protocols for LFS across Australia will go some way to providing access to optimal care nationally; although, for the predominantly centralised structure of care in New Zealand, widespread access may be harder to establish. These difficulties are likely to be similar in other regions in transition of practice and require increased attention to ensure equitable access to recommended care.

11.6.3 Research recommendations

More detailed investigation into the practices of health professionals providing predictive *TP53* to minors is warranted, especially with the introduction of paediatric surveillance for LFS. Pooling several inherited cancer conditions with implications for AYAs could help to recruit a larger number of genetic health professionals involved in AYA care. This would enable a more confident assessment of how they consider developmental needs of AYAs more generally in practice. A holistic approach, including parent, child and provider perspectives, would help to more accurately gauge experiences and delivery of developmentally appropriate models of care.

11.7 Conclusion

This study offers valuable insight into practices of Australasian genetic and oncological health professionals who care for AYAs with, or at risk of, LFS. These findings suggest providers focus on fostering the autonomy of minors undergoing predictive *TP53* genetic

testing and are increasingly supportive of new risk management guidelines using whole-body MRI.

Author contributions

Rowan Forbes Shepherd was involved in all stages of this work and manuscript preparation. Laura E. Forrest, Louise A. Keogh, Allison Werner-Lin, and Martin B. Delatycki made substantial contributions to the design of the work and interpretation of data, and drafting or critically revising the manuscript for important intellectual content. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Human studies and informed consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Animal studies

No non-human animal studies were carried out by the authors for this article.

11.8 Summary

This chapter described current practices for health professionals in Australasia who care for young people with LFS. It yielded critical insights into how health professionals may operate within a youth-friendly framework for genetic counselling, suggesting a pocket of specialised health professionals in the State of Victoria, Australia, already promote

core features of youth-friendly care. This is the final results chapter and completes the empirical work of the mixed-method project. What remains is to draw together the distinct findings across each chapter and provide a cohesive final research product. To do this, the next chapter discusses the principal findings across each strand of research, integrating perspectives of young people and health professionals to better understand the implications of LFS for adolescents and young adults.

12 Discussion

12.1 Overview

This penultimate chapter provides a discussion of the major findings across the thesis in the context of relevant theory and genetic counselling practice. To extend relevant theory, I broaden the notion of citizenship for the risk society defined by Giddens (1991) and Beck (1992) to include young people as they learn and adapt to their genetic risk of disease. By framing the experiences of young people in this study as the bi-products of how we construct and live with risk in late modernity, I examine how genomics imbues risk discourse into the daily lives of young people with inherited disease. In terms of current practice, I advance a structure to developmentally appropriate genetic counselling that can facilitate the longitudinal care for young people with inherited disease and contribute a detailed understanding of the psychosocial needs for adolescents and young adults. I argue that this kind of specialised care will form part of a modern, rationalised provision of genetic counselling services. Implications for practice are woven throughout but I conclude with an overview of the principal recommendations for genetic counselling practice from this body of work as whole.

12.2 The implications of risk society for young people with genetic disease

The evidence presented throughout this thesis demonstrates that upon learning of their gene status, young people are exposed to the pervading risk discourse of late modernity: i.e., risk society (Beck 1992; Giddens 1991). The risk society thesis advanced by Beck and Giddens offers a provocative analysis of our modern, science and technology-driven society, gripped with the identification, measurement and management of risk (Beck 1992; Giddens 1991). For young people in this study, being labelled ‘at risk’ of cancer due to their genetic make-up meant becoming members of a risk society that increasingly places the locus of responsibility of health on the individual, and being constructed as moral agents charged with controlling their bodies and futures to mitigate the risk of cancer (Fitzpatrick 2000; Hallowell and Lawton 2002; Lupton 1993; Hallowell 1999; Koch and Nordahl Svendsen 2005).

Young people demonstrated a willingness to commit to this discourse and do the ‘right thing’ by undergoing genetic testing to clarify their genetic risk; attending intensive, whole-body cancer risk management, and for most young women, considering or completing a form of risk-reducing mastectomy; and considering and using reproductive technology to prevent the passage of their *TP53* mutation to the next generation (Chapters 7-10). Individuals, however, do not make health decisions in a vacuum, and the preferences of young people in the context of LFS need to be interpreted in relation to normative societal pressures that dictate expected behaviour (Bouder 2018). While the uptake of genetic testing, risk management and reproductive technology stand out as the morally responsible thing to do when living with high cancer risk (Koch and Nordahl Svendsen 2005), and are encouraged by genetic health professionals (Chapter 11), they are all intrinsically linked to the broader effects of our risk society, and each presented interesting and unforeseen psychosocial implications for young people in this study.

A key example was that cancer screening and surveillance with whole-body MRI introduced a fragmented relationship between one’s material body and sense of self (Chapter 9). Being prescribed a cyclical dredging of one’s bodily interior for potentially incurable cancer highlighted a novel intersection between medical imaging technology and embodied experience (Griffiths et al. 2010). The unprecedented granularity and diagnostic power of whole-body MRI represented a new, and powerful addition to the arsenal of technological knowing, rendering the entire body as an object to be

scrutinised in great detail by experts (Reventlow, Hvas, and Malterud 2006). This shifts the locus of control for one's health away from the individual and into the hands of technology, creating a fragmented sense of body and self (Gunderman 2005; Green, Thompson, and Griffiths 2002).

Another example was that altering the materiality of the body through the removal of body parts, either prophylactically or from cancer treatment, blurred the lines between what is self and what is body, and incurred losses to self-identity (Chapter 8 and 9) (Hallowell and Lawton 2002; Merleau-Ponty 1962). These unintended consequences of imaging technology and risk-reducing surgery result in the continual problematisation of our bodies and self, a condition of late modernity (Williams 2000), and have unknown implications for a young person's sense of developing self at a time when identity exploration is a key developmental task.

Risk discourses were also evident from young people's ideas and plans for starting a family with LFS (Chapter 10). Hopes for normative family formation (i.e., natural conception) were all but abandoned as it carried the risk of passing on their *TP53* mutation, which was considered an unacceptable risk to future generations. Any attempt at natural conception in the knowledge of this risk was described by many as 'selfish' or 'irresponsible'. Even at young ages, most nominated pre-implantation genetic diagnosis as their preferred course for starting a family, though few understood its considerable financial, logistical and physical burdens (Chapter 10). Concern for the next generation was also apparent from women's experiences of prenatal diagnosis and termination of pregnancy based on the *TP53*+ve status of their foetus; a process which asked them to accept their pregnancies and think about the needs of the coming baby and yet be willing and prepared to abort the 'genetically damaged foetus' (Rothman and Stacey 1985: 190). Risk discourse therefore created a new normal for family formation, where using complex reproductive technology was seen as the 'right' way to have a family in the context of LFS.

Though reproductive technology represented a means of protecting the next generation, the awareness, distribution and cost of prenatal and IVF services also reveals the social structures that may limit reproductive agency. Those with the socioeconomic resources to indulge in risk modification may find genetic and reproductive technology to be their saviour (Lupton 1993). For others, as evidenced in the interpretive description of young people without knowledge or access to IVF services, or who learned of their

gene status after having children, risk discourse creates anxiety and guilt, and promotes a hopelessness and fear of the future (Chapter 10) (Lupton 1993).

For young people who were yet to reach a life stage where having a family was a key focus, these considerations were out of phase with their developmental trajectory (Chapter 10). Though most deferred reproductive decision-making to when they were ready, having to contemplate reproductive risk was distressing for some. Even for those resolved to have their own biological children without LFS, their genetic status prompted them to consider the risk of serious illness and death as a young parent of young children (Chapter 10). The influence of our risk society had permeated their developmental trajectory, and health risks to self and family were considered at each milestone.

To conclude, thinking of how the risk society of late modernity affects young people with genetic disease helps to identify the suppressed and latent implications of learning one's genetic status of disease at an early life stage. In so doing, it challenges the field of genomics to consider and appreciate the risk discourse it promotes by integrating genomic technology into the daily lives of individuals and their key life decisions.

12.3 Structuring developmentally appropriate genetic counselling

As genomic medicine sweeps across the world, the unique skillset of genetic counsellors in helping individuals and families interpret and adapt to genetic information is in high demand (Ormond et al. 2018). To meet this demand, there are two key movements in the genetic counselling profession at present. The first is a re-organisation of genetic counselling services to meet the needs of populations who need them the most; i.e., for individuals and families with rare genetic disease that confer complex clinical and psychosocial needs (Abacan et al. 2019; Austin, Semaka, and Hadjipavlou 2014). The second is recognising that the profession needs to build the evidence that underpins genetic counselling practice to establish best practices in meeting diverse patient needs (Patch and Middleton 2019).

This thesis makes a novel contribution to both of these movements. Firstly, in terms of re-focussing genetic counselling services to high-needs populations, this thesis demonstrates that young people with, or at risk of, genetic disease are deserving of special attention. Due to their transitional life stage, young people require specialist youth-friendly counselling that considers and appreciates their developmental needs

both during genetic testing (Chapters 6 and 7) and beyond (Chapters 6, 8-10). In so doing, the framework of youth-friendly care identifies and promotes the distinct value of genetic counsellors to managing rare and complex inherited conditions beyond education about genetics and risk (Austin, Semaka, and Hadjipavlou 2014). As the broader movement of precision medicine integrates genomics into other fields of clinical practice (e.g., oncology, psychiatry and beyond), tasks of genetic education and pre-test counselling will be outsourced to other health professionals (Abacan et al. 2019). This provides the opportunity re-organise genetic counselling services to focus on and support high-needs populations like young people and further develop youth-friendly models of practice.

