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

Adapted with permission from IWK Health.

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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
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

BACKGROUND

Canadian data indicates that 4250 reproductive-age individuals Assigned Female at Birth (AFAB) (20-39 years old)[2] and 2500 individuals Assigned Male at Birth (AMAB) 20-39 years old[3] are newly diagnosed with cancer in Canada each year, yet referrals to fertility specialists/clinics and fertility preservation is much lower. This is in part due to lack of knowledge and inefficiency in the current Canadian oncofertility system[4].

Health care providers do not always have the knowledge[5] or consistently discuss infertility risks or deliver fertility preservation information to hematology/oncology patients at risk prior to therapy that may impact fertility nor are these services always accessible[6]. Patients 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[7].

These cancer care guidelines aim to facilitate that discussion and process.

GUIDING PRINCIPLES AND VALUES

All patients 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 and multiple times throughout treatment.

GUIDELINES

1. For all patients of current or future childbearing age/status, health care providers should initiate discussions about the risks to fertility and fertility preservation options with patients at multiple points: prior to the delivery of cancer-directed or cancer-like therapy, at discussion of risks of treatment, and prior to the end of treatment/beginning of survivorship. These discussions should be documented. They 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.”

2. If the health care provider is unable to discuss the infertility risks and fertility preservation options, a referral to an appropriate specialist is required. Patients should be provided with contact information for the local Fertility Clinic (see Appendix C).

3. Access to or wait times for a referral to discuss fertility risk and preservation should not be a factor in the decision to refer for this discussion.

4. Some patients may require immediate initiation of cancer-directed or cancer-like therapy or be too ill to undergo fertility preservation procedures. However, they should still be informed of their infertility risk and be made aware of the reason why they were not a

suitable candidate for fertility preservation interventions prior to starting therapy. These patients may still choose and benefit from being referred to a fertility specialist. This discussion must be documented. In some cases, it is possible that patients may be suitable for fertility preservation interventions at a later date and/or in survivorship.

5. For patients who can consider fertility preservation, the options must be discussed with the patient.

6. The decision to pursue fertility preservation interventions is at the discretion of the patient. The decision not to pursue fertility preservation interventions is also an option and at the discretion of the patient.

7. No patient should be excluded from consideration of discussion of fertility preservation for any reason including prognosis, socioeconomic status, or previous history of sexual reproduction.

8. During this discussion about risks of fertility impairment, the patients will be counselled as to whether they are in the low, intermediate, high, or unknown risk of infertility.

9. During the discussion about fertility impairment and potential fertility preservation options, the patient must be made aware of the associated risks, benefits, and estimated rates of success for a live birth without or with different fertility preservation options (see Appendix D). It should be noted that each patient will have a different level of urgency to start cancer-directed and cancer-like therapy, depending on the type of cancer/other diagnosis necessitating cancer-related or cancer-like therapy and its presentation.

10. During the initial discussion about risks of fertility impairment, the patient should be made aware of costs for fertility preservation procedures, including initial banking costs, subsequent storage costs, and costs of using stored materials for in vitro fertilization. These costs are best provided in consultation with local fertility clinics; see Appendix C.

11. During discussion regarding fertility preservation, it is not permissible to provide false hope that viable offspring will occur in those with low risk of fertility impairment who do not pursue fertility preservation as there are many confounding factors. Consideration should be given in case of a failed first-line cancer treatment.

12. A full discussion regarding contraceptive methods based on the teratogenicity or potential teratogenicity of cancer-directed or cancer-like therapy during and immediately following therapy should take place and revisited during the cancer care continuum.

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

Estimation of Infertility Risk

1. 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, type of surgery, patient age, gender, family

history, and potentially pre-existing issues which may affect fertility. Given that many cancer treatment plans involve a combination of chemotherapy, radiation and/or surgery, estimating the true risk for individual patients is challenging.

2. The risk of infertility in this document is graded broadly as low-risk (<20%), intermediate-risk (20-80%), and high-risk (>80%). 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. Furthermore, this risk assessment is meant to give the provider more information about their patient's treatment and expected outcomes with regard to fertility impairment. Although estimation of impaired fertility can be helpful information, this should NOT be used to make decisions about offering fertility preservation, as each patient may have their own reasons for desiring to pursue or forgo fertility preservation that is independent of the risk of fertility impairment.

