

## American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients

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### ABSTRACT

#### Purpose

To develop guidance to practicing oncologists about available fertility preservation methods and related issues in people treated for cancer.

#### Methods

An expert panel and a writing committee were formed. The questions to be addressed by the guideline were determined, and a systematic review of the literature from 1987 to 2005 was performed, and included a search of online databases and consultation with content experts.

#### Results

The literature review found many cohort studies, case series, and case reports, but relatively few randomized or definitive trials examining the success and impact of fertility preservation methods in people with cancer. Fertility preservation methods are used infrequently in people with cancer.

#### Recommendations

As part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists. Clinician judgment should be employed in the timing of raising this issue, but discussion at the earliest possible opportunity is encouraged. Sperm and embryo cryopreservation are considered standard practice and are widely available; other available fertility preservation methods should be considered investigational and be performed in centers with the necessary expertise.

#### Conclusion

Fertility preservation is often possible in people undergoing treatment for cancer. To preserve the full range of options, fertility preservation approaches should be considered as early as possible during treatment planning.

*J Clin Oncol* 24. © 2006 by American Society of Clinical Oncology

### INTRODUCTION

The diagnosis and treatment of cancer often poses a threat to fertility. Methods of fertility preservation are evolving quickly, yet little has been published in the medical oncology literature regarding this topic. Studies suggest that the ability to have biological children is of great importance to many people. Any oncologist seeing reproductive-aged patients for consideration of cancer therapy should be addressing potential treatment-related infertility with them or, in the case of children, with their parents. Yet, studies suggest that many oncologists either do not discuss the possibility of treatment-related infertility or do so suboptimally. Teaching in many fellowship programs covers sperm banking and techniques such as oophorectomy,<sup>1</sup> while little information is provided concerning other methods of fertility preservation.

The purpose of this guideline is to review the literature pertaining to fertility preservation options for men, women, and children undergoing cancer treatment, and to give guidance to oncologists about these issues. The focus is restricted to interventions aimed at fertility preservation; the guidelines do not address methods of fertility restoration after completion of cancer treatment nor the risks of assisted reproductive techniques, except those unique to cancer patients. The risks of pregnancy to parents and offspring after cancer treatment are reviewed only insofar as they might affect a person's desire to pursue fertility preservation methods before or during active cancer treatment.

#### **Estimating the Risk of Infertility After Treatment for Cancer**

Infertility is functionally defined as the inability to conceive after 1 year of intercourse without

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Submitted March 14, 2006; accepted March 24, 2006.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/06/2418-1/\$20.00

DOI: 10.1200/JCO.2006.06.5888

contraception. Rates of permanent infertility and compromised fertility after cancer treatment vary and depend on many factors. The effects of chemotherapy and radiation therapy depend on the drug or size/location of the radiation field, dose, dose-intensity, method of administration (oral versus intravenous), disease, age, sex, and pre-treatment fertility of the patient. Male infertility can result from the disease itself (best documented in patients with testicular cancer and Hodgkin's lymphoma), anatomic problems (eg, retrograde ejaculation or anejaculation), primary or secondary hormonal insufficiency, or more frequently, from damage or depletion of the germinal stem cells. The measurable effects of chemotherapy or radiotherapy include compromised sperm number, motility, morphology, and DNA integrity. In females, fertility can be compromised by any treatment that decreases the number of primordial follicles, affects hormonal balance, or interferes with the functioning of the ovaries, fallopian tubes, uterus, or cervix. Anatomic or vascular changes to the uterus, cervix, or vagina from surgery or radiation may also prevent natural conception and successful pregnancy, requiring assisted reproductive technology or use of a gestational carrier.

Male and female fertility may be transiently or permanently affected by cancer treatment or only become manifest later in women through premature ovarian failure. The panel wishes to

emphasize that female fertility may be compromised despite maintenance or resumption of cyclic menses. Regular menstruation does not guarantee normal fertility as any decrease in ovulatory reserve may result in a lower chance of subsequent conception and higher risk of early menopause. Even if women are initially fertile after cancer treatment, the duration of their fertility may be shortened by premature menopause.

An estimated 1,372,910 people were diagnosed with cancer in 2005, of whom 4% (approximately 55,000) are under the age of 35.<sup>2</sup> The most common cancers diagnosed in people under the age of 40 years are breast cancer, melanoma, cervical cancer, non-Hodgkin's lymphoma, and leukemia.<sup>3</sup> The Panel recognizes that a table of all common cancer treatments with their associated risks of infertility is desirable. However, available data are poor and heterogeneous, so summarization was felt to be beyond the scope of this guideline. However, Tables 1<sup>3A</sup> and 2, and several additional references<sup>4-12</sup> illustrate the range of risks associated with several cancer therapies. The Panel noted that most of the available literature quantifying infertility risks reports rates of azoospermia and amenorrhea, though these are surrogate measures of infertility. In men and women, the greatest risks associated with chemotherapy involve the alkylating agents (particularly cyclophosphamide,

**Table 1.** Effects of Different Antitumor Agents on Sperm Production in Men<sup>168</sup>

Agents (Cumulative Dose for Effect)	Effect
Radiation (2.5 Gy to testis)	Prolonged azoospermia
Chlorambucil (1.4 g/m <sup>2</sup> )	
Cyclophosphamide (19 g/m <sup>2</sup> )	
Procarbazine (4 g/m <sup>2</sup> )	
Melphalan (140 mg/m <sup>2</sup> )	
Cisplatin (500 mg/m <sup>2</sup> )	
BCNU (1 g/m <sup>2</sup> )	Azoospermia in adulthood after treatment before puberty
CCNU (500 mg/m <sup>2</sup> )	
Busulfan (600 mg/kg)	Azoospermia likely, but always given with other highly sterilizing agents
Ifosfamide (42 g/m <sup>2</sup> )	
BCNU (300 mg/m <sup>2</sup> )	
Nitrogen mustard	
Actinomycin D	
Carboplatin (2 g/m <sup>2</sup> )	Prolonged azoospermia not often observed at indicated dose
Doxorubicin (Adriamycin) (770 mg/m <sup>2</sup> )	Can be additive with above agents in causing prolonged azoospermia, but cause only temporary reductions in sperm count when not combined with above agents
Thiotepa (400 mg/m <sup>2</sup> )	
Cytosine arabinoside (1 g/m <sup>2</sup> )	
Vinblastine (50 g/m <sup>2</sup> )	
Vincristine (8 g/m <sup>2</sup> )	
Amsacrine, bleomycin, dacarbazine, daunorubicin, epirubicin, etoposide, fludarabine, 5-fluorouracil, 6-mercaptopurine, methotrexate, mitoxantrone, thioguanine	Only temporary reductions in sperm count at doses used in conventional regimens, but additive effects are possible
Prednisone	Unlikely to affect sperm production
Interferon- $\alpha$	No effects on sperm production
Examples of new agents:	Unknown effects on sperm production
Oxaliplatin	
Irinotecan	
Monoclonal antibodies (trastuzumab, bevacizumab, cetuximab)	
Tyrosine kinase inhibitors (erlotinib, imatinib)	
Taxanes	

NOTE. Reprinted and modified Table 54.6-3 with permission from DeVita, VT, Jr, Hellman S, and Rosenberg, SA. Cancer: Principles & Practice of Oncology (ed 7). Philadelphia, Pa, Lippincott Williams & Wilkins, 2005.  
Abbreviations: BCNU, carmustine; CCNU, lomustine.

