Fertility Preservation for People with Cancer:

A New Zealand Guideline

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INTRODUCTION

This guideline has been developed for oncologists, haematologists and other health professionals involved in the care of people with cancer. The purpose of the guideline is to provide recommendations regarding best practice and a description of currently available options for fertility preservation for children and adults in New Zealand.

The development of the guideline was initiated by the National Child Cancer Network in response to an identified need for a co-ordinated approach to fertility preservation for paediatric, adolescent and young adult patients with cancer. This intent was signalled to the Cancer Treatment Advisory Group who requested that the guideline be broadened to include patients of all ages. Accordingly, the guideline development group was widened to include representatives from adult medical and radiation oncology and haematology services.

The guideline development group comprised a diverse team of health professionals from throughout New Zealand, representing the disciplines of paediatric and adult haematology and oncology, radiation oncology, gynaecology, fertility, endocrinology, and nursing. A consumer representative was also part of the group. For the development of the late effects section a sub-group was formed. This group included health professionals with expertise in the assessment and care of those at risk of late effects of cancer treatment.

The guideline outlines current evidence and international expert opinion regarding the fertility risks associated with cancer treatments and the available or emerging fertility preservation options for those whose fertility is likely to be affected. As technological advances in fertility preservation become known, and evidence for their safety and efficacy increases, fertility preservation becomes an increasingly important consideration for those with cancer and their health care teams, and those charged with making decisions about funding and access to such technologies. This is particularly so for those whose fertility preservation options are limited by age, availability and/or cost. Where cost is an influencing factor in an individual's decision about whether to pursue an option such as ovarian tissue cryopreservation, equality of access for those from lower socio-economic and minority groups becomes an important ethical and moral consideration for all concerned.

Many cancers can be successfully treated but unfortunately, many cancer treatments can damage fertility in the short and long term. Research indicates that people with cancer are concerned about the effect of their diagnosis and treatment on fertility, and want information about fertility and fertility preservation options at an early stage [1-5]. It is therefore important that health professionals involved in cancer care consider and discuss fertility preservation before recommending gonadotoxic treatment.

The Need for Guidance for Health Professionals

From the time of diagnosis until death people with cancer are now described as cancer survivors and approximately 63% of adults and 80% of children diagnosed with invasive cancer will be alive five years from the time of diagnosis [6-9]. This progressive increase in the number of people surviving a diagnosis of cancer and its treatment can be attributed to more effective treatments, earlier diagnoses, and better supportive care[10, 11]. As this number increases and the duration of survivorship extends, the quality of life enjoyed or endured by these survivors is increasingly and appropriately seen as a key outcome of cancer treatments.

Fertility damage can be a significant and distressing effect of cancer and its treatment [12]. Given the known risks of fertility damage associated with certain cancer treatments, and currently available options for fertility preservation, it is reasonable to expect that people diagnosed with cancer will be appropriately and fully informed of both risks and options in a timely manner. There are current and future options for the protection or preservation of fertility for those facing cancer and its treatment. On an individual basis, these options depend on many factors including gender, age, relationship status, type of cancer and type of treatment.

Research suggests that many health professionals do not routinely discuss fertility and fertility preservation despite recognising the importance of doing so. Barriers to such discussions include time constraints, lack of information about fertility options and costs, lack of clear referral pathways, and concerns about potential treatment delays [13-15]. Poor recall of discussions of fertility issues may also be a factor, particularly in the diagnosis and pre-treatment phase where a large volume of potentially distressing information is given to those newly diagnosed with cancer and their family/whanau [16].

Funding for Fertility Preservation for People with Cancer

The nationwide service specification for Artificial Reproductive Technology Services (ART) describes the minimum services that are required to be funded by District Health Boards in New Zealand for eligible people. This service

specification (to be updated in 2014) includes some services for people whose fertility is, or will be permanently impaired by cancer treatment as listed below:

- Retrieval, freezing, and storage of gametes (eggs and sperm) up to 10 years
- In vitro fertilitization cycle according to relevant CPAC tool, embryo freezing, and storage up to 10 years
- Intracytoplasmic sperm injection
- Frozen embryo replacement

Note: Fertility Preservation Service Users who receive services related to fertility preservation will have their gametes / embryos storage funded up to 10 years. Parliament amended the Human Assisted Reproductive Technology Act (the HART Act) in 2010 to clarify provisions relating to the storage and extending storage of gametes and embryos beyond the original 10-year limit. See Ethics Committee on Reproductive Technology (ECART)'s guidelines issued by Advisory Committee on Reproductive Technology (ACART), on the extended storage of gametes and embryos, to enable applications to ECART to extend the period of storage. http://acart.health.govt.nz/system/files/documents/publications/acart-guidelines-extending-storage-gametes-embryos-2012.pdf

Purpose of this Guideline

The purpose of this guideline is to provide:

- information for health professionals about risks to male and female fertility associated with commonly used cancer treatments
- information about currently available fertility preservation options for people of any age diagnosed with cancer and how these can be accessed
- recommendations for monitoring the reproductive health of cancer survivors

Grading of Recommendations

The recommendations presented in this guideline have been assigned a 'grade of evidence' based on the system employed by the New Zealand Guidelines Group. This involves an analysis of the quality and consistency of the evidence base with consideration for the clinical implications of the evidence within the New Zealand healthcare context. The recommendation grades indicate the overall strength of the evidence for a particular recommendation. It is important to note that the grades indicate the *strength of the evidence* supporting a recommendation, not the *importance of the recommendation* itself.

Grades indicate the strength of the supporting evidence rather than the importance of the evidence	*Grade*
The recommendation is supported by good evidence (based on a number of studies that are valid, consistent, applicable and clinically relevant)	A
The recommendation is supported by fair evidence (based on studies that are valid, but there are some concerns about the volume, consistency, applicability and clinical relevance of the evidence that may cause some uncertainty but are not likely to be overturned by other evidence)	B
The recommendation is supported by international expert opinion	C
The evidence is insufficient, evidence is lacking, of poor quality or opinions conflicting, the balance of benefits and harms cannot be determined	I
Good practice point – where no evidence is available, best practice recommendations are made based on the experience of the Guideline Development Team or feedback from consultation within New Zealand	√

FERTILITY DISCUSSION AND INFORMATION

Research and expert opinion suggest that issues related to fertility and sexuality are of a high level of concern for many people diagnosed with cancer, and that this translates into a need for timely, accessible, appropriate and current information [1, 2, 4, 5, 18-21]. Males and pre-menopausal females of any age who require treatment that poses a risk to future fertility, or the parents/guardians of young children, must be given the opportunity to discuss this risk and the available options to protect or preserve their/their child's fertility. Initial discussions should take place before treatment begins as part of the process of informed consent for cancer treatment, and should be led by the most appropriate member of the oncology team (oncologist, surgeon, nurse specialist) [20, 22]. In many cases, urgent referral to a fertility specialist may be required to allow fertility preservation to be undertaken before the commencement of cancer treatment [23, 24]. These discussions should include partners and family/whanau as appropriate. More than one discussion may be needed to facilitate informed decision-making [25].

Recommendations – Discussion and Information	*Grade of Evidence*
The 'reasonable suspicion' of a cancer likely to require fertility-impairing treatment in a male or pre-menopausal female should prompt discussion of fertility and of options for fertility preservation. Delaying discussion until the diagnosis is confirmed may limit access to some fertility preservation options Consideration should also be given to the risk of relapse and/or the need for more gonadotoxic therapy in the future	√
Fertility risks and any appropriate options for fertility preservation should be discussed **with paediatric and adolescent patients and/or parents (or guardians), and young adult patients** regardless of the person's age, prognosis, treatment plan, perceived level of risk to fertility, sexual orientation or relationship status Fertility risks and any appropriate options for fertility preservation should be discussed with **adult male and pre-menopausal female patients** who are at risk of damage to fertility from planned cancer treatment and those who express concerns regarding fertility or ask questions regarding fertility, regardless of prognosis, sexual orientation or relationship status Patients' options for fertility preservation may be influenced by age, co-morbidities and previous treatments. Initial discussions should be undertaken by the most appropriate member of the oncology team as part of the informed consent process for cancer treatment. Urgent referral to a fertility specialist team may be required. Oncology team discussion with person with cancer/family/whanau should include: • the degree of risk to fertility posed by the treatment plan – short and long term • available and appropriate options for fertility preservation, including investigational options where available and appropriate • the potential impact (if any) of pursuing fertility preservation options on cancer treatment and outcome • the acceptability and potential implications of choosing not to pursue fertility preservation • the need for contraception for those who are sexually active as absolute fertility status is difficult to ascertain, particularly during chemotherapy and in the early post-treatment phase • the risk of premature menopause • changes to sexual function • the provision of appropriate written information Specialist fertility team discussion with person with cancer/family/whanau should include: • reiteration of the points discussed by the referring oncology team, as described above • the potential moral, ethical and legal issues associated with some fertility preservation options such as ownership of embryos or reproductive tissue in the event of death or incapacity • information about success rates, risks and complications, published evidence and costs (if relevant) for all options that are under discussion • information regarding storage and disposal of gametes, and the importance of maintaining contact with the fertility centre until such time as gametes are used or disposed of • It is important that people undergoing fertility preservation measures are informed of the outcome of the preservation processes and the options available to them regarding the use of their stored material	√ √ √

Considerations

Ethical Considerations

There are a number of ethical considerations associated with discussing fertility issues and options with people with cancer and their partners and family/whanau, including:

- difficulties associated with encouraging people with a new cancer diagnosis to make decisions about future fertility while they are still coming to terms with their diagnosis and the often urgent need to commence treatment
- decisions regarding delaying the start of cancer treatment to allow for fertility preservation, particularly if the fertility preservation option is investigational
- consideration of the importance of prognosis

Health professionals working with young people with cancer, particularly younger adolescents and children, need to consider the extent to which the young person is able to participate in decision-making and provide consent or assent. This will depend on their level of development, their understanding of their particular situation, and the degree to which they are physically unwell.

Personal Considerations

- delivery of information must be age-appropriate, particularly in the paediatric and adolescent setting, and involvement of AYA Nurse Specialist or other appropriate team member should be considered [16]
- factors such as ethnicity, sexual orientation, personal/sexual history, relationship status and religious or cultural beliefs about reproduction, masturbation and/or assisted reproductive technologies should be considered and attended to with sensitivity in any discussions around fertility
- the person may or may not want their partner and/or family/whanau, or in the case of children and adolescents their parent/caregiver, to be present for and contribute to discussions regarding fertility risk and options
- where language may be a barrier to full communication and understanding, the assistance of an interpreter should be sought with consideration given to the gender of both parties
- for younger people, having children may not be something they have previously considered
- peoples' feelings about future parenthood may change over time so it is important that the long-term consequences of fertility decisions made prior to treatment are emphasised [22, 26]

There are many reasons why people with cancer may decline available fertility preservation options, including [4, 18, 19, 22-24, 26-28]:

- believing that the risk of fertility damage from their treatment is low
- not understanding or absorbing information about fertility risks due to feeling overwhelmed by their diagnosis, receiving too much information in a short timeframe, or a lack of emphasis placed on fertility risks by health professionals
- placing future fertility/parenthood at a lower priority in light of the diagnosis of a life-threatening illness
- being unwilling to delay the start of cancer treatment to pursue fertility preservation
- feeling overwhelmed at the need for additional procedures related to fertility preservation
- concerns regarding the initial and ongoing costs associated with fertility preservation
- religious, cultural or ethical concerns about fertility preservation methods
- being unable to provide a semen sample due to being too unwell or for other reasons

Cultural Considerations

Cultural concerns, beliefs and practices may have a significant impact on decision-making regarding fertility and fertility preservation for some. This may be of particular concern for Maori as some iwi disagree with storage of tissue samples citing whakapapa. It is therefore important that health professionals involved in fertility discussions and fertility care are aware of such beliefs and concerns, and that appropriate cultural and social support be available to assist with discussions and decision-making regarding fertility issues. Due to limited published research addressing Maori attitudes to and uptake of fertility preservation or assisted reproductive technologies in New Zealand no comment can currently be made regarding the impact of these beliefs and concerns on decisions regarding fertility preservation [29, 30].

MANAGING THE FERTILITY PRESERVATION PROCESS

Successful management of the risks to fertility associated with cancer treatment requires a co-ordinated multi-disciplinary approach using appropriate region-specific providers and pathways. It is particularly important that the oncology and specialist fertility teams have established patterns of referral and communication [4, 27]. Other key team members may include the person's partner and family/whanau, AYA Clinical Nurse Specialists and support staff, local surgical/gynaecology/urology teams, staff at the appropriate tissue storage facility/fertility clinic, members of the research team for investigational procedures, reproductive endocrinology laboratory staff and providers of psychosocial support.

Oncology centres may benefit from the development of a specialist nursing role focused on fertility and sexuality issues. This role can maintain responsibility for co-ordination and promotion of fertility preservation discussion, information and referral, and be the central contact for those with needs related to fertility and sexuality [22, 31, 32].