The second contribution is that this thesis adds to the evidence base on how best to meet the clinical and psychosocial needs of young people, advancing recommendations for developmentally appropriate genetic counselling (Young et al. 2019). Specifically, for LFS, this thesis demonstrates that genetic counsellors require an appreciation for the developmental phases and tasks of adolescence and young adulthood when exploring what LFS means to a young person (Chapter 8), when they undergo genetic testing (Chapter 7), and make decisions about risk management (Chapter 9) and reproduction (Chapter 10). I contend that to meet young people's needs, developmentally appropriate care must be longitudinally-focussed, and in the next section I explain how such a structure can meet the changing needs of young people over time as they intersect with disease phases.

12.3.1 Longitudinal care for young people with inherited disease

At present, clinical care for young people with LFS is not geared towards long-range psychosocial management (Chapters 6 and 11). Interactions between young people and their health professionals are mainly coordinated around medically-related appointments (e.g., genetic testing and risk management), and not necessarily for psychosocial reasons. Yet, young people with LFS and inherited disease more generally face the formidable challenge of focussing on present developmental tasks while also looking to future disease phases and developmental milestones (Forbes Shepherd et al. 2018; Waldboth et al. 2016). They need to master the current situation while charting a course for dealing with the complexities and uncertainties of genetic disease in an unknown future. To address their shifting developmental needs over time it is necessary to establish a longitudinal care plan with built-in periodic 'psychosocial check-ups' (Rolland and Williams 2005: 11). A similar recommendation has been made by several

authors in the field (Werner-Lin 2007; Werner-Lin and Gardner 2009; Hoskins, Werner-Lin, and Greene 2014; Hoskins and Greene 2012), but what is lacking from the current discussion is an extended argument of what longitudinal care may look like, and the empirical and theoretical basis to suggest a possible structure.

In the context of inherited cancer, one possible structure for longitudinal care could be to adapt models of cancer survivorship and survivorship care plans (SCPs). The aim of an SCP is to deliver patient-centred care beyond the diagnosis and treatment of cancer by enhancing communication between the patient, their oncology team, and the primary care provider (Wiley et al. 2015). SCPs have seen widespread use in general oncology and are being adapted for use with AYAs to assist with the dual demands of managing their transition to young adulthood and from cancer patient to cancer survivor (Nathan et al. 2011; Patterson et al. 2015; Fardell et al. 2018; CanTeen 2015). Current SCPs in Australia use a simple document consisting of a treatment summary, a follow-up plan, and a post-treatment supportive care plan, and even include a section for genetic test results, details of any genetic counselling and mechanisms for referral to genetic counselling if needed (Wiley et al. 2015). The early success of SCPs in general oncology provides a ready example of how long-term care, with an appreciation of information and supportive care needs, can be coordinated with a simple tool developed collaboratively between a patient and their health professionals.

Though a ready example, the cancer survivorship model is yet to be successfully adapted for AYAs with, or at risk of, inherited cancer, as they are unable to address the non-symptomatic phases of inherited disease. SCPs are deliberately geared towards individuals who have been diagnosed with cancer and consider the cancer continuum to begin with diagnosis. Unaffected individuals at high genetic risk of cancer are therefore a poor fit for SCPs; having not developed cancer, they lack the necessary physical affliction to qualify for the majority of services aimed at cancer 'survivors' despite having long-term information and supportive care needs of their own. Further, individuals with cancer caused by an inherited cancer syndrome are also a poor fit for SCPs. Their high multiple primary cancer risk in addition to their risk of recurrence means they can cycle between crisis and chronic periods of disease, where their 'survival' may be perceived as being in-between cancers (Rolland and Werner-Lin 2006). Their resultant psychosocial concerns are therefore significantly different to most individuals with sporadic cancer.

It is clear that structuring long-term care for young people with inherited disease must first attend to the unique psychosocial context of AYA development, and second,

attend to the unique aspects of genetic disease. I propose that combining the overarching phase-based framework of the Family System Genetic Illness (FSGI) (Table 5, p. 61) with a framework mapping the developmental tasks of adolescence and young adulthood (Table 7, p. 69) can meet these concerns. The FSGI has been used as a research tool to explore facets of individual and familial experience with genetic disease and genetic counselling, but has not been formally or extensively used in genetic counselling practice (Werner-Lin, Ersig, et al. 2018; Werner-Lin 2010, 2008b, 2008a, 2007; Sparbel et al. 2008; Hamilton, Williams, Skirton, et al. 2009). I contend that its attention to the developmental trajectories of genetic disease, the individual, and family can be extended to appreciate specific developmental tasks of adolescence and young adulthood in practice. In so doing, it can help genetic counsellors meet the psychosocial demands of a genetic disease over time in relation to AYA development, both looking backward to understand how experiences before genetic testing shape current outlook, and looking forward to important developmental milestones that could be impacted by different phases of genetic disease.

12.3.1.1 Attending to the interface between disease and individual development is critical

Both genetic disease and psychosocial theories of human development share the unifying concept of stage progression, which provides a basis for thinking about the interface between genetic disease and AYA development (Figure 13, p. 275). Just as Rolland (2005) suggests that using family life cycle models can facilitate a more nuanced understanding of the impact of disease on the family unit, theories of AYA development are useful in proactively thinking about the nature and strains on a young person over the course of genetic disease. In this way, Rolland's (2005) view of the family developmental life cycle is equally applicable to AYA development: 'by adopting a longitudinal developmental perspective, a clinician will stay attuned to future developmental transitions' (Rolland 2005: 2590).

In my proposed structure, the interface between disease phases and AYA development becomes the critical focus for genetic counsellors. Figure 13 (p. 275) depicts my proposed framework, where the time phases of genomic disease (top) map the unfolding disease trajectory for any individual (and their family) across pre-symptomatic and post-clinical onset phases. The core developmental tasks of AYAs (bottom) run in parallel to the illness trajectory, but are not on the same timeline: every individual brings their own unique combination of developmental tasks to each disease phase depending

on their position along the developmental trajectory. Both trajectories are nested within the family life cycle and familial experiences and knowing of disease. For those already clinically diagnosed (e.g., with cancer), their own personal experiences and knowing of disease also come to bear.

By first appreciating the demands of the disease phase (e.g., long-term adaptation), and a young person's personal and familial experiences of disease up to that point, a clinician can then look to a patient's developmental tasks at that time in their life (e.g., emerging adulthood) and consider how they may intersect now, and how they might intersect for future disease (e.g., post-clinical onset) and developmental phases (e.g., young adulthood). In this way, the organisation of services could consist of periodic assessment and re-evaluation of the young person in relation to different phases of genetic disease: i.e., 'the time phases and transition points can inform the timing of psychosocial consultations' (Rolland and Williams 2005: 18). Optimally, this would be facilitated by a genetics-led multidisciplinary team with mental health integration.

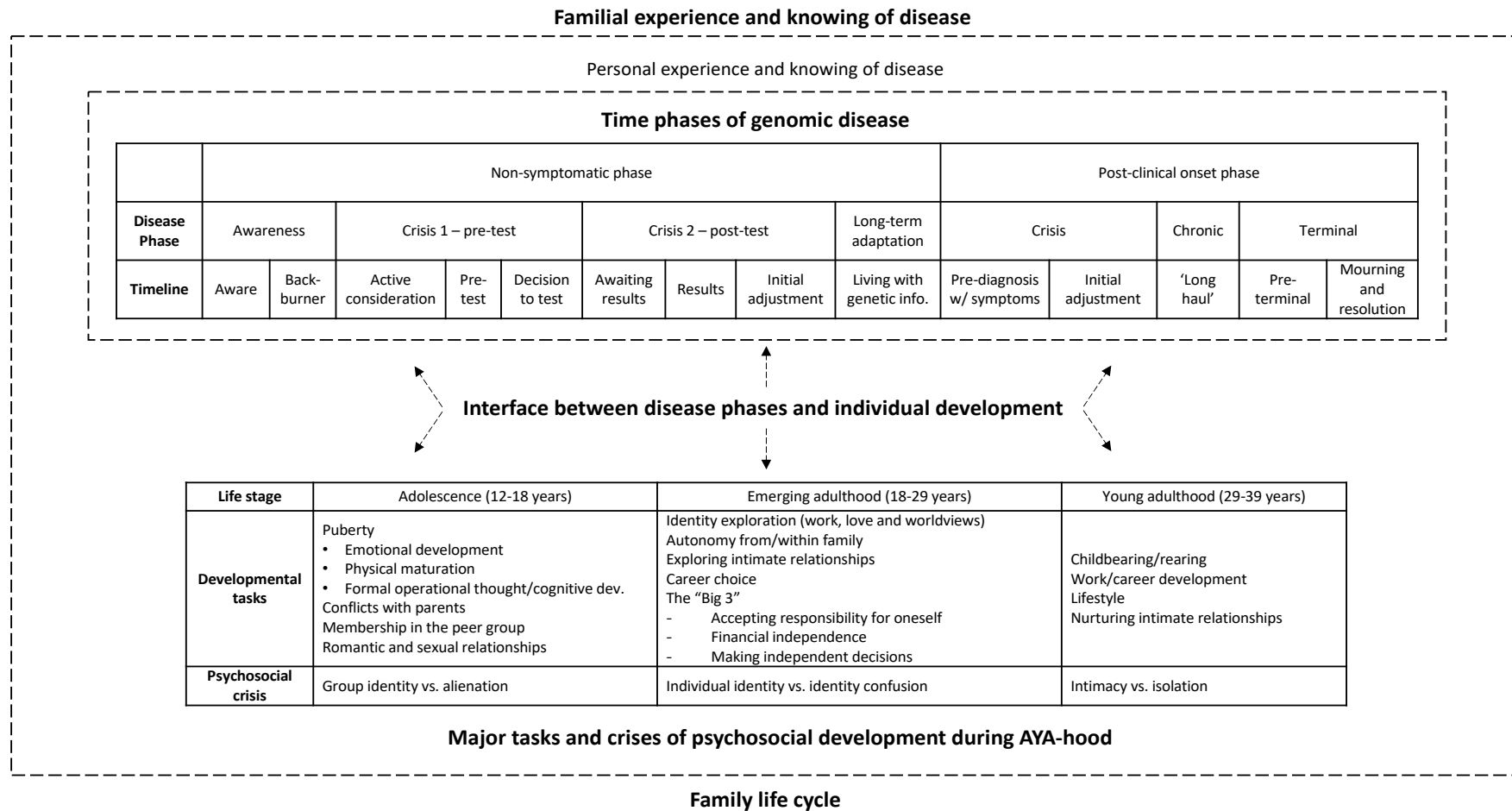


Figure 13. A phase-based structure for developmentally appropriate genetic counselling

12.4 Practice recommendations

To compliment my proposed structure for developmentally appropriate genetic counselling, this thesis advances six recommendations for genetic counselling practice. Each one is described with reference to the LFS-specific evidence supporting it, but are also relevant to other inherited conditions (Box 2, p. 280).