**Table 2.** Risks of Permanent Amenorrhea in Women Treated With Modern Chemotherapy and Radiotherapy

Degree of Risk	Cancer Treatment
High risk (> 80%)	Hematopoietic stem cell transplantation with cyclophosphamide/total body irradiation or cyclophosphamide/busulfan External beam radiation to a field that includes the ovaries CMF, CEF, CAF × 6 cycles in women age 40 and older (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin)
Intermediate risk	CMF, CEF, CAF × 6 cycles in women age 30-39 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin) AC × 4 in women age 40 and older (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide)
Lower risk (< 20%)	ABVD (doxorubicin/bleomycin/vinblastin/dacarbazine) CHOP × 4-6 cycles (cyclophosphamide/doxorubicin/vincristine/prednisone) CVP (cyclophosphamide/vincristine/prednisone) AML therapy (anthracycline/cytarabine) ALL therapy (multi-agent) CMF, CEF, CAF × 6 cycles in women less than 30 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin) AC × 4 in women less than 40 (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide)
Very low or no risk	Vincristine Methotrexate 5-fluorouracil
Unknown risk (examples)	Taxanes Oxaliplatin Irinotecan Monoclonal antibodies (trastuzumab, bevacizumab, cetuximab) Tyrosine kinase inhibitors (erlotinib, imatinib)

\*These are general guidelines based on best available literature. Additional factors, particularly pre-treatment ovarian reserve, specific treatment regimen, and age determine individual risk for immediate infertility, or for premature ovarian failure after resumption of menses. Please see text for details.

ifosfamide, nitrosoureas, chlorambucil, melphalan, busulfan, and procarbazine). Total-body irradiation as used in myeloablative stem-cell transplantation is highly associated with infertility, while lesser doses or limited radiation fields have less gonadal toxicity.<sup>13,14</sup> Several agents are associated with a low or no risk of infertility: methotrexate, fluorouracil, vincristine, bleomycin, and dactinomycin. There are little human data available for the newer agents such as taxanes. Given the paucity of data regarding rates of male and female infertility following most current cancer treatments and the large number of patient factors that influence fertility, oncologists may have difficulty providing precise guidance to patients about their risks for infertility.

**Questions** The committee addressed the following clinical questions:

1. Are cancer patients interested in interventions to preserve fertility?
2. What is the quality of evidence supporting current and forthcoming options for preservation of fertility in males?
3. What is the quality of evidence supporting current and forthcoming options for preservation of fertility in females?
4. What is the role of the oncologist in advising patients about fertility preservation options?

**Practice Guidelines** Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, utilization of clinical guidelines may provide the following:

1. Improvement in outcomes
2. Improvement in medical practice
3. Means for minimizing inappropriate practice variation
4. Decision support tools for practitioners
5. Points of reference for medical orientation and education
6. Criteria for self-evaluation
7. Indicators and criteria for external quality review
8. Assistance with reimbursement and coverage decisions
9. Criteria for use in credentialing decisions
10. Identification of areas where further research is needed

In formulating recommendations for fertility preservation options, ASCO considered these tenets of guideline development, emphasizing review of data from appropriately conducted and analyzed clinical trials. However, it is important to note that guidelines cannot always account for individual variation among patients. Guidelines are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result. (Accordingly, ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe the use of procedures and therapies in clinical practice; they cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment is needed. In that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions and settings for further research.)

## METHODS

### Panel Composition

The ASCO Health Services Committee (HSC) convened an Expert Panel consisting of experts in clinical medicine and research relevant to fertility preservation in cancer patients, including adult and pediatric oncology, obstetrics-gynecology, andrology, reproductive endocrinology and infertility, health services research,

psychosocial oncology, and bioethics. A patient representative was also part of the Panel. Panel members are listed in the Appendix.

### **Literature Review and Analysis**

The following electronic databases were searched from 1987 through March 2005: MEDLINE, PreMEDLINE, and the Cochrane Collaboration Library. The National Cancer Institute's (NCI) PDQ database of clinical trials, and the National Library of Medicine's (NLM) *ClinicalTrials.gov* database were also searched for ongoing trials. Results were supplemented with hand searching of selected reviews and personal files. The following MeSH terms and text words were used in a core search: "fertility," "infertility," and "neoplasms." In separate searches, results were cross-referenced with "pregnancy," "pregnancy outcomes," "reproductive techniques," "premature ovarian failure," and "premature menopause." Supplemental searches were done for each intervention using terms specific for that intervention (eg, "sperm banks," "semen preservation"). Due to the very limited number of randomized controlled trials in this field of research, study design was not limited to randomized controlled trials, but was expanded to include cohort designs, case series, and where no other data were available, case reports and selected abstracts. Letters, commentaries, and editorials were excluded.

Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria: (1) the study discussed a fertility intervention and reported primary data; and (2) the study population consisted of cancer patients scheduled for or undergoing cancer treatments that threaten fertility (other populations could be considered where data were lacking in cancer patients). Articles were excluded from further consideration if they did not report specifically on a fertility intervention and did not report primary data. However, due to the limited nature of the data in many areas, the Panel made an a priori decision to also retain high-quality reviews or background papers, and these articles were described as such in the coding process.

An initial article abstract screen was performed by ASCO staff. The ASCO Panel reviewed all remaining potentially relevant abstracts identified in the original literature searches to select studies pertinent to its deliberations. Two Panel members independently reviewed each abstract for its relevance to the clinical questions, and disagreements were resolved by third-party review. Full text articles were then reviewed for all selected abstracts. The Panel designed a coding sheet to complete the review of identified potentially relevant studies, and the Co-Chairs assigned each Panel member a subset of articles to review. Data were extracted on the source of the threat to fertility, the intervention being considered, the outcomes assessed, the number of patients and types of cancer, and study design. Primary outcomes of interest included pregnancies and live births, but the following were also considered: fertility maintenance; resumption/maintenance of menses; number of oocytes recovered; number of embryos recovered; fertilization rates; and in vitro fertilization (IVF) outcome. Also considered were the risks associated with the fertility intervention, quality of life, patient and/or family satisfaction, patient education or increased awareness, and economic evaluation (eg, cost-effectiveness, cost utility).

### **Consensus Development Based on Evidence**

The entire Panel participated in monthly teleconferences. Preliminary teleconferences refined the questions addressed by the guideline; subsequent teleconferences addressed the process of the systematic review and the allocation of writing assignments for

respective sections. All members of the Panel participated in the preparation of the guideline. Feedback from external reviewers was also solicited. The content of the guideline and the manuscript were reviewed and approved by the Health Services Committee (HSC) and by the ASCO Board of Directors before dissemination.

### **Guideline and Conflict of Interest**

All members of the Expert Panel complied with ASCO policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel completed ASCO's disclosure form and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

### **Revision Dates**

At annual intervals, the Panel Co-Chairs and two Panel members designated by the Co-Chairs will determine the need for revisions to the guideline based on an examination of current literature. If necessary, the entire Panel will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revision of the guideline to the HSC and the ASCO Board for review and approval.

## RESULTS

### **Literature Search**

Preliminary searches identified 1,675 potential articles. The initial abstract screen performed by ASCO staff eliminated 807 abstracts that failed to meet any of the inclusion criteria. The ASCO Panel conducted dual independent review of all remaining 868 potentially relevant abstracts identified in the original systematic review. The Panel eliminated 463 abstracts at this stage of the review; the remaining 405 articles were reviewed in full for the interventions and outcomes described above. One hundred twenty-nine articles that did not report primary data on a fertility preserving intervention were excluded from further consideration. Two hundred thirty-three articles met the inclusion criteria, and an additional 43 articles met the a priori criteria as supplementary studies or reviews.

