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*"It wasn't just for me": Motivations and implications of genetic testing for women at a low risk of hereditary breast and ovarian cancer syndrome*

Running title: GENETIC TESTING WITH LOW HEREDITARY BREAST AND OVARIAN CANCER RISK

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## Abstract

### Objective

Genetic testing for hereditary breast and ovarian cancer (HBOC) due to pathogenic variants in *BRCA1* or *BRCA2* is why most women present to familial cancer centers. Despite being assessed as low risk for HBOC, many women proceed with genetic testing. This study explored the genetic testing experiences of unaffected women at low risk of HBOC to clarify what motivates these women to have testing, and what are the implications of the results.

### Methods

A qualitative approach was taken. Participants included women who had genetic testing for HBOC from 2016-2018 at the Parkville Familial Cancer Centre in Melbourne, Australia. In-depth, semi-structured interviews were conducted, and thematic analysis was undertaken on transcripts; transcripts were coded, codes were organized into a hierarchical system of categories/subcategories, and key themes were identified.

### Results

Analysis of 19 transcripts identified five themes: family underpinned all motivators for HBOC genetic testing; health professionals were influential throughout the process; participants were planning for a positive result; results influenced screening-anxiety and frequency; and negative results gave participants relief in many different ways. The three participants with positive results reported feeling shocked at the results and empowered giving this information to family members.

## Conclusions

Women at low HBOC risk may be motivated to seek genetic testing, and access to this is increasingly offered through non-genetic health professionals. Professionals can support clients through genetic testing by recognizing familial experiences, providing accurate information, addressing risk perceptions, and understanding cancer anxiety felt by many women.

Keywords: *BRCA1*, *BRCA2*, cancer, coping, decision making, genetic counselling, genetics, oncology, psychosocial, qualitative

## 1. Introduction

Awareness and uptake of genetic testing for hereditary breast and ovarian cancer syndrome (HBOC) has dramatically increased since the publicization of the topic by actor Angelina Jolie.<sup>1,2</sup> In light of Jolie's article detailing her experience of carrying a *BRCA1* pathogenic variant, many more women are being referred to familial cancer centers globally to obtain risk-management advice and access genetic testing for HBOC.<sup>1,3</sup> HBOC is caused by pathogenic variants in the DNA repair genes *BRCA1* and *BRCA2*, and drastically increases a female's lifetime risk (to age 80) of breast cancer to 69-72%, and of ovarian cancer to 17-44%.<sup>4</sup> Importantly, risk of HBOC is distinct from the risk of breast and ovarian cancer and each is assessed separately. An individual can simultaneously be at a low risk of HBOC and a high risk of breast/ovarian cancer as cancer can be hereditary, polygenic, and environmental.<sup>5</sup>

Given that HBOC is uncommon, affecting approximately 1 in 400 women,<sup>5</sup> many women are assessed as low risk of having a pathogenic variant.<sup>6</sup> There is a professional awareness of an increasing number of women proceeding with genetic testing for HBOC despite a low risk assessment, often paying out-of-pocket for testing. This has been facilitated by recent technological advances making testing more efficient through multi-gene panels, leading to a reduced cost.<sup>7</sup> Approaches to genetic testing for women at a low risk of HBOC have been rapidly changing, and novel approaches include group genetic counselling and non-genetic health

professionals offering testing.<sup>8</sup> Some have even suggested that genetic testing for HBOC be offered to all women, regardless of risk, as a population-screening approach.<sup>9</sup>

While awareness has increased and cost has improved, the motivations behind testing and the implications of the results for women at a low risk of HBOC remain unclear. Existing literature has been principally focused on the experiences of women at a high risk, but has provided some useful insights outlined below.

