The Impact of the Law in Helping or Hindering Fertility Preservation for Children with Cancer Facing Gonadotoxic Therapies

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Children diagnosed with cancer who require treatment with chemotherapy and/or radiation therapy have ever-increasing survival rates. However, as a result of such treatment they face the added, and significant, burden of infertility into their futures. Options for fertility preservation and future reproduction for such children do exist, but some such options continue to be considered experimental. Collaborative multidisciplinary teams support children and their families to make decisions about such options in the treatment environment. When collection of gonadal tissue from children is consented to in such circumstances, it is subject to stringent institutional clinical and human research ethics review, often in both the pediatric oncology setting and the fertility setting in which it will be preserved, examined and, potentially, used. Laws and guidelines may support the collection and use of reproductive tissue from children for treatment and research, subject to the meeting consent requirements concerning the child and/or their parent(s). This article examines such laws across Australia. It also examines the legal complexities found in some jurisdictions that may hinder research and practice, consequently having a negative impact on the prospects for children with cancer, in relation to their fertility preservation and possibilities for future reproduction.

I. INTRODUCTION

A diagnosis of cancer may impact significantly on any person, varying dependent on the type of cancer, treatment prospects, and the person's physical, emotional, and social resources and support systems. While pediatric oncologists traditionally have focused on providing the most effective treatments available to help prolong the life of their cancer patients, increased survival rates of more than 90–95% in young people diagnosed with particular cancers[1] has meant that attention is increasingly also focused on their longer-term quality of life, and psychological, and social wellbeing – which include factors affecting their ability to have and raise a family. However, one of the most common and most devastating side effects of cancer treatment is infertility. For younger patients (and their parents in cases involving minors) receiving a diagnosis of cancer this also may mean having to consider possible effects of cancer treatment(s) on fertility and the need to make decisions regarding whether it is possible, and if so how, to preserve fertility. They may consider changes in standard treatment protocols or undertake steps to preserve gametes or gonadal tissue where there is a high risk of infertility, noting such measures carry their own risks and uncertainties.

In women who face imminent loss of fertility following exposure to cytotoxic therapy for malignant disease, pathways are available for preservation of future reproductive potential. While collection and cryopreservation of mature eggs (oocytes) is now well established in terms of efficacy with thousands of babies born, time constraints often result in ovarian tissue collection and storage being the only realistic option. This tissue contains immature oocytes within primordial follicles and, following

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[1] F Saletta, MS Seng and LM Lau, "Advances in Paediatric Cancer Treatment" (2014) 3 *Translational Pediatrics* 156.

extensive research to validate the methodology, re-implantation after cryopreservation and storage has resulted in over 100 births from tissue collected from adults.

Although immature oocytes are also present in prepubescent ovaries, there are significant biological differences and successful use of this stored tissue in achieving pregnancy has only recently been reported[2]. As with adult tissue, extensive research will be required to ensure that clinical application is appropriate.

Regarding males, while cryopreservation of sperm has long been a relatively straightforward option for adult and adolescent males who are at risk of losing fertility as a consequence of cytotoxic therapies, the situation is quite different for prepubescent boys. In such cases, the only option is cryopreservation of testicular tissue in which the only potential for future fertility resides in stem cells. Without extensive research, it is impossible to determine whether this tissue is likely to offer any prospect for parenthood in the years to come.

In light of the above, it is clear that research specifically involving the use of gametes and/or gonadal tissue from minors will be essential in order to ensure that future clinical use is based on evidence of potential success and is safe. It will also serve to inform the medical practitioners who will be responsible for managing patients' expectations. This article examines the advances in science in this important area, as well as the laws and guidelines in Australia, concerning research and practice relevant to children.

In Part II of this article a brief overview of methods relevant to preserving gametes, embryos, or gonadal tissue for use at a future time is provided. Part III then highlights the importance of research in this area, noting progress in relation to adults that has led to more than one hundred births worldwide, issues relevant to prepubescent boys and girls, and research regarding assessment of risk associated with the potential presence of malignant cells in cryopreserved gonadal tissue. Part IV considers relevant laws and guidelines in Australia regarding the collection, storage and use of gametes and tissues from minors with cancer. This part highlights variation across the country, including laws in New South Wales and Victoria that pose restrictions or prohibitions on research respectively. In Part V we explore the question of whether the law in these States is helping or hindering the preservation of fertility for children with cancer. Part VI calls for changes needed to support fertility preservation in children, and Part VII concludes the article.

II. PRESERVING GONADAL TISSUE, GAMETES, AND EMBRYOS

Fertility specialists working with young cancer patients may work to preserve gametes, embryos, or gonadal tissue for use at a future time. Methods differ depending on whether the young cancer patient is male or female.