Recommendations – Multi-disciplinary Approach	*Grade of evidence*
Oncology services have a responsibility to ensure that they establish and maintain a co-ordinated and accessible multi-disciplinary approach to fertility preservation including, but not limited to: • oncologist and oncology nursing team • fertility specialist and associated nursing, laboratory and storage facilities • local surgical, gynaecology, urology teams and radiation oncology teams • AYA and other clinical nurse specialists • providers of psycho-social support Oncology services should nominate key team members and/or a specialist role to co-ordinate and promote this approach	√
People with a cancer diagnosis who indicate an interest in pursuing fertility preservation must be urgently referred as appropriate, to: • a local sperm banking facility for post-pubescent males • a fertility specialist for pre-menopausal females of any age who wish to pursue fertility preservation • a fertility specialist/urologist for post-pubescent males who are unable to produce semen for sperm banking by masturbation • psycho-social support at any stage	√

It is common for those newly diagnosed with cancer to have very limited time available between confirmation of the suspected cancer diagnosis and the commencement of potentially life-saving treatment. Emergent life-saving treatment takes priority over fertility preservation, but may compromise future fertility preservation options. The guideline group, therefore, recommend that in a premenopausal female or a male, the 'reasonable suspicion' of a diagnosis of cancer likely to require fertility-impairing treatment should prompt fertility preservation discussions and, as appropriate, interventions.

Consideration of fertility issues, decision-making around fertility preservation, and the pursuit of fertility preservation options can lead to psychological distress [33-35]. Distress may occur at the time that discussions and interventions take place or at any future stage. It is important that both general psychological support and ongoing information and discussion are provided by members of the oncology and fertility teams. Specialist psychological support should be available, and referred to as appropriate.

Guideline Implementation

Written protocols should be developed by oncology and fertility services to clearly outline the service/region-specific implementation of these guideline recommendations [18, 23, 24, 27]. Within this, the roles of the key team members involved in fertility preservation should be clearly stated, with appropriate region-specific information highlighted. Clear communication pathways between services should be developed and maintained within each region to facilitate information sharing and best outcomes:

- where a referral to specialist fertility services is made a detailed referral should be provided, including:
    - cancer diagnosis, including stage and grade of disease and prognosis, if known
    - anticipated/proposed treatment plan
    - assessment of degree of risk to fertility posed by the anticipated/proposed treatment plan
    - time available until start of treatment, and indication of urgency of treatment commencement
    - relationship/family status, presence of existing children
    - relevant medical, mental health and/or substance abuse history
- after assessment, a detailed description of any fertility preservation plan should be provided by the specialist fertility team to the oncology team
- after completion of fertility preservation processes, a detailed description of fertility preservation outcomes should be provided by the specialist fertility team to the oncology team, including:
    - fertility preservation processes undertaken and their outcome
    - the likely use of any stored gametes
    - any further recommendations for management or collection of tissue for fertility preservation

- any peri-operative complications or other relevant clinical information

OPTIONS FOR FERTILITY PRESERVATION

There is currently a limited range of options to preserve or protect the fertility of men and women diagnosed with cancer. The options available to an individual depend on many factors including gender, age, current relationship status, type of cancer, type/intensity/duration of treatment and co-morbidities. It is recommended that fertility preservation be undertaken prior to the commencement of chemotherapy due to the risk of DNA damage to sperm and oocytes from chemotherapy agents [36-40].

Recommendations – Current Fertility Preservation Options for Males and Females with Cancer	*Grade of Evidence*
The most effective and established means of preserving fertility in post-pubertal females with cancer are: • embryo and oocyte cryopreservation where appropriate prior to commencement of cancer treatment The most effective and established means of preserving fertility in post-pubertal males with cancer is: • sperm cryopreservation prior to commencement of cancer treatment	B
Most other procedures are still considered investigational • If the efficacy of a particular method of fertility preservation is not established then this needs to be clearly stated in discussions and consent procedures • Investigational procedures should be undertaken in the context of a protocol approved by the relevant national Ethics Committee (Ethics Committee on Assisted Reproductive Technology or a general Health and Disability Ethics Committee) particularly in the paediatric and adolescent population	√ C
Discussion about fertility preservation options should include an explanation of the processes involved, success rates, risks and side effects, and costs, including: • the potential for increased risk of birth defects associated with assisted reproduction, particularly intracytoplasmic sperm injection (ICSI) • advice that the risk of birth defects associated with oocyte and ovarian tissue cryopreservation is not known	√
Preservation of reproductive tissue during chemotherapy is not currently recommended due to the possibility of DNA damage to the stored tissue	C
The use of fertility preservation measures must be individualised and personalised in consultation with the person with cancer, their family/whanau and the multidisciplinary treatment team	√

Females

Most cancer treatments have the potential to affect fertility. The major effect of cancer treatment on female reproductive potential is through damage to the ovary and the oocytes with accelerated oocyte depletion. Due to the limited number, irreplaceable nature and decreasing quality of oocytes over time, rates of successful conception and pregnancy diminish rapidly from the age of 30 even without cancer treatments [41]. Accordingly, the risk of premature ovarian failure from chemotherapy or radiation therapy increases rapidly from 30 years of age.

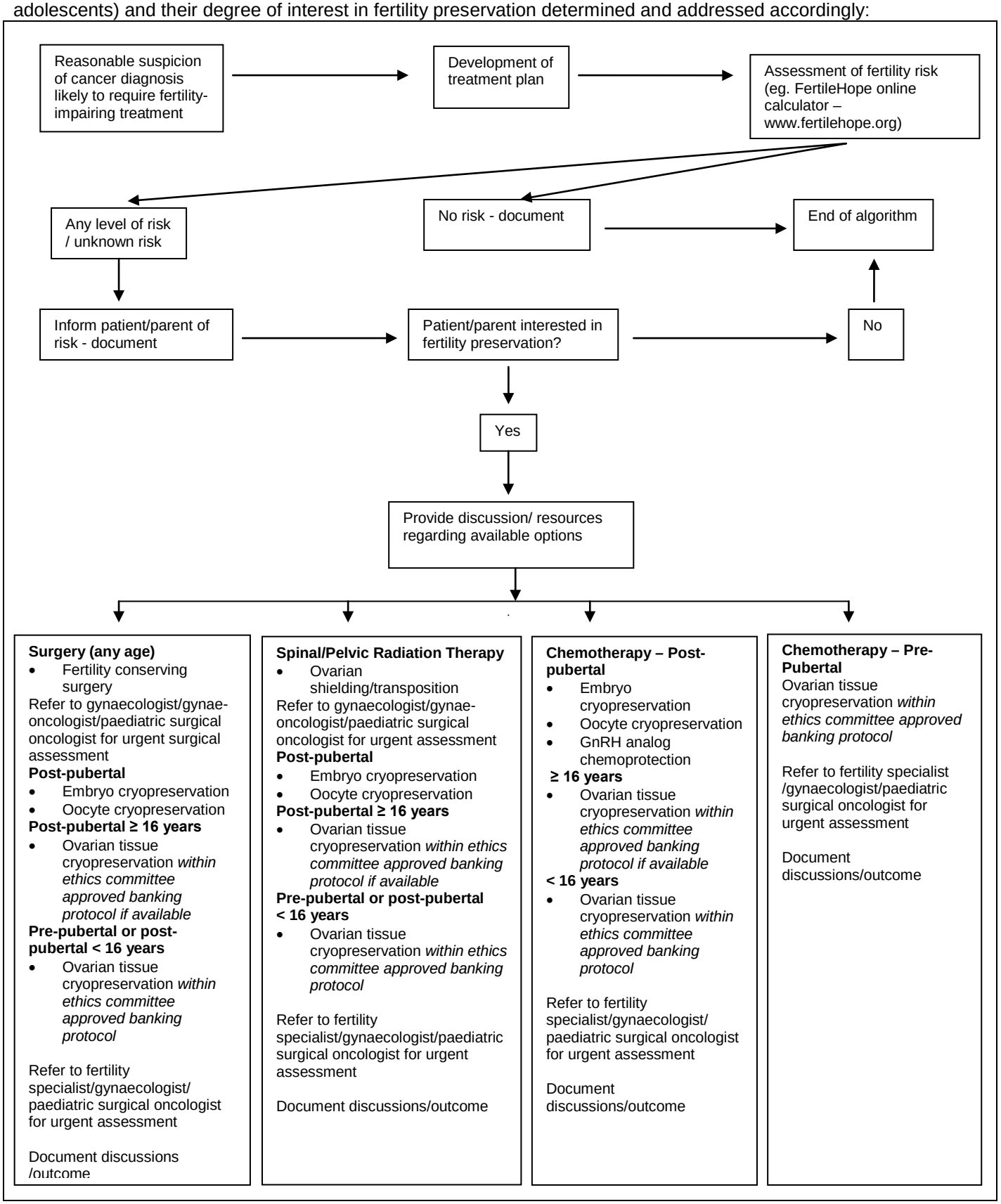
Even though women may continue to menstruate throughout gonadotoxic treatment or resume menstruating after completion of treatment, it is possible that damage to the ovarian reserve will result in premature menopause [42, 43]. An individual woman's risk of ovarian damage or failure is influenced by her age, pre-existing fertility status and the type, intensity and duration of the treatment. In addition, radiation to the uterus can cause irreversible damage via disruption to uterine vasculature and a decrease in uterine weight and length. This can lead to problems with implantation and uterine growth during pregnancy. Surgery involving reproductive or other abdomino-pelvic organs can affect fertility through anatomic or vascular changes. Hormone changes resulting from cranial irradiation may negatively impact on female fertility [4]. Females who have had cancer treatment at any age should be counselled that they may have a shortened reproductive life span with an earlier menopause. Prior treatment with chemotherapy has been shown to significantly reduce the efficacy of assisted reproductive technologies undertaken after the end of cancer treatment [44, 45].

Research suggests that children born to cancer survivors are not at increased risk of birth defects, genetic disorders or chromosomal abnormalities [46-48]. There is, however, a known increased risk of birth defects associated with assisted reproductive technologies [49-53]. This risk may not be significant for IVF when rates of birth defects are adjusted for parental factors, but there are risks associated with ICSI [54]. Pregnancy following cancer should be considered a 'high risk' pregnancy and managed by a multidisciplinary team. Women who have been treated for hormone-sensitive cancers such as breast cancer do not appear to be at increased risk of relapse during subsequent pregnancy [55].

Recommendations – Fertility Preservation for Females	*Grade of Evidence*
Damage to fertility due to cancer or its treatment may lead to emotional distress, as can the processes and procedures associated with fertility preservation and treatment • Availability of and referral for psycho-social support is recommended	√
Embryo and oocyte cryopreservation are established procedures that: • should be discussed, as appropriate, with females from menarche to menopause prior to potentially sterilising surgery, chemotherapy or pelvic radiation • may be suitable for post-pubertal women who: o are medically fit for the procedure o are expected to be able to tolerate the treatment regimen o have sufficient time (10-17 days) before the commencement of their cancer treatment o are informed of the potential risks of hormonal treatment including the risks of cancer progression	B
Ovarian tissue cryopreservation and storage is an investigational procedure that: • should only be undertaken in the context of an ethics committee approved tissue-banking protocol o where this is not available, ovarian tissue cryopreservation may be undertaken in those aged ≥ 16 years provided fully informed consent is gained, including information that the use of cryopreserved ovarian tissue to achieve pregnancy is not yet considered to be a routine clinical practice • should be discussed with females/parents or guardians of females who: o are pre-pubertal and/or o do not have the option of embryo/oocyte cryopreservation	B
Ovarian tissue must be tested for the presence of cancer cells or markers prior to transplantation (transplantation of ovarian tissue is not currently approved in New Zealand)	B
In vitro maturation of oocytes (IVM) is an emerging technology and may be an option but current success rates remain inferior to standard IVF	I
The efficacy of GnRH analogues for ovarian protection for post-pubertal women has not been established, with successive clinical trials producing conflicting evidence • GnRH analogues should therefore NOT be used as the only option for fertility preservation unless informed consent is gained, including discussion of the lack of evidence for the efficacy of this approach • Care should be taken when using GnRH analogues in women with potentially endocrine-sensitive tumours such as breast cancer	B √
Fertility conserving/sparing surgery should be considered and offered wherever possible when pelvic/gynaecologic surgery is indicated Ovarian shielding/transposition should be considered wherever possible when pelvic/abdominal radiation therapy is indicated	C C

Female Fertility Preservation Algorithm

Consideration of the potential impact of cancer treatment on fertility and options for fertility preservation should be included in diagnosis and treatment planning for premenopausal women with cancer or a reasonable suspicion of cancer. Any level of risk to fertility must be disclosed to the person (and/or parents/guardians for children and adolescents) and their degree of interest in fertility preservation determined and addressed accordingly:



Assessment of Fertility Risk

Assessment of the potential for non-surgical cancer treatments to affect female fertility is currently hampered by the use of amenorrhea as a marker of fertility in the majority of reports and the tools developed from them. The presence or absence of menstruation is a poor representation of fertile potential, and any assessment of fertility risk should reflect this. More reliable measures, such as Anti-Mullerian Hormone, Follicle Stimulating Hormone and Inhibin B, are being investigated for their use as markers of ovarian reserve but it will be some time before fertility risk assessment tools reflect research findings based on these [56, 57]. Until this happens, tools such as that provided by FertileHope.org (adapted below) offer a means to *loosely* assess risk on an individual basis.

