A Guideline for Fertility Planning Regarding Pre- and Post-Exposure to Cancer-Directed or Cancer-Like Therapy for Pediatric Hematology/Oncology Patients

Adapted with permission from IWK Health and BC Children's Hospital.

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This guideline and all related materials were reviewed and approved by provincial working groups/specialists and by a patient and family advisor working group. See Appendix A.

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ABBREVIATIONS

AFAB - Assigned Female at Birth
AMAB - Assigned Male at Birth
AMH - Anti-Mullerian Hormone
AOF - Acute Ovarian Failure
CED - Cyclophosphamide Equivalent Dosing
CPAC - Canadian Partnership Against Cancer
FP - Fertility Preservation
FSH - Follicle Stimulating Hormone
GnRH - Gonadotropin-releasing hormone
Gy - Gray
HCP - Health Care Provider
HSCT - Hematopoietic Stem Cell Transplant
IUI - Intrauterine Insemination
IVF - In Vitro Fertilization
IVM - In Vitro Maturation
LH - Lutenizing Hormone
PM - Premature Menopause
POI - Premature Ovarian Insufficiency
RPLND - Retroperitoneal Lymph Node Dissection
TTC - Testicular Tissue Cryopreservation

BACKGROUND

These guidelines are based on the current evidence of the impact of surgery, chemotherapy, and radiotherapy on fertility in children treated with cancer-directed and cancer-like therapies. These guidelines are designed to provide physicians and nursing staff, in the division of hematology/oncology, with a document to provide clear and consistent information, and to facilitate access to further consultation and fertility preservation options. The document also addresses management of gonadotoxicity after completion of treatment. This document addresses:

1. The risks of fertility impairment for patients who are to receive or have received cancer-directed therapy or cancer-like therapy.
2. Available fertility preservation measures for pediatric patients that are to receive or have received cancer-directed or cancer-like therapy.
3. Counselling pediatric cancer survivors of their infertility risks and available resources.
4. Standards for assessing pubertal and gonadal function in patients who have received cancer-directed and cancer-like therapy.

GUIDING PRINCIPLES AND VALUES

All patients (and/or family) undergoing cancer-directed therapy or cancer-like therapy have a right to[1]:

1. Know the risks of potential fertility impairment from their therapy.
2. Knowledge and choice regarding fertility preservation options.
3. Understand the feasibility and potential outcome of the different fertility preservation options.
4. Discuss this information prior to exposure to therapy.

GUIDELINE STATEMENTS

1. All patients to receive, or those who have received cancer-directed and cancer-like therapy (chemotherapy, radiation therapy or surgery that may impact gonadal function) regardless of fertility risk must be made aware of the following:

   1.1. The impact their therapy may have on their fertility.

   1.2. Available standard fertility preservation (FP) options and their feasibility.

2. For younger patients, discussions about post-pubescent fertility may be primarily with family/caregivers. As the patient reaches pubertal/reproductive ages, it is important that the patient is included in these conversations and questions/concerns addressed.

3. Patients with an intermediate or high risk of infertility (see Risk Charts for Individuals Assigned Female and Male at Birth in Estimation of Infertility Risks) need to be made aware of the associated risks, benefits and estimated rates of success for a live birth (this does not account for the infertility risk of 1/6 people that is already present in the general population); see Appendix C. This disclosure needs to happen prior to exposure to cancer-directed or cancer-like therapy whenever possible.

4. Discussions on the impact of cancer-directed and cancer-like therapy on patient's fertility are recommended at 1-year post-therapy, or upon entry to, and routinely during pediatric long-term cancer survivorship clinic. These discussions should be documented and are to occur with the patient and/or their parents/legal guardians depending upon the patient's age and level of autonomy and competence. These discussions should be guided by the adapted Canadian Partnership Against Cancer (CPAC) prompt: "Some cancer treatments could impact fertility or reproductive health and the ability to have biological children now and in the future. I would like to speak to a healthcare professional about this."

5. All childhood survivors who have received cancer-directed or cancer-like therapies and are at risk of pubertal/gonadal impairment should have regular assessment of sexual development starting 1 year after the end of therapy until mature. Post puberty, they should continue to have ongoing assessment of gonadal and sexual function as some patients are at risk of hormonal impairment.

6. Patients, family members, and hematology/oncology health professionals are entitled to have access to easy-to-understand and up-to-date knowledge about fertility preservation available for pediatric hematology/oncology patients.

7. Any patients who may have genetic risk factors related to their cancer diagnosis are entitled to a discussion and referral to appropriate genetic testing.

GUIDELINES

For all hematology/oncology patients **prior to therapy**:

Literature suggests that patients are often dissatisfied with the fertility preservation (FP)

discussions that occur at the time of diagnosis. Health care providers have not consistently delivered FP information to patients at risk and non-disclosure can be associated with future negative feelings, such as resentment and anger.[1] This non-disclosure can be due to the lack of knowledge of the Health Care Professional (HCP).[2] Furthermore, parents and survivors have indicated that they would like to be informed at the time of diagnosis, regardless of the actual risk of fertility impairment, and despite other factors, such as cost, experimental nature of interventions, and the likelihood of surviving.[3-9] Some barriers to FP are non-modifiable such as poor prognosis of severe disease, time constraints for starting treatment and cultural and/or religious beliefs. It has been reported that patients' and families' stress level at the time of diagnosis can be a barrier to discussion. In these cases, psychological and emotional support should be provided by HCPs.[2]

Importantly, the possible impact of cancer-directed and cancer-like therapies should not be underplayed, even when a particular therapy's risk is unknown (e.g., tyrosine kinase inhibitors, mTOR inhibitors and monoclonal antibodies). Care providers should not falsely reassure patients and families that there will be viable offspring if the cancer-directed or cancer-like therapies are low risk to fertility. Likewise, caregivers should not falsely reassure patients and families that FP will definitely result in viable offspring, as there are multiple limitations to assisted reproduction.[10]

1. For all patients, a discussion about the risks to fertility and associated standard FP options is required with the patient and/or family prior to the delivery of cancer-directed or cancer-like therapy.[1,11]

2. Some patients may require immediate initiation of cancer-directed or cancer-like therapy or be too ill to undergo FP procedures. These patients and families should be informed of the infertility risk and be made aware of the rationale for forgoing FP interventions prior to starting therapy. In some cases, it is possible that patients may be suitable for FP interventions after initiation of therapy, at a later date and/or in survivorship. When appropriate patients should be offered a referral to fertility specialists.

3. The decision to pursue FP interventions is at the discretion of the patient and family; the decision to not pursue FP interventions is a valid choice. No patient should be excluded from consideration of discussion of fertility preservation for any reason including age, developmental stage, perceived intellectual ability, prognosis, risk of infertility, socioeconomic status, sociocultural considerations, or previous history of being pregnant or having children.[1]

4. During the discussion about risks of fertility impairment and potential FP options, the patient and/or family members the likelihood of achieving viable offspring with various FP options should be made clear. The realistic feasibility of FP in individual patients should also be made clear, given that each patient will have a different level of urgency to start cancer-directed and cancer-like therapy.

5. During the initial discussion about risks of fertility impairment, the patient and family should be made aware of cost of FP procedures, including initial banking costs,

subsequent storage costs, and costs of using stored materials for assisted reproductive technologies. These costs are best provided in consultation with local fertility clinics; see Appendix D. Social work should be consulted to discuss funding opportunities/programs. It is important to note that there are currently no reimbursement mechanisms for ongoing yearly storage fees or subsequent use of oocytes or sperm for assisted reproductive techniques and these fees will be the responsibility of the patient and/or guardians. For some families, the cost of FP is prohibitive. During or after the disclosure, the patient and/or family should be offered relevant educational material about FP to consider and given the opportunity to ask questions.

For all hematology/oncology patients **who have received** cancer-directed or cancer-like therapy:

1. Cancer-directed or cancer-like therapy can affect both gonadal function and fertility. These issues need to be assessed post treatment as a part of routine physical examinations (i.e., Tanner Staging).

2. Some patients may have had the opportunity to utilize FP technology prior to cancer-directed or cancer-like therapy. These patients should be included in discussions regarding ongoing testing options and storage plans.

3. Some patients at risk of developing gonadal dysfunction/infertility may have a window for FP in early adulthood. It is important that these patients be identified and offered referral to a fertility specialist to consider FP options as appropriate.