In males, the toxic effects of chemotherapy and radiation may result in long-lasting and persistent damage to sperm cells. The most common, and only established clinical strategy to preserve fertility for males is cryopreservation of sperm before delivery of treatment for their cancer. The feasibility depends upon the sexual maturity of the patient, and thus is possible only for post-pubertal males and adult men. Currently, no fertility-preserving options are available for prepubescent boys, who are not yet producing sperm.[2] However, experimental techniques are currently being researched and developed to provide future alternatives for patients that preserve their testicular tissue/cells.[3] In order

2 S Matthews et al. Successful Pregnancy in a Women Previously Suffering from β-Thalassemia Following Transplantation of Ovarian Tissue Cryopreserved Before Puberty. (2018) 70 Minerva Ginecologica 432

[2] E Goossens and H Tournaye, "Male Fertility Preservation, Where Are We in 2014?" (2014) 75 *Annales d'Endocrinologie* 115.

[3] C Wyns et al, "Long-term Spermatogonial Survival in Cryopreserved and Xenografted Immature Human Testicular Tissue" 23 (2008) *Human Reproduction* 2402; E Goossens, D Van Saen and H Tournaye, "Spermatogonial Stem Cell Preservation and Transplantation: from Research to Clinic" (2013) 28 *Human Reproduction* 897.

to take advantage of these and future technologies, patients must harvest and preserve their testicular tissue prior to disease or treatment associated fertility decline.[4]

Preservation of female fertility is more complicated than in males. If the cancer treatment can be delayed, it may be possible to undergo ovarian stimulation and retrieve and freeze mature eggs or produce embryos that can be frozen for later transfer to the individual or a gestational carrier. Oocyte cryopreservation (egg-freezing), once deemed experimental due to the technical challenges associated with the size and structural complexity of oocytes, is no longer deemed as such, and is another option for girls who are post-pubescent. It has also been widely applied for preservation of fertility in young adults at risk of permanently losing their ability to produce viable gametes, and therefore their fertility, as a consequence of impending cytotoxic treatments for malignant disease. However, in the case of adult females undergoing this treatment there is often insufficient time available to collect mature oocytes, so cryopreservation of ovarian tissue is the only option.

For pre-pubertal girls, for whom oocyte and embryo freezing is not an option, ovarian tissue freezing is also becoming a viable option. Once ovarian tissue has been frozen, it is anticipated that it will be thawed and implanted after cancer treatment or that techniques for maturing oocytes in vitro will be developed in the future. However, further research needs to be conducted.

III. The Importance of Research in the Development of Cryopreservation Technology for Cancer Patients

The importance of research in the development of cryopreservation technology for cancer patients is undeniable. Specifically, the knowledge gained from research has been a prerequisite for the evolution of clinical practice using adult cryopreserved ovarian tissue in fertility preservation. Studies conducted have been subject to approval by ethics committees and were carried out on a small proportion of the cryopreserved tissue donated by consenting patients.

A. Successes and Ongoing Research for Peri-, Post-pubertal and Adult Women

Post-thaw transplantation in cancer survivors who had stored tissue prior to cytotoxic therapy was preceded by a series of research studies that were crucial in demonstrating that primordial follicles in frozen tissue could not only survive but could also go on to develop into advanced follicles containing mature oocytes. This research involved establishing optimal methodology for cryopreservation and confirmation of follicle survival by microscopic examination.[5] Obtaining evidence for viability and retention of developmental potential was a bigger challenge. However, such evidence was obtained from research using an experimental model known as xenografting in which the thawed tissue was grafted into a special strain of mice that do not reject tissue from other species.[6] These studies demonstrated that primordial follicles in the grafted cryopreserved tissue had not only survived but were able to undergo development to more advanced stages, and that the oocytes within the follicles could undergo normal maturation. Importantly, these results were repeated using tissue cryopreserved from a wide range of patients.[7]

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[4] C Wyns et al, "Options for Fertility Preservation in Prepubertal Boys" (2010) 16 *Human Reproduction Update* 312; C Wyns et al, "Fertility Preservation in the Male Pediatric Population: Factors Influencing the Decision of Parents and Children" (2015) 30 *Human Reproduction* 2022; WLC Ho et al, "Paediatric & Adolescent Fertility Preservation Task Force, Melbourne. A Short Report on Current Fertility Preservation Strategies for Boys" (2017) 87 *Clinical Endocrinology* 279.

[5] DA Gook, DH Edgar and C Stern, "Effect of Cooling Rate and Dehydration Regimen on the Histological Appearance of Human Ovarian Cortex Following Cryopreservation in 1, 2-Propanediol" (1999) 14 *Human Reproduction* 2061.

[6] DA Gook et al, "Development of Antral Follicles in Human Cryopreserved Ovarian Tissue Following Xenografting" (2001) 16 *Human Reproduction* 417; DA Gook et al, "Oocyte Maturation, Follicle Rupture and Luteinization in Human Cryopreserved Ovarian Tissue Following Xenografting" (2003) 18 *Human Reproduction* 1772.

[7] DA Gook et al, "Diagnostic Assessment of the Developmental Potential of Human Cryopreserved Ovarian Tissue from Multiple Patients Using Xenografting" (2005) 20 *Human Reproduction* 72.

It was on the basis of the above research findings, that clinical grafting of tissue was undertaken and, although ovarian tissue cryopreservation is still considered experimental, over 100 live births have been reported worldwide using tissue collected from post-pubescent girls/women.[8] There has also been one live birth following tissue collected from a peri-pubescent girl.[9] (NB with the techniques being about 20 years old, many of the younger patients are yet to reach an age where they may wish to commence trying for a family.)