While health professionals rely on analytical tools and algorithms to estimate the risk of HBOC, client risk perceptions are often shaped by lived experiences and emotions.<sup>10,11</sup> There is a well-documented proclivity for women to overestimate their risk of HBOC.<sup>12,13</sup> One survey found up to 84% of women with a relevant family history overestimate their risk of breast cancer.<sup>14</sup>

Another study found inaccurate risk-perception around HBOC may be associated with lower levels of genetic knowledge and higher levels of health anxiety.<sup>15</sup> Health anxiety around cancer has also motivated women at an increased risk of breast cancer to have risk-reducing surgeries.<sup>12</sup>

Individuals can sometimes feel a sense of responsibility to benefit their family members by having genetic testing.<sup>16</sup>

Genetic testing for HBOC can either result in a pathogenic variant, a variant of unknown significance (VUS), or a negative result. One study suggested a VUS or negative result led women to underestimate their residual risk of breast/ovarian cancer.<sup>17</sup> This study also found that a negative result led to anxiety-relief for women.<sup>17</sup> Studies into population-level genetic testing for

HBOC in the Ashkenazi-Jewish community found pathogenic variants were detected without a significant short-term impact on psychological outcomes.<sup>18</sup> Another study looked at unaffected women with a pathogenic variant in the family, and found positive results increased vulnerability whilst simultaneously being perceived as beneficial information.<sup>19</sup> One benefit of identifying a pathogenic variant is that it enables high level surveillance and preventative options. For women with HBOC unaffected by cancer, a bilateral mastectomy reduces breast cancer risk by 90-95%,<sup>20</sup> and research has indicated that cancer anxiety is relieved after surgery.<sup>21</sup>

All qualitative studies to date on motivations and implications of genetic testing for HBOC have been conducted using a cohort of participants at a high risk of HBOC or affected by breast or ovarian cancer. There is a gap in the literature around the motivations and implications for women at a low risk of HBOC having genetic testing. This study aims to explore the genetic testing experiences for women at a low risk of HBOC, and to elucidate what motivates these women to have genetic testing and what implications the results have for them.

## 2. Methodology

A qualitative approach was taken to investigate the genetic testing experiences of women at a low HBOC risk. Qualitative research fosters a space for participants to share their lived experiences, allowing for the collection of rich data through their recounting these experiences.<sup>22</sup> Social constructionism was the chosen epistemology as it postulates that meaning is collectively constructed by the interaction between a person's individual, social, and historical contexts.<sup>22</sup> A phenomenological approach was taken because of the highly exploratory nature of the study and the desire to gain detailed information about participants lived experiences.<sup>23</sup> Researcher reflexivity is an important aspect of rigorous research and adopted by researchers: by being aware of preconceived biases and reflecting on the researcher's own role, data collection and analysis become more impartial and reliable.<sup>24</sup> Interviews were conducted by GG, a genetic counselling student trained in non-directive counselling/questioning with neutral framing. Researchers CB, KS, ST and AS are practicing genetic counsellors with prior experience in qualitative research. All researchers contributed to study design and data analysis.

### 2.3 Study Design

This study was conducted at the Parkville Familial Cancer Centre and granted ethical approval by the Peter MacCallum Cancer Centre Ethics Committee (reference number HREC/46620/PMCC-2018). Semi-structured interviews were utilized to gather rich, experiential data around the phenomenon. An interview schedule (Supplementary Table 1) was developed from a review of relevant literature and clinical experience of the research team. Open-ended questions with

neutral framing were used to ask about key events in the genetic testing process, family dynamics, emotions, motivations for testing, and implications of results. Participants were given a participant information package and asked to provide informed consent before being interviewed.

## 2.4 Sampling

Participants were selected through purposive sampling, where deliberate filters are used to select individuals deemed most knowledgeable about the phenomenon in question.<sup>24</sup> Participants were recruited based on the following criteria: (1) English-speaking, (2) aged 18 and over, (3) underwent genetic testing for HBOC, (4) pre-test HBOC risk of less than 10% calculated by the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm,<sup>11</sup> (5) unaffected by breast or ovarian cancer before genetic testing, and (6) results returned 2016-2018. Potential participants were mailed invitations and information, and telephoned if no response was received.

