Practically, fertility preservation approach is more towards scientific evidence rather than a real practice reflection. However, these guidelines are consensus based, not evidence based. Ideally, it is every woman right to choose her fertility plan not only to survive after cancer treatment. In reality, fertility is a crucial part of women life that cannot be taken apart. Owing to advances in cancer treatment there are long term survivorship that favor the possibility of childbearing.

Since 2004, Oncofertility discipline has been established to provide cancer patients to decide about their own plans concerning fertility in the future but with the emphasis to prioritize their cancer optimum management. Initially, fertility preservation is not a one size fits all; each patient plan should be individualized and managed by inputs from different prospective. Instantly, the polling with or against fertility preservation will depend on cancer origin, stage, histological type, grade, management protocols and prognosis; moreover, the fertility and future family planning.

Despite the great harmony of fertility preservation in cancer patient, there are variety of conditions where fertility preservation might be an option as an example risk of premature ovarian insufficiency or delay childbearing (AGE banking) for professional purposes as Female fertility decreases gradually but significantly after age 32 years, and faster after 37 years, which compromises fertility.

To reiterate, fertility preservation is a very complex entity that need cumulative experience and collaborative inputs from different disciplines; gynecology oncology, medical oncology, reproductive specialist and highly specialized nurses to tentatively balance chances of compromising cancer survival and preserving fertility. An entire ample information should be given to each candidate of fertility preservation in order to make their decision.
Noticeably meetings with designated team showed be arranged to allow for open discussion and pinpointing any concerns.
Healthcare providers regarding reproductive management of cancer patients should:

(1) fully understand and comply with the guidelines principles expressed in “perspectives on harvesting, freezing, and storage of gametes and ovarian tissue based on medical indications” and “Perspectives on Sperm Cryopreservation”,
(2) understand the impact of specific cancer treatments on germ cells and fertility,
(3) consider the need for fertility preservation by taking into consideration the patient’s malignancy and general physical condition and the impact of cancer treatment on germ cells and fertility,
(4) understand methods for preservation of gonadal function,
(5) understand fertility issues in patients with hereditary malignancy, and (6) refer cancer patients to reproductive medicine specialists after discussion with each patient and family members, and provide support for patients making decisions about fertility preservation.
(7) financial landscape should be explored as it is considered as a major barrier especially with high out of pocket cost.
Decision tree for fertility preservation: criteria to decide for or against fertility preservation in women


<p>| Non-oncological conditions requiring fertility preservation. |
|-----------------|------------------|
| <strong>Indication</strong> | <strong>Disease</strong> |
| Autoimmune diseases (6, 7) | Systemic lupus erythematosus (SLE) |
| | Behcet's disease |
| | Chronic granulomatous disease (CGD) |
| | Scleroderma |
| Hematopoietic stem cell transplantation (7, 8) | Autoimmune diseases unresponsive to immunosuppressive therapy |
| | Haematological diseases (sickle cell anaemia, thalassaemia major, polycythaemia) |
| Medical conditions causing POI (9) | Altered hypothalamic-pituitary-gonadal axis (10, 11) |
| | Ovarian oophoritis |
| | Benign ovarian tumours |
| | Mosaic Turner's syndrome |
| | Fragile X; Mental retardation 1 (12) |
| | Galactosaemia (13) |
| | Beta-thalassaemia |
| | (14) |
| | Endometriosis (15) |</p>
<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk of permanent amenorrhea</th>
<th>Agent/regime</th>
</tr>
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<tbody>
<tr>
<td>High risk</td>
<td>80%</td>
<td>HSC-TX with cyclophosphamide/TBI or cyclophosphamide/busulfan&lt;br&gt;External beam radiotherapy including the ovaries&lt;br&gt;BEACOPP escalated (≥ 30 years)&lt;br&gt;6× CMF, CEF, CAF, TAC (≥ 40 years)&lt;br&gt;Procarbazine&lt;br&gt;Chlorambucil</td>
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<tr>
<td>Intermediate risk</td>
<td>40-60%</td>
<td>BEACOPP escalated (&lt; 30 years)&lt;br&gt;6× CMF, CEF, CAF, TAC (30–39 years)&lt;br&gt;4× AC (≥ 40 years)&lt;br&gt;4× AC or EC → Taxanes&lt;br&gt;Monoclonal antibody: bevacizumab&lt;br&gt;30%&lt;br&gt;12–54% MTX (cumulative risk increased in repeated treatment of autoimmune disorders)</td>
</tr>
<tr>
<td>Low risk</td>
<td>&lt; 20%</td>
<td>ABVD (≥ 32 years)&lt;br&gt;4–6× CHOP&lt;br&gt;CVP&lt;br&gt;AML therapy (anthracycline/cytarabine)&lt;br&gt;ALL therapy (multi-agent)&lt;br&gt;6× CMF, CEF, CAF, TAC (≤ 30 years)&lt;br&gt;4× AC (≤ 40 years)</td>
</tr>
<tr>
<td>Very low or no risk</td>
<td>–</td>
<td>ABVD (&lt; 32 years)&lt;br&gt;Methotrexate&lt;br&gt;Fluorouracil&lt;br&gt;Vincristine&lt;br&gt;Tamoxifen</td>
</tr>
<tr>
<td>Unknown risk</td>
<td>–</td>
<td>Monoclonal antibodies: trastuzumab, cetuximab&lt;br&gt;Tyrosine kinase inhibitors: erlotinib, imatinib</td>
</tr>
</tbody>
</table>

