Oncofertility in adult and pediatric populations: options and barriers

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Abstract: Cancer and its treatments can affect fertility in a variety of ways, and recent advances in cancer detection and treatment have led to an increasing number of cancer survivors for whom future fertility is a primary concern. Oncofertility is the study of interactions between cancer, anti-cancer therapy, fertility, and reproductive health. Fertility preservation aims to optimize fertility potential before initiation of gonadotoxic therapies. Sperm cryopreservation from an ejaculated sample is the gold standard for adults and post-pubertal adolescents, though added maneuvers such as medical therapy, penile vibratory stimulation, and electroejaculation can be employed when appropriate. When all these approaches fail, testicular sperm extraction can be used to obtain and cryopreserve testicular sperm from the azoospermic patient. Fertility preservation in the pre-pubertal pediatric patient is still experimental, but recent scientific breakthroughs with use of spermatogonial stem cells and testicular tissue transplantation offer great promise for the future. While there may be several practical, cultural, religious, and other barriers to fertility preservation, the establishment of a dedicated fertility preservation team can help to overcome these obstacles and optimize the utilization of fertility preservation in cancer patients of all ages.

Keywords: Azoospermia; fertility preservation; oncofertility

Introduction

Fifty percent of men will receive a diagnosis of cancer during their lifetime, making cancer among the most common disease states. While the overall incidence of cancer in men is declining, significant advances in early detection and therapy have contributed to increasing numbers of cancer survivors who may have reduced fertility and sexual function (1). Moreover, the improved efficacy of novel cancer therapies is often accompanied by undesirable effects on fertility and sexual function (2). Combined with the increasing age of childbearing, these factors have led to an increase in the cohort of male cancer survivors for whom fertility preservation is an important consideration (3).

A growing body of evidence has shown that fertility potential and reproductive health are among the most important concerns for cancer survivors. According to Lehmann *et al.*, over two-thirds of childhood cancer survivors reported that they would feel distressed if their parenthood goals remained unfilled (4). Other studies have demonstrated that patients with infertility secondary to cancer treatment have increased risk of emotional distress (5-9), and infertility in this setting is associated with significant long-term effects on quality of life (10). For young cancer patients, post-malignancy marriage and parenthood considerations are often considered equally important as treatment of the underlying malignancy and can play a significant role in treatment decisions (2,11).

Oncofertility is the study of interactions between cancer, anti-cancer therapy, fertility, and reproductive health.

The field of oncofertility arose from the reproductive concerns of cancer patients to meet their unique medical and psychosocial needs. Fertility preservation is a vital component of oncofertility, which employs medical, surgical, and laboratory interventions to preserve reproductive potential in cancer patients before the detrimental effects of cancer and its treatments occur.

Herein we review the effects of cancer and cancer treatment on fertility, options for fertility preservation in male adult and pediatric patients, barriers to care, and the role of a resolute fertility preservation team in overcoming those barriers.

Effects of cancer on fertility

Cancer is a systemic illness that can affect fertility through multiple distinct mechanisms. Malignancy can alter normal endocrine physiology, which is essential for spermatogenesis. Inflammatory processes and constitutional symptoms can exert both direct and indirect impacts upon spermatogenesis. Psychological morbidity such as anxiety and depression can suppress spermatogenesis and impair sexual function.

Spermatogenesis is dependent upon the normal endocrine function of the hypothalamic-pituitary-gonadal (HPG) axis. Disruption of the axis at any step can result in the suppression of endogenous testosterone production and impaired spermatogenesis. A variety of malignancies may alter the HPG axis, particularly testicular cancers that can produce beta-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP). Elevated levels of β-hCG are associated with poorer semen quality in patients with testicular cancer, suggesting it plays an inhibitory role in spermatogenesis through negative feedback (12-14). Similarly, elevated levels of AFP have been correlated with decreased sperm count and inhibition of spermatogenesis (14,15).

Beyond the endocrinopathy effects of cancer, the immunological response to malignancy may also affect fertility. Many tumors generate lymphocytic infiltration, which can lead to elevation of pro-inflammatory cytokines (16). Rat models have demonstrated that altered homeostasis of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α impair the blood-testis barrier, thereby exposing spermatozoa to elevated levels of reactive oxygen species (ROS) that can cause germ cell apoptosis and sloughing (17-20). Anti-sperm antibodies, found predominantly in testicular cancer, may further impair spermatogenesis,

though the evidence is equivocal (21,22).