## 2.7 Analysis

This study adopted inductive thematic analysis as it is a qualitative approach which enables the identification and extraction of themes directly from participant interviews.<sup>25</sup> Interviews were audio-recorded and transcribed verbatim. Each transcript was read multiple times and analyzed for important, recurring ideas. Sections of text were coded to reflect experiences, emotions, thoughts, understandings, etc., and re-coded after a comprehensive coding scheme was

established. Four researchers (GG/AS/KS/CB) independently coded select transcripts and subsequently compared them to improve rigour.<sup>24</sup> Related codes were organized into potential themes. Themes were discussed amongst the research team and compared across transcripts. Illustrative quotes were selected to exemplify each theme. No statistical methods were used.

### 3. Results

#### 3.1 Participants

Of the 37 women invited to participate, five declined and 13 were unreachable. Nineteen interviews were conducted – four face-to-face and 15 via telephone. Interviews ranged from 26-85 minutes (mean of 45 minutes). Participants ranged from 31 to 67 years old.

All participants but one had a family history of breast and/or ovarian cancer. Sixteen participants had a mother with cancer, 14 of whom died as a result. Family histories varied: collectively, 14 first-degree relatives (FDRs) had breast cancer and three FDRs had ovarian cancer. Further, FDRs had one of the following: brain cancer, gallbladder cancer, lung cancer, pancreatic cancer, and prostate cancer. Two participants did not have any FDRs with cancer, and one participant had four FDRs with cancer. Fourteen tests detected no variants, two returned VUS results in *BRCA2*, and three identified pathogenic variants in *BRCA2*.

Table 1 provides an overview of participant demographics and includes pre-test HBOC risk, as well as pre and post-test participant risk perception. Eleven participants had careers in healthcare.

## 3.2 Themes

### 3.2.1 Family underpinned all motivators.

All participants with family experiences of cancer reported their family history as a motivation for genetic testing.

Having cancer everywhere around us and watching people die, like I mentioned, my brother [saying] ‘if I only knew this and I only knew that’ [...] ‘I could have done this better, I could’ve done that better,’ so I guess that’s sort of, for me, it was easy to make that [genetic testing] decision.

(Jorja, 51-60)

Many participants were motivated to stay healthy and alive for their children, others were motivated to know for themselves, and most were motivated by both.

becoming a mother, I just wanted to know – if I have the genes, I wanted to take the necessary steps to avoid becoming ill

(Heidi, 41-50)

Just going through the experience of losing a close family member with cancer and seeing what they go through. It mainly came down to, one: I don’t want to go through that if I can avoid it, and two: I don’t want my family to have to go through what I did.

(Abbie, 31-40)

Watching family members struggle with cancer also influenced participant cancer anxiety.

I didn’t want them [ovaries] there, worrying me, I guess. They feel like ticking time bombs [...] after seeing my mom die of ovarian cancer, it did worry me

(Bella, 31-40)

Some women did not have extensive family history knowledge. This led participants to have less faith in risk assessments, and seek genetic testing to compensate:

they can't really discern what my risk is because my family history is not all there. I've got part of it missing, and as I said, my mother was essentially an only child and that

meant for me that, yes, they could tell me a level of risk, well it's just an estimate and it's just based on the information they have, not all the information.

(Ophelia, 41-50)

### 3.2.2 Health professionals were influential throughout the process.

Health professionals proved to be influential throughout the process of genetic testing, most often by promoting genetic testing. Some participants were alarmed by statements made by various health professionals.

she [breast surgeon] said, 'oh my god, if I had your family history, I would be going to investigate for the BRCA gene' [...] it just gave me a shake-up.

(Jorja, 51-60)

'it's not a matter of if, it's a matter of when for you.' That was what was stated to me by my breast surgeon. [...] I was told it [my risk of breast cancer] was 80%.

(Celine, 41-50)

Most participants had positive experiences speaking to genetic health professionals. For some participants, genetic counsellors were key to relieving stress and correcting misinformation.

She [genetic counsellor] very much made me calm within the first 10 minutes [...] She was wonderful in clarifying facts very early on and pretty much being able to assure me that the information [from the surgeon] may not be accurate, and she'd give me more information.

(Celine, 41-50)

### 3.2.3 Planning for a positive result.

Before and after consenting to genetic testing, many women were planning for a positive result.