HSC-TX hematopoietic stem cell transplantation, TBI total body irradiation, CMF cyclophosphamide, methotrexate, fluorouracil, CEF cyclophosphamide, epirubicin, fluorouracil, CAF cyclophosphamide, doxorubicin, fluorouracil, TAC docetaxel, doxorubicin, cyclophosphamide, BEACOPP doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, procarbazine, AC doxorubicin, cyclophosphamide, EC epirubicin, cyclophosphamide, MTX methotrexate, ABVD doxorubicin, bleomycin, vinblastine, dacarbazine, CHOP cyclophosphamide, doxorubicin, vincristine, prednisone, CVP cyclophosphamide, vincristine, prednisone, AML acute myeloid leukaemia, ALL acute lymphatic leukaemia

Risk to fertility by gonadotoxic agents and regimes.
Fertility preservation techniques in women. Experimental procedures are indicated in discontinuous boxes, while established ones (i.e. those proven to restore fertility, with live births reported) are indicated in shaded boxes. Vitrified-thawed oocytes can be fertilized by IVF/ICSI for embryo transfer. Immature oocytes can be matured in vitro (IVM) for IVF/ICSI. Research is undergoing on the potential use of oogonial stem cells to repopulate follicle-depleted ovaries or differentiating follicle somatic cells and oocytes from embryonic stem cells or induced pluripotent stem cells to assemble de novo follicles for transplantation or IVM and IVF/ICSI. *Cryopreserved. OT. ovarian tissue.

The Barcelona International Society for Fertility Preservation–ESHRE–ASRM 2015 Expert Working Group made the following recommendations:

_ Several oncological and non-oncological diseases may affect current or future fertility, either due to the disease itself or to gonadotoxic treatment, and need an adequate FP approach. These patients should be counselled regarding potential fertility loss and should be referred to fertility specialists to discuss options for FP and current results._

_ Women wishing to postpone maternity and transgender individuals before starting hormone therapy or undergoing surgery to remove/alter their reproductive organs should also be counselled accordingly._

_ Embryo and oocyte cryopreservation are first-line FP methods in postpubertal women._

_ Metaphase II oocyte cryopreservation (vitrification) is the preferred option._

_ Cumulative evidence for restoration of ovarian function and spontaneous pregnancies after ART following orthotopic transplantation of cryopreserved ovarian tissue supports its future consideration as an open clinical application._

_ The establishment of international registries on the short and long-term outcomes of FP techniques is strongly recommended._