Recommendation 1

The first recommendation is to explore, in detail, a young person's psychosocial history of inherited disease as much as possible during pre-test genetic counselling. This recommendation is consistent with current youth-friendly genetic counselling frameworks (Young et al. 2019), which promote the importance of youth-friendly engagement and communication to build rapport. Familial and/or personal experiences of cancer were powerful influences on how young people approached genetic testing for LFS, on their anticipated gene status, and on their outlook if found to be *TP53*+ve (Chapters 7-10). Assessing family and personal history of cancer is therefore not only an important tool in genetic risk assessment, but also a critically important tool to understand how they may anticipate and make meaning of outcomes from predictive and diagnostic genetic testing. Although evidence from the interpretive description is LFS-specific, the systematic review (Chapter 6) indicated previous life experiences played a similar role for young people with a range of other inherited conditions (e.g., HD or NF1), which is supported by research with adults from families with HBOC and Lynch syndrome (d'Agincourt-Canning 2005; McAllister 2002). Therefore, this may be an appropriate genetic counselling approach for young people across inherited conditions (Young et al. 2019).

Recommendation 2

The second recommendation is that pre-test genetic counselling for young people should be family-focussed and include regular opportunities for young people to spend time alone with the genetic counsellor. Interviews with young people, reports of health professional practices for genetic testing, and the systematic review all showed young people's growing autonomy and interdependence with family complicated the process of genetic testing around the age of majority, and even into the early 20s (Chapters 6, 7 and 11). Health professionals showed they were sensitive to obviously divergent views of genetic testing between adolescents and family in hypothetical scenarios and were supportive of adolescent autonomy if faced with parental disagreement for or against

testing (Chapter 11). Yet young people's accounts of parent-driven genetic testing suggested more subtle dynamics can be at play, highlighting the difficulties in discerning between parental encouragement, concern, and pressure for testing, even when in the best interests of their child (Werner-Lin, Zaspel, et al. 2018).

These findings demonstrate the need for careful family-focussed genetic counselling with opportunities for time alone with the genetic counsellor to understand each member's beliefs, concerns, emotions and motivations for testing. This recommendation also forms an important part of the Young et al. (2019) youth-friendly framework, which suggests integrating time alone with a young person as a usual part of practice. A significant feature distinguishing youth-specific genetic counselling from adult and paediatric care is the shifting role of parents in directing the care of their children and providing consent on their behalf (Werner-Lin, Zaspel, et al. 2018). To account for this transitional phase in the family and for young people's highly varied decision-making capacity for genetic testing, this format could be applicable for young people up to the age of 25. Separate conversations may also alert providers to the presence of red flags for depression or anxiety, and enable referral to appropriate services (Werner-Lin, Zaspel, et al. 2018).

Recommendation 3

The third recommendation is specific to inherited cancer conditions that affect multiple organs, and stipulates the need to be open and clear about the nature of intensive whole-body cancer risk management, including: its medical limitations (e.g., screening and surveillance are not preventative, and whole-body MRI currently has a high false-positive rate), known psychosocial challenges (e.g., emotional and logistical burdens), and unknown implications (e.g., long-term psychological consequences of repeated scanning). All young people in this project described whole-body risk management as a critical means to regain control over their cancer risk, which was one of their key motivations for pursuing genetic testing, and health professionals were supportive of its implementation in clinical practice to improve longevity (Chapters 7, 9 and 11). A key concern, however, is that the rhetoric of preventative care promoted by genetic services can present risk management as a moral act and something that ought to be undertaken without due consideration of its limitations and implications, especially at an age where young people may lack the life experience and independence to make an informed choice.

In many cases, young people felt obliged to enrol in experimental risk management protocols because it was ‘the right thing to do’ to stay healthy (Chapter 9). It is therefore critical to outline the known emotional and logistical burdens of intensive risk management; what it may be like to develop a new relationship between one’s material body and sense of self with repeated whole-body MRIs; and, the unknown implications of long-term engagement for potentially their whole life. Part of this recommendation is to help young people with high genetic risk of multiple cancers to develop a sense of mastery of their condition outside of biological control and avoid an over-reliance on experimental risk management as a primary means of coping.

Recommendation 4

The fourth recommendation is specific to LFS and stipulates the need to directly acknowledge the high level of persistent uncertainty that can come with confirming one’s *TP53*+ve status. Two types of uncertainty arose from accounts of young people with a confirmed *TP53* mutation, requiring different genetic counselling approaches. The first type of uncertainty concerned if they would develop cancer and how this might affect their life decisions (e.g., reproductive decision-making, see Chapter 10). Young people had varied, distant or entirely absent (i.e., *de novo*) family narratives of cancer that could help them anticipate expected outcomes from the variable penetrance and phenotype of LFS (Chapter 7). Spending time to process emotional reactions like ambivalence and frustration, and developing strategies to counter them over the course of a lifetime is therefore a key task of genetic counselling in this context.

The second type of uncertainty did not concern *if* young people would develop cancer (many had accepted this fate upon learning of their gene status), it concerned the *what* and *when* of their future cancer, and if they would survive it (Chapters 7 and 8). Experiences of bereavement during their formative years due to the high penetrance of LFS-causing *TP53* variants among family meant many young people had structured their life cycle to conform to an expectation of disability and death at an early age (Chapter 8). It may therefore be important to introduce a preventative clinical framework for young people to help structure these thought processes and plan for a life beyond a certain age, or plan for a life without pervasive feelings of impending loss incensed by living with LFS. These interventions could help young people acknowledge the possibility of disability and death, and establish meaningful life goals and relationships within a context of heightened uncertainty (Rolland 1990).

Recommendation 5

The fifth recommendation is that youth-friendly genetic counselling must address reproductive decision-making and the role of reproductive technology in family formation. Similar to previous recommendations, the evidence from this thesis supports that this guidance must be communicated in a developmentally appropriate manner that is open, non-judgemental and informative (Peters-Brown and Fry-Mehlretter 1996; Griswold et al. 2011). Many young people felt that starting a family without LFS was the ‘right thing’ to do, and nominated PGD and PND as their preferred option for reproduction (Chapter 10). Very few, however, had a clear understanding of the emotional and financial costs of using reproductive technology, especially young men in the sample. Moreover, a young person’s familial and personal history, developmental stage, sexuality, gender, and their partner’s views played key roles in reproductive decision-making (Chapter 10). It is therefore important to understand the social factors surrounding a young person’s plans for starting a family; encouraging them to consider all options available to them may help allay the perception that there are inherently ‘right’ or ‘wrong’ options. Instead, allow them to choose what will work best for them, and if they are not developmentally ready to engage in reproductive decision-making, make clear plans to revisit it at a time that may be more developmentally appropriate.

Recommendation 6

The sixth and final recommendation is that long-term follow-up is required to facilitate ongoing support as young people reach new phases of development and genetic disease. Areas of potential concern that were highlighted in the interpretive description and systematic review include: long-term engagement in risk management, shifting relationships with family, developing and maintaining romantic relationships, and reproductive decision-making (Chapters 6-10). By coordinating psychosocial check-ups at regular intervals with a genetic counsellor, similar in format to general cancer survivorship plans, will help to facilitate long-term follow-up. To compliment this, and to encourage informal, self-motivated and community-derived support, it is important to also provide links with LFS-specific support groups (e.g., the LFS Association or Living LFS).

Finally, psychosocial care for AYAs with inherited cancer should be mediated by a genetically-oriented multidisciplinary team that integrates youth-friendly genetic counselling, family practice, and mental health providers (Hoskins, Werner-Lin, and Greene 2014). A key way to do this may be to establish collaborative networks with AYA-

specific cancer support services (e.g., Youth Cancer Services) to institute formalised referral pathways.

Box 2. Summary of practice recommendations

1. During pre-test genetic counselling, explore in detail a young person's psychosocial history of inherited disease, focussing on both familial and personal life experiences.
2. Pre-test genetic counselling up to the age of 25 should be family-focussed, with regular built-in opportunities for young people to spend time alone with a genetic counsellor.
3. For multi-organ cancer syndromes, be open about the medical limitations, known psychosocial challenges, and current unknowns of whole-body cancer risk management.
4. Directly acknowledge the high level of persistent uncertainty that can come with confirming one's gene status and collaboratively identify strategies that can help long-term adaptation.
5. Be non-directive and informative about the use of reproductive technology. Encourage young people to consider all options available to them for family formation and that none are inherently 'right' or 'wrong'. Make plans to revisit reproductive decision-making if a young person is not developmentally ready.
6. Make a plan for long-term follow-up care to provide adequate ongoing support as young people reach new phases of development and genetic disease. Initiating psychosocial check-ups at key transitional life and illness stages could help to facilitate this process.