Risks associated with such methods include ischaemic damage to the tissue pending transplant and revascularisation, and the theoretical possibility of reintroducing malignant tumour cells.[10] However, research is being conducted to evaluate how to overcome these and other problems so that this technique may be used without delaying treatment or using hormones to stimulate the ovaries.[11]

Further research is also being conducted to develop new technology for maturing oocytes in culture (in vitro maturation; IVM) from small follicles,[12] not exposed to the hormones necessary for ovulation. Once normality of the developing oocyte is determined, these will be cryopreserved and enhance the potential reproductive material available for future fertility.[13]

B. Prepubescent Girls and Boys

While tissue (ovarian or testicular) may be cryopreserved for prepubescent girls and boys, who do not produce mature gametes, questions remain to be answered before the likelihood of successful clinical use of this tissue can be determined.

In the case of ovarian tissue cryopreserved for prepubescent girls, the population of primordial follicles differs from that in the adult ovary. The hormonal changes that accompany the onset of puberty, and may influence these follicles, have not yet occurred. Additionally, during puberty there is a major diminution of the primordial follicle pool. It cannot, therefore, be assumed that the developmental competence of this tissue is similar to that of the adult.

Research to advance clinical application in this area would seek to establish that the cryopreservation methodology is appropriate for this specific tissue by determining the post-thaw survival of the primordial follicles and, if survival is achievable, to establish the developmental competence of the follicles/gametes within the tissue. Such research would require xenografting of the thawed tissue and subsequent evaluation of the follicular development following the rationale used to assess the viability of adult tissue. If satisfactory outcomes are achieved, clinical grafting may be considered. Research to establish the mechanism of maturation in these oocytes matured in culture is also required to maximise the potential from the pre-pubertal/adolescent ovary. Specifically, due to the different hormonal milieu, the potential of these oocytes is otherwise unknown.

For prepubescent boys who are having testicular tissue cryopreserved, the need for research to provide information on the potential of this tissue is particularly urgent. In these boys, there are no mature or immature gametes (sperm) in the testicular tissue and the only reproductive potential resides in a population of stem cells known as spermatogonia. It is only after puberty, and the accompanying endocrine changes that occur, that some spermatogonial stem cells may be reactivated and give rise to

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[8] J Donnez and MM Dolmans, "Fertility Preservation in Women" (2017) 377 *The New England Journal of Medicine* 1657.

[9] I Demeestere et al, "Live Birth after Autograft of Ovarian Tissue Cryopreserved during Childhood" (2015) 30 *Human Reproduction* 2107.

[10] MM Dolmans et al, "Reimplantation of Cryopreserved Ovarian Tissue from Patients with Acute Lymphoblastic Leukemia Is Potentially Unsafe" (2010) 116 *Blood* 2908; T Greve et al, "Cryopreserved Ovarian Cortex from Patients with Leukemia in Complete Remission Contains No Apparent Viable Malignant Cells" (2012) 120 *Blood* 4311.

[11] C Andersen et al, "Assisted Reproductive Techniques after Autotransplantation of Frozen/Thawed Ovarian Tissue" (2007) 22 *Human Reproduction* i41, Abstract O-104; CJ Stern et al, "First Reported Clinical Pregnancy Following Heterotopic Grafting of Cryopreserved Ovarian Tissue in a Woman after a Bilateral Oophorectomy" (2013) 28 *Human Reproduction* 2996.

[12] RB Gilchrist et al, "Oocyte Maturation and Quality: Role of Cyclic Nucleotides" (2016) 152 *Reproduction* R143.

[13] X Wang et al, "Improving Fertility Preservation for Girls and Women by Coupling Oocyte In Vitro Maturation with Existing Strategies" (2016) 12 *Women's Health (London, England)* 275.

primary spermatocytes. In turn, these primary spermatocytes may give rise to secondary spermatocytes which can undergo further maturation into spermatids and, finally, form mature spermatozoa (the mature male gamete). A number of key questions must be answered before clinical application, such as grafting of this tissue, can be considered. These are:

- Are spermatogonial stem cells from pre-pubertal testicular tissue capable of reactivating and developing into mature sperm in the absence of exposure to the pubertal environment in vivo?
- If so, is this developmental potential preserved during the process of cryopreservation?
- Are the gametes likely to be normal in terms of physiology and genetics/epigenetics?

Without access to human pre-pubertal testicular tissue for research, these questions cannot be addressed in a satisfactory manner.

The role of research in answering these questions is, again, paramount but may be prevented by prevailing legislation relating to the use of gametes from minors for research. (See further discussion at Part IV).

C. Research Regarding Assessment of Risk Associated with the Potential Presence of Malignant Cells in Cryopreserved Gonadal Tissue

In addition to the need to assess the clinical potential of pre-pubertal tissue to restore fertility post-treatment for malignant disease, access to the tissue is critical to allow research into the possibility that the tissue contains malignant cells. This, of course, is true for tissue stored from all patients (male and female, adult and pre-pubertal) since the information will be specific to the individual. If malignant cells are present, the grafting of this tissue back to patients whose cancer has been cured by cytotoxic therapy may be contra-indicated on the basis of the possibility of reintroducing the original disease. This consideration is particularly important in the case of tissue collected from patients with a diagnosis of leukaemia when the disease is likely to be widely disseminated.