3. Chemotherapy: Gonadotoxic alkylating chemotherapy agents are often categorized in terms of cyclophosphamide equivalent dosing (CED) as shown in Table 1 (Appendix E). A CED of > 4000 mg/m^2 is associated with a significant risk of infertility[8]. This is often the case in patients receiving chemotherapy for sarcomas or hematopoietic stem cell transplant (HSCT). Note: in individuals Assigned Male at Birth (AMAB), spermatogenesis is impaired at a lower CED than testosterone. An online calculator to determine CEDs is available at https://fertilitypreservationpittsburgh.org/fertility-resources/fertility-risk-calculator.

4. Other forms of systemic therapy such as tyrosine kinase inhibitors, mTOR inhibitors, and monoclonal antibodies have an unknown risk to fertility. Hormone therapy can also impact fertility. Therefore, patients receiving these agents should also be provided with information on possible infertility and fertility preservation.

5. Radiation
    a. Individuals Assigned Female at Birth (AFAB): Radiation to the pelvis in AFAB individuals increases the risk of infertility.
    b. Individuals Assigned Male at Birth (AMAB): Radiation to the testes and pelvis has the potential to impact both fertility and testosterone production. Data from children, adolescents, and young adults indicates that sterility is highly likely if the dose to the testes is above 6 Gy, and testosterone production is at risk if dose to the testes is above 12 Gy.
    c. AFAB and AMAB individuals: Radiation to the hypothalamic-pituitary-axis is associated with an increased risk of subfertility or infertility, especially in doses exceeding 30 Gy. Total body irradiation also increases the risk.

6. Surgery
    a. AFAB individuals: Bilateral oophorectomy and/or hysterectomy will result in loss of fertility and/or the ability to carry a child. It will also result in early menopause which can have impact on quality of life. Oophoropexy and unilateral oophorectomy may impact fertility as well.
    b. AMAB individuals: Orchiectomy (unilateral), retroperitoneal lymph node dissection, major pelvic surgery, spinal or para-spinal surgery (especially low- lumbar/sacral), prostatectomy, cystectomy may affect fertility. Bilateral orchiectomy will result in loss of

fertility. It will also impact on future testosterone production which impacts sexual function.

c. Both genders: Hypothalamic-pituitary-axis surgery can affect fertility.

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

8. Adjuvant medications may be prescribed for several years in some cancers such as breast cancer. While taking these medications natural conception is not recommended and contraception should be used to prevent pregnancy. Some medications might have unknown risks of teratogenicity (e.g. biologic agents).

9. A summary of the risk of fertility impairment in AFAB individuals with some agents is summarized in Table 2 (Appendix F). Fertility impairment results due to premature ovarian insufficiency (POI) which can lead to acute ovarian failure (AOF) or premature menopause (PM). POI refers to AFAB individuals experiencing ovarian failure before age 40 years and can result from both chemotherapy and radiation therapy. AOF is a permanent loss of ovarian function within 5 years of cancer treatment and commonly associated with full abdominal or pelvic radiation or HSCT and can occur with chemotherapy.

10. A summary of the risk of fertility impairment in AMAB individuals with some agents is summarized in Table 3 (Appendix G).

Fertility Preservation Options for Individuals Assigned Female at Birth (AFAB)

Fertility preservation options for AFAB individuals include ovarian transposition, conservative gynecologic surgery, radiation sparing approaches, ovarian suppression therapy, oocyte cryopreservation, and ovarian tissue cryopreservation and transplantation[9,10].

1. Ovarian Transposition (Oophoropexy)
   For patients undergoing pelvic radiation, surgically moving the ovaries out of the field may provide some benefit. However, due to radiation scatter, ovarian transposition does not always protect the ovaries and patients should be advised of the possible lack of success regarding the procedure. There is also controversy regarding the efficacy of this procedure. If performed, it should be done as close to the time of radiation treatment onset due to the risk of remigration of the ovaries. There is risk to the blood supply of the ovary during this procedure.

2. Conservative Gynecological Surgery
   This 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]. It is possible that this strategy may impact the chances of successful cancer therapy or may increase the risk of disease recurrence. The principle of initial cancer therapy is to cure the patient of their cancer, and if there is cancer recurrence there is almost always a higher risk of treatment failure, death and subsequent infertility secondary to salvage therapy. This must be discussed with the patient.

3. Radiation Sparing Approaches
   This will involve treating the smallest possible volume and shielding of the gonadal regions during radiation therapy to reduce scatter radiation and ovarian damage.