Broader systemic effects of malignancy may exert a negative impact upon reproductive potential in a variety of ways. Cancer-induced anorexia-cachexia syndrome can result in severe malnutrition and, in turn, impaired spermatogenesis (23-25). A simple fever can impair sperm motility, morphology, and concentration, particularly in patients with Hodgkin's lymphoma (26-28). The psychological morbidity of anxiety and depression that often accompanies a diagnosis of malignancy can be associated with decreased testosterone, elevated follicle-stimulating hormone (FSH), and abnormal semen parameters (29). Likewise, the decline in sexual function due to psychological or physiological mechanisms may have an indirect impact on fertility (30,31).

Effects of cancer treatment on fertility

Treatment of malignancy with chemotherapy, surgery, or radiotherapy can compromise fertility. This may occur through a direct spermatotoxic effect upon germ cells, alteration of the HPG axis, impairment of sexual physiology, or a variety of other mechanisms.

Because chemotherapeutic agents target rapidly dividing cells, spermatozoa are particularly susceptible to the cytotoxic effects of these drugs. Through disruption of DNA synthesis and replication, alkylating agents such as cyclophosphamide and busulfan are the most spermatotoxic chemotherapeutic agents, impairing fertility in up to 60% of patients (32-34). Effects on spermatogenesis are often irreversible, as approximately 68% of these patients remain azoospermic 20 years after cessation of therapy (35). Green et al. developed the cyclophosphamide equivalent dose (CED), a metric for quantification of future risk of infertility, which may help patients and clinicians when devising a treatment regimen (36). However, the authors found that even at low doses, some patients developed azoospermia; as such, there are no definitively "safe" doses of cyclophosphamide. Platinum-based agents, such as cisplatin and carboplatin, are similarly gonadotoxic (37). However, platinum-based agents are associated with more favorable recovery of spermatogenesis over time, as approximately 80% of patients had successful sperm retrieval within 8 years of cisplatin cessation (38-40). Other chemotherapeutic agents such as antimetabolites and vinca alkaloids exert a more blunted impact upon spermatogenesis (41-44).

Radiation therapy can have a detrimental effect on spermatogenesis, as the immature cell types in the

testis make it among the most radiosensitive organs. The gonadotoxic effect of radiation is dependent on several variables, including the field of treatment, total dose, and fractionation schedule. There is a clear dose-dependent relationship concerning radiotherapy and gonadotoxicity, yet even low doses of less than 0.8 Gy can cause oligozoospermia and doses above 2 Gy can result in irreversible azoospermia.

Surgical management of cancer can have a wide range of negative effects on sexual function and fertility potential. Retroperitoneal and radical pelvic surgery may disrupt branches of the pudendal nerve, lumbar sympathetic, pelvic, and hypogastric plexuses, which are essential for normal erectile and ejaculatory function (45-48). During retroperitoneal lymph node dissection (RPLND) for testis cancer, the postganglionic sympathetic nerves and hypogastric plexus overlying the aorta may be jeopardized, resulting in anejaculation or retrograde ejaculation in up to 89% of patients (49). While the nerve-sparing approach has led to outstanding improvements in ejaculatory function with 99% of chemotherapy-naïve RPLND patients reporting antegrade ejaculation, functional outcomes are decreased with post-chemotherapy RPLND, wherein 89% of men report antegrade ejaculation (46). Likewise, men who undergo radical surgery for non-testicular malignancies such as muscle-invasive bladder cancer, retroperitoneal sarcoma, paratesticular rhabdomyosarcoma, and colorectal cancer will often develop transient or permanent ejaculatory and erectile dysfunction despite modern techniques for preservation of sexual function (50-54). Beyond sexual function, men with testis cancer who undergo unilateral orchiectomy may have a decrease in semen parameters from the surgery itself, though the majority of these men will recover normal spermatogenesis if no further treatment is needed (55).

Options for fertility preservation

Multiple professional societies have issued guidelines and statements about the importance of fertility preservation and options for management in cancer patients (*Table 1*). All agree that healthcare providers should discuss the possibility of infertility with all male patients newly diagnosed with cancer (*Figure 1*). The initial discussion should take place soon after diagnosis and prior to initiation of therapy (56). All physicians who care for cancer patients must be comfortable initiating a conversation regarding fertility preservation, as physician recommendations strongly influence a patient's

decision to pursue sperm cryopreservation (8).