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
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<tr>
<td>NCCN Breast Cancer 2017²¹</td>
<td>Randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-positive tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. Smaller historical experiences in patients with ER-positive disease have reported conflicting results with regard to the protective effect of GnRH agonist therapy on fertility.</td>
</tr>
<tr>
<td>NCCN AYA Oncology 2017¹⁰</td>
<td>Some data suggest that menstrual suppression with GnRH agonists may protect ovarian function. However, evidence that menstrual suppression with GnRH agonists protects ovarian function is insufficient, so this procedure is not currently recommended as an option for fertility preservation.</td>
</tr>
<tr>
<td>AlOM 2016¹⁶</td>
<td>Temporary ovarian suppression with LHRHα during chemotherapy should be recommended to all premenopausal patients with breast cancer undergoing chemotherapy who are interested in ovarian function and/or fertility preservation.</td>
</tr>
<tr>
<td>SEOM 2016¹⁶</td>
<td>The use of GnRHα could be an option to discuss with patients with early-stage receptor-negative breast cancer if embryo or oocyte cryopreservation not feasible. The use of GnRHα to preserve fertility in women with other cancer should not be recommended.</td>
</tr>
<tr>
<td>BCY 2 2016¹⁷</td>
<td>The most recent data suggested a protective ovarian effect of LHRHα in both patients with hormone receptor-positive and -negative disease with no signal for harm from a breast cancer recurrence standpoint. The BCY 2 Panel therefore agreed this strategy can be discussed with patients interested in potentially preserving fertility and/or ovarian function.</td>
</tr>
<tr>
<td>St Gallen 2015¹⁰</td>
<td>LHRH agonist therapy during chemotherapy proved effective to protect against premature ovarian failure and preserve fertility in young women with ER-negative breast cancer undergoing chemotherapy.</td>
</tr>
<tr>
<td>ESMO 2013¹⁸</td>
<td>The use of GnRH analogs concomitantly with chemotherapy should not be regarded as a reliable means of preserving fertility. Data on long-term ovarian function and pregnancy rates in these cohorts are warranted.</td>
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Abbreviations: ALOM, Italian Association of Medicine; AYA, Adolescent and Young Adult; BCY, International Consensus Conference for Breast Cancer in Young Women; ER, estrogen receptor; ESMO, European Society for Medical Oncology; GnRHα, gonadotropin-releasing hormone agonist; LHRH, luteinizing hormone-releasing hormone; LHRHα, luteinizing hormone-releasing hormone agonist; NCCN, National Comprehensive Cancer Network; SEOM, Sociedad Española de Oncología Médica.
**Breast cancer**

Fertility preservation is recommended in women with breast cancer with a good prognosis, with a moderate to high POI risk and/or age > 35 years at the time of expected pregnancy.

- In hormone-insensitive breast cancer, GnRH agonists, ovarian stimulation for oocyte cryopreservation and ovarian tissue cryopreservation can be offered. • In hormone-sensitive tumours, GnRH agonists and ovarian stimulation for oocyte cryopreservation should be discussed individually.
- If the time interval before chemotherapy is < 2 weeks, e.g., in a neo-adjuvant situation, stimulation is not an option and ovarian tissue cryopreservation should be considered.
- A combination of fertility preserving measures, and freezing the ovarian tissue followed by ovarian stimulation with or without GnRH agonists can be offered.

**Hodgkin’s lymphoma**

Fertility preservation is recommended in women < 40 years with high POI risk (e.g., 6Å~BEACOPPescalated).

- In women with a low or moderate POI risk (e.g., 2Å~ABVD or 2Å~ABVD plus 2Å~BEACOPP escalated) fertility preservation can be considered.
- GnRH agonists, ovarian stimulation with oocyte cryopreservation and ovarian cryopreservation are adequate options for fertility preservation in HL.
- Laparoscopy for ovarian cryopreservation may not be possible in HL, if a mediastinal tumour impairs intubation.
• A combination of fertility preserving measures, GnRH agonists, and freezing of ovarian tissue followed by ovarian stimulation may be an option, if gonadotoxic risk is high, prognosis is good and time is sufficient.

**Borderline ovarian tumour and epithelial**

BOT and in early ovarian cancer FIGO IA G1 after complete staging, fertility sparing surgery to allow for pregnancy is feasible, followed by the completion of surgery after delivery.