A meta-analysis was not performed because the studies were judged to be too small and heterogeneous for meaningful quantitative synthesis.

Cohort studies or case series were identified in embryo and oocyte cryopreservation, ovarian tissue preservation, conservative surgical treatment of tumors, ovarian transposition (during radiotherapy), trachelectomy, sperm banking, rectal electroejaculation, hormonal manipulation, intracytoplasmic sperm injection, and testicular sperm extraction. Case reports were available for the other methods of fertility preservation.

Of the outcomes assessed, 111 studies reported on pregnancies, live births, or IVF outcome. Of these 111 studies, the majority were case series or case reports.

**Limitations of the Literature**

Review of the fertility preservation literature reveals a paucity of large and/or randomized studies. Most data come from cohort studies, case series, small nonrandomized clinical trials or case reports. Fertility preservation methods are still applied relatively infrequently in the cancer population, limiting greater knowledge about success and effects of different potential interventions. Other than risk of tumor recurrence, less attention is paid to the potential negative effects (physical and psychological) of fertility preservation attempts.

Little is known about the emotional impact of infertility or utilization of fertility preservation options on cohorts that are diverse in ethnicity and socioeconomic status, groups that face even greater barriers to fertility preservation.<sup>15,16</sup>

The Panel encourages additional well-designed studies evaluating methods of fertility preservation in people with cancer to help answer these questions. However, the Panel also notes that the traditional gold standard of randomized, controlled, and blinded therapeutic studies may not be possible in this area.

**I. Are Cancer Patients Interested in Fertility Preservation Interventions?**

The available evidence suggests that fertility preservation is of great importance to many people diagnosed with cancer, and that infertility resulting from cancer treatment may be associated with psychosocial distress. Although cancer survivors can become parents through options such as adoption and third-party reproduction (using gamete donation or a gestational carrier),<sup>17</sup> most prefer to have a biological offspring,<sup>18-20</sup> even if they have concerns about birth defects that could be caused if the parent had cancer treatment before conception<sup>21</sup> or anxiety about their own longevity or their child's lifetime cancer risk. One study in men suggested that having banked sperm was a positive factor in coping emotionally with cancer, even if samples were never used.<sup>22</sup> Cancer survivors who are free of disease typically view themselves as healthy enough to be good parents, and in fact view their experience of illness as one that can enrich their parental role. Most put a higher value on family closeness after cancer and believe they are less bothered by daily stresses.<sup>19,20,23</sup> It may be impossible for physicians to know how important fertility preservation is to their patients unless they ask, since many patients may not bring up the topic. A recent report by the President's Cancer Panel recommends that all cancer

patients of reproductive age be informed about the possibility of treatment-related infertility.<sup>24</sup> Figure 1 and Table 3 provide guidance to oncologists in initial discussions.

Surveys of cancer survivors have identified an increased risk of emotional distress in those who become infertile because of their treatment.<sup>19,20,25-28</sup> These studies mirror what has been observed in infertile noncancer populations where research clearly shows that long-term quality of life is affected by unresolved grief and depression,<sup>16</sup> as well as reduced life satisfaction and increased anxiety.<sup>29-31</sup> Some evidence suggests that patients may choose a less efficacious treatment strategy in order to avoid greater toxicity and long-term complications. For example, if given a choice, young women with early-stage breast cancer may choose a less toxic regimen of chemotherapy even if it confers slightly less protection from recurrence.<sup>27</sup>

Parents may also be interested in fertility preservation on behalf of their children with cancer. Impaired future fertility is difficult for children to understand, but potentially traumatic to them as adults. Use of established methods of fertility preservation (semen cryopreservation and embryo freezing) in postpubertal minor children requires patient assent and parental consent. Unfortunately, the modalities that are available to prepubertal children to preserve their fertility are limited by patients' sexual immaturity and are essentially experimental. Efforts to preserve fertility of children using experimental methods should only be attempted under institutional review board (IRB)-approved protocols, where proper attainment of informed consent from a legally authorized representative(s) (ie, parent[s] or guardian[s]) and of childhood assent can be ensured.<sup>32-34</sup> It has been suggested that to overcome some of the practical obstacles involved in studying experimental fertility preservation in children, the consent process should be performed in two stages.<sup>35-36</sup> The decision to harvest gametes would be made at the time of cancer treatment, and consent for the procedure would rely on parents/guardians. The decision of how to use the gametes after they have been isolated could be made at a future point by the patient. Then, the adult patient would be better able to express personal preferences about the handling of the tissue.

**II. What Is the Quality of Evidence Supporting Current and Forthcoming Options for Preservation of Fertility in Males?**

The Panel reviewed the available information supporting sperm cryopreservation, testicular hormonal suppression, and

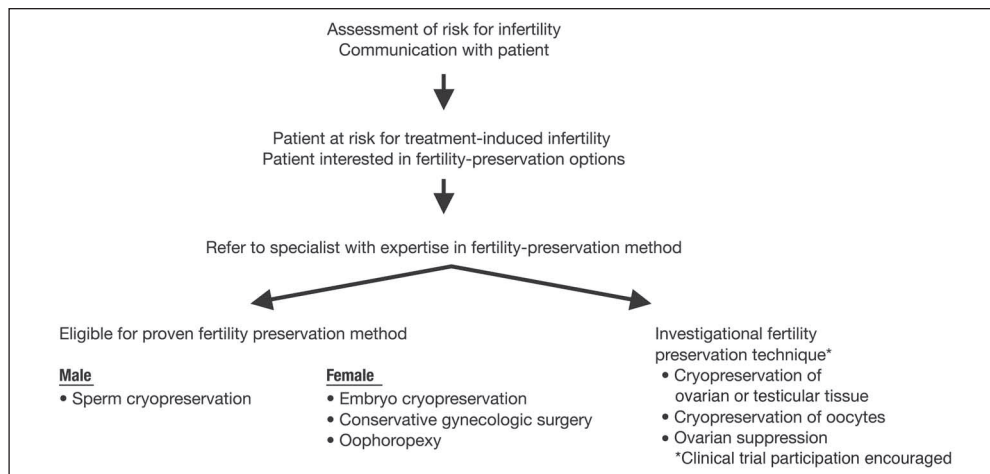


Fig 1. Flow diagram.

**Table 3.** Points of Discussion Between the Patient and Physician: Fertility Preservation Methods in Cancer Patients

- Cancer and cancer treatments vary in their likelihood of causing infertility. Individual factors such as disease, age, treatment type and dosages, and pre-treatment fertility should be considered in counseling patients about the likelihood of infertility.
- Patients who are interested in fertility preservation should consider their options as soon as possible to maximize the likelihood of success. Some female treatments are dependent upon phase of the menstrual cycle and can only be initiated at monthly intervals. Discussion with reproductive specialists and review of available information from patient advocacy resources (for example, FertileHope, the Lance Armstrong Foundation/Livestrong, the Susan G. Komen Breast Cancer Foundation) can facilitate decision-making and treatment planning.
- The two methods of fertility preservation with the highest likelihood of success are sperm cryopreservation for males and embryo freezing for females. Conservative surgical approaches and transposition of ovaries or gonadal shielding prior to radiation therapy may also preserve fertility in selected cancers. At this time (2006), other approaches should be considered investigational.
- Data are very limited, but there appears to be no detectable increased risk of disease recurrence associated with most fertility preservation methods and pregnancy, even in hormonally sensitive tumors.
- Aside from hereditary genetic syndromes and in utero exposure to chemotherapy, there is no evidence that a history of cancer, cancer therapy, or fertility interventions increase the risk of cancer or congenital abnormalities in the progeny.
- Treatment-related infertility may be associated with psychosocial distress, and early referral for counseling may be beneficial in moderately distressed people.

testicular tissue cryopreservation. The available evidence suggests that sperm cryopreservation is an effective method of fertility preservation in males treated for cancer. In contrast, gonadoprotection through hormonal manipulation is ineffective. Testicular tissue or spermatogonial cryopreservation and transplantation or testis xenografting are in the early phases of experimentation and have not yet been successfully tested in humans. Table 4 summarizes the fertility preservation options in males. The Panel notes that available interventions are unlikely to delay initiation of cancer treatment once a patient is successfully referred.