4. Infertility cannot be assumed and counseling on safe sex practices should occur with all patients.

Estimation of Infertility Risk

Estimating the risk of infertility following cancer-directed or cancer-like therapy depends on several factors, including the disease, stage, site, cumulative treatment dose and type of chemotherapy, dose of radiation therapy, patient age, and sex. Given that many pediatric cancer treatment plans involve a combination of chemotherapy, radiation, and/or surgery, estimating the true risk for individual patients is challenging.[10,11] Importantly, children born to persons who received chemotherapy alone are expected to have similar risks of congenital abnormalities whether conception occurred naturally or through assisted reproductive technologies.[12] A report from the St. Jude Lifetime Cohort Study reported an incidence of documented gonadal dysfunction in 24.3% Assigned Female at Birth (AFAB) and 55.6% of Assigned Male at Birth (AMAB) survivors of pediatric cancer (n=1067) (Lehmann V 2019, JCO).

The risk of infertility in this document is graded broadly as minimally increased risk (<20%), moderately increased risk (20-80%) and high level of risk (>80%) (Meacham JAYAO 2020). This wide range is applied due to individual variations between patients that are not fully understood, multimodal therapy, and different mechanisms of therapies on fertility.[13] Furthermore this risk assessment is meant to provide the HCP with more information about a

patient's treatment and expected outcomes regarding fertility impairment. Although risk estimation of impaired fertility can be helpful, this should NOT be used to make decisions about offering FP, as each patient may have individual reasons for desiring to pursue or forego FP that is independent of the risk of fertility impairment. Gonadotoxic chemotherapies, such as alkylators, are often categorized in terms of cyclophosphamide equivalent dosing (CED); an online calculator to determine CEDs is available at https://fertilitypreservationpittsburgh.org/fertility-resources/fertility-risk-calculator/ and is shown in Appendix E.

Patients with solid tumors are generally at higher risk of infertility than those with hematologic malignancies due to the amount of gonadotoxic agents they receive. Patients who undergo hematopoietic stem cell transplant (HSCT) or those who receive radiotherapy to gonadal and pituitary tissue are also at heightened risk for infertility. Common therapy related causes of infertility or subfertility include:

Chemotherapy:

- AFAB individuals: Increased sensitivity to gonadotoxic chemotherapy at older age or post- puberty. CED may be used to calculate gonadotoxic chemotherapy infertility risk.
- AMAB individuals: CED may be used to calculate gonadotoxic chemotherapy infertility risk. Note that spermatogenesis is impaired at lower CED than testosterone production. Prepubertal status does not protect from gonadal injury in AMAB patients.

Radiation:

- AFAB individuals: Survivors who are treated with pelvic radiation, in addition to infertility risk, also have a higher risk of stillbirth or miscarriage, neonatal death, and having offspring who are premature, have low birth weight and are small for gestational age.
- AMAB individuals: Radiation to the testes and pelvis has the potential to impact both fertility and testosterone production. Sterility is highly likely if radiation dose to the testes is above 4 Gy, and testosterone production is at risk if dose to the testes is above 12 Gy.[14]
- Both sexes: Radiation to the hypothalamic-pituitary-axis is associated with an increased risk of subfertility or infertility, especially in doses exceeding 30 Gy.[15]

Surgery:

- AFAB individuals: Oophoropexy, bilateral oophorectomy, hysterectomy.
- AMAB individuals: Orchidectomy (unilateral or bilateral), retroperitoneal lymph node dissection, major pelvic surgery, testicular cancer surgery, spinal or paraspinal surgery (especially low- lumbar/sacral), prostatectomy, cystectomy.
- Both sexes: Hypothalamic-pituitary-axis surgery associated with pituitary dysfunction.

Other risks:

- Chronic graft versus host disease of genital tissues may also impact fertility.

(A) Level of Risk of Gonadal Failure/Infertility above that of General Population for Individuals Assigned Female at Birth (AFAB) (Pediatric Initiative Network)

AFAB Risk Chart			Minimally Increased Risk (<20%)	Significantly Increased Risk (20-80%)	High level of Increased Risk (>80%)
Alkylators CED gm/m2		Prepubertal	CED < 8	CED 8-12	CED > 12
		Pubertal	CED < 4	CED 4-8	CED > 8
Heavy Metal mg/m2			Cisplatin Carboplatin		
Hematopoietic Stem Cell Transplant					Alkylator +/- total body irradiation myeloablative and reduced intensity regimens
Radiation Exposure	Ovary	Prepubertal		< 15 Gy	≥ 15 Gy
		Pubertal		< 10 Gy	≥ 10 Gy
	Hypothalamus		22-29.9 Gy	30-39.9 Gy	≥ 40 Gy
Surgery					

*Note that risks may be additive, and presence of multiple risk exposures may escalate patient to higher risk group based on clinical judgment.

(B) Level of Risk of Gonadal Failure/Infertility above that of General Population for Individuals Assigned Male at Birth (AMAB) (Pediatric Initiative Network)

AMAB Risk Chart		Minimally Increased Risk (<20%)	Significantly Increased Risk (20-80%)	High level of Increased Risk (> 80%)
Alkylators CED gm/m2		CED < 4		CED ≥ 4
Hematopoietic Stem Cell Transplant				Alkylator +/- total body irradiation myeloablative and reduced intensity regimens
Heavy Metal mg/m2		Cisplatin Carboplatin	Cisplatin > 500	
Radiation Exposure	Testicular	0.2-0.6 Gy	0.7-3.9 Gy	≥ 4 Gy
	Hypothalamic	26-29.9 Gy	30-39.9 Gy	≥ 40 Gy
Surgery			RPLND	

Fertility Planning Guidelines for Individuals Assigned Female at Birth (AFAB)

1. All new patients, or patients with a relapse, receiving a new treatment with curative intent should be offered the opportunity to discuss the impact of cancer treatment on fertility.

2. Each fertility preservation procedure has risks and benefits and may not be accessible for all patients based on age, cost, and clinical care factors.

3. Referral to Pediatric & Adolescent Gynecology, Endocrinology, Adult Gynecology should be considered for all pubertal AFAB patients (Tanner 4-5 or age ≥12 y); and for pre-pubertal AFAB patients with moderate to high risk of ovarian insufficiency.

4. The risk of fertility impairment may be useful information for the physician and staff to aid them in their understanding of potential outcomes and late effects (see Appendix C). The risk of infertility to AFAB patients falls into three categories:

    1. acute ovarian failure (AOF)
    2. premature ovarian insufficiency (POI)
    3. Hypothalamic-pituitary failure

    AOF is often associated with full abdominal or pelvic radiation, or hematopoietic stem cell transplantation (HSCT), and occurs immediately following treatment. POI is associated with chemotherapy regimens with gonadotoxic chemotherapy such as alkylating agents and refers to AFAB patients experiencing ovarian failure before 40 years of age. In general, pediatric patients are more likely to develop POI rather than AOF due to their greater ovarian reserve than adults.[10]

    Patients at risk for AOF (e.g. those undergoing HSCT or abdominal/pelvic radiation) may wish to consider oocyte preservation prior to starting therapy as post-therapy fertility preservation may not be feasible. Ovarian tissue cryopreservation can also be considered in select cases as this procedure is no longer considered experimental by the American Society for Reproductive Medicine and European Society of Human Reproduction and Embryology. More than 200 live births have occurred following this procedure, 10 of these in patients under 21 years of age. However, a risk of re-implantation of malignant cells exists and procedures to reduce this risk are in the experimental stage. This risk appears to be higher in leukemia patients, and specifically those with active leukemia at the time of ovarian tissue preservation.[16, 17,18]

Fertility Preservation Options for Pre-menarchal Individuals Assigned Female at Birth (AFAB):

Options for fertility preservation for *pre-menarchal* AFAB individuals may occur in select cases and could include conservative surgery strategies to preserve ovarian tissue or methods to minimize radiation exposure such as surgical ovarian transposition or gonadal shielding.[1,21] Another option available is ovarian tissue cryopreservation which is no longer considered experimental in the Atlantic Provinces. The proposed approach to fertility care in pre-menarchal AFAB patients is shown in Appendix F.