Likelihood of Amenorrhea	Treatment	Potential Usage
HIGH - >70% will develop amenorrhea post-treatment	Fractionated radiation therapy - whole abdominal or pelvic radiation > 6 Gy (adult women)	Many cancers
	Fractionated radiation therapy - whole abdominal or pelvic radiation > 15 Gy (pre-pubertal girls) > 10 Gy (post-pubertal girls)	Wilms tumour, neuroblastoma, sarcomas, Hodgkin lymphoma
	Fractionated radiation therapy - total body irradiation	Conditioning for haematopoietic stem cell transplant
	Fractionated radiation therapy – cranial radiation > 40 Gy	Brain tumours
	Chemotherapy – CEF, CMF, CAF x 6 cycles in women aged 40+	Breast cancer
	Chemotherapy – cyclophosphamide: 7.5g/m2 in girls aged < 20 5g/m2 in women aged > 40	NHL, neuroblastoma, ALL, sarcomas, breast cancer
	Chemotherapy – alkylating agents for conditioning for haematopoietic stem cell transplant eg cyclophosphamide, busulphan, melphalan	Conditioning for haematopoietic stem cell transplant
	Chemotherapy – any alkylating agent eg cyclophosphamide, ifosfamide, busulphan, BCNU, CCNU + total body irradiation or pelvic radiation	Conditioning for haematopoietic stem cell transplant, ovarian cancer, sarcomas, neuroblastoma, Hodgkin lymphoma
	Chemotherapy – protocols containing procarbazine eg ChlVPP, BEACOPP	Hodgkin lymphoma
INTERMEDIATE – 30-70% will develop amenorrhea post-treatment	Fractionated radiation therapy – whole abdomen or pelvic radiation 10 - 15 Gy in pre-pubertal girls	Wilms tumour
	Fractionated radiation therapy – whole abdomen or pelvic radiation 5 - 10 Gy in post-pubertal girls	Wilms tumour, neuroblastoma
	Fractionated radiation therapy – spinal radiation with ovaries shielded or transposed ≥ 25 Gy	Spinal tumours, brain tumours, neuroblastoma, relapsed ALL/NHL
	Chemotherapy – cyclophosphamide 5g/m2 in women aged 30-40	Mulitple cancers, Breast cancer
	Chemotherapy – protocols containing cisplatin	Cervical cancer
	Chemotherapy - FOLFOX4	Colon cancer
	Chemotherapy – • AC x 4 in women aged 40+ • CEF, CMF, CAF x 6 cycles in women aged 30-39 • Anthracycline/taxane containing regimens in women aged 30-39	Breast cancer
LOWER - < 30% will develop amenorrhoea post-treatment	Chemotherapy – • AC x 4 in women aged < 30 • CMF, CEF, CAF x 6 cycles in women aged < 30	Breast cancer
	Chemotherapy – non-alkylating eg ABVD, COP, CHOP	NHL, Hodgkin lymphoma
	Chemotherapy – non-alkylating eg anthracycline + cytarabine	AML
	Chemotherapy – multi-agent	ALL (standard/high risk)
VERY LOW – negligible effect on menstruation	Radiation therapy – radioactive iodine	Thyroid cancer
	Chemotherapy – vinblastine, methotrexate	Multiple cancers

UNKNOWN	Chemotherapy – Oxaliplatin Irinotecan Taxanes – appear to have additive impact but research ongoing Biological therapies	Multiple cancers

(Table adapted to reflect current New Zealand oncological practice [16, 58-61].

Oocyte and Embryo Cryopreservation

Embryo cryopreservation is an established procedure, and is highly successful with 80 - 90% of good quality embryos expected to survive the thawing process [36, 53, 62, 63]. Currently, the chance of a live birth per thawed embryo replaced in a woman under 35 years of age is about 35% [63, 64].The success of this process is dependant on the woman's age at the time that in vitro fertilisation and cryopreservation took place.

Oocyte vitrification is an established procedure with survival rates of thawed oocytes of approximately 90%. Two or three embryos may be expected from every 10 good quality oocytes obtained at the retrieval procedure, with implantation rates similar to those from frozen embryos. Oocyte cryopreservation may be a viable alternative for women who are not in long-standing relationships. The process of vitrification is increasingly being used for the freezing of oocytes and embryos [62, 65-69].

In-vitro maturation of oocytes (IVM**)** is an emerging, but still investigational, technique, which involves collection of immature oocytes from small follicles. This usually takes place early in the menstrual cycle and with limited or no ovarian stimulation. IVM may be of particular benefit for younger women, particularly those with limited time prior to the commencement of chemotherapy, or those with an oestrogen-sensitive tumour [62, 70].

Risks and Considerations:

- Neither embryo nor oocyte cryopreservation provide a guarantee of future fertility
- The process of ovarian stimulation and oocyte retrieval requires 10 to 17 days before the start of chemotherapy or pelvic radiotherapy
- Theoretical concerns exist regarding the use of ovarian stimulation in women with oestrogen-receptor positive breast cancers. The use of an aromatase inhibitor as ovarian stimulator has been described as a safe alternative in a number of reports [71, 72]
- Medically unwell women may face increased risks related to anaesthetic and oocyte collection processes
- Consideration should be given to the appropriateness of the processes involved in oocyte retrieval in women who have not been sexually active, as this usually involves trans-vaginal procedures [73, 74]
- Embryo cryopreservation carries the 'social risk' that the couple may separate and the former male partner may no longer consent to the use of the stored embryos
- It is possible that children born as a result of assisted reproductive technologies may have an increased risk of congenital abnormalities compared to naturally conceived children [53]
- New Zealand legislation limits storage of sperm, oocytes, embryos and ovarian or testicular tissue to a maximum of ten years. After this time, an application to the Ethics Committee on Assisted Reproductive Technology (ECART) must be made by the owner requesting ongoing storage [75].

Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation is a relatively new technology and still considered investigational in relation to the future reimplantation of the tissue for the purpose of restoring fertility. However, it appears to hold promise, in particular for pre-pubertal girls and women for whom embryo or oocyte cryopreservation is not possible [4, 62, 76, 77]. There is no current consensus on the lower and upper ages at which ovarian tissue cryopreservation should be performed. The likelihood of achieving pregnancy and live birth after reimplantation of ovarian tissue is partly dependent on the age of the woman at the time the tissue was retrieved. With this in mind, upper age limits of 30-35 years [62] or 40 years [4, 78] have been proposed. At the time that this guideline was drafted, no pregnancies had been reported in those aged over 35 years. As this is the only possible option for pre-pubertal females, it is argued that this technique should be made available in anticipation of future expertise and success in reimplantation and subsequent restoration of fertility [4, 62, 76, 77].

The process requires a laparoscopic procedure to remove part of an ovary or a whole ovary, which is then sliced into very small segments and cryopreserved. Retrieval of ovarian tissue can take place during another planned surgical procedure. The cryopreserved tissue can subsequently be re-implanted either on or very close to the remaining ovary or outside the pelvic cavity with the aim of restoring ovarian function for at least a period of time. Natural conceptions can occur after re-implantation of ovarian tissue on or close to the remaining ovary where the fallopian tubes are

intact, but IVF is often required to obtain oocytes which can be fertilised in vitro [79]. In excess of 20 live births have been reported after transplantation of cryopreserved ovarian tissue, but it is difficult to determine the true pregnancy and live birth rate as it is unclear how many women have had ovarian tissue replaced without reporting pregnancy and/or live birth, and in some cases pregnancies may have arisen from the residual untransplanted ovary [77, 79-81].

At the time of guideline preparation New Zealand legislation permits the retrieval and cryopreservation/storage of ovarian tissue, but not reimplantation [82, 83]. As yet, no application to the Ethics Committee on Assisted Reproductive Technology (ECART) to re-implant ovarian tissue has been made in New Zealand. Such an application would require approval from the Advisory Committee on Assisted Reproductive Technology (ACART). Current practice at many international sites and the recommendations of existing guidelines and reports suggest that ovarian tissue cryopreservation and storage should be undertaken within a suitable ethically-approved protocol where this is available. This recognises that the techniques involved in the reimplantation of tissue remain investigational, particularly for girls who were pre-pubertal at the time of tissue retrieval, and emphasises the associated need for rigorous information and consent procedures for the protection of patients, caregivers, health professionals and health services [4, 20, 62, 67, 78, 80, 84-86].

The recommendation of this guideline, therefore, is that ovarian tissue cryopreservation/storage should be undertaken in the context of a formal ovarian tissue banking protocol that has approval from the appropriate national ethics committee. However, where this is not possible or available, ovarian tissue cryopreservation may be undertaken in those aged ≥16 years provided fully-informed consent is gained, including information that the use of cryopreserved ovarian tissue to achieve pregnancy is not yet considered to be a routine clinical practice and is not currently permitted in New Zealand [82, 83].

Risks and Considerations:

- There are surgical risks associated with the retrieval of ovarian tissue, similar to those associated with standard laparoscopic or mini-laparotomy surgery. These risks are considered low but include anaesthetic risks and complications such as bleeding and infection; in many cases, ovarian tissue retrieval may take place at the same time as another surgical procedure
- Removal of some ovarian tissue for storage may compromise remaining ovarian function
- Adhesion formation may reduce the chances of spontaneous conception
- Ovarian tissue cryopreservation does not provide a guarantee of future fertility and the process of tissue reimplantation is not yet approved in New Zealand
- Medically-unwell women may face increased risks related to anaesthetic and tissue collection processes
- It is possible that children born as a result of IVF have a minimally increased risk of congenital abnormalities compared to naturally conceived children
- New Zealand legislation limits storage of sperm, oocytes, embryos and ovarian or testicular tissue to a maximum of ten years. After this time, an application to the Ethics Committee on Assisted Reproductive Technology (ECART) must be made by the owner requesting ongoing storage [75]
- There may be a delay of initiation of cancer treatment to allow for surgery and recovery, although this is likely to be minimal
- Very limited data exists on obstetric complications in pregnancies achieved after ovarian tissue cryopreservation and reimplantation. Other than early miscarriage, no pregnancy complications have been reported. There is currently no published data on longer term outcomes for children born as a result of this process

There is a risk of tumour cell transmission in the grafted tissue. A recent review categorised leukaemia, neuroblastoma and Burkitt lymphoma as high risk for ovarian metastasis; at moderate risk are some breast cancers, colon cancer, adenocarcinoma of cervix, non-Hodgkin lymphoma and Ewing Sarcoma; at low risk are some breast cancers, squamous cell carcinoma of cervix, Hodgkin lymphoma, osteogenic carcinoma, rhabdomyosarcoma (non-genital) and Wilms tumour [78, 87]. The risk may be minimised by undertaking a comprehensive assessment of slices of the tissue using techniques most appropriate for each particular tumour type (e.g. immunohistochemistry or molecular testing), looking for the presence of cancer cells or markers, both at the time of tissue excision and prior to reimplantation [77, 80, 88-90].

Comparison of Invasive Female Fertility Preservation Techniques

	Embryo Cryopreservation	Oocyte Cryopreservation	Ovarian Tissue Cryopreservation
Invasiveness of procedure	Minimal	Minimal	Moderate
Time required	10-17 days	10-17 days	½ day
Need for partner	Yes	No	No
Survival rate after freeze/thaw	90%	90%	Reasonable
Likelihood of success	Excellent if enough embryos	Good if enough oocytes retreived	Unknown
Availability in New Zealand	Yes	Yes	Recommended within ethics committee approved banking protocol
Limitations	Hormone-sensitive tumours	Hormone-sensitive tumours	Caution required with some malignancies. Reimplantation of tissue not yet approved in New Zealand

Ovarian Suppression with GnRH Analogues During Chemotherapy

The administration of gonadotrophin-releasing hormone (GnRH) analogues during chemotherapy suppresses menstruation and may reduce the gonadotoxic effects of chemotherapy on ovarian function. Clinical trials examining ovarian function after chemotherapy with or without GnRH analogues have reported conflicting outcomes [91-97]. Therefore the routine use of GnRH analogues to preserve ovarian function is not currently recommended [20].

The most commonly-used GnRH analogue in New Zealand is a depot preparation injected monthly or 3-monthly. When used for durations longer than six months, additional low-dose oestrogen replacement should be considered to reduce the consequences of protracted hypo-oestrogenism (unless the woman has an oestrogen-sensitive tumour).

Risks and Considerations:

- The hypo-oestrogenic state induced by GnRH analogue use may cause hot flushes and reduction in vaginal secretions
- There is a risk of bone depletion when GnRH analogues are used for prolonged periods (i.e. > 6 months) without low-dose oestrogen treatment
- GnRH analogues may usefully suppress menstruation during chemotherapies anticipated to cause severe thrombocytopenia.
- If used to preserve ovarian function, GnRH analogues are best used within a clinical trial where available [4, 67]

Males

Most cancer treatments have the potential to affect fertility. The major effect of cancer treatment on male reproductive potential is via chemotherapy- or radiation-induced damage to sperm, although surgery to reproductive or pelvic organs may also affect fertility. An individual male's fertility outcome is influenced by the type and extent of his disease and the treatment he receives [98].