The gold-standard approach to fertility preservation in adult men is sperm cryopreservation. Modern assisted reproductive technologies including *in vitro* fertilization (IVF) with intracytoplasmic sperm injection (ICSI) have enabled couples to achieve pregnancy with just a single sperm and a single oocyte. Fertility preservation patients should be counseled about the requirement of IVF-ICSI for any future use of cryopreserved sperm. Furthermore, patients should be informed regarding the harmful effects of the cryopreservation process, which can lead to decreased sperm concentration, motility, and DNA integrity (65,66). Nonetheless, prior studies have shown equivalent pregnancy rates after ICSI using fresh versus cryopreserved ejaculated spermatozoa, and multiple studies have demonstrated success with IVF-ICSI in the setting of male fertility preservation (67,68).

When possible, men presenting for fertility preservation should undergo semen analysis via masturbation. This approach to specimen collection is cost-effective and easily performed in an outpatient or inpatient setting. Avoiding potentially spermatotoxic exposures such as wet heat (e.g., sauna, hot tub) prior to sperm banking, and maintaining a period of abstinence for 2–3 days before collection is recommended (69). Men with sperm in the ejaculate should continue with cryopreservation. While the ideal quantity of cryopreserved sperm is unknown, patients should aim to cryopreserve multiple vials to ensure enough specimen is available for future use. In our practice, we encourage patients to cryopreserve 10–12 vials, when possible. Depending upon a patient's semen parameters, this may require repeated specimen collections in a brief time period.

Erectile dysfunction is prevalent among men with cancer and can hinder the ability to provide an adequate specimen (70). Treatment of erectile dysfunction in the setting of fertility preservation should follow standard treatment paradigms (71). First-line therapy consists of phosphodiesterase-5 (PDE-5) inhibitors followed by intracavernosal injections, both of which supply fast-acting therapy. Other standard treatments for erectile dysfunction such as a medicated urethral system for erections (MUSE) and vacuum erection devices may be tried but can be difficult to access, cumbersome, and less effective in time-sensitive scenarios.

In some men, collection via masturbation is not possible due to retrograde ejaculation or anejaculation resulting in aspermia or dry ejaculate. Men with aspermia who can achieve orgasm should undergo post-ejaculate urinalysis

Table 1 Summary of male fertility preservation guidelines (adapted with permission from Halpern *et al.*, "Guideline based approach to male fertility preservation", Urologic Oncology 2019)

Professional society	Publication year	Highlights
American Society of Clinical Oncology (ASCO)	2006, 2018 (56,57)	All health care providers caring for cancer patients should counsel regarding potential infertility prior to initiation of any therapy
		Patients interested in fertility should be referred to reproductive specialists
		Sperm banking should be discussed with all postpubertal males scheduled to receive cancer treatment
National Comprehensive Cancer Network (NCCN)	2012, 2014 (58,59)	Adolescents and young adults with cancer should be considered a unique age group with unique medical and psychosocial considerations, including fertility
		Sperm banking should be offered to all male patients at the time of diagnosis
		Oncology centers should develop a systemic and patient-centered program for offering cryopreservation to all male patients
European Society for Medical Oncology (ESMO)	2013 (60)	Plan sperm banking in males scheduled to receive treatment that could affect future fertility
		Collection of one to three samples recommended
American Academy of Pediatrics (AAP)	2008 (61)	Consider ethical, cultural, and other unique factors that may impact communication with the patient and parents
		Devise talking points based on age and developmental stage of the patient
American Society for Reproductive Medicine (ASRM)	2005, 2013, 2018 (62-64)	Ejaculated sperm cryopreservation is the standard method of fertility preservation in postpubertal males and may be aided by use of phosphodiesterase type 5 (PDE-5) inhibitors, vibratory stimulation, or electroejaculation when appropriate
		Consider cryopreservation of surgically extracted sperm in males who cannot ejaculate or who have either azoospermia or oligozoospermia in an ejaculated sample
		Cryopreservation of testicular tissue in prepubertal boys is investigational at this time and should not be employed in routine clinical practice

(PEU) to rule out retrograde ejaculation. Sperm found in the PEU indicates retrograde ejaculation, and medical therapy with alpha-agonists such as pseudoephedrine and midodrine or tricyclic antidepressants such as imipramine may be used in an off-label fashion to help restore antegrade ejaculation (72). Shoshany *et al.* reported improved semen parameters in 70% of patients treated with pseudoephedrine for retrograde ejaculation (73). In patients unresponsive to medical therapy or when time constraints limit, urinary sperm retrieval can be attempted following urine alkalization, though pregnancy rates using this procedure are highly variable ranging from 20% to 50% (72,74,75).