Options include:

Shielding of the gonadal regions

This is a standard procedure for reducing scatter radiation and ovarian damage.[1,21]

Conservative Gynecologic Surgery and Radiation Therapy Options

Conservative gynecologic surgery is a strategy utilized to spare fertility by performing less radical surgeries with the intent of sparing as much of the reproductive organs as possible.[1,22] It is possible that this strategy may impact the chances of cure and/or or may increase the risk of disease recurrence.

Ovarian Transposition (Oophoropexy)

	Oophoropexy (Ovarian transposition)
Description	Surgical fixation of ovaries to upper abdominal wall or other site that is outside the radiation field.
Eligibility	• Clinically stable to tolerate sedation and procedure. • Radiation therapy that includes exposure to ovaries estimated at doses ≥ 2Gy. • Treatment for cancer has intent to cure.
Requirements	• Surgical consultation. • Procedure has to be scheduled immediately prior to radiation due to risk of remigration of the ovaries.
Advantages	Decreases risk of radiation exposure.
Risk or disadvantages	• Risk of general anesthetic and laparoscopy. • Ovaries may not remain outside of radiation field for full course of RT. • Risk to the blood supply of the ovary during the procedure. • Due to radiation scatter, ovarian transposition does not always protect the ovaries and patients should be advised of the possible lack of success of the procedure[1].
Estimated costs	None.

Ovarian Tissue Cryopreservation and Transplantation

	Ovarian Tissue Cryopreservation (OTC)
Description	Under general anesthesia, one whole ovary is laparoscopically removed. The specimen is processed and individually frozen for future use. One small biopsy may be sent to pathology for evaluation. At a future date, the ovarian tissue can be re-inserted surgically (autologous transplantation), with the hopes that it will resume hormone production and oocyte production in vivo. This may possibly result in a pregnancy and may require in-vitro fertilization (IVF).

Eligibility	• Any age. • Prior to treatment initiation. • Clinically stable to tolerate anesthesia and laparoscopy. • Moderate or high risk of ovarian insufficiency. • Treatment for cancer has intent for cure and reasonable expectation for long-term survival (*OTC guidelines suggest >50% 5 y EFS*). • Low risk of malignant infiltration to ovaries. Excludes patients with leukemia/lymphoma.
Requirements	• Surgical consultation. • Optimally done in coordination with a planned general anesthetic procedure in the operating room.
Advantages	• Can be performed at any age and pubertal stage. • Minimal delay for start of treatment. • Does not require donor sperm. • Ovarian tissue may also allow for return or induction of hormonal function in AFAB patients with gonadal failure.
Risks or disadvantages	• Risk of surgical procedure. • Risk of re-implantation of tumor cells especially in patients with leukemia and hematological malignancies. There is also a theoretical risk that the same re-implantation of cancer may occur with other tumors that have metastatic potential. Procedures to reduce this risk are currently being studied.[16,17] This procedure will be considered on a case-by-case basis for these patients. • Increasing reports of successful pregnancies but data is still limited for live births from pre-pubertal tissue. • Ethically appropriate – e.g. does not lead to delays in emergency therapy, if required based on oncologists' discretion.
Estimated costs	• Check with local fertility clinic (Appendix D) for most up-to-date cost for specimen processing and storage. • Funding may be available to assist with upfront processing and potentially initial storage. • There is no cost for surgical procedure.
Additional considerations	• For low-risk patients, may be considered at request of patient/family or at discretion of treating team. • As of 2019, OTC is no longer considered an experimental procedure. • Recommend delaying collection until 24 hours after undergoing a nuclear medicine test (e.g. PET/CT or MIBG). • Patients at high risk for malignant infiltration (e.g. leukemia, lymphoma, possibly metastatic disease) would not be advised to have re-transplantation of the ovarian tissue. Patients with metastatic disease can be considered for OTC on a case-by-case basis. • At this time, no technology exists for maturation of oocytes in vitro from ovarian tissue but this may be developed in the future. Cryopreservation for this purpose is considered **experimental**.

Fertility Preservation Options for Post-menarchal Individuals Assigned Female at Birth (AFAB) prior to cancer treatment:

The proposed approach to fertility care in *post-menarchal* AFAB patients is shown in Appendix G. Options for fertility preservation are:

1. Shielding of the gonadal regions
2. Conservative gynecologic surgery and radiation therapy options
3. Ovarian transposition (Oophoropexy)
4. Ovarian suppression therapy
5. Oocyte cryopreservation
6. Ovarian tissue cryopreservation

Note: 1, 2, 3 and 6 were discussed in the previous section.

Ovarian Suppression Therapy

	GnRH Agonist Menstrual Suppression
Description	GnRH agonists are given by monthly injection to induce hypo-estrogenism and suppression of menstrual cycles. The primary purpose of this is to prevent heavy menstrual bleeding during cancer therapy. Possible benefit to reduce risk of ovarian insufficiency by reducing gonadotoxicity through hypogonadism and decreased utero-ovarian perfusion.[34,35] This concept is theoretical and should not be the primary indication for use.
Eligibility	• Post-menarchal. • Moderate or high risk of thrombocytopenia.
Requirements	• Monitoring by ECG for prolonged QTc at baseline and at 2 weeks into therapy. • Ability to take Vitamin D supplementations (1000 IU daily) with adequate calcium intake.
Advantages	• Effective to prevent heavy menstrual bleeding due to thrombocytopenia. • No gynecology consult required. • Does not delay start of treatment. • Does not increase risk of venous thromboembolism (compared to estrogen oral contraception for suppression).
Risks or disadvantages	• Side effects: possible menopausal symptoms, e.g. hot flashes. Recommend gynecology consult if side effects persist as they may be manageable with low-dose estrogen and progesterone. • Risk of reduced bone density. • Evidence of effectiveness to reduce risk of ovarian insufficiency is limited.[23]
Estimated costs	Expense to patient/family.
Additional considerations	• Ideally administer >2 weeks prior to onset of thrombocytopenia. • Ideally administer in luteal phase of menstrual cycle. • Should not be used in place of proven fertility preservation methods.[34]

	• Do not recommend for use for greater than one year.

Oocyte Cryopreservation

	Oocyte Cryopreservation
Description	Unfertilized oocytes are harvested and frozen for future use. The process takes about 2 weeks total. Hormone therapy is used to augment the natural menstrual cycle and stimulate maturation of a higher number of oocytes. Ideally administer hormone therapy in the luteal phase of menstrual cycle. Requires daily hormone injections. The process is monitored by transabdominal ultrasounds. Once the oocytes have matured, they are harvested using ultrasound guided transvaginal (or possibly transabdominal) needle while under general anaesthetic or sedation. They are immediately frozen. All stages of the process occur at a fertility clinic. At a future date when the patient is desirous of pregnancy, the oocytes are thawed, fertilized in-vitro and then transferred to the uterus.
Eligibility	• Post-menarchal (Tanner stage 4-5 and onset of menses). • Prior to treatment initiation. • Moderate or high risk of ovarian insufficiency. • Clinically stable to tolerate ovarian stimulation medications and/or procedures. • Able to defer start of treatment for up to 14 days. • Treatment for cancer has intent for cure
Requirements	• Two-week window to undergo stimulation and harvest prior to start of treatment, with possible additional time for recovery. • Pre-collection blood work (infectious screen). • Clinical evaluation by oncology care provider regarding eligibility. • Referral and consultation directly to fertility clinic; or referral to Reproductive Gynecology prior to referral if additional counseling desired. • Patient must be age ≥12 y and ≥ 36 kg to be eligible for general anesthetic at fertility clinic.
Advantages	• Higher documented rate of successful future IVF pregnancy (relative to ovarian tissue cryopreservation). • Does not require sperm from a partner or donor. • Option to potentially preserve fertility in cases of impairment. • Self-reassurance if successful oocyte retrieval.
Risks or disadvantages	• Delay in start of therapy. • Possible side effects of ovarian stimulation medications, including headache, flushing, and ovarian hyper-stimulation syndrome. • Injections and procedures may not be tolerable for some patients. • Multiple collections may be recommended if low number of oocytes collected. • Egg retrieval occurs via a transvaginal probe (possibility of using

	transabdominal US depending on body habitus and patient/family level of concern) and requires sedation with anesthesia. • Rate of successful pregnancy with unfertilized oocytes is lower than with embryo cryopreservation. • Unknown if the delay may impact cancer outcomes in some cases. • Long term storage issues, risk of storage failure, and ethical considerations if the patient passes away. • Social discomfort in some cases with discussing oocyte cryopreservation.
Estimated costs	• Check with local fertility clinic (Appendix D) for most up-to-date cost for procedure, specimen processing and storage. • Funding may be available to assist for upfront processing and potentially initial storage. *Financial options should be discussed directly with fertility clinic if present barrier to access.*
Additional considerations	• For low-risk patients, may be considered at request of patient/family or at discretion of treating team. • Recommend to delay collection until 24 hours after undergoing a nuclear medicine test (e.g. PET/CT or MIBG). • It is estimated that per collection patients will freeze 5-15 eggs.[25] • Chance of pregnancy with 8-12 eggs is ~40-50%[26] but depends on the number of eggs frozen and the age of the patient at the time of freezing.[25] • Approximately only 5-10% of patients will return to use the frozen oocytes.[27]

Fertility Preservation Options for Individuals Assigned Female at Birth (AFAB) After Completion of Cancer-Directed or Cancer-Like therapy:

Discussion to start when the patient/family are ready and referrals/testing no earlier than 1 year after treatment for cancer complete; it is recommended that this be done in late adolescence/early adulthood as waiting too long could result in low yield for oocyte harvest.