• In ovarian cancer FIGO IA G2 after complete staging, fertility sparing surgery and achievement of pregnancy can be considered in individual cases, followed by the completion of surgery and chemotherapy.

• Ovarian stimulation with oocyte cryopreservation can be offered to all patients with BOT, when ovarian reserve is compromised by surgery.

• Ovarian tissue cryopreservation is not recommended in ovarian carcinoma, because of the high risk of relapse, but can be considered in individual cases if bilateral salpingo-oophorectomy is required.

**Cervical cancer**

Fertility sparing surgery such as cone-biopsy or LLETZ is recommended in microinvasive cervical carcinoma FIGO IA1 with one risk factor and in FIGO IA2 without risk factors and if R0 resection is achieved.

• In FIGO IA1 with two risk factors and in FIGO IA2 with one risk factor, fertility preserving surgery in the form of radical trachelectomy according to D’Argent is possible, when staging confirms N0.

• In FIGO IB1 < 2 cm, radical trachelectomy with preservation of the ovaries is possible, the increased oncological risk must be individually assessed.

• In FIGO IB ≥ 2 cm, uterus preservation is not possible.

• In cervical adenocarcinoma FIGO < IB2, the ovaries may be preserved in an individual decision.

• Craniolateral transposition of ovaries is an eligible procedure before radiotherapy. If the uterus cannot be preserved, ovarian stimulation and oocyte cryopreservation followed by surrogacy is an option, if legal in the respective country.
• Downstaging cervical cancer by neo-adjuvant chemotherapy to preserve the uterus is controversially discussed.

Clinical effects of radiotherapy to the uterus.

Endometrial carcinoma and endometrial hyperplasia

In endometrial hyperplasia without atypia, cyclic progestin therapy is indicated (e.g., 10–20 mg MPA/day), with follow-up hysteroscopy and curettage after 3–6 months before a pregnancy is achieved.

• In endometrial hyperplasia with atypia, MPA 100 mg/day or a progestin-releasing IUD is indicated, with follow-up hysteroscopy and curettage after 3 and after 9 months, before pregnancy can be achieved.

• In individual cases of progesterone receptor-positive endometrial carcinoma FIGO IA G1, tumour removal by hysteroscopy and curettage is possible for fertility preservation, followed by progestin therapy with 250 mg MPA for 6–12 months with follow-up in three-monthly intervals. The realization of a pregnancy is then possible within a limited time frame. After pregnancy or in case of relapse, completion of surgery is indicated.

• Fertility preservation is not possible in progesterone receptor-negative endometrial carcinoma FIGO IA G1, or in tumours with higher stages or higher grading. In these cases, hysterectomy with bilateral salpingo-oophorectomy is indicated.

Rheumatic and autoimmune disorders

Fertility preservation should be recommended in young women with autoimmune disorders, when cyclophosphamide therapy is indicated.

• GnRH agonists are an eligible option for fertility preservation in autoimmune diseases.
• Ovarian stimulation and cryopreservation of oocytes can be applied in individual cases, if risk of exacerbation is low and sufficient time is available. Effective thrombosis prophylaxis is required.
• Cryopreservation of ovarian tissue is an option, if ovarian reserve is sufficient.

Other malignant diseases
Ewing sarcoma

GnRH agonists and, if the time interval before oncological therapy is sufficient, ovarian stimulation with oocyte cryopreservation can be considered.
Ovarian tissue cryopreservation is possible.
A risk of ovarian metastasis must be discussed.
Ovarian transposition is possible, if pelvic radiotherapy is performed.

Osteosarcoma

Comparable to Ewing sarcoma, GnRH agonists and, if the time interval before oncological therapy is sufficient, ovarian stimulation with oocyte cryopreservation can be considered.
Ovarian tissue cryopreservation is possible, if the risk of ovarian metastasis is discussed.
Ovarian transposition is possible, if pelvic radiotherapy is performed.

Colorectal carcinoma

If chemotherapy is indicated, GnRH agonists, ovarian stimulation for cryopreservation of oocytes, and ovarian tissue cryopreservation are possible options for fertility preservation.
Ovarian transposition should be considered, if radiotherapy is performed.
Gestational surrogacy after cryopreservation of oocytes or ovarian tissue may be an option, if legal in the respective country.