Adequate identification of leukaemic cells in tissue collected from patients, adults or minors, cannot be achieved by microscopic examination alone so research studies are required to glean the relevant information. One suitable approach is to xenograft tissue into immuno-deficient mice as described earlier. While this has been important in demonstrating the viability of stored tissue in terms of the potential for follicle development, studies employing this technique can also be designed to detect the presence of small numbers of malignant cells in the tissue which can proliferate and, in some cases, go on to form tumours in the host animals. In order to screen for this possibility when tissue is cryopreserved for minors, it would be necessary to have access to a small portion of the stored tissue donated for xenografting studies. Under the above circumstances, it is clear that information from the research studies would be crucial in informing subsequent clinical management, but, in relation to minors, is again impeded by legislative restrictions and prohibitions on research.

IV. Relevant Laws and Guidelines Regarding the Collection, Storage and Use of Gametes and Tissue from Minors with Cancer

A. Legislation Regarding Assisted Reproductive Technologies

Four States in Australia, including Western Australia, South Australia, New South Wales, and Victoria have legislation governing various aspects of assisted reproduction. Western Australian and South Australian legislation concerning assisted reproductive treatment, however, does not contain provisions directly governing the collection, and/or use of, or research upon gonadal tissue and/or gametes from children. In contrast, provision does exist in the New South Wales and Victorian legislation in relation to obtaining and storing gametes from children and is also relevant to whether research may be conducted on tissue or gametes.

New South Wales

In New South Wales, s 29 of the *Assisted Reproductive Technology Act 2007* (NSW) (*ART Act*) prohibits an Assisted Reproductive Technology (ART) provider from providing treatment to a child, or obtaining a gamete from a child for use in ART treatment or for research in connection with ART treatment,[14] unless it has been certified by a registered medical practitioner that there is a reasonable risk of the child becoming infertile before becoming an adult. A child facing gonadotoxic cancer treatment likely to compromise their fertility would satisfy the exclusion. In such cases, the New South Wales *ART Act* provides that an ART provider may *obtain* a gamete from the child for the purpose of *storing* the gamete for the child's future benefit.[15] The gamete obtained from the child must be stored until such time as the child becomes an adult and is able to provide his or her consent in relation to the gamete.[16]

The law in New South Wales means that for the adolescent (post-pubertal) with cancer who face gonadotoxic treatments, *sperm* or *ova* may be collected and stored for future use. The collection of gonadal *tissue* would also be permissible, noting that as such tissue may contain ovarian follicles or spermatogonial stem cells (albeit immature in prepubescent children) the same provisions of the *ART Act* apply. However, given the provisions in the New South Wales Act only permit the *collection* and *storage* of gametes from a child, a literal interpretation of the Act prevents dealing with the cells in any way until the child is an adult and can provide consent. The Act does not provide for substitute consent, for example, by parent(s) or guardian(s). This may inhibit the ability to test the material for example, for the existence of cancerous cells, prior to storage regardless of whether such testing would be considered as use, or research.

Victoria

In Victoria, s 26 of the *Assisted Reproductive Treatment Act 2008* (Vic) prohibits the use of gametes produced by a child, or embryos formed from gametes produced by a child, unless a doctor has certified there is a reasonable risk of the child becoming infertile before becoming an adult. Again, the Victorian *ART Act* would apply to cases of children facing gonadotoxic cancer treatments. In such cases the Victorian legislation permits that gametes may be *obtained* from the child for the purposes of *storing* the gametes for the child's future benefit. Section 26(3) prohibits the use of such gametes obtained from the child:

- in the treatment of another person, including a relative of the child;
- for research purposes; or
- after the death of the person who produced the gametes.

There is a penalty of 240 penalty units or two years' imprisonment or both for breach of the Act.

The Victorian legislation, like that in New South Wales, therefore allows for gametes or tissue to be *collected* and *stored* for children with cancer who face the risk of infertility due to gonadotoxic treatments. The stored tissue may be used for the child's future "benefit" which would presumably include their fertility treatment. However, the Victorian legislation does not make provision for the child to reach the age of maturity and consent to any kind of research. The tissue also cannot be donated after the child's death.

Arguably the wording of the Victorian legislation would allow testing of the tissue before storing it, as it would be of future benefit for the child to know whether the tissue may contain cancerous cells. However, this may depend upon whether such testing is considered experimental and is thus classified as research – which is prohibited under the Victorian *ART Act*. In practice, it has meant that diagnostic testing (histology, immunohistochemistry, and genetic assessment) is permitted, but not xenografting which would be classified as "research". Unfortunately, the diagnostic tests have been unable to detect presence of leukaemic cells in tissue.

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[14] There is a penalty of 800 penalty units in the case of a corporation or 400 penalty units in any other case for breach of this provision: *Assisted Reproductive Technology Act 2007* (NSW) s 29(1).

[15] *Assisted Reproductive Technology Act 2007* (NSW) s 29(2).

[16] *Assisted Reproductive Technology Act 2007* (NSW) s 29(3).