There is limited financial assistance for families post treatment and it is dependent on which province you are from. Please refer to the funding brochure (see APPHON website)

Oocyte cryopreservation for post pubertal AFAB patients.

Ovarian tissue cryopreservation may be considered in the rare times when there is an inability to access the ovaries transvaginally, or unable to tolerate a retrieval under conscious sedation or concern about high estrogen levels during ovarian stimulation.

Fertility Assessment for Individuals Assigned Female at Birth (AFAB) After Completion of Cancer-Directed or Cancer-Like Therapy:

Once a patient has completed their planned therapy a physician assessment should be conducted at each pediatric hematology/oncology clinic visit starting at 1 year off treatment including:

1. If moderate or high risk of pituitary dysfunction: annual LH, FSH, estradiol starting at age 11 years (as part of their periodic complete pituitary surveillance).
2. If moderate or high risk of peripheral gonadal insufficiency: annual LH, FSH, estradiol

starting at age 11 years.

- If abnormal and pre/peri-pubertal, have not reached adult height or have other hormone deficiencies, refer to Endocrinology.
  - Hormone therapy initiation would be considered by endocrinology at approximately the age of 12-13 years, if no signs of puberty, or at older ages if there is pubertal arrest or amenorrhea. Hormone doses and route of administration depend on age, pubertal status, medical history, and risk factors.
- If abnormal and have completed puberty and reached adult height, refer to Gynecology or Reproductive Endocrinology and Infertility services
- Consider Anti-Mullerian Hormone (AMH) testing starting at age 12-years with patient consent.
  - If normal, repeat every 1-2 years (before transition to adult care).
  - If abnormal, consider referring for fertility preservation.
- Consider referral to Endocrinology and to Gynecology for evaluation and counseling regarding fertility preservation.

3. If low risk for central or peripheral hypogonadism, clinical observation only for pubertal progression, growth, menstrual irregularities and/or symptoms of menopause
   - If concerns for precocious puberty, delayed puberty or ovarian insufficiency:
     - send LH, FSH
     - If age >12y, also send AMH
   - If abnormal, refer to above high-risk care pathway

Regardless of risk, refer to endocrinology for assessment if 13 years and no breast development, >15 years and no menarche, secondary amenorrhea >6 months. Consider also consulting gynecology in older adolescents (> 16 years).

Discussions should be offered yearly in follow-up after completion of cancer-directed or cancer-like therapy or when treatment plans change or evolve, as well as if pregnancy is being considered. The discussions should continue throughout survivorship.

Fertility Planning Guidelines for Individuals Assigned Male at Birth (AMAB)

1. All new patients, or patients with relapse, receiving a new treatment should be offered the opportunity to discuss the impact of cancer treatment on fertility, this includes patients who will receive radiation to the hypothalamic-pituitary-axis only.
2. At the time of diagnosis, the risk of fertility impairment may be useful information for HCP and the patient/family (see Appendix C).
3. Many young AMAB patients will experience temporary azoospermia during treatment, which is expected to begin recovery by 1-2 years after completion of treatment, with possible ongoing recovery up to a decade later. This is an important consideration for patients with relapse, as there may be sufficient recovery to have an opportunity for fertility preservation prior to start of more intensive second line therapy.
4. Discussions on sperm banking can be challenging and the HCP should consider if it is culturally safe and acceptable for the patient and family to proceed with discussions.

Fertility Preservation Options for Pre-Pubescent Individuals Assigned Male at Birth (AMAB):

Options for fertility preservation for pre-pubescent or early pubertal AMAB patients (Tanner stage 1 or 2 with testes generally <8-10ml and no history of nocturnal ejaculations or ejaculation by masturbation) include radiation sparing techniques such as gonadal shielding and in some cases testicular tissue cryopreservation which currently is an experimental method. In patients receiving treatment with high risk for infertility, testicular tissue cryopreservation should be offered when available. The proposed approach to fertility care in pre-pubertal AMAB patients is shown in Appendix H.

Options include:

Shielding of the gonadal regions

This is a standard procedure for reducing scatter radiation and testicular damage.

Testicular Tissue Cryopreservation (Experimental)

	EXPERIMENTAL **Testicular Tissue Cryopreservation**
Description	Unilateral biopsy of testicular tissue under general anesthetic.
Eligibility	• Tanner stage < 3 or absence of mature sperm on semen analysis. • High risk of infertility from treatment. • No known malignant infiltration of testes. • Treatment with intent for cure and reasonable expectation of long-term survival. • Prior to start of gonadotoxic treatment. • Requested by family. • Low risk of malignant infiltration to testicles. Excludes patients with leukemia/lymphoma.
Requirements	Urology consultation.
Risks or disadvantages	• **Experimental procedure** – no known technology to stimulate production of mature sperm from pre-pubertal tissue – no live births to date. • Theoretical future risk of re-transplantation of malignant cells. • Risk of additional sedation, if not combined with other essential procedure. • Healing time after incision. • ***Not currently available in Atlantic Canada; it is estimated to be available in late 2025.***
Estimated costs	• Check with local fertility clinic (Appendix D) for most up-to-date cost for procedure, specimen processing and storage. • Funding may be available to assist for upfront processing and potentially initial storage. • No cost for biopsy procedure.

Additional considerations	Ethical consideration as this is an experimental procedure.

Fertility Preservation Options for Post-Pubescent Individuals Assigned Male at Birth (AMAB):

The preferred option for fertility preservation for *post-pubertal* AMAB patients (Tanner stage 3 or higher) is sperm banking. Electroejaculation is currently not available in the Atlantic provinces for semen retrieval but has been used at other institutions if the patient is unable to produce an adequate semen sample for cryopreservation due to illness, stress, motor disability, or early puberty.[24] Sperm extraction and cryopreservation is an excellent option for post-pubertal AMAB patients who are unable to produce an ejaculate. This is not the same as testicular tissue cryopreservation (TTC) and is not experimental. The proposed approach to fertility care in post-pubertal AMAB patients is shown in Appendix I.

Sperm Collection (Banking)

	Sperm Collection
Description	Sperm sample produced via masturbation.
Eligibility	• Tanner stage ≥ 3. • Any risk of infertility. • Medically able and willing to produce semen sample by masturbation. • Prior to start of treatment (*preferable**).
Requirements	• Pre-collection blood work (infectious screen).
Advantages	• Option to potentially preserve fertility in cases of impairment. • Self-reassurance if successful sperm banked.
Risks or disadvantages	• Patient may not be willing or able to produce sample. • Multiple collections may be required if low sperm count. • Patient may have suboptimal sperm production if recent cancer treatment. • Associated financial costs. • Long term storage issues, risk of storage failure. • Social discomfort in some cases with discussing sperm cryopreservation.
Estimated costs	• Check with local fertility clinic (Appendix D) for most up-to-date cost for procedure, specimen processing and storage. • Funding may be available to assist for upfront processing and potentially initial storage.
Additional considerations	• Recommend to delay collection until 24 hours after undergoing a nuclear medicine test (e.g. PET/CT or MIBG). **Collection after start of therapy may be associated with reduced sperm count and increased risk of chromosomal abnormalities and congenital anomalies.* • Boys as young as early adolescence (11-12 years) can and do masturbate. Healthcare providers should not hesitate to discuss with young adolescents.