**Sperm cryopreservation.** Due to recent advances in IVF technology and sperm banking procedures, even men with extremely reduced sperm count and motility are candidates for sperm cryopreservation. It is strongly recommended that sperm be collected before initiation of cancer therapy because the quality of the sample and sperm DNA integrity may be compromised even after a single treatment ses-

sion.<sup>37,38</sup> In addition, depending on the type of cancer—particularly testicular cancer and Hodgkin's lymphoma<sup>39</sup>—and the overall condition of the patient, sperm quality may be poor even in patients who have not yet started treatment.<sup>37,38,40,41</sup> Many patients have to start chemotherapy immediately or soon enough to limit the number of ejaculates to one or two samples. Even in these instances, it is reasonable to make every effort to bank sperm<sup>38</sup> since recent progress in andrology laboratories and in the use of assisted reproductive techniques, particularly the technique of intracytoplasmic sperm injection (ICSI) allows the successful freezing and future use of a very limited amount of sperm. There are case reports and small case series of successful collection of sperm from a postmasturbation urine sample, rectal electroejaculation under anesthesia,<sup>42,43</sup> and testicular sperm aspiration,<sup>44</sup> but these are uncommon and/or investigational methods. Oncologists should make every effort to discuss sperm banking with appropriate patients,<sup>38,45-47</sup> though a recent survey<sup>48</sup> suggests

**Table 4.** Summary of Fertility Preservation Options in Males

Intervention	Definition	Comment	Considerations
Sperm cryopreservation (S) after masturbation	Freezing sperm obtained through masturbation	The most established technique for fertility preservation in men; large cohort studies in men with cancer	<ul style="list-style-type: none"> <li>• Outpatient procedure</li> <li>• Approximately \$1,500 for three samples stored for 3 years, storage fee for additional years*</li> </ul>
Sperm cryopreservation (S) after alternative methods of sperm collection	Freezing sperm obtained through testicular aspiration or extraction, electroejaculation under sedation, or from a post-masturbation urine sample	Small case series and case reports	Testicular sperm extraction-outpatient surgical procedure
Gonadal shielding during radiation therapy (S)	Use of shielding to reduce the dose of radiation delivered to the testicles	Case series	<ul style="list-style-type: none"> <li>• Only possible with selected radiation fields and anatomy</li> <li>• Expertise is required to ensure shielding does not increase dose delivered to the reproductive organs</li> </ul>
Testicular tissue cryopreservation Testis xenografting Spermatogonial isolation (I)	Freezing testicular tissue or germ cells and reimplantation after cancer treatment or maturation in animals	Has not been tested in humans; successful application in animal models	Outpatient surgical procedure
Testicular suppression with gonadotropin releasing hormone (GnRH) analogs or antagonists (I)	Use of hormonal therapies to protect testicular tissue during chemotherapy or radiation therapy	Studies do not support the effectiveness of this approach	

Abbreviations: S, standard; I, investigational.

\*Costs are estimates.

that oncologists lack knowledge about recent advances in assisted reproductive techniques.

Sperm cryopreservation in boys and young men involves additional considerations. Spermatogenesis, the production of sperm, occurs at approximately 13 to 14 years, but once sperm are present, the patient's age does not seem to affect quality of sperm produced.<sup>49</sup> However, prepubertal boys have not yet developed gametes, and collection of semen through masturbation in adolescents may be compromised by embarrassment and issues of informed consent. For example, one study suggested adolescent boys may be more successful if a parent does not accompany them to the sperm bank.<sup>50</sup>

**Hormonal gonadoprotection.** The efficacy of gonadoprotection through hormonal manipulations has only been evaluated in very small studies in cancer patients. Hormonal therapy in men is not successful in preserving fertility when highly sterilizing chemotherapy is given,<sup>51,52</sup> nor did it speed recovery of spermatogenesis in 18 men after nonsterilizing treatment compared to concurrent controls.<sup>53,54</sup> Based on observations in rats, a small prospective study evaluated the effects of hypothalamic-pituitary-gonadal suppression plus testosterone in seven men rendered azoospermic after chemotherapy or radiation treatment for childhood cancer. No recovery of spermatogenesis was seen after 12 weeks of suppression.<sup>55</sup> In contrast, a very small study evaluating testosterone in men without cancer treated with cyclophosphamide for glomerulonephritis suggested some benefit.<sup>56</sup>

**Other methods to preserve male fertility.** Other methods, such as testicular tissue cryopreservation and reimplantation<sup>57</sup> or grafting of human testicular tissue to SCID mice to facilitate spermatogenesis,<sup>58,59</sup> remain experimental and have not been tested in humans. Of note, such approaches are also the only methods of fertility preservation potentially available to prepubertal boys.

**Other considerations of fertility preservation options in males.** Epidemiological studies confirm that most young male patients with cancer are not referred for sperm banking.<sup>12,37,38</sup> Reasons for this apparent underutilization are likely multifactorial. Physicians may not discuss or emphasize opportunities to preserve fertility before treatment.<sup>60</sup> Psychological, logistic and financial constraints on patients may further limit sperm banking. Men may be traumatized about their diagnosis or lack interest in fertility preservation at the time of diagnosis. However, two recent surveys suggest that for men who desire future children, lack of timely information is the most common reason for not banking sperm.<sup>19,20</sup> Responsibility for organizing an appointment with the cryopreservation laboratory often falls to the patient. Most insurance companies in the United States do not cover sperm cryopreservation. However, even in the United Kingdom, where the national health system subsidizes sperm banking for young cancer patients, many young men are not given referrals.<sup>61</sup>

Even when sperm is banked, most studies suggest that a minority (up to 30%, but < 10% in most cohorts) of men return to use their stored specimens.<sup>41,62-64</sup> Storage fees are rarely a reason that men have cryopreserved semen destroyed.<sup>65</sup>

In the absence of a heritable cancer syndrome, there is no evidence that a prior history of cancer increases the rate of congenital abnormalities or cancer in a man's offspring.<sup>66</sup> However, recent studies suggest the sperm of untreated men with cancer may have poor DNA integrity even before treatment.<sup>67,68</sup> Small studies suggest transient higher rates of aneuploidy after chemotherapy and radiotherapy,<sup>69-71</sup> though DNA integrity of sperm seemed similar to age-matched controls in one cohort of pediatric cancer survivors.<sup>72</sup>