4. Ovarian Suppression Therapy
   Using gonadotropin-releasing hormone (GnRH) analogs does not guarantee gonadal protection. 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[1,22]. This should not be the primary indication for use.

5. Oocyte Cryopreservation
   Given the time required, logistics (hormonal stimulation of ovulation, transvaginal ultrasounds, oocyte harvesting) and financial cost to the patient, many patients will be unable to avail of this procedure prior to initiation of therapy. However, all patients at risk for AOF should be offered consultation with a reproductive specialist as post-therapy fertility preservation may not be feasible. Those at risk for POI may also wish to pursue oocyte cryopreservation after completion of chemotherapy if ovarian reserve remains sufficient post-treatment.

6. Ovarian Tissue Cryopreservation and Transplantation
   Ovarian tissue cryopreservation and future re-implantation is an option to restore ovarian function for patients who are unable to cryopreserve oocytes for any reason. Although ovarian tissue cryopreservation is no longer considered 'experimental', it is not performed routinely in most centres and is considered on a case-by-case basis in Atlantic Canada.

   There is a real concern with reintroducing cancer cells with re-implantation of ovarian tissue and it is considered a contraindication in patients with leukemia[12]. There is a theoretical risk that the same re-implantation of cancer may occur with other tumors that have metastatic potential. In the future, there may be methods for using cryopreserved ovarian tissue without re-implantation into a patient, such as in vitro maturation (IVM) of oocytes, these techniques are the subjects of ongoing research.

   Ovarian tissue retrieval is typically done via laparoscopy and will require additional procedure time and cost.

   For AFAB patients who would like to discuss further or consider oocyte cryopreservation or ovarian tissue cryopreservation and transplantation, an algorithmic approach is outlined in Appendix H: Fertility Care Outline for Individuals Assigned Female at Birth. This algorithm also outlines exclusion criteria for these 2 methods which include: urgent need to begin cancer therapy, patient too ill requiring inpatient medical care, platelet count less than 50 x 10^9/L or ANC <0.5 x 10^9/L, or patient unable to commit to the process.

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, an assessment should be conducted if the patient is interested or when they are considering conceiving. To note, some patients at risk of developing gonadal dysfunction/infertility may have a window for fertility preservation. It is

important that these patients be identified and offered referral to a fertility specialist to consider fertility preservation options as appropriate.

1. Medication use, especially hormonal therapies, and contraception.

2. Assessment of sexual function.

3. Hormone screening including FSH, LH, and Estradiol (on days 2-4 of the menstrual cycle). FSH, LH, and estradiol levels cannot be accurately measured while an AFAB individual is taking hormone-releasing birth control (such as oral contraceptives or hormone- releasing intrauterine devices).

4. Anti-mullerian hormone (AMH) levels can be offered and drawn in any AFAB individual at risk of infertility and are not affected by exogenous hormone replacement. The cost of testing for AMH levels may not be covered by provincial medical insurance for at-risk survivors and may be ordered by any endocrinologist or fertility specialist with a potential cost to the patient for this test.

5. A referral to the following specialists should be considered, as necessary:
    a. Endocrinology for hypogonadism. Patients with infertility or subfertility caused by central hypogonadism may wish to discuss hormonal options for fertility purposes. In the event wait times are high for endocrinology, referrals may be directed to fertility specialists.
    b. Gynecology for peri-menopausal symptoms (some fertility specialists manage this as well).
    c. Reproductive gynecology for fertility preservation counseling or infertility assessment. For patients at risk of POI, decisions regarding oocyte cryopreservation or ovarian tissue cryopreservation with transplantation may be informed by declining levels of anti-mullerian hormone, declining oocyte reserve by ultrasound, or evidence of early menopause based upon history and hormonal lab values.

6. Cancer-directed or cancer-like therapy, can affect gonadal function as well. It is important this late side effect is included in post-treatment assessments.

7. For patients who had the opportunity to utilize fertility preservation technology prior to cancer-directed or cancer-like therapy, discussions regarding utilization and ongoing storage should be had.

8. Discussion 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 Preservation Options for Individuals Assigned Male at Birth (AMAB)

The options for fertility preservation for AMAB individuals include:

1. Radiation Sparing Approaches
   This will involve treating the smallest possible volume and shielding of the gonadal regions during radiation therapy to reduce scatter radiation and testicular damage.