12.5 Strengths and limitations of this work

The strengths of this body of work lie in the breadth, volume and rigour of research undertaken, and its relative success in the field as evidenced by three chapters being published in respectable peer-reviewed journals. Throughout, there is close attention to the links between my philosophical and theoretical positions, and how they influenced my research decisions. The entire qualitative enquiry is based on a strong and comprehensive foundation with the systematic review, the largest and most in-depth of its kind to date. The principal qualitative study rigorously applies a novel methodology in genetic counselling research, increasing the profile and credibility of interpretive description to genetic counselling researchers.

In terms of the qualitative sample, I was able to recruit a large number of young people with, or at risk of, LFS (n=30), providing a robust basis for in-depth qualitative enquiry. Using multiple sites across Australia for recruitment also increases the

transferability of knowledge to similar clinical contexts nationally. A relatively large number of males ($n=10$) also participated, who are notoriously difficult to recruit to psychosocial research and are gravely underrepresented in the literature to date (Wakefield et al. 2017; Forbes Shepherd et al. 2018). The depth and quality of interviews, and the strong theoretical basis of the inquiry also contributed to a high level of information power from the sample, enabling a robust analysis (Malterud, Siersma, and Guassora 2016). A particular strength of Study 2 was that it developed several novel findings, documenting many experiences of young people with LFS for the first time in the literature: namely, genetic testing experiences for LFS (Chapter 7), reproductive decision-making for young people at high risk of multi-organ cancer (Chapter 10), and negotiating a new relationship with one's body when engaging in intensive cancer surveillance (Chapter 9). Many findings also supported evidence from other research, especially relating to familial and personal experiences of cancer and their relationship with risk perception (Chapter 8), underlining the contribution of this project to research in the field at present.

Though modest in size and scope, the survey hones in on the core genetic and oncology services provided to young people with LFS. Also, due to the specialist nature of LFS-related care, the survey potentially captures a large proportion of health professionals who care for young people with LFS in Australasia. While this does not indicate a broader sense of generalisability, it increases the credibility of the descriptive findings in an Australasian context. As a mixed-method project, another strength of this work is that it successfully documents the same genetic counselling issues from two different perspectives (i.e., young people and health professionals) using different methods; therefore, providing a more holistic and in-depth understanding than one perspective alone. This enabled the development of clear, evidence-based recommendations for practice grounded in findings from this thesis.

The strengths of this research in terms of its breadth also contribute in some part to its limitations. The primary research questions of this exploratory project were geared towards gaining a broad understanding of the psychosocial implications of LFS for young people. Reflecting this aim, the sampling criteria for both phases of research were also broad, resulting in heterogeneous samples. The wide age range, gene status, types of testing, and cancer history meant interview participants were dissimilar in many respects, increasing the breadth of experiences covered in interviews but limiting the depth of exploration in some themes as they were based on fewer comparable

experiences. Similarly, the survey sample captured the many types health professionals who care for this population, but not in sufficient numbers to make meaningful comparisons between professions, thereby diluting the confidence of some findings across different types of health professionals and types of practice (e.g., genetic testing, or risk management, or psychosocial support).

The project may have been better served from stricter sampling criteria that focussed on one particular group within the LFS population (e.g., only individuals with a *de novo* mutation, only males, or only unaffected individuals with a *TP53* mutation), or one particular group of health professionals (e.g., genetic counsellors) providing one type of service (e.g., psychosocial support) to draw out stronger interpretive conclusions with less variability. Also, as with any interview research, regardless of sampling criteria, findings ultimately reflect the experiences of those who participated, which may be substantially different to those who declined to participate.

One final limitation concerns the ability of the survey to explore developmentally appropriate practice with robust terms of reference. Without a normative model of practice for young people with genetic disease to refer to at the time of the survey design, it was difficult to identify and describe core youth-friendly practices to assess in the survey. This resulted in a more general assessment of practices that are common to standard models of clinical genetics (e.g., focussing on the proband irrespective of age during pre-test genetic counselling).

13 Conclusion

To conclude, this thesis has extensively explored the implications of LFS for adolescents and young adults in Australia. By including the perspectives of young people from families with LFS and the health professionals who care for them, I was able to make two distinct contributions to knowledge in this field. The first contribution addresses one of the main aims of interpretive description: to produce knowledge that can be applicable in clinical practice. The confluence of evidence from all three studies in this project made clear recommendations for developmentally appropriate genetic counselling. One of the principal recommendations was that youth-friendly genetic counselling must be longitudinal and attentive to two key trajectories. The first is the developmental trajectory of young people as they progress through the formative and transitional years of adolescence and young adulthood. The second is the trajectory of genetic disease over non-symptomatic and post-clinical onset phases. Nested within familial and personal experiences of inherited disease, the intersections of each distinct trajectory over time could become areas of focus for genetic counsellors working with young people to inform their approach and the salient issues worth addressing (e.g., acceptance and belonging among peers, growing independence from family, and reproductive decision making).

The second contribution to knowledge was theoretical. The strong collection of qualitative data from this thesis was able to clearly link the influence of our modern risk society on the decisions and experiences of young people who live with LFS, and how this might apply to other inherited conditions with implications for young people. Exploring the implications of genomic technology for young people through the lens of the risk society thesis offered an alternative and provocative analysis of how biomedical

risk can shape expected behaviour, add layers of moral judgement to healthcare decisions, and problematise the body.

13.1 Agenda for future research

While this project is extensive in scope, there are many key areas that merit further investigation. One area would be to compare the qualitative findings with other similar data internationally that focusses on the psychosocial and clinical needs of young people with LFS. This would enable a deeper understanding of cultural differences between experiences of LFS in varied health systems. To do this, one option would be to combine interview data from this dissertation with data from extensive family interviews at the NCI that include young people, and conduct wide-ranging comparative analyses. One area could be to focus on experiences of anticipatory loss for young people with LFS—i.e., the experience of bereavement prior to an expected change—due to living with high cancer risk. This would extend the latest work out of the NCI (Werner-Lin et al. 2020) and contribute to my upcoming postdoctoral fellowship at the Clinical Genetics Branch. Additionally, to develop a more nuanced understanding of experiences with LFS across different cultures and health contexts, future research could focus on individuals and families with the Brazilian founder *TP53* mutation (R337H).

Another potentially fruitful strand of research would be to develop a longitudinal psychometric study of young people with LFS assessing their psychological functioning over time compared to clinical controls. Or, alternatively, to focus on different subsets of young people who have developed cancer at different life stages (e.g., childhood, adolescence, emerging adulthood), and compare how their experiences may be similar or different to design effective psychosocial interventions. A more wide-ranging focus could be to investigate the range of coping styles young people may use in their adaptation to LFS, and how this varies based on gender, developmental stage, prior experiences with cancer (either personal or familial), and over time. This research could ascertain salient ways of coping for young people in this context and identify those that could be targetable for clinical intervention.

Perhaps most importantly, a future research goal should be to develop a mixed-method research program investigating the psychosocial and clinical needs of young people across inherited conditions (e.g., familial testicular cancer, inherited bone marrow failure syndrome, and neurofibromatosis). This will move the field out of siloed research projects focussing on one condition and begin systematically exploring

commonality of young people's experience across conditions with similar implications. A wide-ranging research program would allow for more in-depth exploration of the moral and technological imperatives of genetic testing; screening, surveillance and treatment; and reproductive technology among young people living with high genetic risk of disease. In turn, these efforts will enable the development of youth-specific practices *across* genetic counselling, and contribute to a diverse evidence base generated by different methodologies and representing different groups.

As part of this program, an additional area could be to explore the intersection of masculinity and coping for young men with high genetic risk of cancer. Accounts of young men in this study stood in stark contrast to young women in many respects, and their general lack of engagement in genetic counselling research to date is worthy of addressing. Potential areas of research could focus on their risk perceptions and coping styles in the face of high cancer risk, and the reproductive decision-making of men at the life stage where starting family is a core developmental task. Lastly, continued research into health professional practice for young people with inherited disease is required to better understand the delivery of developmentally appropriate care, and how the structure proposed here may help to facilitate longitudinal care.

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15 Appendices

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Appendix 1 – Supplementary material

Table 30S. Summary of scoring process for critical appraisal using the SRQR checklist

Scoring instructions	For each criterion, mark whether the study fully meets the criteria (score with 2), partially meets criteria (score with 1), does not meet criteria (score with 0). Tally the total score across all 21 items in the SRQR checklist and give a final score out of 42. Convert to a percentage for the final percentage score.
Example item	Item 5 – Qualitative approach and research paradigm Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/interpretivist) is also recommended; rationale.
Example score	Does the study meet this criterion? Yes=2, Partial=1, No=0 Repeat for each criterion.

Abbreviations: SRQR, standards of reporting qualitative research. Example items reproduced from SRQR guidelines (O'Brien et al. 2014).

Table 31S. Types of care provided by health professionals to AYAs with, or at risk of, LFS

Types of care provided	Genetic counsellors (n=24)	Physicians (n=17)	Oncology nurse (n=2)	Total (n=43)
All types of care, n (%)	15 (62.5)	9 (52.9)	0 (0)	24 (55.8)
Predictive genetic testing to AYAs	17 (70.8)	11 (64.7)	0 (0)	28 (65.1)
Risk management	22 (91.7)	15 (88.2)	2 (100)	39 (90.7)
Psychosocial support	22 (91.7)	13 (76.5)	0 (0)	35 (81.4)
Sees under 18-year-olds in practice	22 (91.7)	12 (70.6)	0 (0)	34 (79.1)

Table 32S. Health professionals' experiences with facilitating predictive *TP53* genetic testing

	Number of times		Profession	
	≤5	≥6	Genetic counsellors	Physicians
Facilitated PGT for AYAs (n=26)	19	7	15	11
Facilitated PGT for minors ^a (n=14)	12	2	7	7

Abbreviations: PGT, predictive genetic testing

^aMinors are under 18 years of age.