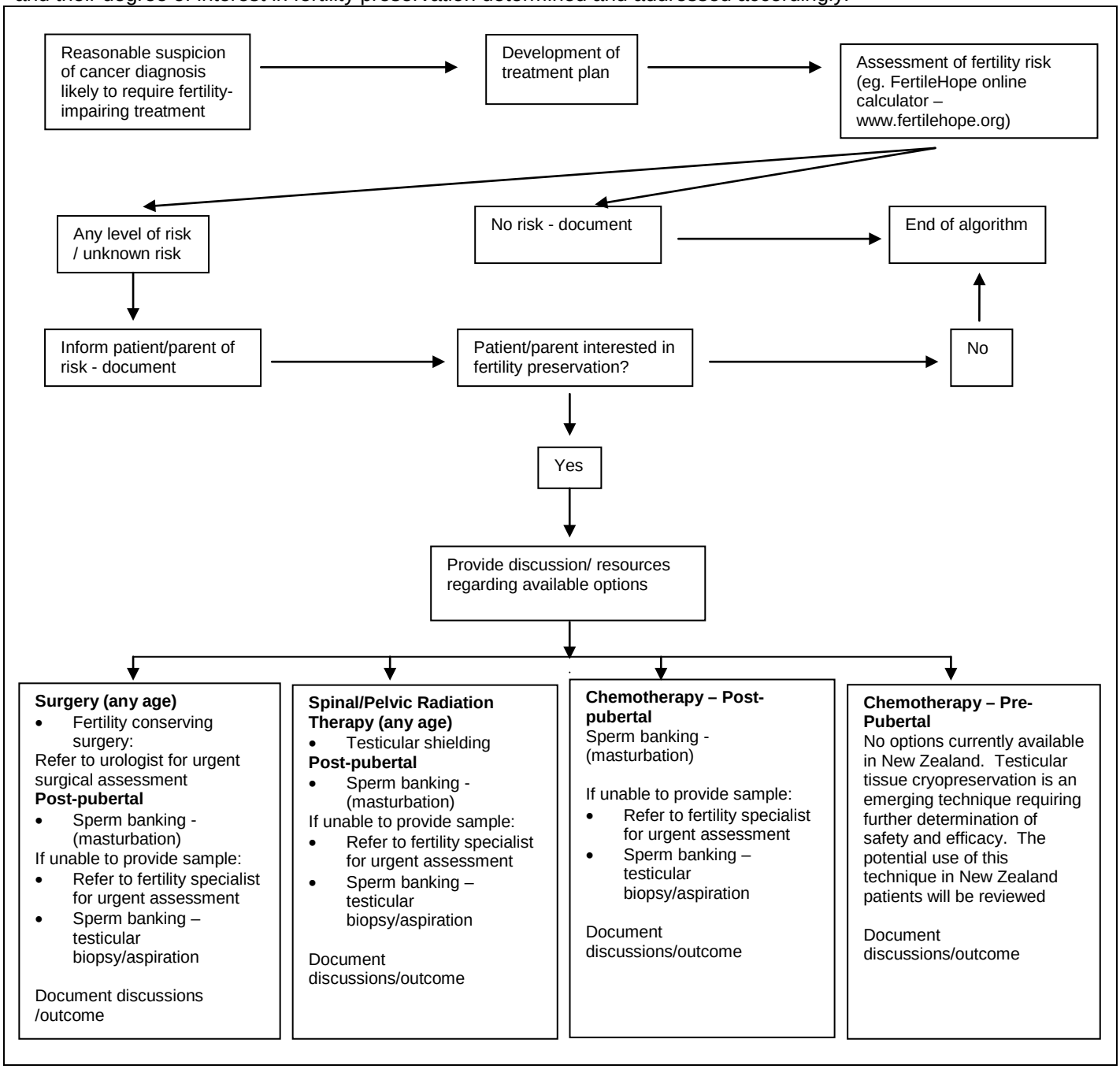
Research suggests that children born to cancer survivors are not more likely to have birth defects, genetic disorders or chromosomal abnormalities [46-48]. However, higher rates of sperm aneuploidy have been reported for up to 18 months after chemotherapy and radiotherapy in males with Hodgkin Lymphoma and testicular cancer, suggesting that there may be risks associated with fathering children or providing sperm for banking during this time [40]. There is an increased risk of birth defects associated with assisted reproductive technologies [49-53]. Recent research suggests this risk may not be significant for IVF when rates of birth defects are adjusted for parental factors, but there are risks associated with ICSI [54].

Recommendations – Fertility Preservation for Males	*Grade of Evidence*
Damage to fertility due to cancer or its treatment may lead to emotional distress, as can the processes and procedures associated with fertility preservation and treatment • Availability of and referral for psycho-social support is recommended	√
Sperm cryopreservation is the only well-established method of preserving fertility in post-pubertal males.	B

• It should be offered to all post-pubertal males prior to chemotherapy, radiotherapy or surgery that may damage the testes or reproductive function • It may be offered to pubertal males (Tanner stages 2-4)	C
Epididymal or testicular aspiration or biopsy should be offered to post-pubertal males and pubertal males (Tanner stages 2-4) who are unable to ejaculate, and considered for those with azoospermia	√
Fertility conserving surgery should be employed wherever possible when pelvic/testicular surgery is indicated Testicular shielding should be employed wherever possible when pelvic/abdominal radiation therapy is indicated	C

Male Fertility Preservation Algorithm

Consideration of the potential impact of cancer treatment on fertility and options for fertility preservation should be included in diagnosis and treatment planning for people of any age with cancer or a reasonable suspicion of cancer. Any level of risk to fertility must be disclosed to the person (and/or parents/guardians for children and adolescents) and their degree of interest in fertility preservation determined and addressed accordingly:



Assessment of Fertility Risk

Assessment of the potential impact of non-surgical cancer treatments on male fertility is based on the risk of azoospermia post-treatment and the length of time until sperm production resumes. Tools such as that provided by FertileHope.org (adapted below) offer a means to *loosely* assess risk on an individual basis.

Likelihood of Azoospermia	Treatment	Potential Usage
HIGH – prolonged azoospermia common post-treatment	Fractionated radiation therapy – total body irradiation	Conditioning for haematopoietic stem cell transplant
	Fractionated radiation therapy – testicular radiation dose > 2.5 Gy in men	Testicular cancer, ALL, NHL
	Fractionated radiation therapy – testicular radiation dose > 6 Gy in boys	ALL, NHL, sarcomas, germ cell tumours
	Fractionated radiation therapy – cranial radiation > 40 Gy	Brain tumours
	Chemotherapy – protocols containing procarbazine eg COPP, ChlVPP, BEACOPP	Hodgkin lymphoma
	Chemotherapy – alkylating therapy for haematopoietic stem cell transplant conditioning eg cyclophosphamide, busulphan, melphalan	Conditioning for haematopoietic stem cell transplant
	Chemotherapy – any alkylating agent eg procarbazine, cyclophosphamide + total body irradiation or pelvic/testicular irradiation	Testicular cancer, conditioning for haematopoietic stem cell transplant, ALL, NHL, sarcomas, neuroblastoma, Hodgkin lymphoma
	Chemotherapy – protocols containing temozolamide or carmustine (BCNU)	Brain tumour
	Chemotherapy – cyclophosphamide >7.5g/m2	Sarcomas, NHL, neuroblastoma, ALL
INTERMEDIATE – prolonged azoospermia not common at standard dose but can occur	Fractionated radiation therapy – testicular radiation dose by scatter 1-6 Gy	Wilms tumour, neuroblastoma
	Chemotherapy – • BEP x 2-4 cycles • cumulative cisplatin dose < 400mg/m2 • cumulative carboplatin dose ≤ 2g/m2	Testicular cancer
LOWER – typically temporary azoospermia post-treatment	Fractionated radiation therapy – testicular radiation dose < 0.2 – 0.7 Gy	Testicular cancer
	Chemotherapy – non-alkylating chemotherapy eg ABVD, OEPA, NOVP, CHOP, COP, anthracycline/cytarabine	Hodgkin lymphoma, NHL, AML
VERY LOW/NO – no effects on sperm production	Fractionated radiation therapy – testicular radiation dose < 0.2Gy	Multiple cancers
	Radiation therapy – radioactive iodine	Thyroid cancer
UNKNOWN	Irinotecan Biological therapies	Colon cancer Multiple cancers

(Table adapted to reflect current New Zealand oncological practice [16, 58-61])

Cryopreservation of Semen

Semen cryopreservation (sperm banking) before treatment starts is the only well-established method to preserve fertility potential in post-pubertal males. Post-pubertal males at any risk of post-treatment infertility should be offered the opportunity to bank sperm. This is most commonly achieved using ejaculated sperm, and the chances of a future pregnancy are increased when more than one sample is provided. In addition, assisted reproductive technology may be required to achieve pregnancy with cryopreserved semen. Successful pregnancies using sperm stored for up to 28 years have been reported [99].

Semen quality is frequently decreased in males with cancer prior to the commencement of treatment [100]. Poor semen quality has been reported in males with Hodgkin Disease and testicular cancer [101, 102]. This may mean assisted reproductive technologies such as intra-cytoplasmic sperm injection may be necessary to achieve a pregnancy. Men should not, however, be discouraged from banking sperm even when sperm quality is reduced.

Cryopreservation of Epididymal or Testicular Extracted Sperm

If semen collection by ejaculation is not possible or successful it may be possible to obtain sperm by direct testicular or epididymal aspiration or biopsy [103]. For males undergoing orchidectomy for testicular cancer, sperm suitable for use in ICSI may be extracted from the testis during surgery [104].

Cryopreservation of Testicular Tissue Before Puberty

Testicular tissue from prepubertal boys has been cryopreserved in some international centres in the expectation of successful future transplantation of spermatogonial stem cells [4, 105]. This is an area of active international research and not an established procedure in New Zealand, but will be reviewed as new evidence emerges.

Risks and Considerations:

- Sperm banking is recommended before cancer treatment starts to avoid increased sperm aneuploidy rates and increased sperm DNA damage
- Discussion regarding sperm banking must be undertaken with sensitivity in adolescents and it is preferable that the majority of the discussion take place without parents present
- More than one attempt may be needed to obtain a suitable semen sample for banking
- The collection of more than one semen sample over a period of days is preferable for maximising future fertility potential, however newer techniques such as ICSI (intracytoplasmic sperm injection) allow for successful cryopreservation and future use of small numbers of sperm
- Semen must be transported to the fertility centre laboratory at room temperature and received at the laboratory within an hour of collection
- Sperm quality has been found to be poor, including aneuploidy and increased rates of DNA damage in association with testicular cancer, Hodgkin lymphoma and other cancers even prior to treatment and this risk should be made clear
- There are risks such as pain, bleeding, swelling and infection when epidiymal/testicular extraction of sperm is used
- New Zealand legislation limits storage of sperm, oocytes, embryos and ovarian or testicular tissue to a maximum of ten years. After this time, an application to the Ethics Committee on Assisted Reproductive Technology (ECART) must be made by the owner requesting ongoing storage [75].

Males should have their fertility status evaluated approximately 1 year after completion of treatment to assess for return of natural fertility, in which case, consideration should be given to the destruction of banked sperm.

LONG TERM FOLLOW UP

Current evidence suggests that the impact of cancer and its treatment on fertility and sexual health is an important consideration for many cancer survivors [4, 5, 14, 19, 21, 67, 106-114]. There is limited high level evidence on which to base recommendations for long term followup after cancer treatment, particularly for those treated for cancer as adults. The type of post-treatment follow up indicated for cancer survivors in relation to fertility and sexual health should be determined according to gender, diagnosis, type of cancer treatment received, age at diagnosis and treatment, and other patient-specific factors. There are differences in long term follow-up recommendations for paediatric/AYA cancer survivors versus adult survivors related to clinical indication and the pragmatics of resource and service provision. Long term follow-up may also be undertaken within a primary care environment.

For paediatric, adolescent, and young adult cancer survivors an initial clinical review of reproductive, endocrine and sexual health should be undertaken approximately six months after the end of treatment [4, 67, 107]. A plan for follow up should then be drawn up as appropriate with an emphasis on good communication between paediatric (if appropriate) and adult services, the patient's General Practitioner and other relevant health care providers. A comprehensive follow-up service for those with a higher degree of need would involve a multidisciplinary team including oncology, psychology, nursing, specialist fertility and endocrinology services, with access to social work and peer support. While it may not be possible to have all members available at one site, clearly defined referral and communication paths must be established between team members. Follow-up services should be able to accommodate the changing needs of survivors over time.

In acknowledgement of the current lack of evidence on which to base recommendations for long term followup of those treated for cancer as adults, limited recommendations are made here.

Psycho-Social Assessment

Cancer survivors of both genders (and their partners) may experience psychological distress related to the effects of cancer treatment on their reproductive and sexual function and intimate relationships. Pursuing or choosing not to pursue fertility preservation pre-treatment and/or fertility interventions post-treatment may both result in distress, as may the belief that these options were not adequately addressed at diagnosis. Assessment of the psychological health and needs of cancer survivors, particularly relating to the reproductive and sexual sequelae of cancer and its treatment should therefore be a key part of long term follow-up, and provision should be made for specialist psychological input where indicated [3, 12, 14, 18, 19, 35, 67, 111-113, 115-123].

Pre-treatment discussions regarding fertility, fertility preservation, and the effect of cancer and its treatment on fertility and sexuality are often undertaken at a time of great stress [16]. Care should be taken to assess the level of understanding the patient and their family/whanau have of the information they were given during their diagnosis and treatment, and to update them on any further developments in the field [124].

Recommendations – Long Term Follow Up	*Grade of Evidence*
Paediatric and adolescent/young adult cancer survivors should have access to systematic long term follow up of their reproductive, endocrine and sexual health	C
Adult cancer survivors should have access to follow-up for reproductive and sexual health as appropriate for their age and the treatments received	I
This should include the opportunity, if indicated, to meet with a fertility specialist after treatment completion to review, and where appropriate, assess their reproductive, endocrine and sexual health, and plan for future care or intervention	√
Some cancer survivors have psychological health needs related to the impact of the cancer and its treatment on their reproductive and sexual function.	B
Referral for psychological support should be available. .	√
Depending on the treatments received, pregnancy after cancer treatment may be considered 'high risk' due to the potential impact of some cancer treatments on the health of both mother and baby	C

Females

Girls and women who have undergone cancer treatment may be at increased risk of infertility, premature ovarian failure, sexual dysfunction and associated emotional distress. The degree of risk to fertility and sexual function is influenced by the cancer diagnosis, the type, intensity and duration of treatment, the age at which the diagnosis and treatment occurred, and the woman's pre-existing fertility status and functioning. For paediatric and adolesecent/young adult survivors reproductive and sexual health should be checked, as appropriate, as part of overall treatment follow-up. For adult cancer survivors, reproductive and sexual health should be assessed as clinically indicated.