2. Surgical Conservative Approaches
   This is a strategy utilized to spare fertility by performing fewer radical surgeries with the intent of sparing as much of the nerves and reproductive organs as possible. For example, nerve sparing retroperitoneal lymph node dissection or partial orchiectomy in patients with only one testicle.[1] It is possible that this strategy may impact the chances of successful cancer therapy or may increase the risk of disease recurrence. The principle of initial cancer therapy is to cure the patient of their cancer, and if there is cancer recurrence there is almost always a higher risk of treatment failure, death, and subsequent infertility secondary to salvage therapy. This must be discussed with the patient.

3. Ejaculated Sperm Cryopreservation
   This involves obtaining a semen sample from the AMAB individual. This can be arranged relatively quickly (within 24-48 hours) as long as the patient is in Halifax Regional Municipality or near the city of Moncton. Patients outside of Halifax or Moncton will need to travel to the clinic area.

4. Testicular Sperm Extraction
   In individuals who are unable to produce a sample by masturbation and ejaculation, a testicular biopsy to extract viable sperm is an option.

For AMAB patients who would like to discuss further or consider sperm cryopreservation, referral to a local fertility clinic (see Appendix C) is required as outlined in Appendix I.

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

Once a patient has completed their planned therapy, an assessment should be conducted if the patient is interested or when they are considering conceiving. To note, some patients at risk of developing gonadal dysfunction/infertility may have a window for fertility preservation. It is important that these patients be identified and offered referral to a fertility specialist to consider fertility preservation options as appropriate.[13]

1. After completion of cancer-directed or cancer-like therapy, semen analysis testing should be offered to survivors. This testing can be arranged through their oncology team, family physicians, or local fertility clinics (see Appendix C) depending on the clinical scenario
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. AMAB individuals who do not sperm bank prior to treatment and are at risk for future gonadal

toxicity should be offered a referral to reproductive endocrinology for counseling, assessment, and possible sperm banking at a local fertility clinic; see Appendix C.

4. For patients with declining testosterone levels and/or rising FSH and LH levels, there may be a potential window for successful sperm banking prior to initiating exogenous testosterone replacement. Exogenous testosterone should not be initiated unless patients understand that starting testosterone will render them sterile, and reversing its effects down the road is not guaranteed. If these patients have low sperm count, they should consider sperm cryopreservation prior to starting exogenous testosterone.

5. Cancer-directed or cancer-like therapy, can affect gonadal function (semen parameters, testosterone, LH) as well. It is important this late side effect is included in post-treatment assessments.

6. For patients who had the opportunity to utilize fertility preservation technology prior to cancer-directed or cancer-like therapy, discussions regarding utilization and ongoing storage should be had.

7. Additional discussions and/or referrals may 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.

Effect on Offspring

Children born to individuals Assigned Male at Birth (AMAB)[14] or Assigned Female at Birth (AFAB) who received chemotherapy alone are expected to have similar risks of congenital abnormalities whether conception occurred naturally or through assisted reproductive technologies.

AFAB individuals treated with pelvic radiation 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.

Costs

All sperm, oocyte and ovarian tissue cryopreservation will take place at a local fertility clinic (see Appendix C).

It is important to note that there are currently no reimbursement mechanisms for ongoing yearly storage fees or subsequent use of oocytes or semen for artificial reproductive techniques and these fees will be the responsibility of the patient. Private drug plans and provincial funding will sometimes cover the cost of medications related to oocyte cryopreservation and fertility treatments.

Costs for initial banking of sperm or oocytes may be partially reimbursed in select cases and discussion with the oncology team or local fertility clinics (see Appendix C) may provide the most up to date information. Fertile Future through their Power of Hope cost reduction program can assist some individuals Assigned Male at Birth (AMAB) (fertilefuture.ca/programs/cost-

reduction-program-for-men).

For some patients, the cost of fertility preservation is prohibitive. During or after the disclosure, the patient should be offered relevant educational material about fertility preservation to consider and given the opportunity to ask questions.

Process

1. Access to or wait times for a referral to discuss fertility risk and preservation should not be a factor in the decision to refer for this discussion.

2. The referral process should be as seamless and automatic as possible.

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APPENDICES

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Appendix A - Guideline Reviewed and Approved at the Provincial Level

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*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 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.

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

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

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.

Assisted reproduction – Techniques used to treat infertility or subfertility. It includes fertility treatment techniques that manipulate a 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 is considered as AOF.

Premature ovarian insufficiency - When an AFAB individual's ovaries stop ovulating and producing estrogen before she is 40years old.

In vitro fertilization - A medical procedure whereby an egg is fertilized by sperm outside the body.