Non-Hodgkin lymphoma (NHL)

GnRH agonists are an option for fertility preservation.
Ovarian transposition can be considered, if pelvic radiotherapy is performed. Ovarian stimulation for cryopreservation of oocytes, and ovarian tissue cryopreservation are not recommended, because of the risk of ovarian metastasis.

**Acute lymphoblastic leukaemia (ALL)**

GnRH agonists are an option for fertility preservation. GnRH agonist-induced amenorrhoea prevents menstrual bleeding during oncological therapy. Ovarian stimulation with cryopreservation of oocytes is often not possible due to the limited time available. Ovarian cryopreservation is experimental because of the high risk of ovarian malignant cells. In vitro growth (IVG) or xenotransplantation may become future strategies.

**Acute myeloid leukaemia (AML)**

Comparable to ALL, GnRH agonists are an option for fertility preservation in AML and GnRH agonist-induced amenorrhea prevents menstrual bleeding during oncological therapy. Ovarian stimulation with cryopreservation of oocytes is often not possible due to the limited time available. Ovarian tissue cryopreservation is experimental because of the high risk of ovarian malignant cells. In vitro growth (IVG) or xenotransplantation may become future strategies.

**Future tasks**
<table>
<thead>
<tr>
<th></th>
<th>Establish a system for treatment selection and guidance on oncofertility, including an informed assent form (for children and adolescents) and an informed consent form (for adults)</th>
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<tr>
<td>2.</td>
<td>Management of patients who do not want fertility preservation or in whom fertility preservation is contraindicated Medical intervention to maintain and improve the QOL of cancer survivors who underwent treatment before 2012</td>
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<tr>
<td>3.</td>
<td>Obtaining further knowledge about oncofertility and promotion of information delivery (including peer support groups for cancer survivors)</td>
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<td>4.</td>
<td>Consider public financial assistance for fertility preservation therapy</td>
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<td>5.</td>
<td>Nurture expert healthcare providers dealing with oncofertility</td>
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<tr>
<td>6.</td>
<td>Promote technical innovations in the oncofertility field</td>
</tr>
</tbody>
</table>
Recommendations

- Recommendation 1.1. People with cancer are interested in discussing fertility preservation. Health care providers caring for adult and pediatric patients with cancer (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, surgeons, and others) should address the possibility of infertility as early as possible before treatment starts.

- Recommendation 1.2. Health care providers should refer patients who express an interest in fertility preservation (and those who are ambivalent) to reproductive specialists.

- Recommendation 1.3. To preserve the full range of options, fertility preservation approaches should be discussed as early as possible, before treatment starts. The discussion can ultimately reduce distress and improve quality of life. Another discussion and/or referral may be necessary when the patient returns for follow up after completion of therapy and/or if pregnancy is being considered. The discussions should be documented in the medical record.

Adult Men

- Recommendation 2.1. Sperm cryopreservation: Sperm cryopreservation is effective, and health care providers should discuss sperm banking with postpubertal males receiving cancer treatment.

- Recommendation 2.2. Hormonal gonadoprotection: Hormonal therapy in men is not successful in preserving fertility. It is not recommended.

- Recommendation 2.3. Other methods to preserve male fertility: Other methods, such as testicular tissue cryopreservation and reimplantation or grafting of human testicular tissue, should be performed only as part of clinical trials or approved experimental protocols.

- Recommendation 2.4. Postchemotherapy: Men should be advised of a potentially higher risk of genetic damage in sperm collected after initiation of therapy. It is strongly recommended that sperm be collected before initiation of treatment.
because the quality of the sample and sperm DNA integrity may be compromised after a single treatment. Although sperm counts and quality of sperm may be diminished even before initiation of therapy, and even if there may be a need to initiate chemotherapy quickly such that there may be limited time to obtain optimal numbers of ejaculate specimens, these concerns should not dissuade patients from banking sperm. Intracytoplasmic sperm injection allows the future use of a very limited amount of sperm; thus, even in these compromised scenarios, fertility may still be preserved.