	• It is estimated >95% of patients who receive fertility preservation counseling will attempt to produce a semen sample.[28] • About 90-95% will be successful in producing a viable sample.[28] • 15% of these patients are estimated to use cryopreserved sperm for fertility treatment.[29] • The success rate depends on the type of fertility treatment (IVF or IUI) and the age of the birthing partner.[29]

Sperm Extraction

	Surgical Testicular Sperm Extraction
Description	Surgical sperm extraction from testis under general anesthetic.
Eligibility	• Tanner stage ≥ 3. • Moderate or High risk of infertility. • No known malignant infiltration of testes. • Unable or unwilling to produce semen sample for sperm banking. • Prior to start of treatment (*preferable**).
Requirements	Pre-collection blood work (infectious screen).
Risks or disadvantages	• Risk of additional sedation, if not combined with other essential procedure. • Sperm extracted are only suitable for in vitro fertilization (IVF). • Healing time after incision. • Cost.
Estimated costs	• Check with local fertility clinic (Appendix D) for most up-to-date cost for procedure, specimen processing and storage. • Funding may be available to assist for upfront processing and potentially initial storage.
Additional considerations	• For low-risk patients, may be considered at request of patient/family or at discretion of treating team. • Ideally is done at time of other procedure (port-a-cath, bone marrow biopsy etc.). • Recommend to delay collection until 24 hours after undergoing a nuclear medicine test (e.g. PET/CT or MIBG). **Collection after start of therapy may be associated with reduced sperm count and increased risk of chromosomal abnormalities and congenital anomalies.*

Fertility Preservation Options for Individuals Assigned Male at Birth (AMAB) After Completion of Cancer-Directed or Cancer-Like Therapy:

- Discussion to start no earlier than 1 year after treatment for cancer complete.
- No financial assistance for families.
- Sperm cryopreservation for post pubertal AMAB patients.

- Testicular tissue cryopreservation for pre-pubertal AMAB patients when available.

Fertility Assessment for Individuals Assigned Male at Birth (AMAB) After Completion of Cancer-Directed or Cancer-Like Therapy*:*

1. After completion of cancer-directed or cancer-like therapy, semen analysis testing should be offered to post-pubertal survivors. This testing can be arranged through follow-up team either at local fertility clinic (Appendix D) or regional center depending on facility capabilities.
2. The earliest time that semen analysis should be completed is 1-2 years post completion of chemotherapy. However, note that even if negative at the first testing, resumption of spermatogenesis can occur up to 10 years post-chemotherapy.
3. Post-pubertal AMAB patients who do not sperm bank prior to treatment and are at risk for future gonadal toxicity should be offered a referral to reproductive medicine for counseling, assessment, and possible sperm banking.
4. For patients with declining hormone levels (Testosterone), consideration of sperm cryopreservation should occur prior to initiating exogenous testosterone replacement. Local fertility clinic (Appendix D) to assess patient prior to endocrinology/urology consult and start of exogenous hormone replacement.
5. Physician assessment should be conducted at each pediatric hematology/oncology clinic starting 1 year after end of therapy.
6. If moderate or high risk of pituitary dysfunction: annual LH, FSH, testosterone starting at age 11 years (as part of their periodic complete pituitary surveillance).
7. If moderate or high risk of testicular gonadotoxicity: annual LH, FSH, testosterone starting at age 11 years.
    - If abnormal and pre/peri-pubertal, have not reached adult height or have other hormone deficiencies, refer to Endocrinology.
        - Hormone therapy initiation would be considered by Endocrinology at approximately the age of 14 years, if no signs of puberty, or older ages if there is pubertal arrest, or clinical and biochemical features of hypogonadism. Hormone doses depend on age, pubertal status, medical history, and risk factors.
    - If abnormal and have completed puberty, refer to Urology.
    - Consider referral to Urology for evaluation and counseling regarding fertility preservation starting anytime after puberty. Offer semen analysis post puberty. if youth is able and willing to obtain sample.
8. If low risk for central or peripheral hypogonadism, clinical observation only for pubertal progression, growth, and or features of hypogonadism
    - If any concerns, send LH, FSH, testosterone.
        - If abnormal refer to the fertility clinic.

Regardless of risk and investigations, refer to endocrinology for assessment if 14 years and no testicular enlargement (<4mL), poor growth, or slow/absent progression of secondary sex characteristics.

REFERENCES

1. Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology* 2013; **31**(19): 2500.
2. El Alaoui-Lasmaili K, Nguyen-Thi PL, Demogeot N, et al. Fertility discussions and concerns in childhood cancer survivors a systematic review for updated practice. *Cancer Medicine.* 2022;12:6023-6039.
3. Gupta AA, Donen RM, Sung L, et al. Testicular biopsy for fertility preservation in prepubertal boys with cancer: identifying preferences for procedure and reactions to disclosure practices. *The Journal of urology* 2016; **196**(1): 219-24.
4. Long CJ, Ginsberg JP, Kolon TF. Fertility Preservation in Children and Adolescents With Cancer. *Urology*.
5. Taylor JF, Ott MA. Fertility preservation after a cancer diagnosis: A systematic review of adolescents', parents', and providers' prospectives', experiences and preferences. *J Pediatr Adolesc Gynecol* 201629:585-598.
6. Clasen NHZ, van der Perk MEM, Neggers SJCMM et al. Experiences of female childhood cancer patients and survivors regarding information and counselling on gonadotoxicity risk and fertility preservation at diagnosis: A systematic review. *Cancers*. 2023; 14:1-16.
7. Gerstl B, Sullivan E, Chong S, et al. Reproductive outcomes after a childhood and adolescent young adult cancer diagnosis in female cancer survivors: A systematic review and meta-analysis. *Journal of Adolescent and Young Adult Oncology*. 2018; 6:627-641.
8. Anazodo A, Laws P, Logan S, et al. How can we improve oncofertility care for patients? A systematic scoping review of current international practice and models of care. *Human Reproductive Update*. 2019;25(2):159-179.
9. Ludemann J, Pruett M, Klosky J et al. The evolution of fertility preservation care models in a large pediatric cancer and blood disorders center. *Pediatric Blood and Cancer.* 2022; 70:e30052.
10. Ginsberg JP. Educational paper. *European journal of pediatrics* 2011; **170**(6): 703-8.
11. Fernbach A, Lockart B, Armus CL, et al. Evidence-based recommendations for fertility preservation options for inclusion in treatment protocols for pediatric and adolescent patients diagnosed with cancer. *Journal of Pediatric Oncology Nursing* 2014; **31**(4): 211-22.
12. Ståhl O, Boyd HA, Giwercman A, et al. Risk of birth abnormalities in the offspring of men with a history of cancer: a cohort study using Danish and Swedish national registries. *Journal of the National Cancer Institute* 2011; **103**(5): 398-406.
13. Green DM, Liu W, Kutteh WH, et al. Cumulative alkylating agent exposure and semen parameters in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. *The Lancet Oncology* 2014; **15**(11): 1215-23.
14. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers. Version 5.0. 2018.
15. Koustenis E, Pfitzer C, Balcerek M, et al. Impact of cranial irradiation and brain tumor location on fertility: a survey. *Klinische Pädiatrie* 2013; **225**(06): 320-4.
16. Dolmans MM, von Wolff M, Poirot C, et al. Transplantation of cryopreserved ovarian tissue in a series of 285 women: a review of five leading European centers. *Fertility and Sterility.* 2021;115(5):1102-1115.
17. Dolmans MM, Falcone T, Patrizio P. Importance of patient selection to analyze in vitro fertilization outcome with transplanted cryopreserved ovarian tissue. *Fertil Steril* 2020;114:279-80.