Appendix C - 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 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 conceptia.ca

Appendix D - 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 (AFAB) via Oocyte Cryopreservation	1) IVF stimulation phase lasts 9-11 days and is associated with daily subcutaneous injections ofgonadotropins and GnRH antagonists. Monitoring is required with transvaginal ultrasound and bloodwork every 2-3 days. 2) Egg retrieval occurs via a transvaginal probe and requires conscious sedation. 3) Unknown if the delay may impact 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 some cases with discussing oocytecryopreservation.	1) Option to potentially preserve fertility in cases of impairment. 2) Self-reassuranc eif 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.[15-17]
Fertility Preservation for Individuals Assigned Male at Birth (AMAB) with Sperm 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 some cases with discussing sperm cryopreservation.	1) Option to potentially preserve fertility in cases of impairment. 2) Self-reassuranc eif successful sperm banked	1) It is estimated >95% of patient who pursue fertility preservation counseling will attempt semen sample. 2) About 90-95% will be successful in producing a viable sample. 3) 15% of these patients are estimated to use cryopreserved sperm for fertility treatment. 4) The success rate depends on the type of fertility treatment (IVF or IUI) and the age of the AFAB partner.[18-20]

Appendix E - Table 1: 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

Appendix F - Table 2: Risk of Infertility for Individuals Assigned Female at Birth

CED equivalent (mg/m^2)[8]	**Individual Assigned Female at Birth**
<4,000	Low (<20%)
4000 - 8000	Intermediate (20-80%)
> 8000	High (>80%)
Radiation Exposure[13,21]	
Total Body	High
Whole abdomen or pelvic radiation ≥15Gy pre-pubertal or ≥10 Gy post-pubertal 10 to < 15 Gy pre-pubertal (5 to <10 Gy post-pubertal)	High Intermediate
Cranial >30 Gy Cranial <30 Gy	High Low/Intermediate
Spinal irradiation 24-36 Gy 18-24 Gy	High Intermediate
Other[13]	
Conditioning for Transplant (e.g. Cyclophosphamide, Busulfan, Melphalan)	High
Radioactive iodine	None
Bevacizumab	Intermediate
Cisplatin	Low/Intermediate

Appendix G - Table 3: Risk of Infertility for Individuals Assigned Male at Birth

CED equivalent (mg/m^2)[8]	**Individual Assigned Male at Birth**
<4,000	Low (<20%)
>4000	High (>80%)
Radiation Exposure	
Total Body	High
Testicular or Pelvic >6 Gy Testicular or Pelvic <6 Gy	High Low/Intermediate
Cranial >30 Gy Cranial <30 Gy	High Low/Intermediate
Spinal irradiation 24-36 Gy	High
Other	
Conditioning for Transplant (e.g. Cyclophosphamide, Busulfan,Melphalan)	High
Cisplatin cumulative >400 mg/m^2	Intermediate
Carboplatin dose >2g/m^2	Intermediate
Radioactive iodine	Low
Bevacizumab	Low

Appendix H - Fertility Care Outline for Individuals Assigned Female at Birth

Cancer diagnosis is suspected or confirmed by current health care provider.
1. Patient is given educational materials on oncofertility (APPHON website).
2. HCP simultaneously makes referral to:
   a. Cancer Centre; and
   b. Required or requested specialist(s), including fertility.

Cancer Center

1. Patient arrives for initial consultation.
2. Patient completes the Screening for Distress with CPAC-adapted Prompt for Oncofertility:
   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.
3. Hematologist/oncologist discusses the treatment plan, side effects, and impacts on fertility. Document discussion.

"Yes" to Prompt

Patient is given educational materials on oncofertility (APPHON website).

"No" to Prompt

Ask if patient would like to discuss again later and document discussion. Unless requested not to, revisit prompt regularly to ensure opportunity is available if patient perspective changes.

1. Determine eligibility for oocyte preservation.
2. May consider ovarian tissue cryopreservation on case-by-case basis.

Note: No chemotherapy prior to oocyte harvest.

Eligible for oocyte preservation

Discuss with patient and document discussion.

Educational & Financial Resources: (APPHON website)

Resource Person: Refer to local Fertility Clinic (Appendix C)

Not eligible for oocyte preservation:

1. Urgent need to begin cancer therapy.
2. Ill patient requiring inpatient medical care.
3. Platelet count less than 50 x 10^9/L or ANC <0.5 x10^9/L.
4. Patient unable to commit to process.