Cancer survivors who undertook fertility preservation prior to commencing cancer treatment should be referred for early specialist fertility review after treatment completion. Prior treatment with chemotherapy has been shown to significantly reduce the efficacy of assisted reproductive technologies where pre-treatment fertility preservation has not been undertaken. Early referral for specialist fertility review is therefore recommended for girls and women who

are at increased risk of premature ovarian failure due to the cancer treatments they have received, and who express a desire to have children in the future[44, 45].

Girls should be assessed for overall growth and development during and after cancer treatment and referred for early endocrine review where there are concerns regarding growth velocity or delayed/precocious puberty [106, 108]. Due to the increased risk of premature ovarian failure after cancer treatments it is recommended that early referral for specialist fertility and/or endocrine assessment be discussed with female cancer survivors to support optimal reproductive and sexual health. Hormone replacement may be a safe therapy for survivors of non-hormone dependent cancers to alleviate symptoms of oestrogen deficiency and maintain bone health. Hormone replacement is contra-indicated in women who have been treated for breast and hormone-dependent gynaecological cancers [67, 125-127].

The return of and/or presence of menstruation is often used as a surrogate marker of fertility but does not provide an accurate indication of ovarian reserve and therefore future fertility. Antimullerian hormone (AMH) is currently considered the most useful marker of ovarian reserve for post-pubertal girls and women. Other markers include early follicular phase FSH. Ultrasound scan assessment of ovarian volume of antral follicle count may also be used [16, 42, 128, 129].

It is important to discuss contraception with sexually active cancer survivors, even where fertility is impaired.

Pregnancy after Treatment for Cancer

Current evidence suggests that pregnancy after treatment for cancer is generally safe for both mother and baby, although it is often recommended that pregnancy in cancer survivors be considered 'high risk' and managed through a tertiary obstetric centre if possible[130]. It is generally recommended that pregnancy be avoided by those treated for cancers *other than breast cancer* for 6-12 months after the completion of cancer therapy to minimise risks to both mother and baby [130, 131]. Children born to cancer survivors are not at increased risk of birth defects, genetic disorders or chromosomal abnormalities [46-48].

Pregnancy occurring at least 10 months from the time of diagnosis in women treated for early breast cancer may not have a negative impact on prognosis [55]. It is generally, however, recommended that women avoid pregnancy for at least 2 years after a diagnosis of breast cancer in order to minimise the risk to both mother and baby associated with early relapse, and allow some endocrine therapy where appropriate [130-132].

The risks associated with pregnancy in cancer survivors are reflective of the particular cancer treatments given and therefore it is important that the obstetric team have access to treatment information. Women who have received pelvic radiation therapy are at increased risk of miscarriage, pre-term birth and low-birthweight infants due to damage to the uterine wall and vasculature. The long term impact of cancer therapies on cardiac, renal, respiratory and immune function should be considered in terms of pregnancy risk [67, 106, 108].

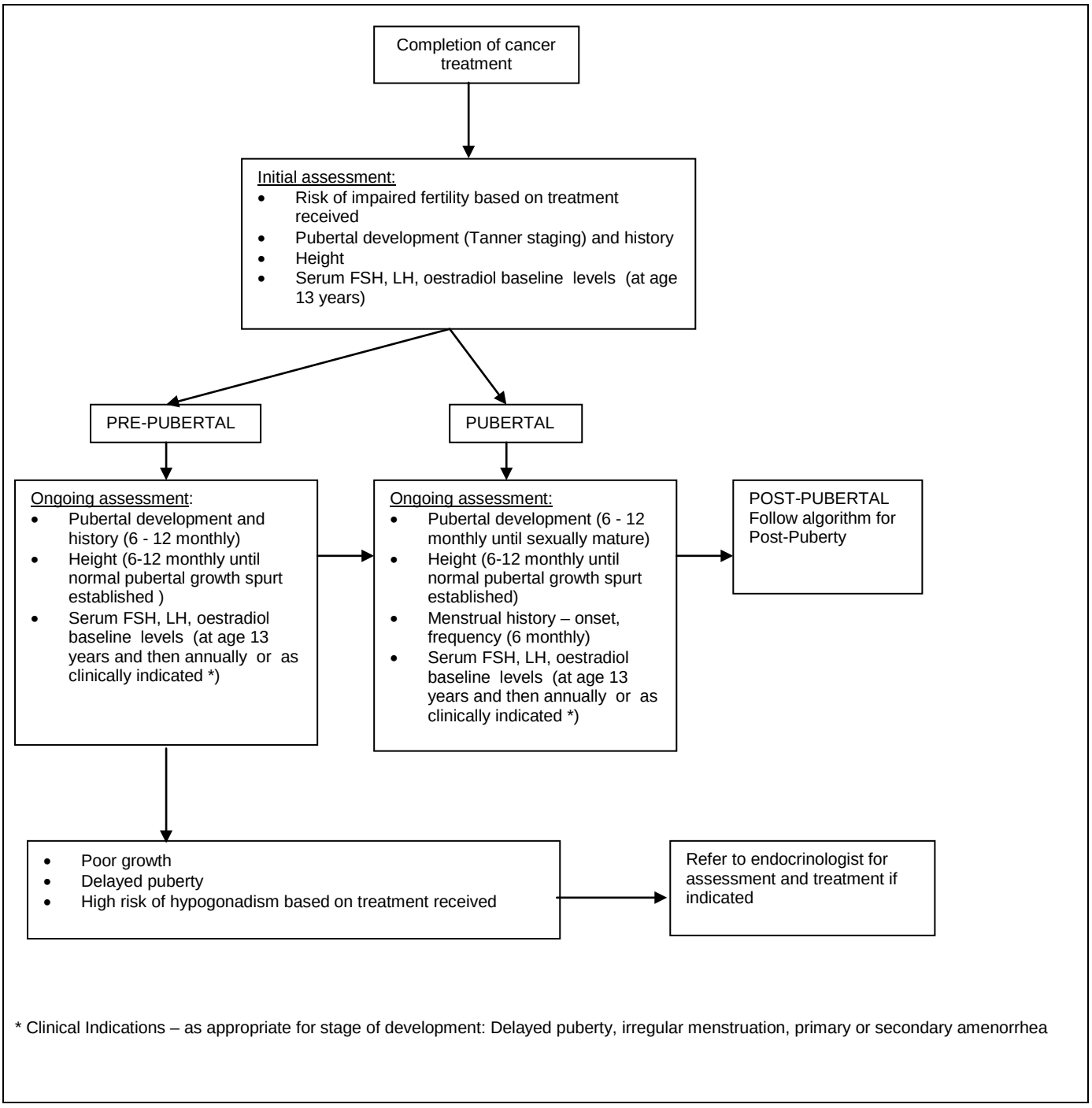
Adoption and Surrogacy Options

Adoption processes in New Zealand are overseen by Child, Youth and Family (http://www.cyf.govt.nz/adoption/).

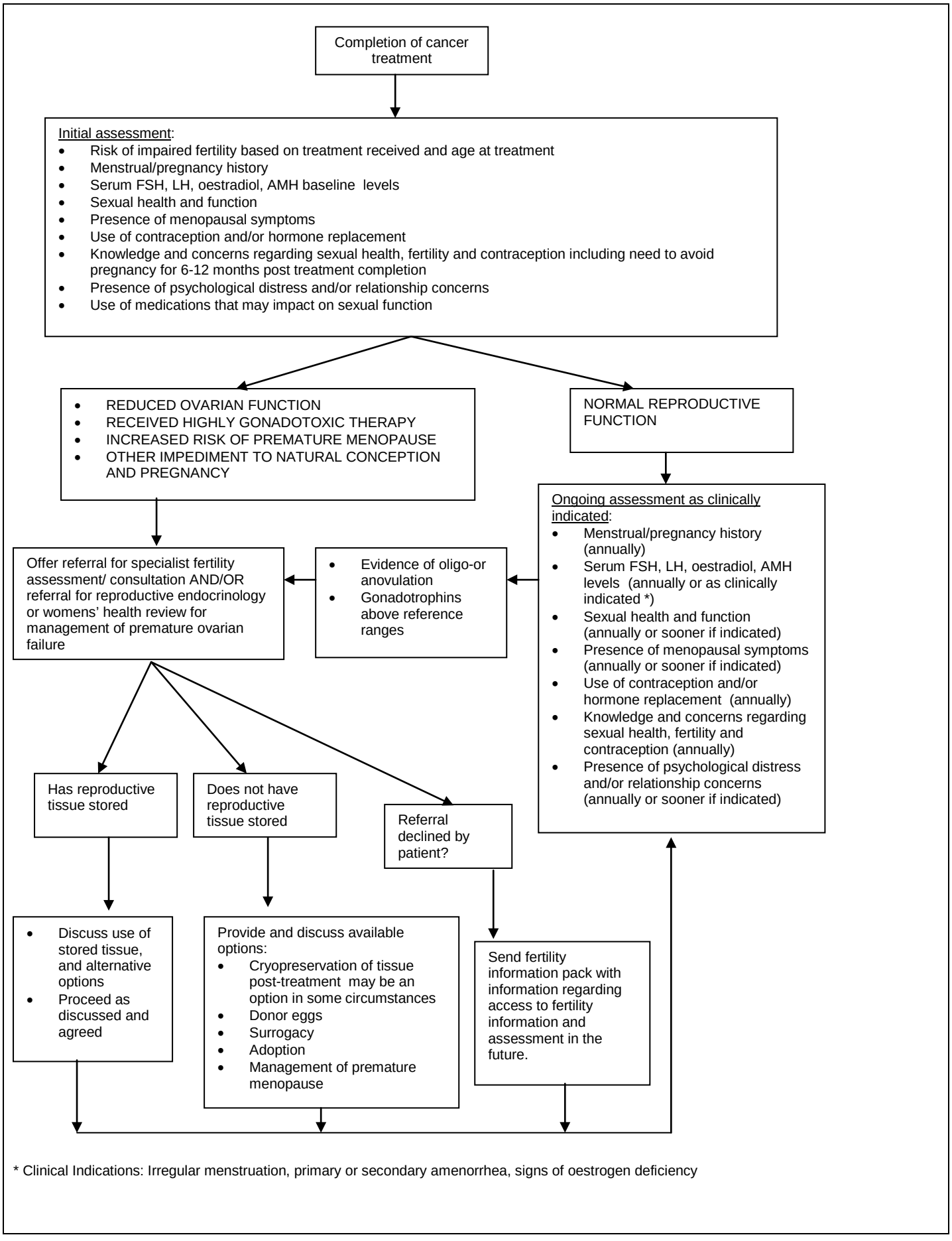
Options for surrogacy are best discussed with a fertility specialist.

Female Long Term Follow-up Algorithms

GIRLS - Prepubertal/Pubertal:

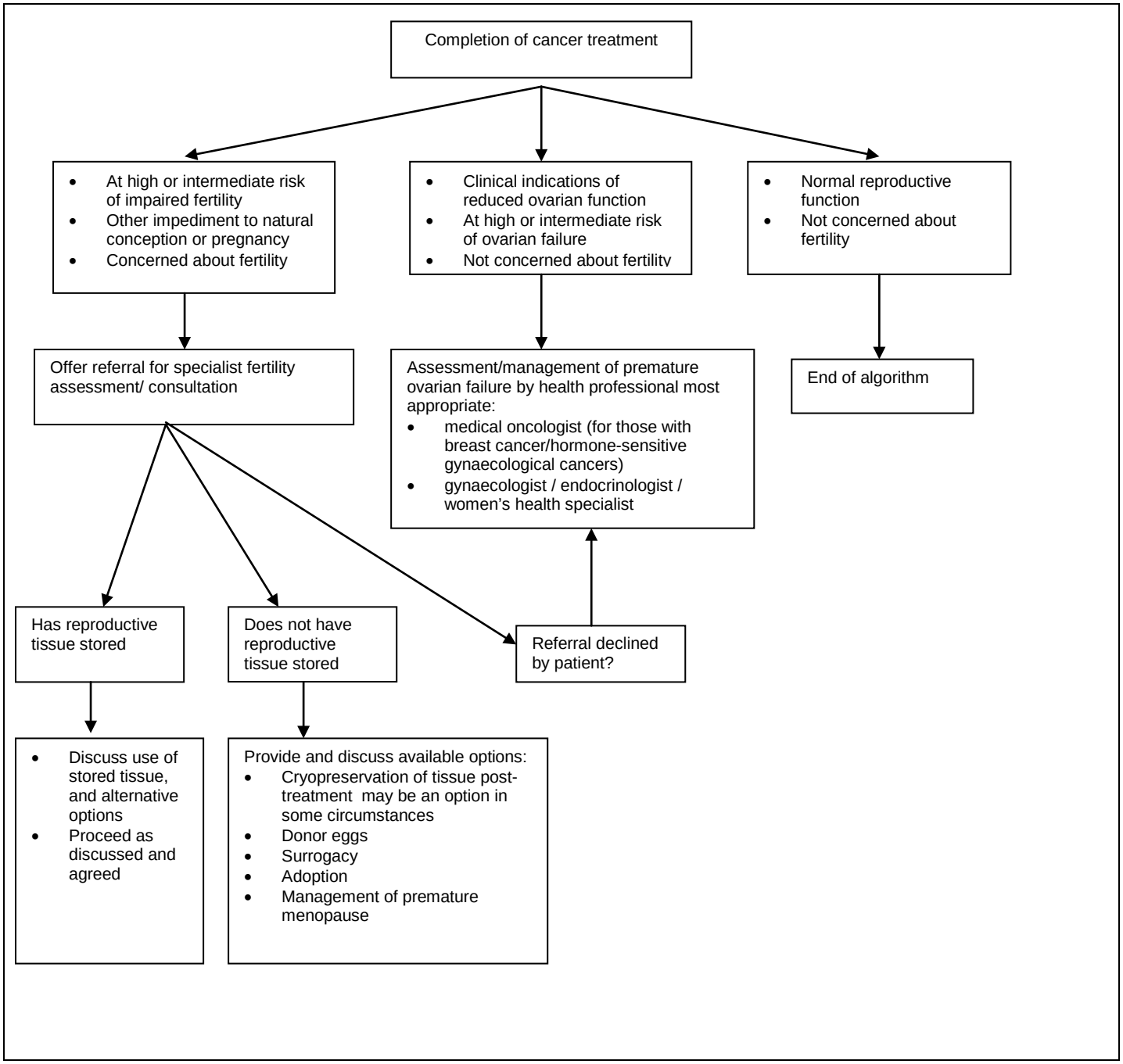


GIRLS - Post-Pubertal and Adolescents/Young Adults:



* Clinical Indications: Irregular menstruation, primary or secondary amenorrhea, signs of oestrogen deficiency

WOMEN:



Males

Boys and men who have undergone cancer treatment may be at increased risk of infertility, sexual dysfunction and associated emotional distress. The degree of risk to fertility and sexual function is influenced by the cancer diagnosis, the type, intensity and duration of treatment, the age at which the diagnosis and treatment occurred, and pre-existing fertility status and functioning. For paediatric and adolescent/young adult survivors reproductive and sexual health should be checked, as appropriate, as part of overall treatment follow-up. For adult cancer survivors, reproductive and sexual health should be assessed, as appropriate, after treatment completion. Cancer survivors who undertook fertility preservation prior to commencing cancer treatment should be referred for early specialist fertility review after treatment completion.

Boys should be assessed for overall growth and development during and after cancer treatment and referred for early endocrine review where there are concerns regarding growth velocity or delayed/precocious puberty. Testicular volume and serum FSH, LH, testosterone and inhibin B (if available) provide useful indicators of gonadal damage [106, 108]. Boys (when age-appropriate) and men should be offered semen analysis 12 months after treatment

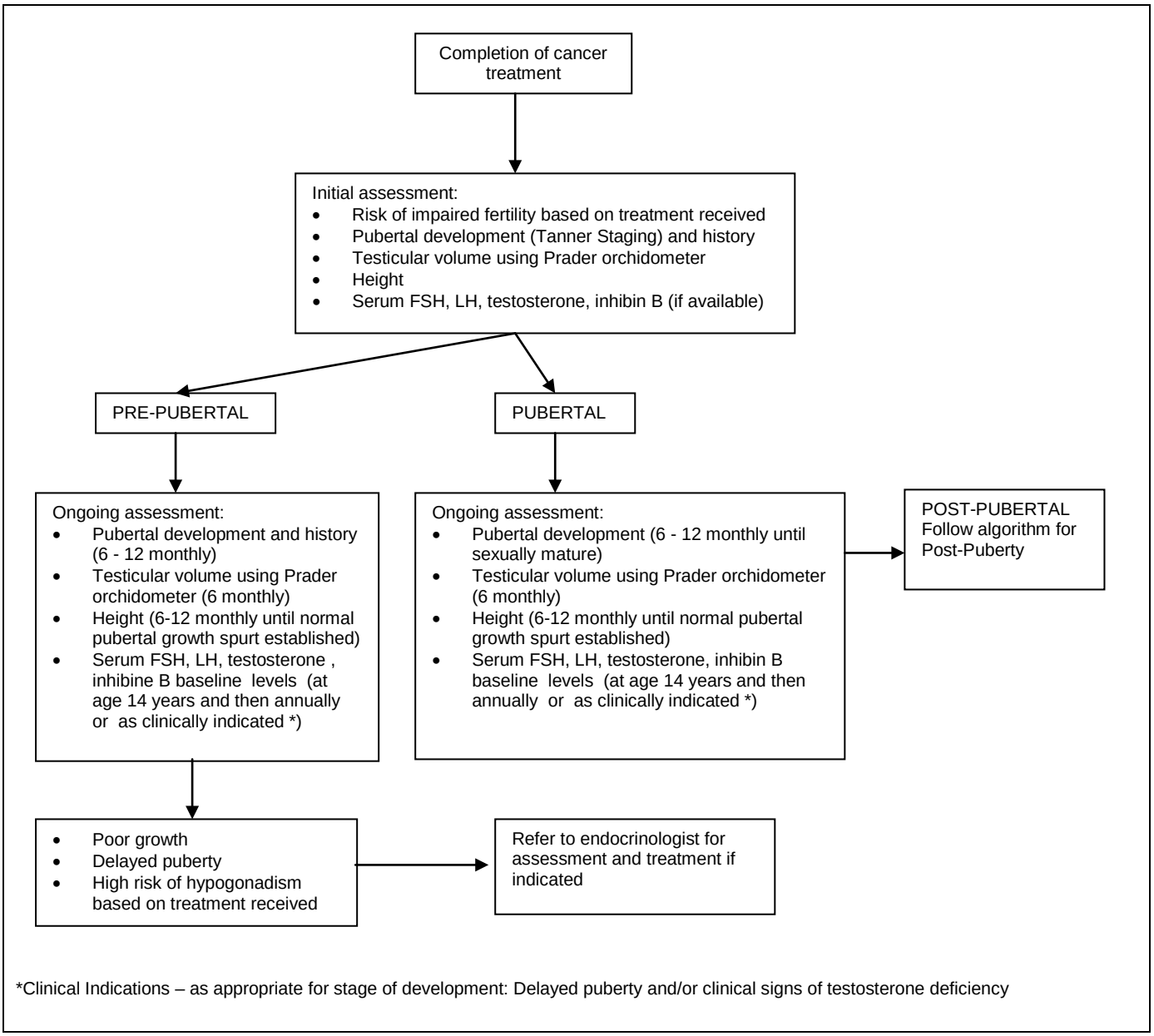
completion [67]. Those whose fertility is shown to be unaffected or restored and who have sperm banked from pre-treatment should be encouraged to arrange for banked sperm to be discarded.

It is important to discuss contraception with sexually active cancer survivors, even where fertility is impaired.

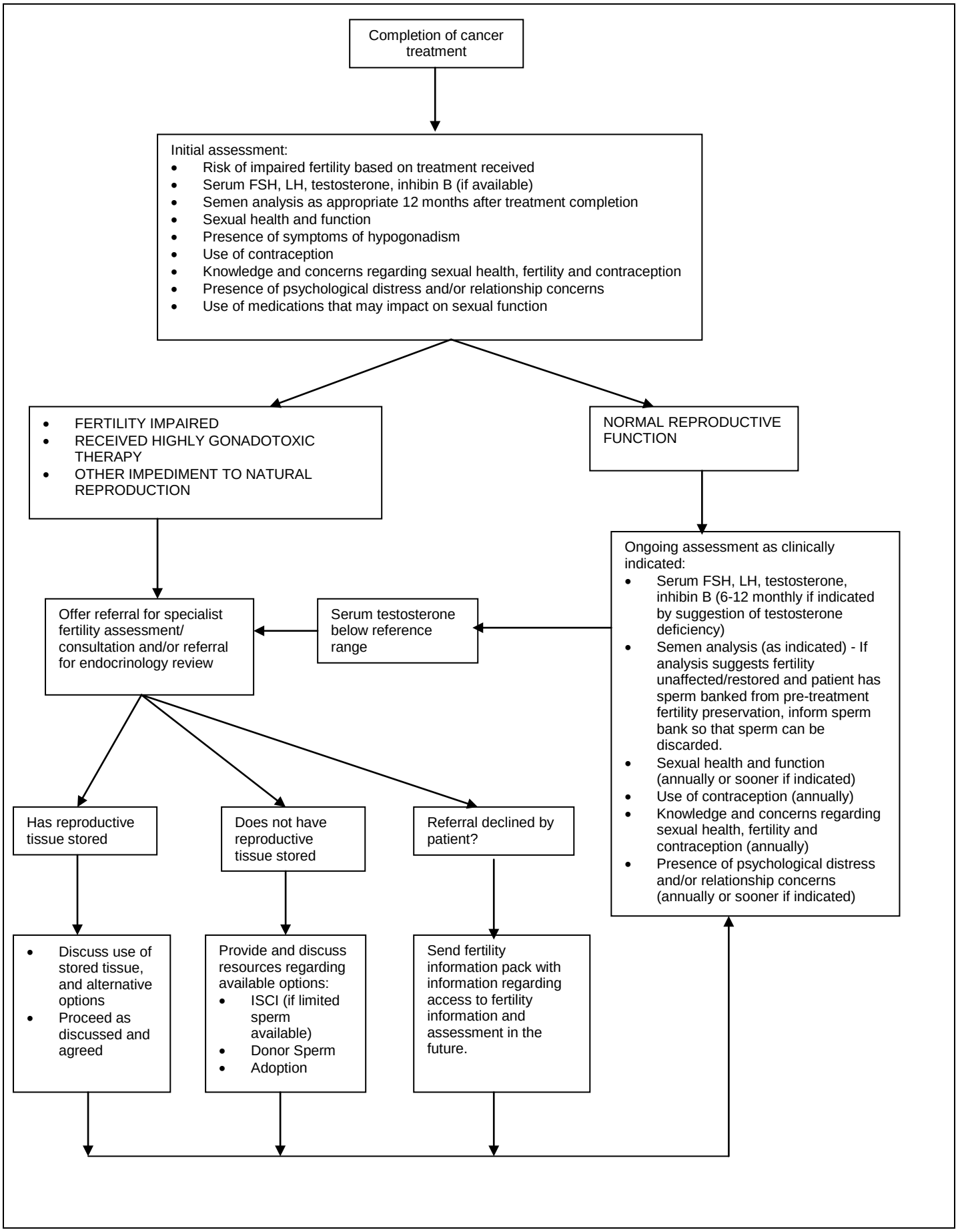
Children born to cancer survivors are not at increased risk of birth defects, genetic disorders or chromosomal abnormalities [46-48].

Male Long Term Follow-up Algorithms

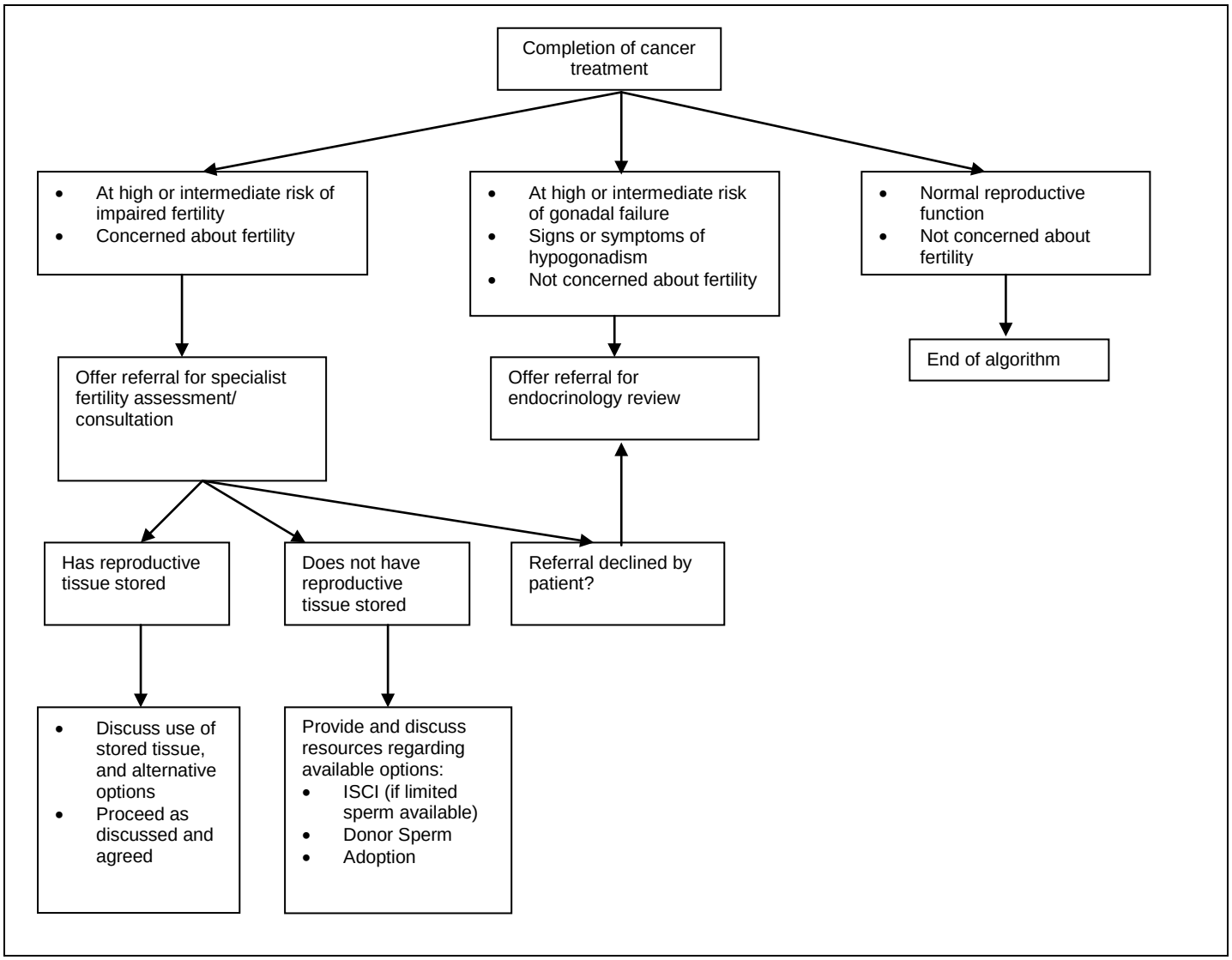
BOYS - Prepubertal/Pubertal:



BOYS - Post-Pubertal and Adolescents/Young Adults:



MEN:



It is acknowledged that there will be variations in the availability of multi-disciplinary team input for long term follow-up around New Zealand.