18. Corkum KS, Rhee DS, Wafford QE, et al. Fertility and hormone preservation and restoration for female children and adolescents receiving gonadotoxic cancer treatments: A systematic review. *Journal of Pediatric Surgery*. 2019;**54**:2200-2209.
19. Senapati S, Morse CB, Sammel MD, et al. Fertility preservation in patients with haematological disorders: a retrospective cohort study. *Reproductive biomedicine online* 2014; **28**(1): 92-8.
20. Anderson RA, Cameron D, Clatot F, et al. Anti-Mullerian hormone as a marker of ovarian reserve and premature ovarian insufficiency in children and women with cancer: a systematic review. Human Reproduction Update. 2022;**28**(2):417-434.
21. Rodriguez-Wallberg KA, Oktay K. Fertility preservation during cancer treatment: clinical guidelines. *Cancer management and research* 2014; **6**: 105.
22. Lange S, Tait D, Matthews M. Oncofertility: an emerging discipline in obstetrics and gynecology. *Obstetrical & gynecological survey* 2013; **68**(8): 582-93.
23. Hickman LC, Llarena NC, Valentine LN, Liu X, Falcone T. Preservation of gonadal function in women undergoing chemotherapy: a systematic review and meta-analysis of the potential role for gonadotropin-releasing hormone agonists. *Journal of assisted reproduction and genetics* 2018; **35**(4): 571-81.
24. Adank MC, van Dorp W, Smit M, et al. Electroejaculation as a method of fertility preservation in boys diagnosed with cancer: a single-center experience and review of the literature. *Fertility and sterility* 2014; **102**(1): 199-205. e1.
25. Magnusson Å, Källen K, Thurin-Kjellberg A, Bergh C. The number of oocytes retrieved during IVF: a balance between efficacy and safety. *Human reproduction* 2018; **33**(1): 58-64.
26. Doyle JO, Richter KS, Lim J, Stillman RJ, Graham JR, Tucker MJ. Successful elective and medically indicated oocyte vitrification and warming for autologous in vitro fertilization, with predicted birth probabilities for fertility preservation according to number of cryopreserved oocytes and age at retrieval. *Fertility and sterility* 2016; **105**(2): 459-66. e2.
27. Cobo A, García-Velasco J, Domingo J, Pellicer A, Remohí J. Elective and Onco-fertility preservation: factors related to IVF outcomes. *Human Reproduction* 2018; **33**(12): 2222-31.
28. Daudin M, Rives N, Walschaerts M, et al. Sperm cryopreservation in adolescents and young adults with cancer: results of the French national sperm banking network (CECOS). *Fertility and sterility* 2015; **103**(2): 478-86. e1.
29. Neal MS, Nagel K, Duckworth J, et al. Effectiveness of sperm banking in adolescents and young adults with cancer: a regional experience. *Cancer* 2007; **110**(5): 1125-9.
30. Dohle GR. Male infertility in cancer patients: review of the literature. *International journal of urology* 2010; **17**(4): 327-31.
31. Bjornard K, Close A, Burns K, et al. Fertility preservation in pediatric solid tumors: A report from the Children's Oncology Group. *Pediatric Blood and Cancer*. 2024;**71**:e30960.
32. Meacham LR, Burns K, Orwig KE, et al. Standardizing risk assessment for treatment-related gonadal insufficiency and infertility in childhood adolescent and young adult cancer: The pediatric initiative network risk stratification system. *Journal of Adolescent and Young Adult Oncology.* 2020;**9**(6):662-666.
33. Schaefer F, Marr J, Seidel C, Tilgen W, Schärer K. Assessment of gonadal maturation by evaluation of spermaturia. *Archives of disease in childhood* 1990; **65**(11): 1205-7.
34. Oktay K, Harvey BE, Partridge AH, et al. Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2018; 36(19):1994-2001.
35. Blumernfeld Z. Fertility Preservation Using GnRH Agonists: Rationale, Possible Mechanisms, and Explanation of Controversy. Clin Med Insights Reprod Health. 2019;13:1-13.

APPENDICES

Appendix A	Guideline Reviewed and Approved at the Provincial Level
Appendix B	Definitions
Appendix C	Risks, Benefits and Estimated Success of Live Birth for Select Fertility Preservation Methods
Appendix D	Fertility Clinics
Appendix E	Cyclophosphamide Equivalent Dosing
Appendix F	Pre-Menarchal Fertility Care Outline for Individuals Assigned Female at Birth
Appendix G	Post-Menarche Fertility Care Outline for Individuals Assigned Female at Birth
Appendix H	Pre-Pubertal fertility Care Outline for Individuals Assigned Male at Birth[33]
Appendix I	Post-Pubertal Fertility Care Outline for Individuals Assigned Male at Birth[33]

Appendix A - Guideline Reviewed and Approved at the Provincial Level

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We are grateful to those named above and the many additional members of the Patient and Family Advisor Working Group who preferred to remain anonymous.
*These patient and family advisors also participated in their respective province's Working Group or the Atlantic Steering Committee.

Appendix B - Definitions

Cancer-directed therapy - Any treatment that is given to modify, control, remove or destroy primary or metastatic cancer tissue is cancer-directed treatment.

Cancer-like therapy - Treatments that are traditionally called chemotherapy agents which may also be used to treat non-malignant conditions.

Hematopoietic stem cell transplant (HSCT) - Involves the intravenous infusion of autologous or allogeneic stem cells collected from bone marrow, peripheral blood, or umbilical cord blood to reestablish hematopoietic and immunologic function in patients whose bone marrow or immune system is damaged or defective. In most cases, HSCT is completed after an intensive dose of chemotherapy called a conditioning regimen in order to allow the patient to accept the new stem cells. The risk of infertility and subfertility associated with HSCT is related to the conditioning regimen (e.g., chemotherapy and/or radiotherapy) rather than the transfer of cells itself.

Fertility preservation - The effort to help cancer patients retain their fertility or utilize treatment options or procedures to maximize future fertility success.

Gy - Gy is the abbreviation for gray, a unit of measurement for absorbed dose of radiation. It represents the amount of energy deposited per unit mass of a substance or tissue when exposed to ionizing radiation. One gray (Gy) equals one joule of energy absorbed per kilogram of matter (1 J/kg). Radiation therapy treatments often specify doses in grays.

Sexual maturity - In this document, individuals Assigned Female at Birth (AFAB) are considered sexually mature once they reach menarche. For individuals Assigned Male at Birth (AMAB), they are considered sexually mature, generally, once they are tanner stage 3 or greater.

Ovarian transposition (Oophoropexy) - A surgery that moves ovaries out of the field of radiation.

Assisted reproduction - Techniques used to treat infertility or subfertility. It includes fertility treatment techniques that manipulate an AFAB individual's egg and/or an AMAB individual's sperm to improve the likelihood of pregnancy.

Subfertility - A delay in conceiving. In subfertility, the possibility of conceiving naturally exists, but takes longer than average.

Infertility - The inability to conceive naturally after one year of trying. In infertility, the likelihood of conceiving without medical intervention is unlikely.

Acute ovarian failure - Loss of ovarian function during or shortly after completion of cancer therapy. If a patient never menstruates or they cease to menstruate within 5 years after cancer diagnosis, this is considered AOF.

Premature ovarian insufficiency - When an AFAB individual's ovaries stop working normally before they are 40 years old.

In vitro fertilization - A medical procedure whereby an egg is fertilized by sperm in a test tube or elsewhere outside the body.

Appendix C - Risks, Benefits and Estimated Success of Live Birth for Select Fertility Preservation Methods

Item	Risks	Benefits	Estimated Success of LiveBirth
Fertility Preservation for Individuals Assigned Female at Birth via Oocyte Cryopreservation	1) IVF stimulation phase lasts 9-11 days and is associated with daily subcutaneous injections of gonadotropins and GnRH antagonists. Monitoring is required with transvaginal ultrasound and bloodwork every 2-3 days. 2) Egg retrieval occurs via a transvaginal probe and requiresgeneral anesthesia. 3) Unknown if the delay mayimpact cancer outcomes in some cases. 4) Long term storage issues, riskof storage failure, and ethical considerations if the patient passes away. 5) Social discomfort in somecases with discussing oocyte cryopreservation.	1) Option to potentially preserve fertility in cases of impairment. 2) Self-reassuranceif successful oocyte retrieval	1) It is estimated that per collection patients will freeze 5-15 eggs. 2) Chance of pregnancy with 8-12 eggs is ~40-50%but depends on the number of eggs frozen and the age of the patient at the time of freezing. 3) Approximately only 5-10% of patients will return to use the frozen oocytes.[25-27]
Fertility Preservation for Individuals Assigned Male at Birth withSperm Cryopreservation	1) Some patients may undergothe procedure and be able to conceive naturally later in life. 2) Associated financial costs. 3) Long term storage issues, riskof storage failure, and ethical considerations if the patient passes away. 4) Social discomfort in somecases with discussing sperm cryopreservation.	1) Option to potentially preserve fertility in cases of impairment. 2) Self-reassuranceif successful sperm banked	1) It is estimated >95% of patient who pursue fertilitypreservation counseling will attempt semen sample. 2) About 90-95% will be successful in producing aviable sample. 3) 15% of these patients are estimated to use cryopreserved sperm forfertility treatment. 4) The success rate depends on the type of fertility treatment (IVF orIUI) and the age of the AFAB partner.[28-30]