Appendix 2 – List of presentations related to this thesis

*Forbes Shepherd, R., Keogh, L.A., Werner-Lin, A., Delatycki, M.B., Forrest, L.E. Negotiating autonomy and interdependence with family: how young people and health professionals navigate genetic testing for Li-Fraumeni syndrome. **Oral** presented at the European Conference of Human Genetics, 2020; Berlin, Germany.

*This presentation was awarded the ESHG New Investigator Award for 2020.

Forbes Shepherd, R., Keogh, L.A., Werner-Lin, A., Delatycki, M.B., Forrest, L.E. Adolescent and young adult experiences of genetic testing for Li-Fraumeni syndrome. **Oral** presented at the National Society of Genetic Counselors (NSGC) 38th Annual Conference, 2019; Salt Lake City, Utah, United States of America.

Forbes Shepherd, R., Keogh, L.A., Werner-Lin, A., Delatycki, M.B., Forrest, L.E. Adolescent and young adult experiences of genetic testing for Li-Fraumeni syndrome. **Keynote** speaker at Familial Aspects of Cancer: Research and Practice (KConFab), 2019; Kingscliff, Australia.

*Forbes Shepherd, R., Keogh, L.A., Werner-Lin, A., Delatycki, M.B., Forrest, L.E. Adolescent and young adult experiences of genetic testing for Li-Fraumeni syndrome. **Oral** presented at the Human Genetics Society of Australasia (HGSA) 43rd Annual Scientific Meeting, 2019; Wellington, New Zealand.

*This presentation was awarded the HGSA New Investigator Award for 2019.

Forbes Shepherd, R., Keogh, L.A., Werner-Lin, A., Delatycki, M.B., Forrest, L.E. 'It really does affect everything, even if you don't have cancer': The experiences of Australian adolescents and young adults with Li-Fraumeni syndrome. **Oral** presented at the 3rd Global Adolescent and Young Adult Cancer Congress, 2018; Sydney, Australia.

Forbes Shepherd, R., Keogh, L.A., Werner-Lin, A., Delatycki, M.B., Forrest, L.E. Vulnerability, Control and Development: The experiences of young Australians with Li-Fraumeni syndrome. **Oral** presented at the 'Growing up in the Genomic Era' Symposium, 2018; Sydney, Australia.

Forbes Shepherd, R., Keogh, L.A., Werner-Lin, A., Delatycki, M.B., Forrest, L.E. 'It really does affect everything, even if you don't have cancer': The experiences of Australian adolescents and young adults with Li-Fraumeni syndrome. **Oral** presented at Familial Aspects of Cancer: Research and Practice (KConFab), 2018; Kingscliff, Australia.

Forbes Shepherd, R., Keogh, L.A., Werner-Lin, A., Delatycki, M.B., Forrest, L.E.
Predictive genetic testing for Li-Fraumeni syndrome in minors: an ethical bind?
Oral presented at the Hastings Centre for Bioethics, 2018; Garrison, New York,
United States of America.

Forbes Shepherd, R., Keogh, L.A., Werner-Lin, A., Delatycki, M.B., Forrest, L.E. The
experiences of Australian adolescents and young adults with Li-Fraumeni
syndrome. **Oral** presented at the Clinical Genetics Branch, National Cancer
Institute, 2018; Rockville, Maryland, United States of America.

Forbes Shepherd, R., Keogh, L.A., Werner-Lin, A., Delatycki, M.B., Forrest, L.E. The
experiences of Australian adolescents and young adults with Li-Fraumeni
syndrome. **Oral** presented at Interfaculty Centre for Biomedical Ethics and Law,
KU Leuven, 2018; Leuven, Belgium.

Forbes Shepherd, R., Keogh, L.A., Werner-Lin, A., Delatycki, M.B., Forrest, L.E. The
psychosocial experiences of Australian adolescents and young adults with Li-
Fraumeni syndrome: a qualitative study. **Poster** presented at European Meeting
on Psychosocial Aspects of Genetics, 2018; Milan, Italy.

Forbes Shepherd, R., Keogh, L.A., Werner-Lin, A., Delatycki, M.B., Forrest, L.E. The
psychosocial experiences of Australian adolescents and young adults with Li-
Fraumeni syndrome: a qualitative study. **Poster** presented at the World Congress
on Genetic Counselling, 2017; Cambridge, UK.

Appendix 3 – Human Research Ethics Committee and Governance letters

Appendix 3A – Peter MacCallum Cancer Centre Human Research Ethics Committee Ethical Approval for HREC/16/PMCC/196

Peter MacCallum Cancer Centre
305 Grattan Street
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Locations
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Bendigo
Box Hill
Moorabbin
Sunshine



PETER MACCALLUM CANCER CENTRE HUMAN RESEARCH ETHICS COMMITTEE [EC00235] ETHICAL APPROVAL

HREC Reference No: HREC/16/PMCC/196

Peter Mac Project No: 16/152

HREC Approval Date: 22 February 2017

Project Title: The lived experiences of young Australians with Li-Fraumeni Syndrome: are their psychosocial needs being met?

Coordinating Principal Investigator: Dr Laura Forrest

I am pleased to advise that the above project has **received ethical approval** from the Peter MacCallum Cancer Centre Human Research Ethics Committee (HREC). The HREC confirms that your proposal meets the requirements of the National Statement on Ethical Conduct in Human Research (2007). This HREC is organised and operates in accordance with the National Health and Medical Research Council's (NHRMC) National Statement on Ethical Conduct in Human Research (2007), and all subsequent updates, and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines).

Ethical approval for this project applies at the following sites:

Site
Peter MacCallum Cancer Centre
Royal Melbourne Hospital
Austin Health
Victorian Clinical Genetics Service (Murdoch Children's Research Institute, Royal Children's Hospital)

Approved Documents

The following documents have been reviewed and approved:

Document	Version	Date
Protocol	3	25 January 2017
Attachment A1 Master Participant Information Sheet and Consent Form Adult providing own consent	2	25 January 2017
Attachment A2 Master Participant Information Sheet and Consent Form Adolescent/Young Adult under 18 years	1	25 January 2017
Attachment B Master Participant Information Sheet and Consent Form Parent/Guardian consenting on behalf of participant	2	25 January 2017
Attachment C Master Cover Letter	1	28 November 2016
Attachment D Phone Script Adult	1.1	28 November 2016
Attachment E Phone Script Child	1.1	28 November 2016
Attachment F Initial Email	1.2	28 November 2016
Attachment G SMS template	1.1	28 November 2016

Attachment H RFS_LFS Study Brochure	1.2	28 November 2016
Attachment I Expression of Interest slip	1	28 November 2016
Attachment J1 Interview Guide (affected carrier)	1	25 January 2017
Attachment J2 Interview Guide (unaffected carrier)	1	25 January 2017
Attachment J3 Interview Guide (unaffected at risk)	1	25 January 2017
Attachment K Web Content	1	28 November 2016

Governance Authorisation

Governance Authorisation is required at each site participating in the study before the research project can commence at that site. You are required to provide a copy of this HREC approval letter to the principal investigator for each site covered by this ethics approval for inclusion in the site specific assessment application.

Conditions of Ethical Approval

- You are required to submit to the HREC:
 - An Annual Progress Report (that covers all sites listed on the approval) for the duration of the project. This report is due on the anniversary of HREC approval. Continuation of ethics approval is contingent on submission of an annual report, due within one month of the approval anniversary. Failure to comply with this requirement may result in suspension of the project by the HREC.
 - A comprehensive Final Report upon completion of the project.
- Submit to the reviewing HREC for approval any proposed amendments to the project including any proposed changes to the Protocol, Participant Information and Consent Form/s and the Investigator Brochure.
- Notify the reviewing HREC of any adverse events that have a material impact on the conduct of the research in accordance with the NHMRC Position Statement: *Monitoring and reporting of safety for clinical trials involving therapeutic products May 2009*.
- Notify the reviewing HREC of your inability to continue as Coordinating Principal Investigator.
- Notify the reviewing HREC of the failure to commence the study within 12 months of the HREC approval date or if a decision is taken to end the study at any of the sites prior to the expected date of completion.
- Notify the reviewing HREC of any matters which may impact the conduct of the project.
- If your project involves radiation, you are legally obliged to conduct your research in accordance with the Australian Radiation Protection and Nuclear Safety Agency Code of Practice 'Exposure of Humans to Ionizing Radiation for Research Purposes' Radiation Protection series Publication No.8 (May 2005)(ARPANSA Code).

Please note: Template forms for reporting Amendments, Adverse events, Annual/Final reports, etc. can be accessed from: <https://www2.health.vic.gov.au/about/clinical-trials-and-research/clinical-trial-research/how-to-make-an-hrec-application-for-clinical-trials> or www.petermac.org/research.

The HREC may conduct an audit of the project at any time.

Yours sincerely,



Dr Dianne Snowden
 Manager Human Research Ethics & Governance
 Ethics Committee Secretariat
 T: 8559 7540
 E: ethics@petermac.org

Appendix 3B – Peter MacCallum Cancer Centre Human Research Ethics Committee Ethical Approval (most recent amendment)

Peter MacCallum Cancer Centre
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Sunshine



MEMORANDUM

To: Dr Laura Forrest
From: Ethics Committee Secretariat
CC: Mr Rowan Forbes Shepherd; OCR
Date: 07 February 2019
Re: **Peter Mac Project No:** 16/152
AU RED HREC Reference No: HREC/16/PMCC/196
Study Title: The lived experiences of young Australians with Li-Fraumeni Syndrome: are their psychosocial needs being met?