Anejaculation is the complete lack of ejaculation and is accompanied by lack of antegrade release of semen from the urethra. It can result from a variety of conditions, including hypogonadism, neurologic impairment, and medication side effects. While some men will respond to alpha-agonist therapy, many will require added intervention such as penile vibratory stimulation (PVS) and electroejaculation (EEJ).

PVS employs mechanical stimulation of the dorsum and frenulum of the penis, which stimulates the sacral spinal ejaculatory reflex until antegrade ejaculation occurs. Success rates range from 77% to 86% in men with spinal cord injury above T10 in whom the ejaculatory reflex is still intact. In men with lower spinal cord injury, the ejaculatory reflex is typically compromised, and success rates are lower at approximately 17% (76). Advantages of PVS include ease of use, low cost, and low morbidity. As such, PVS should be considered as the first choice in men with anejaculation who are refractory to medical therapy.

EEJ is recommended for patients in whom PVS does not restore antegrade ejaculation. EEJ utilizes a transrectal probe for direct transmission of electrical current to the prostate and seminal vesicles resulting in ejaculation with approximately 95% success (77). In combination with assisted reproductive technology (ART), EEJ offers
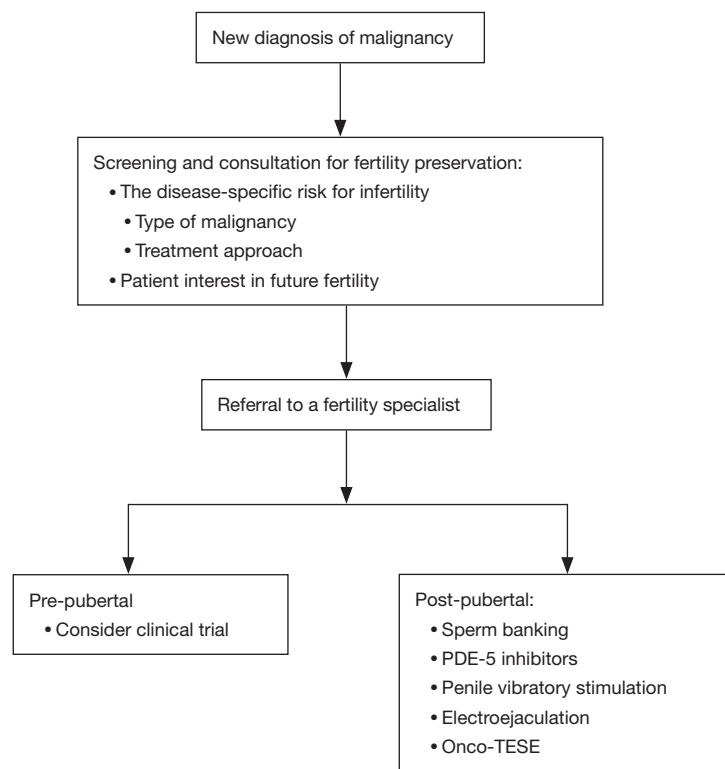
Figure 1 Approach to fertility preservation in the male cancer patient with a new diagnosis of malignancy (adapted with permission from Halpern *et al.*, "Guideline based approach to male fertility preservation", *Urologic Oncology* 2019). PDE, phosphodiesterase; TESE, testicular sperm extraction.

reasonable cycle fecundity of 8.7% and 37.2% using intrauterine insemination (IUI) and IVF, respectively (78). Multiple studies have also demonstrated success using EEJ in the adolescent cancer population with sperm retrieval rates ranging from 45% to 60% (79,80). In contrast to PVS, EEJ is invasive and painful. While patients with spinal cord injury who lack sensation below the waist can undergo EEJ in the ambulatory setting without an anesthetic, most men will require anesthesia (81).