Men should be advised of a possible, not yet quantifiable, higher risk of genetic damage in sperm stored after diagnosis of cancer or initiation of cancer therapy. In noncancer populations, there is no evidence of an increased risk of adverse outcomes if cryopreserved rather than fresh sperm are used for assisted reproductive techniques. Intracytoplasmic sperm injection (ICSI) allows successful fertilization with a single sperm but has raised concerns about the health of offspring conceived by this method. Although no studies have shown an increased rate of adverse outcomes compared with traditional in vitro fertilization techniques (both may be associated with a higher rate of major birth defects than unassisted conception),<sup>73</sup> the technique is relatively new, and long-term follow-up of progeny is recommended.<sup>74,75</sup>

### **III. What Is the Quality of Evidence Supporting Current and Forthcoming Options for Preservation of Fertility in Females?**

Fertility preservation options in females depend on the patient's age, type of treatment, diagnosis, whether she has a partner, the time available and the potential that cancer has metastasized to her ovaries.<sup>76</sup> The panel reviewed the available information supporting embryo and oocyte cryopreservation (with or without hormonal stimulation), ovarian tissue cryopreservation, ovarian suppression, ovarian transposition, and trachelectomy. Conservative surgical and radiation therapy approaches to specific cancers are also available but are not discussed further. Table 5 summarizes the options for fertility preservation in females. The Panel notes that due to requirements for scheduling and procedures, some interventions may entail a delay in cancer treatment and wishes to emphasize that early referral to a subspecialist can minimize this delay.

**Embryo cryopreservation.** Embryo cryopreservation is considered an established fertility preservation method as it has routinely been used for storing surplus embryos after in vitro fertilization for infertility treatment. This approach typically requires approximately two weeks of ovarian stimulation with daily injections of follicle-stimulating hormone from the onset of menses. Follicle development is monitored by serial ultrasounds and blood tests. At the appropriate time, an injection of HCG is administered to start the ovulatory cascade, and oocytes are subsequently collected by ultrasound guided transvaginal needle aspiration under intravenous sedation. Oocytes are fertilized in vitro and cryopreserved after fertilization. Because stimulation must be started at the onset of menses and takes two weeks, a delay of 2 to 6 weeks in chemotherapy initiation may be required if reproductive specialists do not see women early in their menstrual cycle. Most insurance companies do not offer assisted reproductive techniques as benefits so this approach may be associated with high out-of-pocket costs for most women. A partner or sperm donor is also required.

Live birth rates after embryo cryopreservation depend on the patient's age and the total number of embryos cryopreserved and may be lower than with fresh embryos. Oocyte collection can be performed without ovarian stimulation ("natural cycle-IVF") but the embryo yield is extremely low.<sup>77,78</sup> For women with hormone-sensitive tumors,<sup>79</sup> alternative hormonal stimulation approaches such as letrozole or tamoxifen have been developed to theoretically reduce the potential risk of estrogen exposure. Short term breast cancer recurrence rates after ovarian stimulation using letrozole or tamoxifen concurrent with follicle stimulating hormone (FSH) administration have been compared to nonrandomized controls and no increase in

Table 5. Fertility Preservation Options in Females

Intervention	Definition	Comment	Considerations*
Embryo cryopreservation (S)	Harvesting eggs, in vitro fertilization, and freezing of embryos for later implantation	The most established technique for fertility preservation in women	<ul style="list-style-type: none"> <li>● Requires 10-14 days of ovarian stimulation from the beginning of menstrual cycle</li> <li>● Outpatient surgical procedure</li> <li>● Requires partner or donor sperm</li> <li>● Approximately \$8,000 per cycle, \$350 per year storage fees</li> </ul>
Oocyte cryopreservation (I)	Harvesting and freezing of unfertilized eggs	Small case series and case reports; as of 2005, 120 deliveries reported, approximately 2% live births per thawed oocyte (3-4 times lower than standard IVF)	<ul style="list-style-type: none"> <li>● Requires 10-14 days of ovarian stimulation from the beginning of menstrual cycle</li> <li>● Outpatient surgical procedure</li> <li>● Approximately \$8,000 per cycle, \$350/yr storage fees</li> </ul>
Ovarian cryopreservation and transplantation (I)	Freezing of ovarian tissue and reimplantation after cancer treatment	Case reports; as of 2005, two live births reported	<ul style="list-style-type: none"> <li>● Not suitable when risk of ovarian involvement is high</li> <li>● Same day outpatient surgical procedure</li> </ul>
Gonadal shielding during radiation therapy (S)	Use of shielding to reduce the dose of radiation delivered to the reproductive organs	Case series	<ul style="list-style-type: none"> <li>● Only possible with selected radiation fields and anatomy</li> <li>● Expertise is required to ensure shielding does not increase dose delivered to the reproductive organs</li> </ul>
Ovarian transposition (oophoropexy) (S)	Surgical repositioning of ovaries away from the radiation field	Large cohort studies and case series suggest approximately 50% chance of success due to altered ovarian blood flow and scattered radiation	<ul style="list-style-type: none"> <li>● Same day outpatient surgical procedure</li> <li>● Transposition should be performed just before radiation therapy to prevent return of ovaries to former position</li> <li>● May need repositioning or in vitro fertilization (IVF) to conceive</li> </ul>
Trachelectomy (S)	Surgical removal of the cervix while preserving the uterus	Large case series and case reports	<ul style="list-style-type: none"> <li>● Inpatient surgical procedure</li> <li>● Limited to early stage cervical cancer; no evidence of higher cancer relapse rate in appropriate candidates</li> <li>● Expertise may not be widely available</li> </ul>
Other conservative gynecologic surgery (S/I)	Minimization of normal tissue resection	Large case series and case reports	<ul style="list-style-type: none"> <li>● Expertise may not be widely available</li> </ul>
Ovarian suppression with gonadotropin releasing hormone (GnRH) analogs or antagonists (I)	Use of hormonal therapies to protect ovarian tissue during chemotherapy or radiation therapy	Small randomized studies and case series. Larger randomized trials in progress	<ul style="list-style-type: none"> <li>● Medication given before and during treatment with chemotherapy</li> <li>● Approximately \$500/mo</li> </ul>

Abbreviations: S, standard; I, investigational.  
\*Costs are estimates

cancer recurrence rates has been noted in these initial studies.<sup>77,78</sup> Only a small percentage of cancer survivors have yet returned to utilize their embryos but the initial pregnancy rates are encouraging.<sup>77,79</sup> Nevertheless, long-term follow-up with a larger number of patients is needed to evaluate the safety and efficacy of this approach. The panel also notes that letrozole and tamoxifen should not be given to a woman after pregnancy is established.<sup>80,81</sup> Recently, standard ovarian stimulation with coapplication of a progestin-releasing IUD has been reported to allow successful preservation of embryos in a patient with endometrial cancer.<sup>82</sup>

**Oocyte cryopreservation.** Cryopreservation of unfertilized oocytes is another option for fertility preservation, particularly in patients for whom a partner is unavailable, or who have religious or

ethical objections to embryo freezing. The oocytes are thawed later and fertilized in vitro. Ovarian stimulation and harvesting requirements are identical to those of embryo cryopreservation, and thus this technique is associated with similar concerns regarding delays in therapy and potential risks of short-term exposure to high hormonal levels. As with embryo cryopreservation, letrozole or tamoxifen can be used. Research indicates that unfertilized oocytes are more prone to damage during cryopreservation procedures than embryos, and as a result, the overall pregnancy rates may be lower than standard IVF procedures.<sup>83</sup> There have been approximately 120 deliveries with this approach,<sup>83</sup> and efforts to improve the efficiency of cryopreservation may increase success rates.<sup>84,85</sup> Further research is needed to delineate the current success rates and safety, as well as to improve the efficiency

of this procedure. Oocyte cryopreservation should only be performed in centers with the necessary expertise, and the Panel recommends participation in IRB-approved protocols.