B. The NHMRC Ethical Guidelines

In all States and Territories in Australia, the National Health and Medical Research Council, *Guidelines on the Ethical Use of Assisted Reproductive Technology in Clinical Practice and Research* (2017) (*NHMRC Ethical Guidelines*) are relevant. Adherence to the *NHMRC Ethical Guidelines* is required as a condition for accreditation for fertility clinics across the country, and as a condition for registration under South Australian legislation. If the guidelines are inconsistent with statute or common law ruling, the legislation and/or common law rules would prevail.

The *NHMRC Ethical Guidelines* recognise the collection and storage of a person's gonadal tissue and/or gametes as something that may occur in an attempt to help the person retain their ability to procreate. They emphasise the importance of informed decision-making and the management of expectations within the context of available clinical evidence. They also provide specific guidance regarding the collection and storage of gonadal tissue or gametes for fertility preservation from persons unable to provide valid consent, such as children.

The *NHMRC Ethical Guidelines* state collection and storage of gonadal tissue or gametes for a child or young person should be assessed and may be ethically acceptable if:

- storage of the gonadal tissue or gametes is the best means of preserving the fertility of the child or young person;
- the risks and discomfort of the procedure to the child or young person can be minimized;
- the child or young person, if capable, and their parent(s), guardian or otherwise authorised person consents to the proposed collection and storage;
- the collection and storage is not for the reproductive needs of another individual.[17]

Where there is any doubt about the ethical acceptability of the proposed collection and storage of gonadal tissue or gametes for a child or young person, the *NHMRC Ethical Guidelines* state that a clinician should seek advice from an independent body. As mentioned previously, seeking such advice from institutional clinical ethics response teams and/or human research ethics committees in such cases is standard practice. For example, at the Royal Children's Hospital in Melbourne, procedures are undertaken as a novel technology under institutional governance, with clinical ethics governance for individual cases and research governance for data collection.[18]

The *NHMRC Ethical Guidelines* further require that person(s) authorised to consent to the collection and storage of gonadal tissue or gametes from a child or young person are provided with all relevant information and have access to appropriate counselling services.[19] Clinics must also ensure that valid consent for each specific procedure is obtained from the person(s) authorised to consent to the collection and storage of gonadal tissue or gametes from a child or young person. In addition, the developing capacity of a child or young person to participate in decision-making should be respected. The guidelines provide that when the child or young person is not legally competent but sufficiently understands the issues, clinicians should encourage the child to take part in the decision-making process. Where appropriate, clinics must ensure that the child or young person is also provided with all relevant information and has access to appropriate counselling services. Pursuant to the *NHMRC Ethical Guidelines*, when the child or young person reaches the appropriate age of consent,[20] clinics must manage the transition of responsibility for the stored gametes from the person(s) authorised to consent, to the individual. The individual's valid consent must then be obtained for the continued storage of their gonadal tissue or gametes.

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[17] National Health and Medical Research Council, *Guidelines on the Use of Assisted Reproductive Technology in Clinical Practice and Research* (2017) [8.4.1].

[18] See further RJ McDougall et al, "Ethics of Fertility Preservation for Prepubertal Children: Should Clinicians Offer Procedures Where Efficacy Is Largely Unproven?" (2018) 44 *Journal of Medical Ethics* 27.

[19] National Health and Medical Research Council, n 17, [8.5.1].

[20] As noted above, at law the age of consent in most States and Territories of Australia is 18, except South Australia where it is 16 unless the child is considered to be "Gillick Competent".

The *NHMRC Ethical Guidelines* do not provide further guidance on the use of such tissue or gametes. Presumably, the use, would be permitted subject to obtaining legally valid consent.

C. Consent to Medical Procedures, Treatment and Research Relevant to Minors

A health care professional cannot treat a person, and research cannot be conducted, if they have not obtained legally valid consent from the patient or participant, or in the case of minors, from a person who is recognised as having authority to consent on their behalf.

Parental Authority

In Australia, generally a child's parent(s) (or appointed guardian(s)) are the main source of authority for health care procedures and treatment. This authority comes from a parent/guardian's duty to maintain and protect the child. The consent of either parent is usually sufficient authorisation for a doctor or other health care professional to examine and treat a child or young person, unless a court order specifies otherwise. However, parental decision-making in relation to children is limited to the extent that any decision regarding consent to, or refusal of, medical treatment or intervention, must be in the child's *best interests*. Parents are also not able to consent to treatment made illegal by statute. Such parental authority exists across most States/Territories of Australia until the child reaches the age of 18,[21] except in South Australia which recognises medical decision-making capacity for children above the age of 16.

Parental authority to make decisions about health care/medical procedures for their child(ren) is not absolute. A child may consent to their own health care/medical procedures and treatment if they demonstrate "*Gillick* competence".[22] Such competence is not decided upon by the age of the child, but rather by evaluating whether he/she demonstrates sufficient understanding and intelligence to consent to health care treatment themselves. Such children are considered "mature minors". Again, a decision made by a *Gillick*-competent minor must be considered to be in their best interests (eg children may not be able to refuse treatment needed to save their life or prevent serious harm).