We are pleased to advise that the amendment submission dated 08 January 2019 has **received ethical approval** from the Peter MacCallum Cancer Centre Human Research Ethics Committee. This submission also satisfies **Peter Mac Research Governance** requirements and may now be conducted at the Peter MacCallum Cancer Centre.

Ethical approval for this amendment applies at the following sites:

Site
Peter MacCallum Cancer Centre
Royal Melbourne Hospital
Austin Health
Victorian Clinical Genetics Service (Murdoch Children's Research Institute, Royal Children's Hospital)
Royal Brisbane and Women's Hospital, (QLD)
King Edward Memorial Hospital, (WA)

The following documents have been reviewed and approved:

Document	Version	Date
Protocol 'The lived experiences of young Australians with Li-Fraumeni Syndrome: are their psychosocial needs being met?'	8	08 January 2019

Governance Authorisation is required at each participating site named above before the amendment can commence at each site. Principal Investigators must be provided a copy of this approval and consult with their Research Governance Office regarding submission requirements.

Should you have any questions about your project please contact the Ethics Committee Secretariat on (03) 8559 7540 or ethics@petermac.org. Submission guidelines, forms and standard operating procedures are available on the ethics website: www.petermac.org/research/doing-research-us/ethics-governance

Kind Regards,

Robyn Summerhayes
Ethics Committee Secretariat

The Peter MacCallum Cancer Centre Human Research Ethics Committee and its subcommittees are organised and operate in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Research Involving Humans (2018), and all subsequent updates, and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines). Please be advised that the Principal Researcher and Associate Researchers named on the application did not participate in deliberative discussions or decision-making regarding the project.

Appendix 3C – Peter MacCallum Cancer Centre Governance Authorisation approval letter

Peter MacCallum Cancer Centre
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GOVERNANCE AUTHORISATION

SITE SPECIFIC ASSESSMENT (SSA) APPROVAL TO CONDUCT A RESEARCH PROJECT PETER MACCALLUM CANCER CENTRE

Reviewing HREC: Peter MacCallum Cancer Centre Ethics Committee [EC00235]
HREC Reference No: HREC/16/PMCC/196
HREC Approval Date: 22 February 2017

Peter Mac Project No: 16/152
SSA Reference No: SSA/17/PMCC/37
SSA Authorisation Date: 14 March 2017

Project Title: The lived experiences of young Australians with Li-Fraumeni Syndrome: are their psychosocial needs being met?

Principal Investigator: Dr Laura Forrest/Mr Rowan Forbes Shepherd

I am pleased to advise that the above project is authorised to be conducted at the Peter MacCallum Cancer Centre. This approval is subject to compliance with the conditions set out below and any conditions specified by the reviewing HREC.

Approved Documents:

Document	Version	Date
Protocol	3	25 January 2017
PMCC Participant Information and Consent Form Adult providing own consent (<i>based on Master Participant Information and Consent Form Adult providing own consent version 2 dated 25 January 2017</i>)	1.0	6 March 2017
PMCC Participant Information and Consent Form Adolescent/Young Adult under 18 years (<i>based on Master Participant Information and Consent Form Adolescent/Young Adult under 18 years version 1 dated 25 January 2017</i>)	1.0	6 March 2017
PMCC Participant Information and Consent Form Parent/Guardian consenting on behalf of participant (<i>based on Master Participant Information and Consent Form Parent/Guardian consenting on behalf of participant version 2.0 dated 25 January 2017</i>)	1.0	6 March 2017
Attachment C Master Cover Letter	1	28 November 2016
Attachment D Phone Script Adult	1.1	28 November 2016
Attachment E Phone Script Child	1.1	28 November 2016
Attachment F Initial Email	1.2	28 November 2016
Attachment G SMS template	1.1	28 November 2016

Attachment H RFS_LFS Study Brochure	1.2	28 November 2016
Attachment I Expression of Interest slip	1	28 November 2016
Attachment J1 Interview Guide (affected carrier)	1	25 January 2017
Attachment J2 Interview Guide (unaffected carrier)	1	25 January 2017
Attachment J3 Interview Guide (unaffected at risk)	1	25 January 2017
Attachment K Web Content	1	28 November 2016

Research governance

As Principal Investigator, you are required to:

1. Comply with the Investigator's responsibilities as outlined in the *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)*.
2. Submit a copy of this letter to the person responsible for radiation safety at Peter MacCallum Cancer Centre. **This condition only applies if** the project involves exposure to ionising radiation that exceeds dose constraints, and the Medical Physicist's report has advised that the project needs to be added to the site's *Licence for Research Involving Human Volunteers* issued by the Department of Health Radiation Safety Section (for more information, visit <http://www.health.vic.gov.au/radiation/>). *Note: If the Medical Physicist's report has advised that the project needs to be added to the site's licence, the project cannot commence at site until you have confirmed that the project has been added to the site's licence.*
3. Notify the Peter MacCallum Cancer Centre Research Governance Office (RGO) of:
 - The actual start date of the project at Peter MacCallum Cancer Centre.
 - Any amendments to the project after these have been approved by the reviewing HREC.
 - Any adverse events involving patients of Peter MacCallum Cancer Centre, in accordance Peter MacCallum Cancer Centre Governance Guideline001 http://www1.petermac.org/Ethics/standardop_proc_guide.html.
 - Any changes to the indemnity, insurance arrangements or Clinical Trial Research Agreement for this project. This includes changes to the project budget or other changes which may have financial or other resource implications at Peter MacCallum Cancer Centre.
 - Your inability to continue as Principal Investigator or any other change in research personnel involved in this project.
 - Failure to commence the study within 12 months of the Governance authorisation date or if a decision is taken to end the study at this site.
 - Any other unforeseen events.
 - Any other matters which may impact the conduct of the project at Peter MacCallum Cancer Centre.
4. Ensure that HREC approval remains current for the entire duration of the project. Investigators undertaking projects without current Reviewing HREC approval risk their indemnity, funding and publication rights.
5. Submit an annual progress report every 12 months for the duration of the project. This report is due on the anniversary of HREC approval. Continued SSA approval is contingent on receipt of an annual report by the RGO. In addition, a comprehensive final report should be submitted to the RGO upon completion of the project.

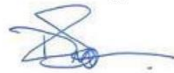
You must also abide by the following requirements:

6. Where applicable, ensure that the CTN has been electronically lodged to the TGA by the sponsor.
7. For clinical trials where Peter MacCallum Cancer Centre is the Sponsor, you are required to contact the Office for Cancer Research [ocr@petermac.org] to organise submission of the electronic Clinical Trial Notification (e-CTN) to the TGA. This must be completed before commencement of your project.
8. It is the Principal Investigator's responsibility to ensure that copies of the complete submitted e-CTN and TGA issued acknowledgement are included in the study Site File for the project at this site.
9. Ensure that the Clinical Trial Research Agreement (CTRA) and Indemnities (or other research agreements as applicable) are fully executed, i.e. signed by all parties; and an original version (or copy) placed in the study file.

Please note: Template forms for reporting Amendments, Adverse events, Annual/Final reports, etc. can be accessed from: <https://www2.health.vic.gov.au/about/clinical-trials-and-research/clinical-trial-research/how-to-make-an-hrec-application-for-clinical-trials> or www.petermac.org/research

The RGO may conduct an audit of the project at any time.

Yours sincerely,



Dr Dianne Snowden
Manager Human Research Ethics & Governance
Ethics Committee Secretariat
T: (03) 8559 7540
E: ethics@petermac.org

Patron: The Honourable Linda Dessau, AM – Governor of Victoria

Appendix 3D – Peter MacCallum Cancer Centre Clinical Research Sponsorship Committee approval letter

Peter MacCallum Cancer Centre

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Moorabbin
Sunshine



14th Feb 2017.

Dear Rowan Forbes Shepherd,

RE: The lived experiences of young Australians with Li-Fraumeni Syndrome: are their psychosocial needs being met?. Protocol Version 3, 25th January 2017.

The Clinical Research Sponsorship Committee has approved the application for Peter MacCallum Cancer Centre to act as Sponsor for the above titled project.

The project may now proceed for Ethical and Governance review. If any changes are made to the protocol during ethics approval then an updated, tracked version should be submitted to the sponsorship committee for review.

Please note the following conditions of sponsorship:

- All SAEs/SUSARs must be reported to and reviewed by the sponsor
- All protocol deviations/violations must be reported to and reviewed by the sponsor
- All protocol amendments must be reviewed and approved by the sponsor prior to ethics submission
- Investigator Brochure updates must be reviewed by the sponsor
- All changes to contracts must be reviewed and approved by the sponsor
- All changes to, or extended absences of, PI's to be reported to the sponsor
- All changes to funding/budgets must be reported to the sponsor
- Sponsor approval required when additional study sites are proposed
- Provide Sponsor with evidence of approval from the relevant HREC(s)/Governance Offices
- Sponsor must be notified of recruitment closure or suspension
- Sponsor must be notified of trial completion

SAEs/SUSARs should be emailed to SafetyReporting@petermac.org

All other sponsor communication should be emailed to ocr@petermac.org

We wish you well with this study.

Kind Regards,


Professor John Seymour
Co-Director, Division of Cancer Medicine
Associate Research Director (Clinical)
Chair, Clinical Research Sponsorship Committee

cc: Hon. The Honourable Linda Dessau, AM – Governor of Victoria

Appendix 3E – Victorian Clinical Genetics Service/The Royal Children’s Hospital Governance Authorisation

GOVERNANCE AUTHORISATION

12 April 2017

Professor Martin Delatycki
Victorian Clinical Genetics Service
Murdoch Childrens Research Institute



Dear Prof Delatycki

Project Title: The lived experiences of young Australians with Li-Fraumeni Syndrome: are their psychosocial needs being met?