Despite the therapies above, a substantial proportion of men pursuing fertility preservation will remain azoospermic. Lass *et al.* reported 13.8% of cancer patients were azoospermic at the time of attempted sperm cryopreservation (82). These patients should be offered oncological testicular sperm extraction (onco-TESE) before initiation of any cancer treatment regimen. Initially coined by Schrader *et al.* in 2003, onco-TESE refers to the technique of testicular sperm extraction (TESE) when employed in the setting of malignancy, either using a conventional approach or a microdissection approach (83,84). Like conventional TESE, onco-TESE

carries a small but significant risk of complications such as hematoma, testicular fibrosis, hypogonadism, and even testicular loss (85). In a small series of 6 patients with either azoospermia, cryptozoospermia, or severe oligozoospermia who underwent onco-TESE, sperm was retrieved in 4 (67%) patients (86). In the setting of testicular cancer, onco-TESE can be performed on the orchiectomy specimen *ex vivo* ("back table" onco-TESE), thereby sparing the morbidity of operation on the contralateral testis (87). For azoospermic men with a new cancer diagnosis, onco-TESE offers the best chance for future fertility, as many of these men will remain azoospermic after the completion of chemotherapy (86).

There is no consensus about monitoring of fertility after cancer. We recommend routine follow-up with repeat semen analysis at 1- and 2-years following completion of gonadotoxic therapy. Even in men with the return of sperm to the ejaculate sooner, we recommend waiting at least 1–2 years following gonadotoxic therapy before trying to conceive due to concerns about potential harm to offspring conceived during this interval. It is critical that providers

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discuss the importance of follow-up at the time of initial fertility preservation, as a large proportion (36%) of men are lost to follow-up after completion of therapy (88).

Fertility preservation in the pediatric patient

Long-term longitudinal studies have demonstrated that men treated for childhood cancer are at significantly increased risk of infertility (89-91). There is great heterogeneity in the types of pediatric malignancy and treatments, which, along with patient age and pubertal state, can variably affect fertility potential. Unfortunately, gonadal shielding during radiation therapy and other preemptive maneuvers have been unsuccessful in consistently protecting future fertility (92).

The most important aspect in the management of pediatric fertility preservation is the determination of pubertal status with a detailed history and physical examination. It is imperative to discern whether the patient has experienced sexual thoughts, nocturnal emission, or masturbation, as this will inform his ability to supply a semen specimen. Physical examination with careful attention to secondary sex characteristics and Tanner staging can also provide insight into the pubertal state.

For peripubertal and post-pubertal adolescents, the gold-standard for fertility preservation is still cryopreservation of an ejaculated semen sample. Feasibility of cryopreservation of an ejaculated semen sample has been demonstrated in patients as young as 11 years, and for this reason, age alone should not be utilized as a determinant of pubertal state (93,94). Peripubertal or post-pubertal males who are unable to supply a semen sample may be candidates for the therapies, including PVS, EEJ, and onco-TESE. Regardless of the mode of specimen collection, patients and their families should be counseled about the need for IVF with any future use of cryopreserved specimen.

Fertility preservation in prepubertal patients is still strictly experimental. Prepubertal patients do not have mature gametes or active spermatogenesis, and as such, they are not candidates for traditional cryopreservation (95). Several alternative experimental approaches have been undertaken to preserve fertility in prepubertal cancer patients. Spermatogonial stem cell transplantation has been described in multiple animal models, and more recent efforts have focused upon cryopreservation of testicular tissue with the goal of future culture and autologous grafting of spermatogonial stem cells. Others have explored the use of decellularized testicles or synthetic bioscaffolds for spermatogonial stem cell culture in attempts to cultivate viable testicular tissue *in vitro* (96,97). Induction of spermatogonial stem cells from embryonic or induced pluripotent stem cells is yet another potential pathway (98).

Most recently, a breakthrough in autologous grafting of testicular tissue demonstrated great promise for future clinical application. Fayomi *et al.* harvested and cryopreserved testicular tissue from prepubertal rhesus macaques monkeys, which resulted in castration (99). Autologous grafting of cryopreserved tissue beneath either the back skin or scrotal skin of the castrated monkeys yielded testosterone production and complete spermatogenesis within 1 year. Using ART, graft-generated sperm successfully fertilized oocytes resulting in the birth of a healthy female. This exciting proof of concept might pave the way for future human studies of testicular tissue cryopreservation in prepubertal children.