Be the decision-maker a *Gillick*-competent minor, or a parent/guardian, when a decision is not considered to be in the minor's best interests, a court may exercise its parens patriae jurisdiction and make a final ruling in that regard. In addition, some treatments that have been deemed "special medical treatments" require court approval – noting that attempts to preserve fertility for cancer patients does not fall into this category.

Importantly, as such procedures are still considered experimental, the retrieval and use of gonadal tissue for fertility preservation continues to be subject to institutional governance. This may include a combination of human research ethics committee review (that would assess the proposed procedure according to guidelines governing responsible human subject research in deciding whether to approve such procedures as research), clinical ethics governance (that may also focus on the clinical and psychosocial benefits and risks to the individual, as well as the values of the person and their family) and/or executive oversight as a new technology.[23] Research on the tissue itself would also be subject to human research ethics committee review. Such committees will examine closely whether requested procedures are in the best interests of a particular child, being guided by ethical guidelines on the conduct of human subject research,[24] which include but are not limited to considerations of beneficence and non-maleficence, as well other explicit laws and guidelines regulating the collection and use of, and/or research upon, reproductive tissue and/or gametes of children. But, ultimately, the "best interests" of the child will be determinative.

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[21] *Family Law Act 1975* (Cth) s 61C.

[22] At common law, the right was established in the English case of *Gillick v West Norfolk AHA* [1986] AC 112, and so is sometimes referred to as "*Gillick competence*".

[23] MA Kemertzis et al, "Fertility Preservation Toolkit: A Clinician Resource to Assist Clinical Discussion and Decision Making in Pediatric and Adolescent Oncology" (2018) 40 *Journal of Pediatric Hematology/Oncology* e133.

[24] National Health and Medical Research Council, *National Statement on Ethical Conduct in Human Research* (2007).

The sorts of factors that may be considered to determine a child's best interests were set out by Nicholson CJ in *Re Marion (No 2)*[25] and again used by him in *Re Alex*.[26] The factors include (but are not necessarily limited to):

- the particular condition of the child or young person who requires the procedure or treatment;
- the nature of the procedure or treatment proposed;
- the reasons why the procedure or treatment be carried out;
- the alternative course of treatment that are available in relation to the condition;
- the desirability of and effect of authorising the procedure for treatment proposed rather than available alternatives;
- the physical effects on the child or young person and the psychological and social implications for the child or young person of authorising or not authorising the proposed procedure or treatment;
- the nature and degree of any risk to the child or young person of authorising or not authorising the proposed procedure or treatment; and
- the views (if any) of the guardian(s) of the child or young person, to the proposed procedure or treatment and to any alternative procedure or treatment.[27]

While individual cases must be assessed on their own merits, and accordingly different decisions may be made depending on the circumstances of each case, considering the "best interests" criteria in relation to attempts to preserve a children's fertility via the collection of reproductive tissue demonstrates that such criteria will be met in light of:

- the significant prospect of infertility resulting from gonadotoxic cancer treatments; the desire to preserve the child's fertility;
- the relatively modest intrusion required (laparoscopy to remove an ovarian biopsy or small incision to remove testicular biopsy) (both of which can be combined with other medically indicated procedures such as central line placement to minimise the potential inconvenience, additional anaesthetic risks, and costs);[28]
- the lack of alternative suitable methods for fertility preservation, particularly for prepubescent children; and
- the minimal physical impact on the child of collecting gonadal tissue, coupled with the likelihood of longer-term positive psychological and sociological consequences in light of possible fertility preservation and future reproduction (even if this cannot be guaranteed).

Combined with parental (and/or a *Gillick*-competent child's) consent,[29] the best interests test in such circumstances would be satisfied. Of course, if the risks of the harvesting procedure outweighed the potential benefits for any particular child, for example when the child is too ill to undergo surgical intervention, this would not be the case and the decision not to proceed may be made.

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[25] *Re Marion No 2* (1992) 17 Fam LR 336, 451.

[26] *Re Alex* (2004) 180 FLR 89; [2004] FamCA 297.

[27] *Re Marion No 2* (1992) 17 Fam LR 336, 351; *Re Alex* (2004) 180 FLR 89, [202]–[213]; [2004] FamCA 297.

[28] P Jadoul, MM Dolmans and J Donnez, "Fertility Preservation in Girls during Childhood: Is It Feasible, Efficient and Safe and to Whom Should It Be Proposed?" (2010) 16 *Human Reproduction Update* 617; E Feigin et al, "Laparoscopic Ovarian Tissue Preservation in Young Patients at Risk for Ovarian Failure as a Result of Chemotherapy/Irradiation for Primary Malignancy" (2007) 42 *Journal of Pediatric Surgery* 862; K Oktay and O Oktem, "Fertility Preservation Medicine: A New Field in the Care of Young Cancer Survivors" (2009) 53 *Pediatric Blood & Cancer* 267.