DEVELOPMENT AND REVIEW OF THE GUIDELINE

This guideline has been developed by a national Fertility Preservation Working Group. This group was initially convened by the National Child Cancer Network to develop a guideline for children and adolescents/young adults with cancer. The group and its remit were then extended to include those of all ages with cancer at the request of the Cancer Treatment Advisory Group. The group is comprised of a multidisciplinary team of health professionals from throughout New Zealand with expert knowledge of oncology and fertility, and a patient representative with personal experience of infertility related to cancer treatment. Additional consultation with expert practitioners was undertaken where required, and the guideline was reviewed by relevant stakeholder groups prior to being finalised.

To ground the development of the guideline in international evidence and current best practice the group reviewed and appraised existing international guidelines, relevant literature, expert recommendations and New Zealand legislation. Particular attention was paid to the recently published Clinical Oncological Society of Australia (COSA) web-based guideline aimed at adolescents and young adults. The recommendations made in these source documents and the bases on which they were made were appraised and considered in light of New Zealand's unique cultural, health and social environment.

This guideline should be used alongside local protocols that specify assessment/referral procedures and key expert practitioners in various aspects of oncology and fertility to facilitate patient access in a timely manner and optimise the outcome of any fertility preservation measures undertaken.

This document is current as at 7th December 2017 pending publication of an in-process international guideline. After publication of the international guideline this document will be reviewed and updated accordingly.

Guideline Development Group Membership

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REFERENCES

1. Davies, N.J., et al., *Information satisfaction in breast and prostate cancer patients: Implications for quality of life.* Psycho-Oncology, 2008. **17**: p. 1048-1052.
2. Jenkins, V., L. Fallowfield, and J. Saul, *Information needs of patients with cancer: Results from a large study in UK cancer centres.* British Journal of Cancer, 2001. **84**(1): p. 48-51.
3. Thewes, B., et al., *The fertility and menopause-related information needs of younger women with a diagnosis of breast cancer: A qualitative study.* Psycho-Oncology, 2003. **12**: p. 500-511.
4. Lee, S.J., et al., *American Society of Clinical Oncology recommendations on fertility preservation in cancer patients.* Journal of Clinical Oncology, 2006. **24**: p. 2917-2931.
5. Beckjord, E.B., et al., *Health related information needs in a large and diverse sample of adult cancer survivors: Implications for cancer care.* Journal of Cancer Survivorship, 2008. **2**: p. 179-189.
6. Alfano, C.M. and J.H. Rowland, *Recovery issues in cancer survivorship: A new challenge for supportive care.* Cancer Journal, 2006. **12**: p. 432-443.
7. New Zealand Health Information Service, *Cancer patient survival covering the period 1994-2003*, 2006, Ministry of Health: Wellington, New Zealand.
8. New Zealand Health Information Service, *Cancer: new registrations and deaths 2002*, 2006a, Ministry of Health: Wellington, New Zealand.
9. Ministry of Health, *Cancer: New registrations and deaths 2009*, 2012: Wellington.
10. Cancer Control Taskforce, *The New Zealand Cancer Control Strategy: Action Plan 2005-2010*, 2005, Ministry of Health: Wellington, New Zealand.
11. Hewitt, M.E., et al., *Perspectives on post-treatment care: Qualitative research with survivors, nurses and physicians.* Journal of Clinical Oncology, 2007. **25**(16): p. 2270-2273.
12. Partridge, A.H., et al., *Web-based survey of fertility issues in young women with breast cancer.* Journal of Clinical Oncology, 2004. **22**: p. 4174-4183.
13. Stead, M.L., et al., *Lack of communication between healthcare professionals and women with ovarian cancer about sexual issues.* British Journal of Cancer, 2003. **88**: p. 666-671.
14. Hordern, A.J. and A.F. Street, *Constructions of sexuality and intimacy after cancer: Patient and health professional perspectives.* Social Science and Medicine, 2007a. **64**: p. 1704-1718.
15. Quinn, G.P., et al., *Discussion of fertility preservation with newly diagnosed patients: Oncologists' views.* Journal of Cancer Survivorship, 2007. **1**: p. 146-155.
16. Levine J, Canada A, and Stern C J, *Fertility preservation in adolescents and young adults with cancer.* Journal of Clinical Oncology, 2010. **28**(32): p. 4831-41.
17. Ministry of Health/DHB Specialist Medical and Surgical Services - Artificial Reproductive Technology Services, Tier Level Two Service Specification (2014), Nationwide Service Framework Library http://www.nsfl.health.govt.nz/apps/nsfl.nsf/pagesmh/299
18. Peate, M., et al., *The fertility-related concerns, needs and preferences of young women with cancer: A systematic review.* Breast Cancer Research and Treatment, 2009. **116**: p. 215-223.
19. Tschudin S and Bitzer J, *Psychological aspects of fertility preservation in men and women affected by cancer and other life-threatening diseases.* Human Reproduction Update, 2009. **15**(5): p. 587-597.
20. Loren AW, et al. *Fertility preservation for patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline update*. Journal of Clinical Oncology, 2013. DOI: 10.1200/JCO.2013.49.2678.
21. Thames Valley Cancer Network, *TVCN Adult Haematology Long Term Follow Up Guideline - Fertility*, 2013, Thames Valley Cancer Network: Oxford.
22. Nagel K and Neal M, *Discussions regarding sperm banking with adolescent and young adult males who have cancer.* Journal of Pediatric Oncology Nursing, 2008. **25**(2): p. 102-106.
23. Achille M A, et al., *Facilitators and obstacles to sperm banking in young men receiving gonadotoxic chemotherapy for cancer: the perspective of survivors and health care professionals.* Human Reproduction, 2006. **21**(12): p. 206-3216.
24. Crawshaw M A, et al., *Male and female experiences of having fertility matters raised alongside a cancer diagnosis during the teenage and young adult years.* European Journal of Cancer Care, 2009. **18**(4): p. 381-390.
25. Balthazar U, et al., *The current fertility preservation consultation model: are we adequately informing cancer patients of their options?* Human Reproduction, 2012. **27**(8): p. 2413-2419.
26. Edge B, Holmes D, and Makin G, *Sperm banking in adolescent cancer patients.* Archives of Disease in Childhood, 2006. **91**(2): p. 149-152.
27. Multidisciplinary Working Group convened by the British Fertility Society, *A strategy for fertility services for survivors of childhood cancer.* Human Fertility, 2003. **6**(2): p. A1-A39.
28. Anderson R A, et al., *Do doctors discuss fertility issues before they treat young patients with cancer?* Human Reproduction, 2008. **23**(10): p. 2246-2251.
29. Walker, T., et al., *The road we travel: Maori experience of cancer.* New Zealand Medical Journal, 2008. **121**(1279): p. 27-35.
30. Reynolds Paul and Smith Cherryl, *The gift of children: Maori and infertility*. 2012, Wellington: Huia Publishers.

31. Canada, A.L. and L.R. Schover, *Research promoting better patient education on reproductive health after cancer.* Journal of the National Cancer Institute Monographs, 2005. **34**: p. 98-100.
32. Foy, S.M. *Provision of a fertility service for women with cancer: Evaluating the educational needs of specialist cancer nurses*. in *15th International Conference on Cancer Nursing*. 2008. Singapore.
33. Alesi, R., *Infertility and its treatment: An emotional rollercoaster.* Australian Family Physician, 2005. **34**(3): p. 135-139.
34. Cousineau, T.M. and A.D. Domar, *Psychological impact of infertility.* Best Practice and Research: Clinical Obstetrics and Gynaecology, 2007. **21**(2): p. 293-308.
35. Johansson, M. and M. Berg, *Women's experiences of childlessness 2 years after the end of in vitro fertilization treatment.* Scandinavian Journal of Caring Science, 2005. **19**: p. 58-63.
36. Bedoschi G and Oktay K, *Current approach to fertility preservation by embryo cryopreservation.* Fertility and Sterility, 2013. **99**(6): p. 1496-1502.
37. Chung K, et al., *Emergency IVF versus ovarian tissue cryopreservation: decision making in fertility preservation for female cancer patients.* Fertility and Sterility, 2013. **99**(6): p. 1534-1542.
38. Morris ID, *Sperm DNA damage and cancer treatment.* International Journal of Andrology, 2002. **25**: p. 255-261.
39. O'Donovan M, *An evaluaton of chromatin condensation and DNA integrity in the spermatozoa of men with cancer before and after therapy.* Andrologia, 2005. **37**: p. 83-90.
40. Tempest H G, et al., *Sperm aneuploidy frequencies analysed before and after chemotherapy in testicular cancer and Hodgkin's lymphoma patients.* Human Reproduction, 2008. **23**(2): p. 251-258.
41. Simon, B., et al., *Preserving fertility after cancer.* CA - A Cancer Journal for Clinicians, 2005. **55**(4): p. 211-228.
42. Partridge, A.H., et al., *Age of menopause among women who remain premenopausal following treatment for early breast cancer: Long-term results from International Breast Cancer Study Group Trials V and VI.* European Journal of Cancer, 2007. **43**: p. 1646-1653.
43. Stroud, J.S., et al., *Effects of cancer treatment on ovarian function.* Fertility and Sterility, 2009. **92**(2): p. 417-428.
44. Das M, et al., *Ovarian reserve and response to IVF and in vitro maturation treatment following chemotherapy.* Human Reproduction, 2012. **27**(8): p. 2509-2514.
45. Barton SE, et al., *Female cancer survivors are low responders and have reduced success compared with other patients undergoing assisted reproductive technologies.* Fertility and Sterility, 2012. **97**(2): p. 381-386.
46. Blatt J, *Pregnancy outcome in long-term survivors of childhood cancer.* Medical and Pediatric Oncology, 1999. **33**(1): p. 29-33.
47. Fossa, S.D., et al., *Parenthood in survivors after adult cancer and perinatal health in their offspring: A preliminary report.* Journal of the National Cancer Institute Monographs, 2005. **34**: p. 77-82.
48. Winther J F, et al., *Chromosomal abnormalities among offspring of childhood-cancer survivors in Denmark: a population-based study.* American Journal of Human Genetics, 2004. **74**(6): p. 1282-1285.
49. Hansen M, et al., *Assisted reproductive technologies and the risk of birth defects: a systematic review.* Human Reproduction, 2005. **20**(2): p. 328-338.
50. Bonduelle M, et al., *A multi-centre cohort study of the physical health of 5-year old children conceived after intracytoplasmic sperm injection, in vitro fertilisation and natural conception.* Human Reproduction, 2005. **20**(2): p. 413-419.
51. Buckett W M, et al., *Obstetric outcomes and congenital abnormalities after in vitro maturation, in vitro fertilization, and intracytoplasmic sperm injection.* Obstetrics and Gynecology, 2007. **110**: p. 885-891.
52. Halliday J L, et al., *Increased risk of blastogenesis birth defects, arising in the first 4 weeks of pregnancy, after assisted reproductive technologies.* Human Reproduction, 2010. **25**(1): p. 59-65.
53. Wennerholm U B, et al., *Children born after cryopreservation of embryos or oocytes: a systematic review of outcome data.* Human Reproduction, 2009. **24**: p. 2158-2172.
54. Davies MJ, et al., *Reproductive technologies and risk of birth defects.* New England Journal of Medicine, 2012. **366**: p. 1803-1813.
55. Valachis A, et al., *Safety of pregnancy after primary breast cancer in young women: A meta-analysis to overcome bias of healthy mother effect studies.* Obstetrical and Gynaecological Survey, 2010. **65**(12): p. 786-793.
56. Usta T and Oral E, *Is the measurement of anti-Mullerian hormone essential?* Current Opinion in Obstetrics and Gynaecology, 2012. **24**: p. 151-157.
57. La Marca A, et al., *Possibilities and limits of ovarian reserve testing in ART.* Current Pharmaceutical Biotechnology, 2012. **13**: p. 398-408.
58. Wallace W H B, Anderson R A, and Irvine DS, *Fertility preservation for young patients with cancer: who is at risk and what can be offered?* Lancet Oncology, 2005(6): p. 209-218.
59. FertileHOPE. *Risk of amenorrhea from chemotherapy and radiation treatments for cancer*. 2007 [cited 2012 7th October 2012]; Available from: www.fertilehope.org.
60. Stern, C.J., et al., *Fertility preservation in female oncology patients.* Australian and New Zealand Journal of Obstetrics and Gynaecology, 2006. **46**: p. 15-23.