Barriers to fertility preservation

There are numerous potential barriers to fertility preservation in both the adult and pediatric cancer patient. These are broad in scope and include patient and provider knowledge gaps, patient and provider discomfort, financial, logistical, and cultural barriers.

The most critical barrier to fertility preservation is the first consultation. A new cancer diagnosis is often accompanied by stress, anxiety, and a desire to start treatment at once. However, the narrow window before initiation of therapy is critical for fertility preservation, as even a single oncologic intervention may transiently or permanently impair fertility (56). Nonetheless, Schover *et al.* found that only 60% of adult men recall being informed about infertility as a possible side effect of their treatment and only 51% were offered sperm banking before therapy (8). Likewise, Quinn *et al.* reported that cancer patients of childbearing age were referred to reproductive endocrinologists less than half of the time (100). Physicians, nurses, and social workers alike may be unfamiliar or uncomfortable discussing fertility preservation with the newly diagnosed cancer patient, which may account for low referral rates (100-104). Oncologists are even less likely to refer patients for cryopreservation in the setting of aggressive cancer with a poor prognosis (8,105). Since a physician's recommendation is an important predictor of fertility preservation, changing physician practice patterns, and closing knowledge gaps are essential to increasing

utilization (8,106).

Logistical considerations can severely limit access to fertility preservation in the acute setting. Many healthcare settings may not have a reproductive urologist on-site or even on-call for urgent consultation. Likewise, clinical facilities may not have the laboratory capabilities to perform sperm cryopreservation or even basic semen analysis (107,108).

Even when appropriate counseling, referral, and resources are provided, financial considerations may impede fertility preservation (102,103). Oncologists tend to overestimate the costs of cryopreservation, and 51% of oncologists believe out-of-pocket costs would prohibit most men from choosing this option (8,109). However, a recent survey found that costs were not an important consideration for patients when deciding to cryopreserve sperm (110). Furthermore, while sperm cryopreservation can be expensive with estimated upfront and 3-year storage total fees approaching $1,500, new legislation in multiple states has mandated insurance coverage for fertility preservation, thereby alleviating the financial burden (57,111,112).

Cultural and religious beliefs may also impede fertility preservation. For example, masturbation is prohibited by certain religions including Roman Catholicism and Judaism, which can hinder the ability to obtain samples for cryopreservation (113). Likewise, certain religions do not support ART, thereby minimizing the utility of cryopreservation as the future use of sperm is severely restricted. Providers should explore these cultural and religious beliefs with patients during the first consultation to integrate these concerns into the plan of care.

Pediatric cancer patients present unique challenges when it comes to fertility preservation. Clinicians and parents alike may feel uncomfortable discussing sexual health and fertility with pediatric patients. Ethical considerations of consent, assent, and adherence to principles of beneficence, nonmaleficence, justice, and autonomy can manifest in many scenarios in both the prepubertal and post-pubertal patient (95).

Role of a formal fertility preservation program

A formal fertility preservation program can help to overcome the barriers above and optimize use of fertility preservation. Such a program should assemble a multidisciplinary team, including oncologists, urologists, reproductive endocrinologists, geneticists, mental health professionals, nurses, and social workers. Formal training

programs and educational initiatives can improve the knowledge base of the team members and increase physician awareness throughout the institution (114). Online resources and patient navigators, available in multiple languages, can increase patient access.

Implementation of a fertility preservation program leads to improved outcomes. Sheth *et al.* reported an increase in the number of male cancer patients receiving fertility preservation consultation and pursuing sperm cryopreservation by 2.4- and 2.7-fold, respectively (114). Likewise, Lopategui *et al.* found a six-fold increase in fertility preservation after the establishment of an oncofertility team (115).

Conclusions

Cancer and its treatments can threaten fertility through a variety of mechanisms. There are many options for fertility preservation in male adult and pediatric cancer patients, and exciting, innovative approaches are on the horizon. Timely consultation, well-trained experts, and a formal fertility preservation program can help to overcome barriers and ensure that patients perfect their future fertility potential.

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Footnote

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