[29] Note, a valid legal consent also requires that the person(s) consenting has capacity to consent, understands the broad nature of the treatment or procedure proposed, and must give consent without undue influence (ie freely and voluntarily): *Gibbons v Wright* (1954) 91 CLR 423. Capacity is generally presumed unless proven not to exist. It includes that a person understands the situation, relevant facts, or basic information in relation to the decisions or choices that need to be made, can evaluate reasonable implications or consequences regarding the decision and choices, is able to use reasoned processes to weigh the risks and benefits, and communicate relatively consistent or stable decisions and/or choices). Making decisions in highly stressful situations (such as for example, recent diagnosis of childhood cancer) does not necessarily negate capacity, but some time may be needed to process information, ensure adequate understanding, and to weigh the pros and cons.

V. IS THE LAW IN NSW AND VICTORIA HELPING OR HINDERING THE PRESERVATION OF FERTILITY FOR CHILDREN WITH CANCER?

The New South Wales and Victorian ART legislative provisions, as they have been drafted, pose significant issues for the collection of gonadal tissue and gametes with the aim of preserving the fertility of prepubescent children. In particular, both States' legislation may prevent research from being undertaken in their locales that may develop understanding and techniques that might assist such children to reproduce in the future. This includes research that may benefit the patient specifically, and research that may benefit others, for example, should the patient die and was able to donate tissue for research. It appears at odds with the furtherance of understanding and knowledge, and future benefits for the patient that within these States the clinical ethics framework is present that the procedures are ethically permissible because (1) the value placed on future fertility by the patient is likely to be high; (2) the procedures are generally low risk medically if there is appropriate exercise of medical judgment; and (3) *there is research being done internationally in order to develop a pathway for which a child may one day be able to use the tissue*. Yet, such research cannot occur where the patient is.

The respective New South Wales and Victorian provisions also raise issues relevant to testing of the gonadal tissue for cancerous cells once it has been collected, which is routinely evaluated for adults using xenografting to ensure that cancerous cells are not implanted back into the adult. While in New South Wales consent may be given to such testing once the child turns 18, this may mean tissue is stored for anywhere up to 18 years without the child or its family knowing whether it may ever be used. In Victoria, the situation is even worse – in that such testing may never happen – it being considered research and thus prohibited. In such circumstances, the only way to know if there are cancerous cells is to wait and treat the person when they become an adult. This creates a risk that cancer could be reintroduced to the patient when the tissue is used. To expect people to undertake such a risk is highly ethically problematic, when there is a possible method that may reduce or avoid it is unacceptable.

In New South Wales, it is noted that the ART provisions, also conflict with s 21Y of the *Human Tissue Act 1983* (NSW) which permits the senior next of kin to authorise the use for therapeutic, medical or scientific purposes of any tissue[30] removed from the body of the child during medical, dental or surgical treatment, unless the child or another next of kin of the same or higher order objects to such use. Such provisions would allow, for example, the parent(s)/guardian(s) of the child to consent to the examination of the tissue for testing or research purposes noting that anything deemed experimental would be subject to institutional Human Research Ethics Committee review. Similarly, if the child was to die after the tissue was removed, in New South Wales pursuant to the *Human Tissue Act 1983* the senior next of kin could authorise the use of the tissue, unless the person objected to the use of the tissue for the purposes to be authorised during their lifetime, or there is another next of kin of the same or higher order objects to such use again subject to Human Research Ethics Committee review if required.[31] Such provisions accord with the status given to parental authority regarding medical decision-making under the *Family Law Act 1975* (Cth), provided they are acting in the best interests of their child, but, add in the possibility for a child to object. However, given the New South Wales *ART Act* specifically regulates matters to do with assisted reproduction, the application of the provisions in the *Human Tissue Act 1983* remain uncertain.

In Victoria, despite the law making an exception to prohibitions on the collection and storage of gametes or gonadal tissue from children in instances where a child is at reasonable risk of becoming infertile before becoming an adult, the prohibitions on research at any time, does not appear at all to serve the child's "future benefit" in the context of cancer.

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[30] Tissue is defined in *Human Tissue Act 1983* (NSW) s 4 as including ova and semen unless specifically excluded by a Part of the Act.

[31] *Human Tissue Act 1983* (NSW) s 21ZA.

The law in both jurisdictions, therefore, may ultimately hinder the preservation of fertility for children, by preventing research at time crucial periods, or at all. This appears to be an unintended consequence of legislation that fails to contextualise or provide nuance regarding when research might actually be acceptable, and in the best interests of children (and their future selves) when faced with cancer and high risk of infertility.

In the other States, there are no such laws. The *NHMRC Ethical Guidelines* allow the collection and storage of gametes and tissue in the circumstance of childhood cancer. Arguably, provided valid legal consent is given by a "*Gillick*-competent child" or his/her parent(s)/guardian(s), and institutional human research ethics committee approval is obtained, research aimed at (1) increasing knowledge and understanding that may lead to better "preservation of fertility" or (2) ensuring cancerous tissue/cells are not re-implanted into the person when they are an adult would be permitted, and is in the best interests of the child.