**Ovarian tissue cryopreservation.** Ovarian tissue cryopreservation is an investigational method of fertility preservation but has the advantage of requiring neither a sperm donor nor ovarian stimulation. Ovarian tissue is removed laparoscopically, a one hour outpatient procedure that requires general anesthesia, and frozen. At a later date, the ovarian tissue is thawed and reimplanted. Primordial follicles can be cryopreserved with great efficiency<sup>86,87</sup> but because of the initial ischemia encountered after ovarian transplantation, a quarter or more of these follicles might be lost, as shown in xenografting studies.<sup>88</sup> To offset this relatively large loss, typically the cortex from an entire ovary is cryopreserved in adults. The benefit of ovarian cryopreservation for women older than 40 years of age is very uncertain because there are too few primordial follicles remaining.<sup>89</sup> Ovarian tissue cryopreservation has been performed in humans for less than a decade, and the first ovarian transplant procedure was reported in 2000.<sup>90</sup> Ovarian tissue can be transplanted orthotopically to pelvis<sup>90-94</sup> or heterotopically to subcutaneous areas such as the forearm or lower abdomen,<sup>95,96</sup> and initial studies reported restoration of ovarian endocrine function after both types of transplantation.<sup>90,93,94,96,97</sup> There have been two reports of live births from orthotopic ovarian transplantation in cancer patients; one conceived spontaneously<sup>91</sup> and the other as a result of in vitro fertilization.<sup>92</sup> In addition, a live birth occurred when fresh ovarian tissue was transplanted between identical twins because of unexplained premature ovarian failure in the recipient, not related to cancer.<sup>98</sup>

One concern with reimplanting ovarian tissue is the potential for reintroduction of cancer cells. In patients without evidence of systemic metastasis to other organs, the likelihood of occult ovarian metastasis appears to be low in the majority of cancers seen in young females,<sup>99,100</sup> and there are no reports of cancer recurrence after ovarian transplantation although fewer than 20 procedures are reported thus far. Thus, ovarian tissue screening to detect malignant cells should be performed to minimize the risk of inadvertent transfer with the ovary. In patients with high risk of ovarian involvement, xenografting and ex vivo follicle growth are experimental but not yet practical possibilities.<sup>101</sup>

Ovarian cryopreservation and transplantation procedures should only be performed in centers with the necessary expertise under IRB-approved protocols that include follow-up for recurrent cancer.

**Ovarian suppression.** Ovarian suppression through gonadotropin-releasing hormone (GnRH) agonist or antagonist treatment during chemotherapy is highly controversial as a method to maintain fertility. A small study evaluating 54 patients compared with retrospective controls suggested a benefit in preserving menstrual function from ovarian suppression with GnRH analogs in women undergoing chemotherapy for Hodgkin's and non-Hodgkin's lymphoma,<sup>102</sup> but a small prospective study of 18 women receiving chemotherapy for Hodgkin's lymphoma did not show a benefit of this approach.<sup>52</sup> Retrospective studies have been criticized for longer follow-up time and higher incidence/dose of usage of alkylating agents in controls.<sup>100</sup> Two small case series of 64 and 24 cancer patients without controls report resumption of menses and/or pregnancies after ovarian suppression.<sup>103,104</sup> Small observational studies also suggest that oral contraceptives may help preserve ovarian function when given during chemotherapy.<sup>105,106</sup> Large randomized clinical studies of ovarian sup-

pression should be performed with fertility preservation, not just menstruation, as the outcome measure. The Southwest Oncology Group is currently conducting a trial aimed at preventing early ovarian failure with GnRH agonists among women with hormone-receptor negative breast cancer who receive chemotherapy. The German Hodgkin's Lymphoma Study Group is conducting a randomized phase II trial evaluating GnRH agonists and oral contraceptives to preserve fertility in women treated for advanced Hodgkin's lymphoma.<sup>105</sup>

Anecdotally, because GnRH analogs are readily available, this strategy has been used widely without clear evidence for efficacy or full understanding of the potential risks and benefits, especially in women with hormone sensitive tumors. At this time, since there is insufficient evidence regarding the safety and effectiveness of GnRH analogs and other means of ovarian suppression on female fertility preservation, women interested in ovarian suppression for this purpose are encouraged to participate in clinical trials.

**Ovarian transposition.** Ovarian transposition (oophorectomy—surgically moving ovaries as far as possible from the radiation field) can be offered when pelvic radiation is used for cancer treatment. The procedure can be done laparoscopically if laparotomy is not needed for the primary treatment of the tumor.<sup>107-109</sup> Because of the risk of remigration of the ovaries, this procedure should be performed as close to the radiation treatment as possible.<sup>110</sup> The overall success rate as judged by preservation of short-term menstrual function is approximately 50%. Scatter radiation and alteration of ovarian blood supply appear to be the main reasons behind the failures.<sup>107,111,112</sup> Total radiation dose and the dose received by the "less-irradiated" ovary also affect the outcome.<sup>113</sup> Ovarian repositioning may not always be needed to restore fertility, as spontaneous pregnancies have been reported in women with transposed ovaries.<sup>114</sup> If infertility develops and in vitro fertilization is needed after ovarian transposition however, the performance of oocyte retrieval becomes more complicated.<sup>112</sup> In this case, either a second procedure is needed to reposition the ovaries to pelvis,<sup>114</sup> or egg collection will have to be performed percutaneously with the risk of reducing the efficiency of this procedure.<sup>112</sup> Other risks include ovarian dysfunction leading to ovarian cysts and the theoretical risk of increased difficulty diagnosing ovarian cancer if the ovaries are no longer palpable on bimanual examination.

**Conservative gynecologic surgery.** It has been estimated that nearly 50% of women diagnosed with cervical carcinoma under the age of 40 are eligible for radical trachelectomy, a procedure in which the cervix is resected but the uterus is spared.<sup>115</sup> The procedure is typically performed vaginally with laparoscopic assistance, but an abdominal variant has also been described.<sup>116</sup> It has been suggested that the procedure be restricted to stage 1A2-IB disease with less than 2 cm in diameter and less than 10 mm invasion.<sup>117,118</sup> The recurrence rates following radical trachelectomy appear to be similar to that of radical hysterectomy but no randomized study exists.<sup>119</sup> To date, at least 236 women underwent the procedure with 63 live births resulting.<sup>120</sup> There is an increased risk in midtrimester losses and preterm birth.<sup>121,122</sup> There is also a higher incidence of infertility due to cervical abnormalities, which would require the use of assisted reproduction technologies.<sup>117,123</sup>

In the treatment of other gynecologic malignancies, interventions to spare fertility have generally centered on doing less radical surgery and/or lower dose chemotherapy with the intent of sparing the

reproductive organs as much as possible for subsequent fertility. Reports are generally limited in size and lack randomized controls. However, they reveal no obvious increased risk of disease recurrence in women treated with fertility sparing approaches. For example, in the two largest published series of 212 women with malignant ovarian germ cell tumors, fertility-sparing surgery with or without chemotherapy did not appear to substantially affect the risk of recurrence compared with historical controls.<sup>124,125</sup>