HREC Reference Number: HREC/16/PMCC/196
SSA Reference Number: SSA/17/RCHM/87
RCH HREC Reference Number: 37057A

I am pleased to advise that the above project has received governance authorisation at the Melbourne Children’s Campus (incorporating The Royal Children’s Hospital, Murdoch Childrens Research Institute and the University of Melbourne Department of Paediatrics).

Governance Authorisation Date: 12 April 2017*

Please note that governance authorisation is ongoing, subject to the submission of an annual report on the anniversary of approval.

Authorised Documents:

In addition to the documents listed on the HREC approval letter, the following documents have been authorised for use at the Melbourne Children’s Campus:

Document	Version	Date
Protocol	3.0	25 January 2017
VCGS PIS- Adolescent/Young Adult under 18 years	2.0	6 April 2017
VCGS Parent/Guardian consenting on behalf of participant	2.0	6 April 2017
VCGS PICF, adult providing own consent	2.0	6 April 2017
Attachment D Phone Script Adult	1.1	28 November 2016
Attachment E Phone Script Child	1.1	28 November 2016
Attachment F Initial Email	1.2	28 November 2016
Attachment G SMS template	1.1	28 November 2016
Attachment H RFS_LFS Study Brochure	2.0	14 March 2017
Attachment I (VCGS) Expression of Interest slip	1.0	28 November 2016
Attachment J1 Interview Guide (affected carrier)	1.0	25 January 2017
Attachment J2 Interview Guide (unaffected carrier)	1.0	25 January 2017
Attachment J3 Interview Guide (unaffected at risk)	1.0	25 January 2017
Attachment K Web Content	2.0	20 March 2017

Conditions of Governance Authorisation

As Principal Investigator, you are required to:

1. Comply with the Investigator’s responsibilities as outlined in the *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)*.
2. Submit a copy of this letter to the person responsible for radiation safety at this site. **This condition only applies if** the project involves exposure to ionising radiation that exceeds dose constraints, and the Medical Physicist’s report has advised that the project needs to be added to the site’s *Licence for Research Involving Human Volunteers* issued by the Department of Health Radiation Safety Section (for more information, visit <http://www.health.vic.gov.au/radiation/>).

Note: If the Medical Physicist's report has advised that the project needs to be added to the site's licence, the project cannot commence at site until you have confirmed that the project has been added to the site's licence.

3. Notify the RGO of:
 - The actual start date of the project.
 - Any amendments to the project after these have been approved by the reviewing HREC.
 - Any adverse events involving patients at this site, in accordance with the NHMRC Position Statement: *Monitoring and reporting of safety for clinical trials involving therapeutic products May 2009*.
 - Any changes to the indemnity, insurance arrangements or Clinical Trial Research Agreement for this project. This includes changes to the project budget or other changes which may have financial or other resource implications at this site.
 - Your inability to continue as Principal Investigator or any other change in research personnel involved in this project.
 - Failure to commence the study within 12 months of the Reviewing HREC approval date or if a decision is taken to end the study at this site.
 - Any other unforeseen events.
 - Any other matters which may impact the conduct of the project at this site.
4. Ensure that HREC approval remains current for the entire duration of the project. Investigators undertaking projects without current Reviewing HREC approval risk their indemnity, funding and publication rights.
5. Submit an annual progress report every 12 months for the duration of the project. This report is due on the anniversary of HREC approval. Continued Governance Authorisation is contingent on receipt of an annual report by the RGO. In addition, a comprehensive final report should be submitted to the RGO upon completion of the project.

You must also abide by the following requirements:

1. Where applicable, ensure that the CTN has been electronically lodged to the TGA by the sponsor.
2. For clinical trials where the site is the Sponsor, you are required to contact MCTC to organise submission of the electronic Clinical Trial Notification (e-CTN) to the TGA. This must be completed before commencement of your project.
3. It is the Principal Investigator's responsibility to ensure that copies of the complete submitted e-CTN and TGA issued acknowledgement are included in the study Site File for the project at this site.
4. Ensure that the Clinical Trial Research Agreement (CTRA) and Indemnities (or other research agreements as applicable) are fully executed, i.e. signed by all parties; and an original version (or copy) placed in the study file.

The RGO may conduct an audit of the project at any time.

If you have any matters that arise regarding conduct of the research at this site, please ensure you contact the Research Governance Manager on 03 9345 5044.

I wish you and your colleagues every success in your research.

Yours sincerely



Eman Nafea, PhD
Research Governance Manager
Research Ethics and Governance
The Royal Children's Hospital Melbourne
Phone : (03) 9345 54491
Email : Eman.Nafea@rch.org.au
Web : www.rch.org.au

Appendix 3F – Royal Brisbane and Women’s Hospital Governance Authorisation



Royal Brisbane and Women’s Hospital
Metro North Hospital and Health Service



**Queensland
Government**

Enquiries to: Dr Marilyn Banks, Executive Director of Research
Research Services, MNHHS-RBWH
Phone: 07 3646 8579

Dr Helen Marfan
Genetic Health QLD
MNHHS-RBWH
Herston QLD 4029

Dear Dr Marfan

Re: HREC/16/PMCC/196: The lived experiences of young Australians with Li-Fraumeni Syndrome: are their psychosocial needs being met?

Thank you for submitting your research protocol approved by the Peter MacCallum Cancer Centre HREC approval originally on the 22 Feb 2017 and then Amendments approved on the 22 March 2017, 25 July 2017, 6 March 2018 and 18 May 2018 twice. I am pleased to inform you that authorisation has been granted for this study to be conducted at the MNHHS-RBWH. Your trial meets the principles and practices set out in the Australian Code for the Responsible Conduct of Research (2007 Universities Australia, updated 2014) and the ICH Harmonised Tripartite Good Clinical Practice (GCP) Guidelines.

The following documents approved by above mentioned HREC are specifically accepted for the MNHHS-RBWH site:

Document	Version	Date
<i>Covering Letter to RGO</i>		17 May 2018
<i>Human Research Ethics Application (Submission Code:</i>		5 Dec 2016
<i>Application: SSA (Submission Code: AU/3/E79638</i>		24 May 2018
<i>Protocol</i>	7	27 April 2018
<i>GHQ PICF Adult providing own consent based on the Mater PICF version 4 dated 18 April 2018</i>	1	18 April 2018
<i>GHQ PICF Adolescent /Young Adult under 18 years based on the Master Adolescent /Young Adult under 18 years PICF version 2 dated 18 April 2018</i>	1	18 April 2018
<i>GHQ PICF Parent/Guardian consenting on behalf of participant based on the Master Parent/Guardian consenting on behalf of participant PICF version 3 dated 18 April 2018</i>	1	18 April 2018
<i>GHQ Phone script_ADULT_LFS</i>	1	21 May 2018
<i>GHQ Phone script_CHILD_LFS</i>	1	21 May 2018

Royal Brisbane and Women’s Hospital – we don’t smoke here anymore

1

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Royal Brisbane and Women’s Hospital
Butterfield Street
Herston

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Post Office
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Phone

(07) 3646 8111

Fax

(07) 3646 4240



Royal Brisbane and Women's Hospital
Metro North Hospital and Health Service



Queensland
Government

<i>GHQ Initial_email_LFS</i>	1	21 May 2018
<i>GHQ SMS_template_LFS</i>	1	21 May 2018
<i>GHQ Study_A4_flyer</i>	1	21 May 2018
<i>GHQ EOI_slip</i>	1	21 May 2018
<i>GHQ Interview guide (affected carrier)</i>	1	21 May 2018
<i>GHQ Interview guide (unaffected carrier)</i>	1	21 May 2018
<i>GHQ Invite letter_carrier</i>	1	17 April 2018
<i>Web content</i>	2	20 Mar 2017

Please email HREC approved amendments to RBWH-RGO@health.qld.gov.au and provide the description and the rationale. This will assist in the governance review to see if any further documentation is required for our MNHHS-RBWH site.

When the study commences please complete the Commencement form and send it to the HREC office with a copy to the Research Governance office. Forms can be found at the MNHHS Research Web site: <https://www.health.qld.gov.au/metronorth/research/ethics-governance/post-approval-reporting/default.asp>.

If you have any questions relating to this authorisation please contact the Research Governance Office on 3646 8579.

I wish you continued success with your research.

Yours sincerely

Merrilyn Banks

Digitally signed by Merrilyn Banks
DN: cn=Merrilyn Banks, o=RBWH, ou=Executive Director
Research, email=merrilyn.banks@health.qld.gov.au, c=AU
Date: 2018.07.09 09:16:23 +10'00'

Dr Merrilyn Banks
Executive Director of Research
Research Services, MNHHS-RBWH

Royal Brisbane and Women's Hospital – we don't smoke here anymore

2

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Appendix 3G – King Edward Memorial Hospital Governance Authorisation



Government of Western Australia
Department of Health

Dr Louise Farrell
Level 2 A block, 374 Bagot Road
SUBIACO Western Australia 6008

31 July 2018

Dr Catherine Kiraly-Borri
KEMH
L3, 374 Bagot Road
SUBIACO Western Australia 6008

Dear Dr Kiraly-Borri

PRN: RGS0000001002
Project Title: The lived experiences of young Australians with Li-Fraumeni Syndrome: are the
ir psychosocial needs being met?
Protocol Number: Version 7, 27 APR 2018

Thank you for submitting the above research project for governance review. I am pleased to advise you that King Edward Memorial Hospital has granted authorisation for this research project to be conducted at the following participating site(s):

King Edward Memorial Hospital

In addition to those approved by the Human Research Ethics Committee (HREC), the approved site specific documents include:

Document	Version	Version Date
GSWA_Attachment H_Study_A4_flyer_v1_21.05.18	1	21/05/2018
GSWA_Attachment L_Invite letter_carrier_v1_17.04.18	1	17/04/2018
GSWA_Attachment A1_PICF_self_LFS_v1_18.04.18	1	18/04/2018
GSWA_Attachment B_PICF_Parent and Guardian_LFS_v1_18.04.18	1	18/04/2018

Site authorisation of this project is valid from 31 July 2018 subject to continued ethical approval from the Peter MacCallum Cancer Centre Human Research Ethics Committee and compliance with the 'Conditions of Site Authorisation for a Research Project' (Appendix A). To find the original letter and any possible attachments, [click here](#) when logged into RGS.