Participants found themselves contemplating surgeries and family planning while awaiting the results:

[I was] worried that it will come back positive and thinking what to do next. And everything is going to change [...] we will have to think about when to do this mastectomy, when to do this oophorectomy

(Rose, 41-50)

yeah, so if I was BRCA positive, I was probably thinking that I would do IVF [in-vitro fertilization] to screen out any BRCA positive [...] embryos.

(Frances, 31-40)

### 3.2.4 Results influenced screening-anxiety and frequency.

One of the implications of these results for women was the effect on screening. After a negative result, many women were assessed as low risk of developing breast cancer (Table 1). In some cases, this changed the amount of breast cancer screening recommended:

I was having annual mammograms and that hasn't changed, but I was having MRIs last year and this year but that's going to stop now that we've had the confirmation about the BRCA gene.

(Gina, 41-50)

As Table 1 indicates, many women altered their perception of their own breast cancer risk after receiving results. As a result, some of these women felt relief from cancer screening anxiety.

I do still feel a little anxious [when having mammograms] but not to the extent that I used to be. If I didn't have this genetic testing, I would be more anxious.

(Ingrid, 51-60)

I think I don't feel as much anxiety about it [screening] because I know I'm low risk. [...] So, yeah, I don't think I worry about it as much anymore.

(Bella, 31-40)

### 3.2.5 Negative results gave relief in many ways.

Relief from results was not limited to screening anxiety. All participants with a negative result or VUS described relief after receiving their results, and for mothers, this relief was often related to their children.

we had counselling after the test with the results and [the genetic counsellor] was very good [...] saying [my daughter]'s risks were, in actual fact, not much higher than anybody else's, so that made me feel better

(Phyllis, 51-60)

Many women described relief from cancer anxiety in different ways. One recurring indication was relief from negative feelings associated with cancer thoughts.

I think, you know, anytime you see an advertisement or anything about breast cancer, it used to give a flutter in my heart, I used to get a bit anxious. Whereas now, it's just like another advertisement. I just think, that's not going to be me.

(Celine, 41-50)

While negative results were reassuring, all participants that received a positive result expressed shock. Evelyn discussed how this result was especially surprising given her initial risk assessment for HBOC:

To go from you've got 2% risk to you actually, you're 100% risk of having the gene mutation, it was really shocking for me to hear.

(Evelyn, 41-50)

Finally, participants felt a sense of power being able to give this information to their family members. When asked how providing this information to family members felt, Daphne replied:

like I said, [giving this information is] powerful. Positive and powerful because you could change people's lives.

(Daphne, 61-70)

### 3.3 Summary of Results

The results highlighted many key themes that were interconnected for participants throughout their genetic testing journeys (Figure 1). Further data supporting the themes is provided in Supplementary Tables 2-6. Mainly, family underpinned all motivators for HBOC genetic testing, health professionals were influential throughout the process, participants were planning for a positive result, results influenced screening-anxiety and frequency, and negative results gave participants relief in many different ways. Positive results were reported to empower women and their families.

## 4. Discussion

This study explored the experiences of genetic testing for HBOC in unaffected women who were given a low risk assessment. This is novel research in this field, as all current literature on the topic of genetic testing for HBOC relates to the experiences of women given a high risk assessment prior to genetic testing and/or women affected by breast or ovarian cancer.

### 4.1 Family Underscoring Genetic Testing Experiences

People use their family narratives and lived experiences<sup>26</sup> to shape their perceptions and values. The findings we present reflect this, as family experience with cancer was a key motivator for genetic testing. This is in line with motivations of women at a high risk of HBOC to undergo genetic testing, where studies show family history has led women to have genetic testing as they perceive this as a way of gaining control over their cancer risk and avoiding the same fate as their mothers.<sup>16,27</sup>

The desire to know about a predisposition to cancer in this cohort often did not come from a self-serving agenda. Women and mothers are disproportionately responsible for family health in Western societies, and passing down a pathogenic variant causes many women guilt.<sup>28</sup> Mothers felt a sense of responsibility to have this information for their children, as informative results could prevent illness in the family. These selfless motivations may be related to the female approach to morality, as described by feminist psychologist Carol Gilligan. She postulates that

women are driven by their relationships with others and value these as a key component of self.<sup>29</sup> This aligns well with the current literature: the idea that motivations behind genetic testing for HBOC are to benefit other family members was originally discussed by Hallowell in 1999. She asserted that women want to understand their genetic risk and sometimes seek testing out of a sense of responsibility to their close family members, especially children.<sup>30</sup> This notion has been affirmed by more recent studies,<sup>16,31</sup> and is perhaps an explanation why some women are more relieved for their children than for themselves.