*Other considerations of fertility preservation options in females.* The possibility that fertility preservation interventions and/or subsequent pregnancy may increase the risk of cancer recurrence has been most concerning in breast cancer and the gynecologic malignancies. To date, the effect of subsequent pregnancy after breast cancer on prognosis has not been studied prospectively.<sup>126</sup> Several case-control and retrospective cohort studies have not shown a decrement in survival or an increase in risk of recurrence with pregnancy.<sup>127-133</sup> While these data are reassuring, the studies are all limited by significant biases, and concerns remain for some women and their physicians.<sup>20,134</sup> Since breast, endometrial, and ovarian cancer cells have been shown to express GnRH receptors, a GnRH agonist could affect cancer cell proliferation or apoptosis.<sup>135</sup> However, GnRH agonists have also been used as treatments for hormone receptor-positive premenopausal breast tumors, and combined trials of GnRH agonists and chemotherapy are underway.<sup>136</sup> In women with hormone receptor-positive breast cancer who undergo successful fertility preservation treatments, continued menstrual cycling after chemotherapy could theoretically increase relapse rates by interfering with one proposed mechanism of action (ovarian suppression) of adjuvant therapy.<sup>137</sup>

There is concern that instrumentation of the pelvis to perform fertility preservation maneuvers can result in local spread of disease. In one case report, a woman with cervical adenocarcinoma developed an abdominal wall metastasis at the site of trocar insertion for laparoscopy done for ovarian transposition for fertility preservation.<sup>138</sup> It is unclear how often this occurs however.

#### **IV. What Is the Role of the Oncologist in Advising Patients About Fertility Preservation Options?**

*Discuss infertility as a potential risk of therapy.* As with the other potential complications of cancer treatment, oncologists have a responsibility to inform patients about the risks that their cancer treatment will permanently impair fertility. Yet, recent surveys of male and female cancer survivors of reproductive age concur that at least half have no memory of a discussion of fertility at the time of their treatment disposition.<sup>19,20,23,139</sup> The few studies of oncologists' practices of discussing infertility confirm patients' reports. In clinical practice many oncologists do not mention even proven techniques such as sperm banking.<sup>48,140,141</sup> Even when patients do recall infertility discussions, many are dissatisfied with the quality and amount of information provided.<sup>27,141,142</sup> Almost all these studies rely on retrospective self-reports from either oncologists or cancer survivors, and the role of recall bias cannot be ascertained. Patients who participate in survey research are usually self-selected, affluent, well-educated, Caucasians.<sup>19,20</sup> Furthermore, the participation rates by physicians have been very low, often under 33%, so that it is unclear whether the results are generalizable.<sup>48,141</sup>

Studies document many reasons why oncologists do not discuss infertility with the frequency that they discuss other treatment related complications such as neutropenia and cardiopulmonary toxicity.

Physicians may be prioritizing discussions about immediate or potentially life-threatening complications instead of discussing infertility. Data regarding the risks of infertility with various chemotherapy regimens are poor or nonexistent. Some physicians do not recognize the importance of fertility to cancer survivors<sup>143</sup> or believe that the cost of fertility preservation interventions is prohibitive. For example, 51% of oncologists in a United States study believed that most men could not afford to bank sperm because of out-of-pocket costs.<sup>141</sup> However, oncologists overestimated these costs<sup>48</sup> and their deterrent effect; in a companion survey of young men, only 7% cited financial reasons for not banking sperm.<sup>19</sup> Oncologists are also less likely to refer patients for sperm banking if the cancer prognosis is poor<sup>141,144</sup> or they believe that patients would not be interested for other reasons. Physicians' emotional discomfort with discussing fertility issues may also play a role<sup>141</sup> along with lack of knowledge and time. While the Panel recommends discussion about risks of treatment-induced infertility at the earliest possible opportunity, the Panel recognizes that raising this issue at the first encounter or at the time of diagnosis may not always be practical or wise. Clinician judgment should be employed in the timing of raising this issue, with the goal of discussion and referral at the earliest possible opportunity.

While professional organizations such as the American Society for Reproductive Medicine and patient advocacy organizations such as Fertile Hope,<sup>145</sup> Lance Armstrong Foundation/Livestrong, and the Susan G. Komen Breast Cancer Foundation do provide patient information, patients may not be aware of these resources and able to access information in a timely fashion when confronted with a new diagnosis of cancer. In addition, a physician's recommendation is a very strong predictor of whether a man banks sperm, almost as influential as the patient's desire for children in the future.<sup>19,146</sup> This finding is reminiscent of the important influence of physician recommendations in promoting smoking cessation and cancer screening<sup>147,148</sup> and suggests that physician encouragement affects patient interest in fertility preservation options. An algorithm for triaging fertility preservation referrals is presented in Figure 1, and suggested talking points are illustrated in Table 3. Ideally, after referral, the decision about who is an appropriate candidate to attempt specific fertility preservation techniques could be rendered by a team including a medical oncologist, reproductive endocrinologist, and a psychosocial provider, all guided by written protocols which can be shared with patients.<sup>149</sup> Patients, and parents of minors, should not be provided with unrealistic expectations about their cancer prognoses, the success rates of fertility preservation interventions or the cost of attempting to preserve fertility, and the option of declining fertility preservation interventions should also be discussed. Potential legal issues, such as ownership of embryos and reproductive tissue in the event of a patient's death, divorce or incapacity, should also be discussed by the reproductive specialist.

*Answer basic questions about whether fertility preservation options decrease the chance of successful cancer treatment, increase the risk of maternal or perinatal complications, or compromise the health of offspring.* Specific risks of fertility preservation options are discussed above in the sections on male and female considerations. Although studies are generally small and either not prospective or have short follow-up, there is no evidence that currently used fertility preservation options directly compromise the success of cancer therapy. There may of course be individual considerations, such as if chemotherapy is delayed to give time to pursue fertility preservation options or in the case of hormonally sensitive tumors.

There have been many published reports regarding parental outcome after interventions to spare fertility through cancer treatment and/or pregnancy following cancer. However, available studies are generally limited to case reports and small series. The few larger studies addressing these issues have generally been comprised of heterogeneous patient populations, retrospective in nature, with relatively short-term follow-up, and lacking randomized controls. Available data are reassuring, however, in that there is no clear increased risk to a survivor's health from available interventions to preserve fertility or from subsequent pregnancy, beyond that of normal populations with similar comorbidities.

In light of the long-term organ toxicity that may result from cancer and cancer therapy, pregnancy after cancer treatment may be complicated by an increased risk of organ impairment, especially of the heart, lungs, and uterus. For example, there is evidence that pregnancy may increase the risk of worsening cardiac ejection fraction in women treated with doxorubicin for childhood cancer,<sup>150</sup> and uterine or total-body irradiation appears to increase the risk of miscarriage, prematurity and low birth weight.<sup>151-154</sup> While several studies have revealed no evidence that use of cryopreserved sperm regardless of mode of extraction or fertilization technique has a detrimental effect on perinatal health of offspring or mother, the available data regarding the effects of female fertility sparing interventions on maternal or fetal perinatal health are limited. The major risk that has been recognized appears to be an increased risk of cervical incompetence, miscarriage, prematurity and low birth weight in women with lower gynecologic malignancies who have undergone conservative surgery such as trachelectomy for fertility preservation,<sup>122,155-157</sup> and the health risks associated with a higher rate of multiple births after assisted reproductive technology. Short and long-term follow-up following fertility sparing interventions for women with cancer is warranted. At the present time, in light of concerns, women with a history of cancer and cancer treatment should be considered high risk for perinatal complications and would be prudent to seek specialized perinatal care.