Discuss with patient and document discussion.

Ovarian tissue cryopreservation considerations when oocyte preservation not feasible:

1. Patient too ill to undergo oocyte preservation.
2. Accessing abdomen for another surgery.
3. Ovarian failure imminent post-cancer therapy.

Discuss case with surgery and reproductive endocrinology and infertility (REI) if potential candidate. Consult as appropriate and document discussion.

Fertility Specialist

Patient is offered consultation (in person or virtual) within one week.

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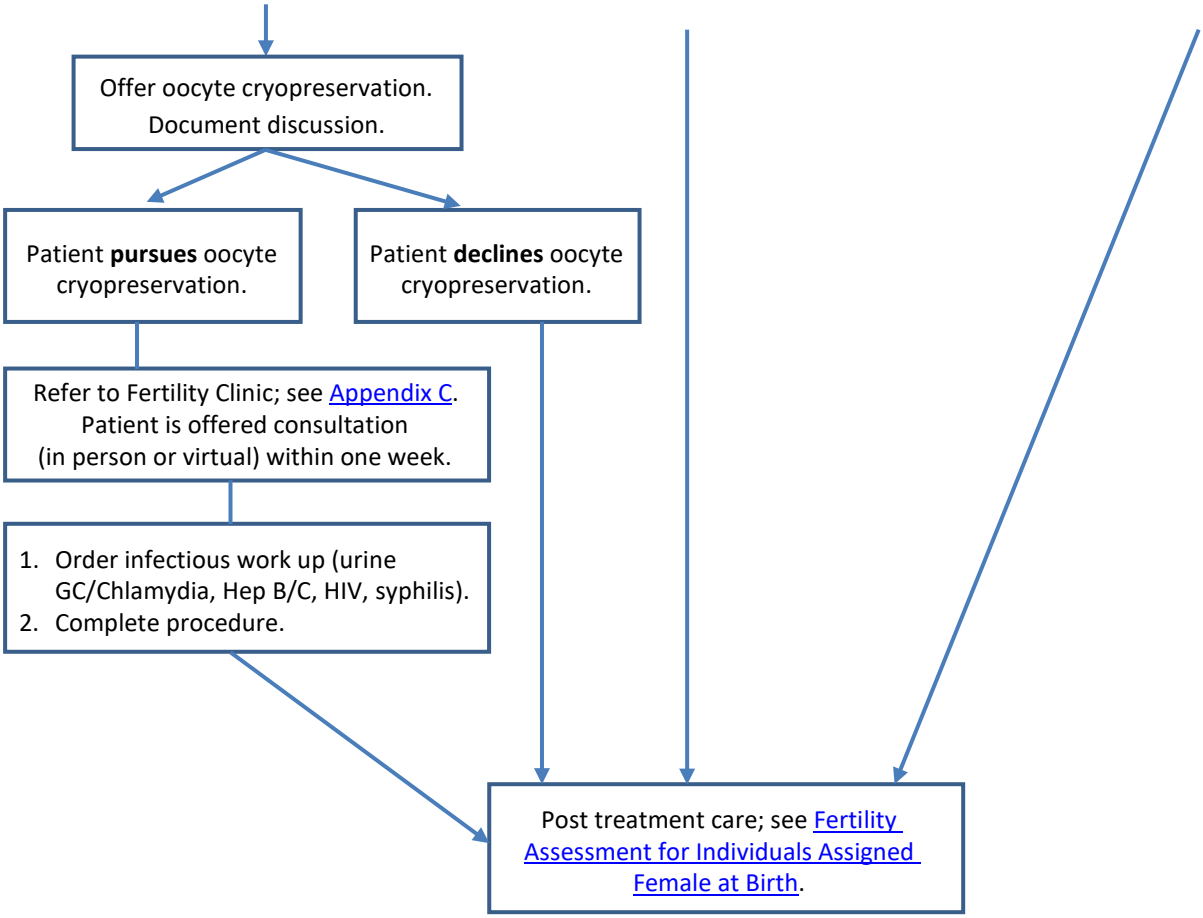
Offer oocyte cryopreservation. Document discussion.
Patient **pursues** oocyte cryopreservation.
Patient **declines** oocyte cryopreservation.
Refer to Fertility Clinic; see Appendix C. Patient is offered consultation (in person or virtual) within one week.
1. Order infectious work up (urine GC/Chlamydia,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

Appendix I - Fertility Care Outline for Individuals Assigned Male at Birth