Intriguingly, some participants without extensive family history information had less faith in risk assessments and were motivated to seek genetic testing to fill this informational gap. This novel finding provides an explanation to why some women proceed with genetic testing for HBOC despite a limited family history. This lack of familial knowledge can fuel cancer anxiety through a negativity bias, where people can assume the worst when evaluating unknown entities.<sup>32</sup>

#### 4.2 The Influence of Medical Professionals

In Western societies, medical professionals are very influential in how patients understand their risks and options.<sup>33</sup> According to the shared decision-making model of care, medical professionals should educate the patient about risks and options and achieve a plan that respects patient values while providing beneficial care.<sup>34</sup> Since giving correct risk information is a vital part of their role, it is concerning when medical professionals provide inaccurate risk

assessments. Statements from non-genetic health professionals influenced the risk perceptions of many participants and acted as motivators for HBOC genetic testing. This is in line with other research that has shown health professionals can cause cancer anxiety and influence risk perception, indirectly motivating genetic testing.<sup>12</sup> Genetic counsellors are well-positioned to provide non-directive and supportive counselling around HBOC risk, and studies show patients feel relief after speaking to a genetic counsellor.<sup>35</sup>

#### 4.3 Cancer Anxiety and A Way to Cope

According to the Transactional Model of Stress and Coping (TMSC), when a stressor is seen as avoidable, people often cope with anxiety by seeking more information and planning ahead.<sup>36</sup> In the case of our participants, information came in the form of genetic test results around their risk of breast or ovarian cancer. These cancers were seen as avoidable since risk-reducing surgery could mitigate the risk for participants and their children, and pre-implantation genetic testing could prevent this risk in future children. Therefore, according to the TMSC, these women may be coping with anxiety around cancer by having genetic testing and planning for a positive result.

Other researchers have reached similar conclusions and assert that pursuing genetic testing is a way to cope with the anxiety of being at-risk for a disease.<sup>37,38</sup> Participants in our study with a negative result were able to relieve their cancer anxiety, at least in part. This relief was expressed through less screening-related anxiety, relief for children, and relief from negative cancer-

associated feelings. Other studies have found similar themes, associating negative genetic testing results with relief from stress.<sup>39</sup>

#### 4.4 Reduced Screening after Negative Results

Many participants were advised to adjust their breast cancer screening, as they were perceived to have a lower breast cancer risk after a negative genetic test result. Excessive screening of low risk individuals can lead to over-diagnosis, where treatment is administered for a tumor that would not progress to be symptomatic.<sup>40</sup> Our findings indicate that negative results for low-risk women can help adjust risk perceptions and reduce unnecessary, resource-intensive screening. This is one area where further research with a quantitative approach would be useful.

#### 4.5 Study Limitations

This was a retrospective study, and in some cases, information gathered around genetic testing was collected three years after the testing occurred. Results around motivations for testing and perception of cancer risk would likely be more salient if collected before testing. Additionally, this study was unable to include women who do not speak English, biasing the sample population to a less diverse group. Whilst demographic details such as level of education were not collected, several participants were health professionals. Studies taking into account socio-demographic variables are needed to determine whether these findings are generalizable. Although qualitative

research can provide rich data around experiences, the nature of this research means that findings presented in this study are not generalizable, and more quantitative research is needed to generalize these findings.

#### 4.6 Clinical Implications

Based on the findings of this study, it is clear that family is central to genetic testing motivations for HBOC in low risk women. Health professionals have a vital role in ensuring women feel heard around their lived experiences with cancer as these experiences greatly influence cancer anxiety and fear around receiving a positive result. Genetic counsellors are well situated to help women cope with shocking positive results.