Aside from hereditary genetic syndromes, however, there is scant evidence that a history of cancer, cancer therapy, or fertility interventions increases the risk of problems in the progeny. Available studies including large registry studies have revealed no increased risk of genetic abnormalities, birth defects, or cancers, aside from hereditary syndromes, in the children of cancer survivors.<sup>72,152,158-161</sup> Data regarding the effects of interventions to spare parental fertility on the health of the progeny are limited to case reports and small series with relatively short follow-up. At present, there does not appear to be a clear detrimental effect from any of the available fertility sparing interventions. However, patients should be encouraged to participate in registries and clinical studies as available to define further the safety of fertility preservation interventions and strategies.

*As needed, refer patients to reproductive specialists and psychosocial providers.* Oncologists should refer interested and appropriate patients to reproductive specialists as soon as possible. Some methods of fertility preservation in females require timing with the menstrual cycle, so expeditious referrals are suggested to avoid missing opportunities. As long as the oncologist presents the options in enough detail

for the patient to decide whether to seek a consultation, the detailed counseling could be done by an infertility specialist. However, oncologists' input will still be invaluable to help guide patients as they think about how to prioritize fertility preservation in the context of their cancer treatment plan. When referring patients, oncologists should remember that many methods are still investigational. Ethical guidelines published by the American Society for Reproductive Medicine states that fertility preservation involving oocyte, ovarian and testicular harvesting for freezing should be performed only in specialized centers working with IRB-approved consents.<sup>162</sup> In addition, the experience of the infertility specialist in working with cancer patients should also be considered.

One option the oncologist should routinely offer is a referral for psychological counseling when a man or woman has moderate to severe distress about potential infertility. Research on infertility patients has shown that structured, cognitive-behavioral counseling can reduce anxiety and depression.<sup>163-165</sup> The American Society for Reproductive Medicine has both a Fertility Preservation Special Interest Group ([http://www.asrm.org/Professionals/PG-SIG-Affiliated\\_Soc/fpsig/fpsig\\_index.html](http://www.asrm.org/Professionals/PG-SIG-Affiliated_Soc/fpsig/fpsig_index.html)) and a Mental Health Professional Group ([http://www.asrm.org/Professionals/PG-SIG-Affiliated\\_Soc/MHPG/index.html](http://www.asrm.org/Professionals/PG-SIG-Affiliated_Soc/MHPG/index.html)).

### **Previous Consensus Statements**

Consensus statements have also been developed by some professional societies, including the British Fertility Society (<http://www.britishfertilitysociety.org.uk/practicepolicy/documents/fccpaper.pdf>),<sup>166</sup> the European Society of Human Reproduction and Embryology (ESHRE) Task Force (<http://www.eshre.com>), and the American Society for Reproductive Medicine.<sup>162,167</sup> The Panel has evaluated the Guidelines produced by reproductive specialist societies and found them to be consistent with the ASCO guidelines.

### **Interpretive Summary**

Fertility preservation is often possible in people undergoing treatment for cancer. Broader application of fertility preservation methods is limited by several factors: lack of knowledge about the risk of infertility with current cancer treatments, failure to discuss and consider options before treatment, lack of insurance coverage for most procedures with consequent high out of pocket costs, and the investigational status of many fertility preservation methods. The Panel recommends that oncologists discuss at the earliest opportunity the possibility of infertility as a risk of cancer treatment, recognizing that in many cases, adequate data are not available to provide accurate predictions for any one individual. For patients at risk for infertility who are interested in evaluating their options for fertility preservation, referral to appropriate specialists as early as possible is recommended. People attempting fertility preservation in the context of cancer treatment are encouraged to enroll in clinical trials that will advance the state of knowledge. Figure 1 and Table 3 provide additional guidance to oncologists in initial discussions. Supplementary materials available for public use such as a summary of guidelines, slide set, and patient information may be found on ASCO's Web site (<http://www.asco.org>).

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### Acknowledgment

The Expert Panel expresses its gratitude to Kevin Fox, MD, Edward Balaban, DO, David Biggs, MD, Dror Meirow, MD, Tommaso Falcone, MD, Clifford Hudis, MD, Halle Moore, MD, Melani Shaum, MD, Pamela Munster, MD, Charles Sklar, MD, Ted Trimble, MD, Steven Wolff MD, Elizabeth Ginsburg MD, Lisa Newman, MD, Todd Crocenzi, MD, Cheryl Perkins, MD, RPh, and the Health Services Committee membership for their thoughtful reviews of earlier drafts. The Panel also thanks Kaitlin Einhaus of ASCO for administrative help.

**ASCO Recommendations on Fertility Preservation**

<b>Appendix. Panel Composition</b>	
Investigator	Institution
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**Authors' Disclosures of Potential Conflicts of Interest**

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

<b>Authors</b>	<b>Employment</b>	<b>Leadership</b>	<b>Consultant</b>	<b>Stock</b>	<b>Honoraria</b>	<b>Research Funds</b>	<b>Testimony</b>	<b>Other</b>
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**Dollar Amount Codes** (A) < \$10,000 (B) \$10,000-99,999 (C) ≥ \$100,000 (N/R) Not Required

\*No significant financial relationships to disclose.

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**Conception and design:** Stephanie J. Lee, Kutluk Oktay  
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## ERRATA

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The June 20, 2006, ASCO special article by Lee et al entitled, "American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients" (J Clin Oncol 24:2917-2931, 2006) contained an error. In Table 1, the dosage for busulfan was given as 600 mg/kg, while it should have been 600 mg/m<sup>2</sup>. This was due to a misprint in the original textbook where the data were taken.

The online version has been corrected in departure from the print.

DOI: 10.1200/JCO.2006.11.904



The November 1, 2006, article by Harvey et al entitled, "Phase III Trial Comparing Three Doses of Docetaxel for Second-Line Treatment of Advanced Breast Cancer" (J Clin Oncol 24:4963-4970, 2006) contained an error.

In the Introduction section, the third sentence of the first paragraph was given as:

"Phase III trials showed higher response rates with second-line single-agent docetaxel compared with doxorubicin (47.8% v 33.3%, respectively;  $P = .008$ ),<sup>3</sup> mitomycin plus vinblastine (30.0% v 11.6%, respectively;  $P < .0001$ ),<sup>4</sup> or methotrexate plus fluorouracil (42% v 21%, respectively;  $P < .001$ )<sup>5</sup> but not compared with fluorouracil plus vinorelbine (38.9% v 43.0%, respectively;  $P = .69$ )<sup>6</sup> and paclitaxel (25.0% v 32.0%, respectively;  $P = .1$ ).<sup>7</sup>"

While it should have read:

"Phase III trials showed higher response rates with second-line single-agent docetaxel compared with doxorubicin (47.8% v 33.3%, respectively;  $P = .008$ ),<sup>3</sup> mitomycin plus vinblastine (30.0% v 11.6%, respectively;  $P < .0001$ ),<sup>4</sup> or methotrexate plus fluorouracil (42% v 21%, respectively;  $P < .001$ )<sup>5</sup> but not compared with fluorouracil plus vinorelbine (**43.0% v 38.9%**, respectively;  $P = .69$ )<sup>6</sup> and paclitaxel (**32.0% v 25.0%**, respectively;  $P = .1$ ).<sup>7</sup>"

The online version has been corrected in departure from the print.

DOI: 10.1200/JCO.2006.11.905

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