Appendix D - Fertility Clinics

Province	Fertility clinics closest to each region
Newfoundland & Labrador	**Newfoundland and Labrador Fertility Clinic** 103 - 35 Major's Path, St. John's NL Phone: 709-777-7444, Fax: 709-752-3648 **Newfound Fertility and Reproductive Services** 1 Paton Street, St. John's NL 709-753-7611; 1-833-333-1715 Physicians at NLFS will refer patients if they require egg or embryo freezing. Patients should not self-refer and oncologist/surgeons/hematologist should refer to this clinic or call switchboard to speak to one of the fertility specialists directly. Patients can be referred to any Health Canada approved Canadian clinic. The most common clinics to which referrals are made include: **Atlantic Fertility** 213 - 1535 Dresden Row, Halifax NS atlanticfertility.ca **Ottawa Fertility Clinic (OFC)** 100 - 955 Green Valley Crescent, Ottawa ON conceive.ca
New Brunswick	**Conceptia** 31 Providence St. 4th floor, Pavillon Hotel-Dieu, Moncton, NB www.conceptia.ca
Nova Scotia	**Atlantic Fertility** 213 - 1535 Dresden Row, Halifax NS atlanticfertility.ca
Prince Edward Island	**Atlantic Fertility** 213 - 1535 Dresden Row, Halifax NS atlanticfertility.ca **Conceptia** 31 Providence St. 4th floor, Pavillon Hotel-Dieu, Moncton, NB www.conceptia.ca

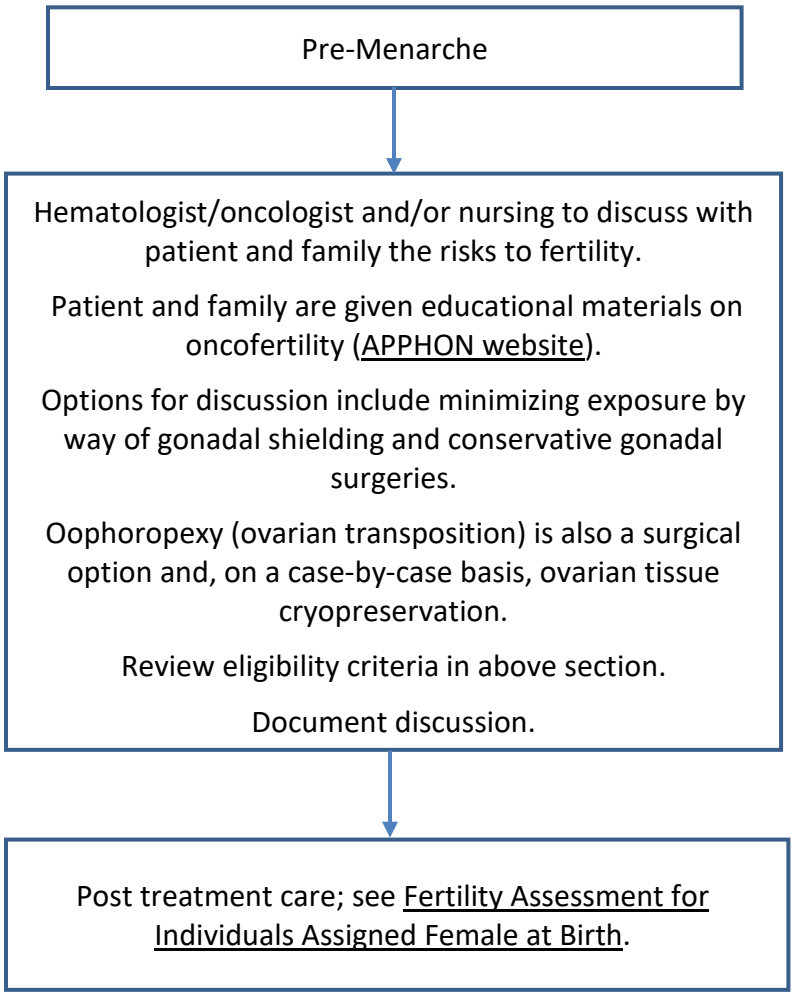
Appendix E - Cyclophosphamide Equivalent Dosing

Cyclophosphamide Equivalent Dosing (CED) calculation*	
Agent dose mg/m2 (CED)	**Correction factor**
Cyclophosphamide	1.0
Ifosfamide	0.244
Procarbazine	0.857
Chlorambucil	14.286
BCNU (Carmustine)	15
CCNU (Lomustine)	16
Melphalan	40
Thiotepa	50
Nitrogen Mustard	100
Busulphan	8.823

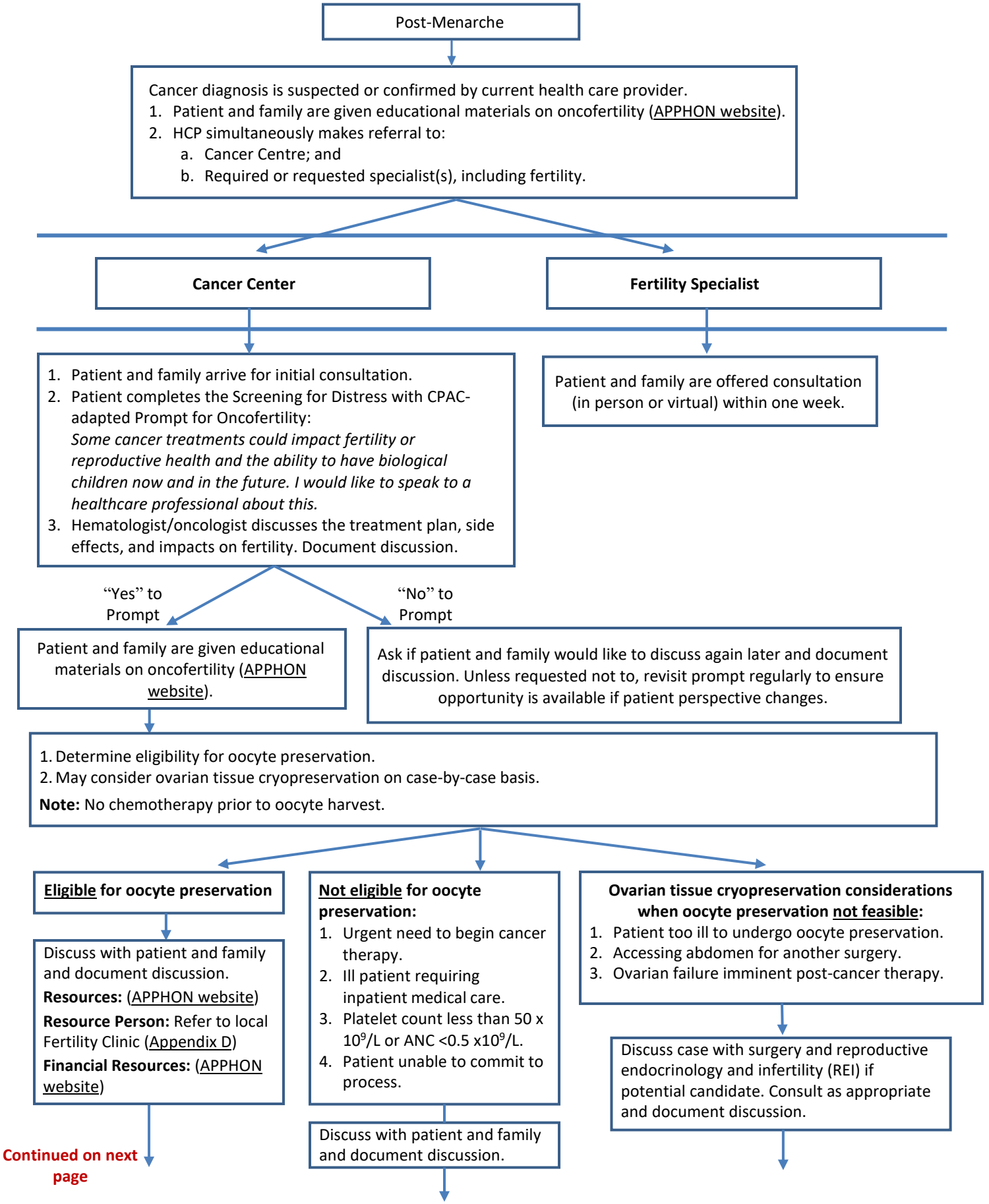
*CED unknown: Treosulfan, Dacarbazine, targeted agents such as mTOR inhibitors, tyrosine kinase inhibitors and monoclonal antibodies