Adult Women

- Recommendation 3.1. Embryo cryopreservation: Embryo cryopreservation is an established fertility preservation method, and it has routinely been used for storing surplus embryos after in vitro fertilization.

- Recommendation 3.2. Cryopreservation of unfertilized oocytes: Cryopreservation of unfertilized oocytes is an option, and may be especially well suited to women who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing. Oocyte cryopreservation should be performed in centers with the necessary expertise. As of October 2012, the American Society for Reproductive Medicine no longer deems this procedure experimental.

- **Qualifying statement.** More flexible ovarian stimulation protocols for oocyte collection are now available. Timing of this procedure no longer depends on the menstrual cycle in most cases, and stimulation can be initiated with less delay compared with old protocols. Thus, oocyte harvesting for the purpose of oocyte or embryo cryopreservation is now possible on a cycle day–independent schedule. Of special concern in estrogen-sensitive breast and gynecologic malignancies is the possibility that these fertility preservation interventions (eg, ovarian stimulation regimens that increase estrogen levels) and/or subsequent pregnancy may increase the risk of cancer recurrence. Aromatase inhibitor–based stimulation protocols are now well established and may ameliorate this concern. Studies do not indicate increased cancer recurrence risk as a result of aromatase inhibitor–supplemented ovarian stimulation and subsequent pregnancy.

- Recommendation 3.3. Ovarian transposition: Ovarian transposition (oophoropexy) can be offered when pelvic irradiation is performed as cancer
treatment. However, because of radiation scatter, ovaries are not always protected, and patients should be aware that this technique is not always successful. Because of the risk of remigration of the ovaries, this procedure should be performed as close to the time of radiation treatment as possible.

- **Recommendation 3.4.** Conservative gynecologic surgery: It has been suggested that radical trachelectomy (surgical removal of the uterine cervix) should be restricted to stage IA2 to IB cervical cancer with diameter < 2 cm and invasion < 10 mm. In the treatment of other gynecologic malignancies, interventions to spare fertility have generally centered on doing less radical surgery, with the intent of sparing the reproductive organs as much as possible. Ovarian cystectomy can be performed for early-stage ovarian cancer.

- **Recommendation 3.5 (updated).** Ovarian suppression: There is conflicting evidence to recommend GnRHa and other means of ovarian suppression for fertility preservation. The Panel recognizes that, when proven fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. However, GnRHa should not be used in place of proven fertility preservation methods.

- **Recommendation 3.6 (updated).** Ovarian tissue cryopreservation and transplantation: Ovarian tissue cryopreservation for the purpose of future transplantation does not require ovarian stimulation and can be performed immediately. In addition, it does not require sexual maturity and hence may be the only method available in children. Finally, this method may also restore global ovarian function. However, it should be noted further investigation is needed to confirm whether it is safe in patients with leukemias.

- **Qualifying statement.** As of the time of this publication, ovarian tissue cryopreservation remains experimental. However, emerging data may prompt reconsideration of this designation in the future (this technique is already considered nonexperimental in some countries, and its experimental status is undergoing evaluation in the United States).
• Recommendation 4.1. All oncologic health care providers should be prepared to
discuss infertility as a potential risk of therapy. This discussion should take place
as soon as possible once a cancer diagnosis is made and can occur simultaneously
with staging and the formulation of a treatment plan. There are benefits for
patients in discussing fertility information with providers at every step of the
cancer journey.

• Recommendation 4.2. Encourage patients to participate in registries and clinical
studies, as available, to define further the safety and efficacy of these
interventions and strategies.

• Recommendation 4.3. Refer patients who express an interest in fertility, as well as
those who are ambivalent or uncertain, to reproductive specialists as soon as
possible.

• Recommendation 4.4. Refer patients to psychosocial providers when they are
distressed about potential infertility.

Special Considerations: Children

• Recommendation 5.1. Suggest established methods of fertility preservation (eg,
semen or oocyte cryopreservation) for postpubertal children, with patient assent
and parent or guardian consent. For prepubertal children, the only fertility
preservation options are ovarian and testicular cryopreservation, which are
investigational.