61. Loren AW, et al., *ASCO Guidelines Data Supplement - Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update*, 2013, American Society of Clinical Oncology.
62. Anderson RA, *Report on the current status of the use of cryopreserved ovarian tissue for the Advisory Committee on Assisted Reproductive Technology (ACART) of New Zealand*, 2010, University of Edinburgh: Edinburgh.
63. Fertility Associates, *Personal communication*, 2012.
64. Wang Y A, Chambers G M, and Sullivan E A, *Assisted reproductive technology in Australia and New Zealand 2008. Assisted reproduction technology series. No. 14. Cat No. PER49*, in *Assisted Reproductive Technology Series*2010, AIHW: Canberra.
65. Smith G D, et al., *Prospective randomised comparison of human oocyte cryopreservation with slow-rate freezing or vitrification.* Fertility and Sterility, 2010. **94**(6): p. 2088-2095.
66. Rienzi L, et al., *Consistent and predictable delivery rates after oocyte vitrification: an observational longitudinal cohort multicentric study.* Human Reproduction, 2012. **27**(6): p. 1606-1612.
67. Clinical Oncological Society of Australia. *Fertility preservation for AYAs diagnosed with cancer: guidance for health professionals*. [cited 2012 7th October 2012]; Available from: http://wiki.cancer.org.au/australia/COSA:AYA_cancer_fertility_preservation.
68. Leader A, et al., *Fertility considerations and preservation in haemato-oncology patients undergoing treatment.* British Journal of Haematology, 2011. **153**(3): p. 291-308.
69. Cobo A, et al., *Is vitrification of oocytes useful for fertility preservation of age-related fertility decline and in cancer patients?* Fertility and Sterility, 2013. **99**(6): p. 1485-1496.
70. Shalom-Paz E, et al., *Fertility preservation for breast cancer patients using IVM followed by oocyte or embryo vitrification.* Reproductive Biomedicine Online, 2010. **21**(4): p. 566-571.
71. Oktay K, et al., *Fertility preservation in breast cancer patients: IVF and cryopreservation after ovarian stimulation with tamoxifen.* Human Reproduction, 2003. **18**(1): p. 90-95.
72. Cakmak H and Rosen MP, *Ovarian stimulation in cancer patients.* Fertility and Sterility, 2013. **99**(6): p. 1476-1484.
73. Hart R, *Preservation of fertility in adults and children diagnosed with cancer.* British Medical Journal, 2008. **27**(337).
74. Oktem O and Oktay K, *Fertility preservation for breast cancer patients.* Seminars in Reproductive Medicine, 2009. **27**: p. 486-492.
75. Ministry of Justice, *Human Assisted Reproductive Technology (Storage) Amendment Act*, 2010: New Zealand.
76. Jadoul P, Dolmans M, and Donnez J, *Fertility preservation in girls during childhood: is it feasible, efficient and safe and to whom should it be proposed?* Human Reproduction Update, 2010. **16**(6): p. 617-630.
77. Michaeli J, et al., *Fertility preservation in girls.* Obstetrics and Gynecology International, 2012. **2012**.
78. The Practice Committe of the American Society for Reproductive Medicine and Practice Committee of the Society for Assisted Reproductive Technology, *Ovarian tissue and oocyte cryopreservation.* Fertility and Sterility, 2008. **90**: p. S241-246.
79. Donnez J, et al., *Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation.* fertility and Sterility, 2013. **99**(6): p. 1503-1513.
80. Rodriguez-Wallberg KA and Oktay K, *Recent advances in oocyte and ovarian tissue cryopreservation and transplantation.* Best Practice and Research: Clinical Obstetrics and Gynaecology, 2012. **26**: p. 391-405.
81. Donnez J, et al., *Children born after autotransplantation of cryopreserved ovarian tissue. A review of 13 live births.* Annals of Medicine, 2011(43): p. 437-450.
82. Ministry of Justice, *Human Assisted Reproductive Technology Act*, 2004: New Zealand.
83. Minstry of Justice, *Human Assisted Reproductive Technology Order* 2005: New Zealand.
84. The Practice Committe of the American Society for Reproductive Medicine and Practice Committee of the Society for Assisted Reproductive Technology, *Ovarian tissue and oocyte cryopreservation: Recently reviewed practice committee report.* Fertility and Sterility, 2006. **86**(5 Supplement 1): p. S142-S147.
85. Wallace W H B and Barr R D, *Fertility preservation in girls and young women with cancer: what are the remaining challenges?* Human Reproduction Update, 2010. **16**(6): p. 614-616.
86. Wallace W H B, Thompson L, and Anderson RA, *Longterm follow-up of survivors of childhood cancer: summary of updated SIGN guidance.* British Medical Journal, 2013. **346**: p. f1190.
87. Dolmans M, et al., *Risk of transferring malignant cells with transplanted frozen-thawed ovarian tissue.* Fertility and Sterility, 2013. **99**(6): p. 1514-1522.
88. Meirow D, et al., *Ovarian tissue banking in patients with Hodgkin's disease: is it safe?* Fertility and Sterility, 1998. **69**(6): p. 996-998.
89. Kim S S, et al., *Ovarian tissue harvested from lymphoma patients to preserve fertility may be safe for autotransplantation.* Human Reproduction, 2001. **16**(10): p. 2056-2060.
90. Bittinger S E, et al., *Detection of Hodgkin lymphoma within ovarian tissue.* Fertility and Sterility, 2011. **95**(2): p. 803-806.
91. Bedaiwy MA, et al., *Gonadotropin-releasing hormone analog cotreatment for preservation of ovarian function during gonadotoxic chemotherapy: a systematic review and meta-analysis.* Fertility and Sterility, 2011. **95**(3): p. 906-914.

92. Ben-Aharon I, et al., *Pharmacological interventions for fertility preservation during chemotherapy: a systematic review and meta-analysis.* Breast Cancer Research and Treatment, 2010. **122**(3): p. 803-811.
93. Clowse M E, et al., *Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis.* Journal of Womens Health, 2009. **18**(3): p. 311-319.
94. Beck-Fruchter R, Weiss A, and S. E, *GnRh agonist therapy as ovarian protectants in female patients undergoing chemotherapy: a review of the clinical data.* Human Reproduction Update, 2008. **14**(6): p. 553-561.
95. Badawy A, et al., *Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomised study.* Fertility and Sterility, 2009. **91**(3): p. 694-697.
96. Partridge AH, *Ovarian suppression for prevention of premature menopause and infertility: empty promise or effective therapy? .* Journal of Clinical Oncology, 2012. **30**(5): p. 479-481.
97. Munster PN, et al., *Randomised trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo) adjuvant chemotherapy for breast cancer.* Journal of Clinical Oncology, 2012. **30**(5): p. 533-538.
98. Meistrich M L, Vassilopoulou-Sellin R, and Lipschultz L I, *Gonadal Dysfunction*, in *Cancer: Principles and Practice of Oncology*, DeVita V T, Hellman S, and Rosenberg S A, Editors. 2005, Lippincott, Williams and Wilkins: Philadelphia. p. 2560-2574.
99. Feldschuh J, et al., *Successful sperm storage for 28 years.* Fertility and Sterility, 2005. **84**(4).
100. Agarwal A and Allamaneni S S, *Disruption of spermatogenesis by the cancer disease process.* Journal of the National Cancer Institute Monographs, 2005. **34**: p. 9-12.
101. O'Flaherty C, et al., *Characterization of sperm chromatin quality in testicular cancer and Hodgkin's lymphoma patients prior to chemotherapy.* Human Reproduction, 2008. **23**(5): p. 1044-1052.
102. Skakkebaek N E, Rajpert-De Meyts E, and Main K M, *Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects.* Human Reproduction, 2001. **16**(5): p. 972-978.
103. Shin D, Lo K C, and Lipschultz L I, *Treatment options for the infertile male with cancer.* Journal of the National Cancer Institute Monographs, 2005. **34**: p. 48-50.
104. Carmignani L, et al., *Testicular sperm extraction in cancerous testicles in patients with azoospermia: a case report.* Human Reproduction, 2007. **22**(4): p. 1068-1072.
105. Wyns C, et al., *Options for fertility preservation in prepubertal boys.* Human Reproduction Update, 2010. **16**(3): p. 312-328.
106. United Kingdom Children's Cancer Study Group Late Effects Group, *Practice Statement: Therapy Based Long Term Follow Up*, 2005.
107. Children's Oncology Group, *Long-term follow-up guidelines for survivors of childhood, adolescent and young adult cancers*, 2008, Children's Oncology Group: Arcadia, CA.
108. Scottish Intercollegiate Guidelines Network, *Long term follow up of survivors of childhood cancer: A national clinical guideline*, 2004, Scottish Intercollegiate Guidelines Network: Edinburgh.
109. Absolom, K., et al., *Ovarian failure following cancer treatment: Current management and quality of life.* Human Reproduction, 2008. **23**(11): p. 2506-2512.
110. Hammond, C.T.C., et al., *Non-Hodgkin's lymphoma survivors' fertility and sexual function-related information needs.* Fertility and Sterility, 2008. **90**(4): p. 1258-1260.
111. Hordern, A.J. and A.F. Street, *Communicating about patient sexuality and intimacy after cancer: Mismatched expectations and unmet needs.* Medical Journal of Australia, 2007b. **186**(5): p. 224-227.
112. Walton, L.M., et al., *Gynaecologic cancer patients' needs and experiences of supportive health services in New Zealand.* Psycho-Oncology, 2009. **19**(2): p. 201-208.
113. Wenzel, L., et al., *Defining and measuring reproductive concerns of female cancer survivors.* Journal of the National Cancer Institute Monographs, 2005. **34**: p. 94-98.
114. Zebrack, B.J., J. Mills, and T.S. Weitzman, *Health and supportive care needs of young adult cancer patients and survivors.* Journal of Cancer Survivorship, 2007. **1**: p. 137-145.
115. Rosen, A., K.A. Rodriguez-Wallberg, and L. Rosenzweig, *Psycho-social distress in young cancer survivors.* Seminars in Oncology Nursing, 2009. **25**(4): p. 268-277.
116. Bloom, J.R., et al., *Then and now: Quality of life of young breast cancer survivors.* Psycho-Oncology, 2004. **13**: p. 147-160.
117. Carter, J., et al., *Cancer-related infertility in survivorship.* International Journal of Gynaecological Cancer, 2010. **20**(1): p. 2-8.
118. Carter, J., et al., *Gynaecologic cancer treatment and the impact of cancer-related infertility.* Gynecologic Oncology, 2005. **97**: p. 90-95.
119. Nakayama, K., et al., *Receiving information on fertility- and menopause-related treatment effects among women who undergo hematopoietic stem cell transplantation: Changes in perceived importance over time.* Biology of Blood and Marrow Transplantation, 2009. **15**(11): p. 1465-1474.
120. Cancer Control Council of New Zealand, *The voice of experience: Part one*, 2009, Cancer Control Council: Wellington, New Zealand.
121. Allan, H., *Experiences of infertility: Liminality and the role of the fertility clinic.* Nursing Inquiry, 2007. **14**(2): p. 132-139.
122. Andrykowski, M.A., E. Lykins, and A. Floyd, *Psychological health in cancer survivors.* Seminars in Oncology Nursing, 2008. **24**(3): p. 193-201.

123. Halkett, G.K.B., et al., *The phenomenon of making decisions during the experience of early breast cancer.* European Journal of Cancer Care, 2007. **16**: p. 322-330.
124. Schover L R, et al., *Knowledge and experience regarding cancer, infertility and sperm banking in younger male survivors.* Journal of Clinical Oncology, 2002. **20**(7): p. 1880-1889.
125. Rees M, *Gynaecological oncology perspective on management of the menopause.* European Journal of Surgical Oncology, 2006. **32**(8): p. 892-897.
126. Hickey M, et al., *Practical clinical guidelines for assessing and managing menopausal symptoms after breast cancer.* Annals of Oncology, 2008. **19**(10): p. 1669-1680.
127. Kendall A, et al., *Caution: Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors.* Annals of Oncology, 2006. **17**(4): p. 584-587.
128. Brougham MFH, et al., *Anti-Mullerian Hormone is a Marker of Gonadotoxicity in Pre-and Postpubertal Girls Treated for Cancer: A Prospective Study.* Journal of Clinical Endocrinology and Metabolism, 2012. **97**(6): p. 2059-2067.
129. Kelsey TW, et al., *Data driven assessment of the human ovarian reserve.* Molecular Human Reproduction, 2012. **18**(2): p. 79-87.
130. Matthews ML, et al., *Cancer, Fertility Preservation and Future Pregnancy: A Comprehensive Review.* Obstetics and Gynaecology International, 2012. **2012**: p. 1-11.
131. De Bree E, et al., *Pregnancy after breast cancer: A comprehensive review.* Journal of Surgical Oncology, 2010. **101**(6): p. 534-542.
132. Azim AA, et al., *Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies.* European Journal of Cancer, 2011. **47**: p. 74-83.