VI. CHANGES NEEDED TO SUPPORT FERTILITY PRESERVATION IN CHILDREN

The law in New South Wales and Victoria regarding collection, storage and use of gametes and gonadal tissue from children may have an adverse impact on children with cancer, hindering research in these jurisdictions that may hold promise for their future fertility and ability to have biologically related children. Such research could also result in the children from whom tissue is collected having cancer reintroduced into their bodies. It is unacceptable that while such research may take place in Western Australia, South Australia, Tasmania, Queensland, [ACT] and the Northern Territory, subject to necessary clinical and human research ethics approvals and consent, it is in the States of Victoria and New South Wales that leading research regarding fertility preservation in adults has taken place, and where significant expertise lies. The only way to address this is to amend the legislation in Victoria (which prohibits research) and in New South Wales (which prevents any research and investigationsbefore the child turns 18). This should happen as a matter of priority, as at present gametes and tissue are being collected and stored, but research to improve understanding and knowledge, and decrease risk, is being stymied. The opportunity is readily present in Victoria, noting there is currently a review of the legislation in that State.[32]

The laws in Victoria and New South Wales are also illustrative of the need to consider how to provide flexibility in regulation, particularly in rapidly advancing areas of science. This is a perennial problem that calls for attention via proactive, flexible forms of governance, rather than intractable regulatory rules.[33] For example, a simple method in the current context would be to provide in the legislation that research is permitted in limited circumstances, subject to consent and necessary approvals, and as specified in directions. The Minister responsible for the Act could then use directions to set the parameters within which research may occur, noting that directions can then be updated more readily when called for in a flexible and responsive manner. Another, would be to not legislate, but rather, as is the situation in most of the States and Territories in Australia, rely on the *NHMRC Ethical Guidelines*, the National Statement on the Ethical Conduct of Research, and scrutiny by institutional clinical and human research ethics committees.

Research on fertility preservation for people with childhood cancer is also a context that may benefit from dynamic consent requirements as research knowledge improves – that is, that consent be revisited over a period of time, as research knowledge evolves. However, this should be qualified by recognising that requirements and patient preferences regarding consent will need to be examined carefully and contextualised – noting that some research has found that a significant number of cancer

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[32] See Victoria State Government, *Review of Assisted Reproductive Treatment* <https://www2.health.vic.gov.au/hospitals-and-health-services/patient-care/perinatal-reproductive/assisted-reproduction/regulatory-review>.

[33] See, eg, R Hagemann, J Skees and A Thierer, "Soft Law for Hard Problems: The Governance of Emerging Technologies in an Uncertain Future" (2018)available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3118539; GE Marchant et al (eds), *The Growing Gap between Emerging Technologies and Legal-ethical Oversight: The Pacing Problem* (Springer, 2011); G Mandel, "Regulating Emerging Technologies" (2009) 1 *Law, Innovation and Technology* 75.

patients would prefer to give one-time blanket consent when they have donated tissue, compared to having to engage with a tiered consent approach, or re-consenting for each additional study.[34]

Finally, but not least, there should be the possibility for directions for the disposition of stored gametes, embryos and gonadal tissue. That is, persons whose gametes, embryos, or tissue are stored to preserve fertility, or their legal guardians should give directions for disposition of that tissue in the future. This might best be done when the gametes, embryos, or gonadal tissue are removed or preserved, but directions can be given or amended at any later time that the patient wishes. This would allow the person (or their parent(s)) to specify what should be done with stored gametes, embryos, or gonadal tissue if he/she dies. This is a standard inclusion in adult consent forms, but due to the prohibitions on research in Victoria and New South Wales for children, is not something that is possible in Victoria, or in New South Wales, before a person reaches the age of 18.

VII. CONCLUSION

A diagnosis of childhood cancer can be devastating. However, in modern times, treatment with chemotherapy and/or radiation therapy has resulted in ever-increasing survival rates. Such treatment, nevertheless, poses the added, and significant, burden of infertility into a child's future. There is, however reason for hope. This article has shown that options for fertility preservation and future reproduction for such children do exist, but some such options continue to be considered experimental. Collaborative multidisciplinary teams support children and their families to make decisions about such options in the treatment environment. When collection of gonadal tissue from children is consented to in such circumstances, it is subject to stringent institutional human research and clinical ethics review, often in both the pediatric oncology setting and the fertility setting in which it will be preserved, examined and, potentially, used. Laws and guidelines may support the collection and use of reproductive tissue from children for treatment and research, subject to the meeting consent requirements concerning the child and/or their parent(s).

This article has shown that laws in Victoria and New South Wales, however, hinder research and practice that may provide further understanding and knowledge, and that they decrease risk of reintroducing cancer into a person from whom gametes or tissue have been collected. Consequently, the laws are having a negative impact on the prospects for children with cancer in relation to their fertility preservation, possibilities for future reproduction, and safety.

The authors call for changes to the law to permit such research, subject to lawful consent and institutional human research ethics committee approval. It is also imperative to recognise that the law struggles in areas of rapidly changing technology, and more flexible regulatory approaches are required. Implementation of dynamic consent in such an environment and allowing disposition regarding what should happen to gametes and tissue should a child die, would also enable advances in this important area.

[34] Z Master et al, "Cancer Patient Perceptions on the Ethical and Legal Issues Related to Biobanking" (2013) 6 *BMC Medical Genomics* 8; KL Braun et al, "Cancer Patient Perceptions about Biobanking and Preferred Timing of Consent" (2014) 12 *Biopreservation and Biobanking* 106.

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