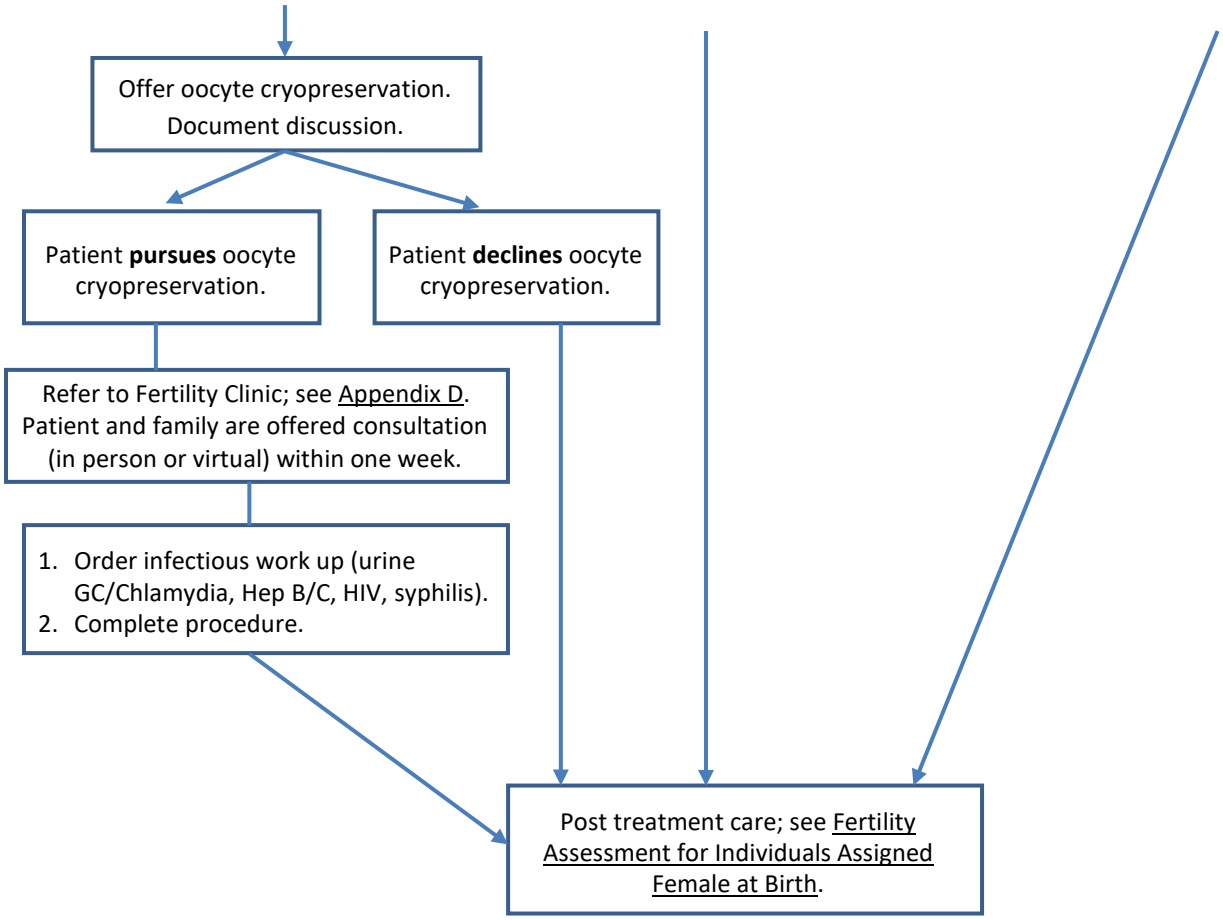
https://fertilitypreservationpittsburgh.org/fertility-resources/fertility-risk-calculator/

Appendix F - Pre-Menarchal Fertility Care Outline for Individuals Assigned Female at Birth

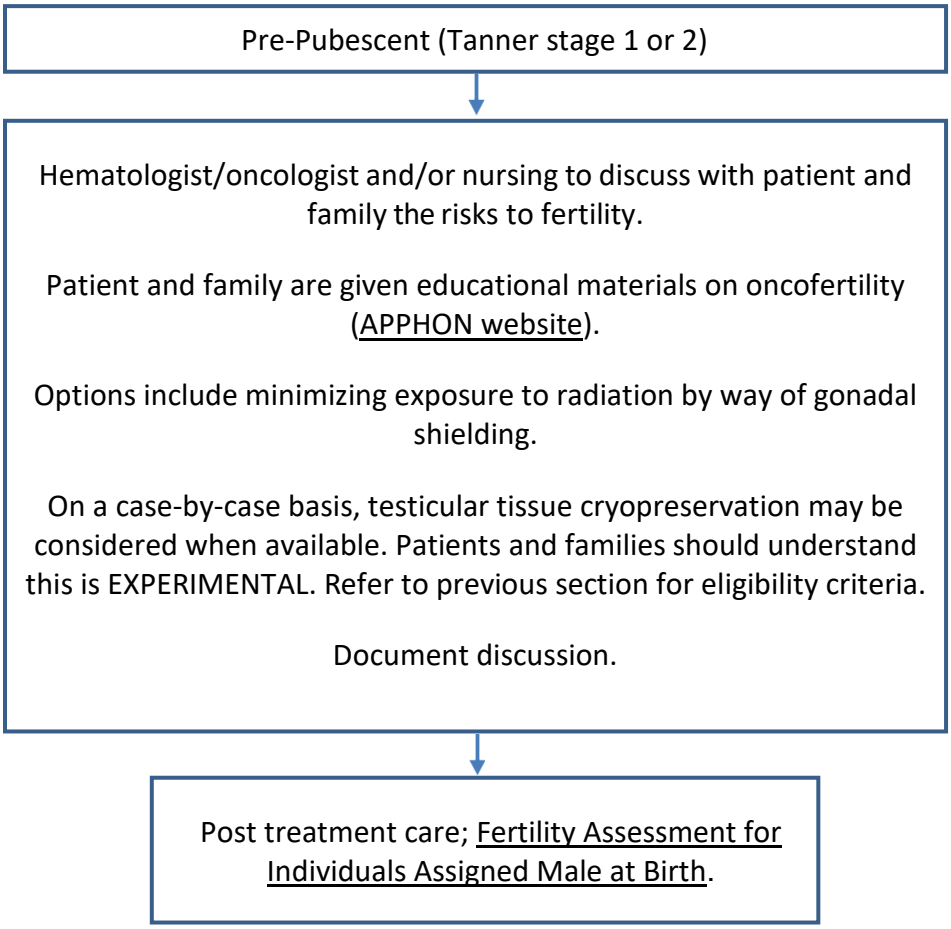


Appendix G - Post-Menarche Fertility Care Outline for Individuals Assigned Female at Birth




Offer oocyte cryopreservation. Document discussion.
Patient **pursues** oocyte cryopreservation.
Patient **declines** oocyte cryopreservation.
Refer to Fertility Clinic; see Appendix D. Patient and family are offered consultation (in person or virtual) within one week.
1. Order infectious work up (urine GC/Chlamydia, Hep B/C, HIV, syphilis).
2. Complete procedure.
Post treatment care; see Fertility Assessment for Individuals Assigned Female at Birth.

Appendix H - Pre-Pubertal Fertility Care Outline for Individuals Assigned Male at Birth[33]



Appendix I - Post-Pubertal Fertility Care Outline for Individuals Assigned Male at Birth[33]