Should you have any queries about King Edward Memorial Hospital's consideration of your project, please contact the Research Governance Office at kemh.rgo@health.wa.gov.au or on 08 6458 1667. The Research Governance Office's Standard Operating Procedures are available from the Research Governance Office.

I wish you every success in your research.

Yours sincerely

Dr Louise Farrell
Acting Director Clinical Services

Appendix 3H – Peter MacCallum Cancer Centre Human Research Ethics Committee Ethical Approval for LNR/17/PMCC/281

Peter MacCallum Cancer Centre

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Sunshine



Peter Mac

Peter MacCallum Cancer Centre
Victoria Australia

MEMORANDUM

To: Mr Rowan Forbes Shepherd
From: Ethics Committee Secretariat
Date: 24 May 2018
Re: **Peter Mac Project No: 17/222L**
HREC No: LNR/17/PMCC/281
Study Title: A national survey of health professionals' practice when caring for young Australians with Li-Fraumeni Syndrome

We are pleased to advise that the amendment submission dated 14 May 2018, has **received ethical approval** from the Peter MacCallum Cancer Centre Human Research Ethics Committee. The amendment also **satisfies Peter Mac Research Governance requirements** and may now be conducted at this site.

The following documents have been reviewed and approved:

Document	Version/Edition	Date
Protocol	3	22 May 2018
Appendix 4- Participant Information Sheet and Consent Form & Survey	1	14 May 2018
Appendix 5a- Invite to survey for clinical genetics services	1	14 May 2018
Appendix 5b- Follow up to survey for clinical genetics services	1	14 May 2018
Appendix 6- Survey Advertisement	1	14 May 2018

Should you have any questions about your project please contact the Ethics Committee Secretariat on (03) 8559 7540 or ethics@petermac.org. Submission guidelines, forms and standard operating procedures are available on the ethics website: <http://www1.petermac.org/Ethics/default.htm>

Kind Regards,

Ethics Committee Secretariat

The Peter MacCallum Cancer Centre Human Research Ethics Committee and its subcommittees are organised and operate in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Research Involving Humans (2007), and all subsequent updates, and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines).

Please be advised that the Principal Researcher and Associate Researchers named on the application did not participate in deliberative discussions or decision-making regarding the project.

Chapter 15: Appendices

Please refer to the Peter MacCallum Cancer Centre Ethics Committee Secretariat website (<http://www.petermac.org/research>) for access to forms, policies and guidelines and other information and news concerning research at Peter MacCallum Cancer Centre.

The Peter MacCallum Cancer Centre Ethics Committee is organised and operates according to the NHMRC National Statement on Ethical Conduct in Human Research (2007) and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and the Health Privacy Principles enumerated in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines).

Please be advised that the Principal Researcher and any Associate Researchers named on the application did not participate in deliberative discussions or decision-making regarding the project.

Yours sincerely,



Dr. Dianne Snowden
Manager, Human Research Ethics & Governance
Ethics Committee Secretariat
T: (03) 8559 7540
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Patron: The Honourable Linda Dessau, AM – Governor of Victoria

Appendix 3I – Peter MacCallum Cancer Centre Human Research Ethics Committee Ethical Approval for LNR/17/PMCC/281 (most recent amendment)

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PETER MACCALLUM CANCER CENTRE AUTHORISATION TO CONDUCT A RESEARCH PROJECT

HREC Reference No: LNR/17/PMCC/281
SSA Reference No: LNRSSA/18/PMCC/2
Peter Mac Project No: 17/222L

Project Title: A national survey of health professionals' practice when caring for young Australians with Li-Fraumeni Syndrome

Principal Investigator: Mr Rowan Forbes Shepherd

Approval Date: 4 January 2018

I am pleased to advise that the above project has **received ethical approval and satisfies Peter Mac research governance requirements** and may now be conducted at Peter MacCallum Cancer Centre. Conduct of the project is subject to compliance with the conditions set out below.

Approved Documents:

Document	Version	Date
Protocol	02	18 December 2017
Appendix 1 Invite Letter Survey Development	2	18 December 2017
Appendix 2 Invite Letter Survey Piloting	1	18 December 2017
Appendix 3 Interview Guide	1	4 December 2017

In order to comply with the National Statement on Ethical Conduct in Human Research (2007 and updates), Guidelines for Good Clinical Research Practice and local research policies and guidelines, you are required to:

- Submit an Annual Progress Report every 12 months for the duration of the project. *Note: Continuation of ethics approval is contingent on submission of an annual report in a timely manner;*
- Submit a comprehensive Final Report upon completion of the project;
- Submit any proposed amendments to the project including any proposed changes to any of the approved documents;
- Notify any unexpected developments in the project with ethical implications;
- Notify any change in Principal Investigators/Associate Investigators involved in the project at Peter MacCallum Cancer Centre;
- Notify if a decision is taken to end the project prior to the expected date of completion.

The Peter MacCallum Cancer Centre Ethics Committee may conduct an audit of the project at any time.

Appendix 4 – Interview guide

Themes	Key questions and follow-ups	Prompts
Introduction	State full name, DOB, carrier and cancer status. Can you tell me a little bit about yourself?	Age, family, work/study, living situation, partner, hobbies/interests
Family	Tell me about your family's experiences with cancer. When did you first become aware of LFS in your family? What was that like? Has anyone in your family had cancer or genetic testing for LFS? What do you know about how they decided to/not to get testing?	How has your experience of LFS changed over time?
Genetic counselling and testing	Can you tell me about your experience of finding out you have LFS? Alternative opening: You said before that you were diagnosed with cancer, can you tell me more of your experience? Tell me about the process of counselling and genetic testing. I am interested in your/your family's decision making around genetic testing for LFS. Can you tell me about that? How do you feel about your decision to undergo genetic testing? What were your thoughts leading up to the disclosure of your genetic test result? What impact has your test result had on your family? If you had friend considering genetic testing for TP53, what advice would you give them?	What lead you to have GT? What was it like making that decision? Who was involved in making that decision? What do you think of getting testing now? What did you think your test result would be? What made you think that way?

Coming of age with Li-Fraumeni syndrome: perspectives of young people and health professionals

Identity	What is it like to have LFS as a young person? What does LFS mean to you? When speaking with other people for the first time, how do you describe LFS? What are your future plans? How does LFS fit into those plans?	Education, employment/career and family.
Risk perception	What have you been told you about your chances of developing cancer (again) as you get older? Do you believe you will get cancer? How does that make you feel?	
If they have developed cancer, ask about the next two topics		
Body image	Since your cancer diagnosis, how do you think about your health? Your body?	Has this changed over time? How?
Fertility	Did you have any discussions regarding fertility before cancer treatment? What was that like? Are you happy that you discussed it?	If not, is it something you are aware of now? Would you have liked to know about it before?
Risk management	What kinds of recommendations have you received to keep on top of your cancer risk? What kinds of screening or risk management advice have you received? What advice have you followed? Tell me what you think of screening. Do you think it helps? How? If you were to offer advice to a friend considering screening, what would you tell them? What are your habits like with alcohol and smoking? How do these fit into your life?	Whole-body risk mgmt. participants: How often are your appointments? What do you have to do? What is it like before and after an appointment? Young women: what have you been told about risk-reducing surgery? How would you feel if you didn't have screening available? Has this changed over time?

Chapter 15: Appendices

Family planning/formation	Do you think you'll have a family in the future (or more children)? Tell me about your plans	How does LFS fit into those plans? What do you think about your children's risk of LFS?
Supports	Who are the most important people in your life? Who else is part of your life? Tell me about your friendship group. Do you talk to your friends about LFS? What's your relationship like with your family? Is LFS something you talk about with family much? Who are the main supports for you in your family? How do they support you? What role do health professionals play in supporting you? How? How do you feel about health professionals constantly checking in on you? (If family members with LFS): how do you support them? (If no fam members): how would you support a young person with LFS if they came to you? Are you in a relationship currently? Can you tell me about it? How does LFS/cancer affect your relationship? Are you dating at the moment? What is that like with LFS? How does LFS influence your future relationship plans?	Has this changed since you learnt about LFS? Parents/siblings. Who comes with you to any appointments you might have? Where are you living at the moment? What are you not getting in terms of support, but that you'd like to have?

Appendix 5 – List of other published work during candidature

Forbes Shepherd, R., Browne, T. K., and Warwick, L. 2017. 'A Relational Approach to Genetic Counseling for Hereditary Breast and Ovarian Cancer', *Journal of Genetic Counseling*, 26: 283-99.

*Rasmussen, V., *Forbes Shepherd, R., Forrest, L. E., James, P. A., and Young, M.-A. 2019. 'Men's experiences of recontact about a potential increased risk of prostate cancer due to Lynch syndrome: "Just another straw on the stack"', *Journal of Genetic Counseling*, 28: 750-59.

*Co-first authors

Tutty, E., Petelin, L., McKinley, J., Young, M.-A., Meiser, B., Rasmussen, V. M., Forbes Shepherd, R., James, P. A., and Forrest, L. E. 2019. 'Evaluation of telephone genetic counselling to facilitate germline BRCA1/2 testing in women with high-grade serous ovarian cancer', *European Journal of Human Genetics*, 27: 1186-96.