The findings also indicate that patients may be alarmed by misinformation or overestimation of risk provided by well-meaning health professionals. General practitioners, breast specialists, and other medical professionals should ensure they make accurate assessments based on reliable risk stratification tools. Health professionals can allay anxiety caused by inaccurate assessments by asking clients what they have been told about their risk to ensure they have an accurate perception.

Finally, these findings demonstrate that clients may cope with anxiety by seeking information and planning for the future. It should be recognized that this desire for information often stems

from cancer anxiety embedded in the psyche of a client from familial experience. Only by properly understanding and addressing the motivations behind information-seeking behavior can health professionals build therapeutic rapport and aid the client in making an informed decision.

#### 4.7 Conclusion

The results suggest that despite an objectively low HBOC risk, women can feel motivated to have genetic testing due to their family experiences with cancer and resultant fears about cancer. Adding to this cancer anxiety were statements implying a high genetic risk from various health professionals. Some women may have coped with cancer anxiety by planning for a positive result, leading women who received a negative result or a VUS to feel relief in many ways. Positive results were shocking but empowering, and enabled proactive risk management.

This exploratory study lays a strong foundation for research in this area, and future studies may take a quantitative approach to see if these findings are generalizable. Further research is needed as more genetic testing for HBOC is being facilitated through non-genetic health professionals. If professionals facilitating this testing can recognize the familial experiences and acknowledge the cancer anxiety many of these women feel while providing accurate assessments, they can help to support clients through their genetic testing decision-making and adaptation to results.

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### Conflict of Interest Statement

The authors declare there are no conflicts of interest.

### Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

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Table 1

*Participant demographics.*

Pseudonym	Age at interview	Length of interview (minutes)	FDR died of cancer <sup>†</sup>	Pre-testing BOADICEA HBOC risk <sup>‡</sup>	Pre-testing perceived risk of breast cancer <sup>§</sup>	Post-testing perceived risk of breast cancer <sup>§</sup>	Post-testing assessed risk of breast cancer <sup>§</sup>
Abbie	31-40	37	Yes	1%	Unsure	Low	Low
Bella	31-40	31	Yes	9%	Low	Low	Low
Celine	41-50	32	No	1%	High	Moderate	Moderate
Daphne	61-70	58	Yes	1%	High	High	High
Evelyn	41-50	77	No	2%	High	High	High
Frances	31-40	33	Yes	2%	Unsure	Low	Low
Gina	41-50	31	Yes	9%	High	Low	Low
Heidi	41-50	36	Yes	6%	High	High	Moderate
Ingrid	51-60	31	No	1%	Unsure	Low	Low
Jorja	51-60	42	Yes	1%	High	High	Moderate
Katrina	61-70	43	Yes	1%	High	Moderate	Low
Lily	51-60	26	Yes	1%	Low	Low	Low
Madeleine	51-60	42	Yes	1%	High	Low	Low
Nora	41-50	85	Yes	9%	Unsure	High	High
Ophelia	41-50	41	Yes	1%	High	Unsure	Low
Phyllis	51-60	31	Yes	6%	Moderate	Low	Moderate
Quinn	51-60	31	No	2%	High	Moderate	Low
Rose	41-50	45	No	3%	Moderate	Low	Low
Sherry	31-40	50	Yes	2%	Moderate	Low	Low

*Note.* Participant demographics and interview information for all 19 participants. Age ranges were used to maintain anonymity.

<sup>†</sup>Collectively for participants, 18 first-degree relatives died of cancer including 14 mothers. Ages of cancer-related death ranged from 35-80 (mean of 57 years).

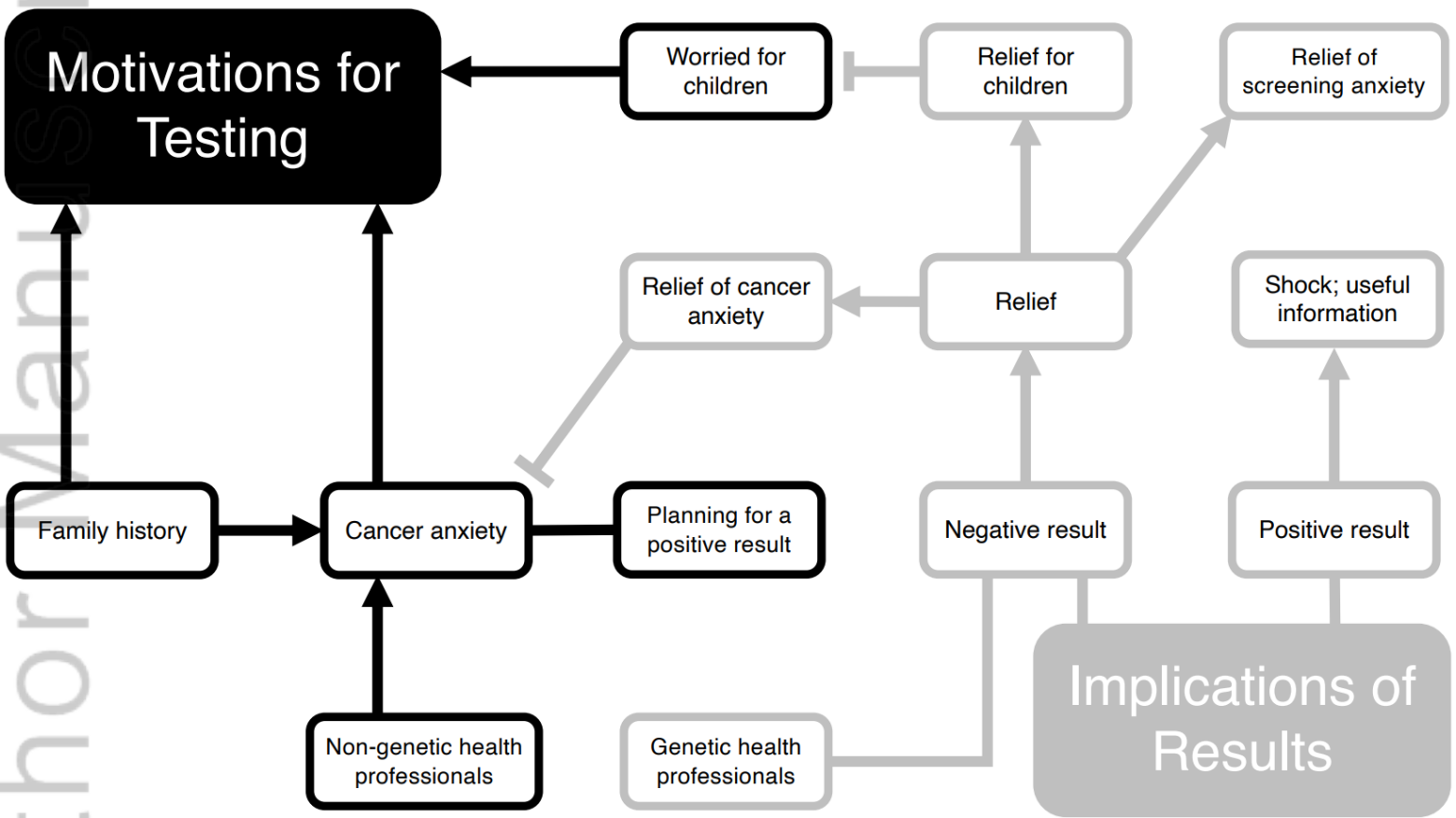
<sup>‡</sup>Risk of hereditary breast and ovarian cancer (HBOC) syndrome is from the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA).<sup>11</sup>

§Pre-testing perceived risk and post-testing perceived risk represents the risk level reported by the participant during their interview when asked by the interviewer. Post-testing assessed risk of cancer represents the risk given to the participant by the Parkville Familial Cancer Centre. Low risk level is less than 18% lifetime risk of breast cancer (LTR, assessed to age 80), moderate risk is 18-30% LTR, and high risk is above 30% LTR.

#### Figure Legend

Figure 1. Themes around motivations for testing and implications of results. This figure demonstrates how themes identified in this study were related to the main research questions and related to each other.

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