Title

Access to Fertility Preservation for Cancer Patients: Ethical, Moral and Theological Considerations

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Access to Fertility Preservation for Cancer Patients:

Ethical, Moral and Theological Considerations

By

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Tables & Graphs

TABLE 1. Distribution of patients enrolled in the Tyrosine Kinase Inhibitor (TKI) study			
Total N = 67; Age median (range) : 48 (21-72)		**N**	%
Race	White	43	66%
	Asian*	11	17%
	Black	5	8%
	Other/Mixed	6	9%
Income	<$40,000	9	13%
	$40-100,000	24	36%
	>$100,000	27	40%
	Prefered not to answer	7	10%
Education	Some college or less	18	27%
	Bachelor's	27	40%
	Graduate	22	33%
Employment	Employed full time	50	82%
	Employed part time	5	8%
	Not employed**	11	18%
Marital Status	Married or domestic partnership	44	66%
	Single/other	23	34%
Paternity	Prior pregnancies with any partner	34	53%
	Desire to have children in the future	21	32%
Cancer Diagnosis	Chronic myelogenous leukemia	34	54%
	Renal cell carcinoma	7	11%
	Gastrointestinal stromal tumor	5	8%
	Hepatocellular carcinoma	2	3%
	Pancreatic Neuroendocrine tumor	1	2%
	Other	14	22%
TKI at visit	Dasatinib	23	34%
	Imatinib	18	27%
	Other**	26	39%

* Indian, Chinese, Filipino, Japanese, Korean, Vietnamese
** Unemployed, retired, or student
*** Sunitinib, Pazopanib, Nilotinib, Bosutinib, Sorafenib, Everolimus, other

Table 2. Fertility Presevation counseling and knowledge at time of diagnosis	N ("No")	%
Did anyone on the medical team (doctors, nurses, therapists, social workers) provide you with information about the risks of cancer treatment to your fertility and ability to father a child?	38	57%
Did you believe that the cancer treatment recommended by your doctors might affect your fertility?	36	54%
Were you concerned about becoming infertile as a result of cancer treatment?	39	58%

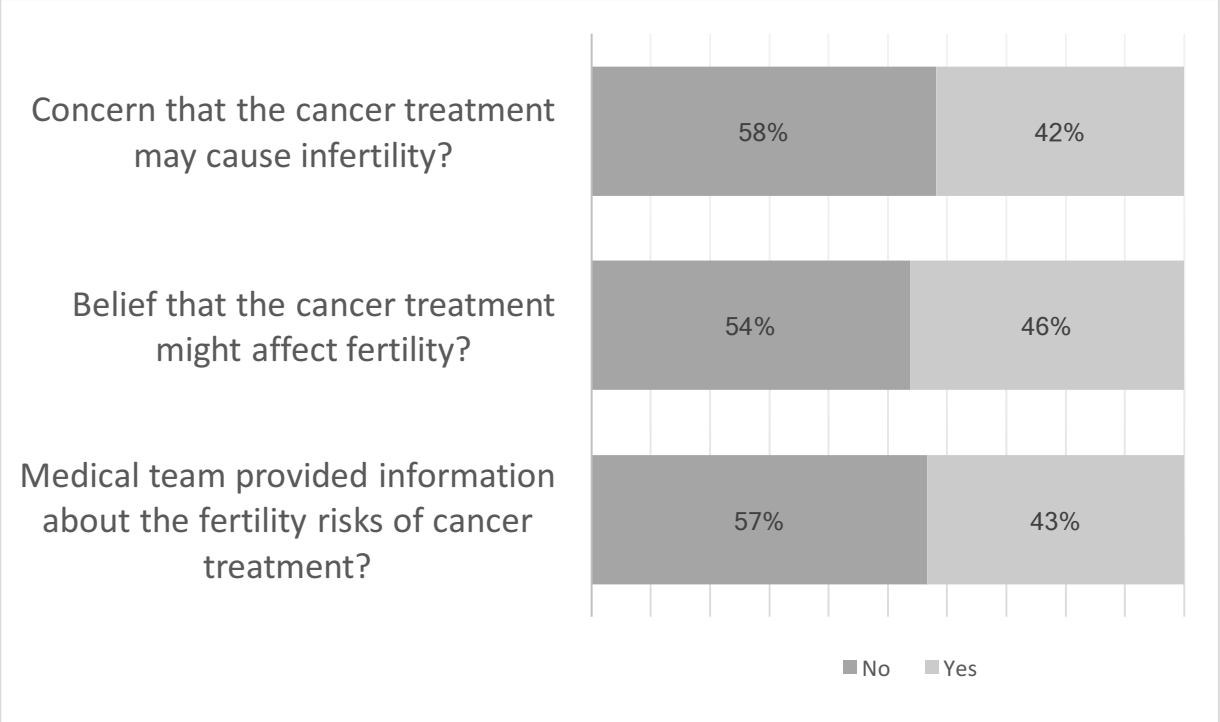
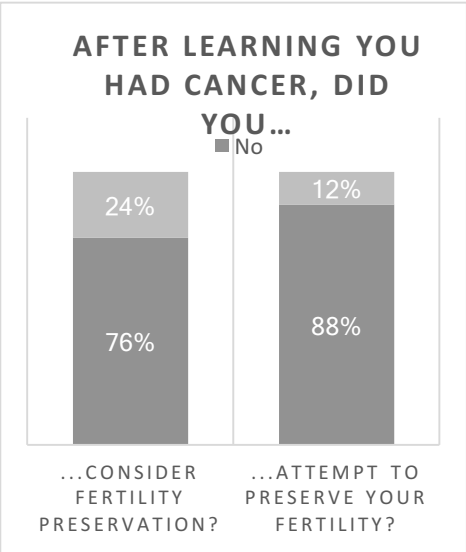


Table 3. Interest in Fertility at Time of Diagnosis		N ("No")*	%
After learning you had cancer, did you…	...CONSIDER fertility preservation?	51	76%
	...ATTEMPT to preserve your fertility?	59	88%
Did your doctor…	...ask you whether having children was important to you?	39	58%
	…provide ways to protect testicles from cancer treatment?	52	78%
	…talk to you about ways to protect your ability to father a child?	43	64%
	…provide fertility specialist referrals?	52	78%
	…share available resources for more information on ways to preserve fertility?	48	72%

* "No" includes "No, not at all". The other possible answers were "Yes but not as much as I wanted to", "Yes almost as much as I wanted to", and "Yes as much as I wanted to".



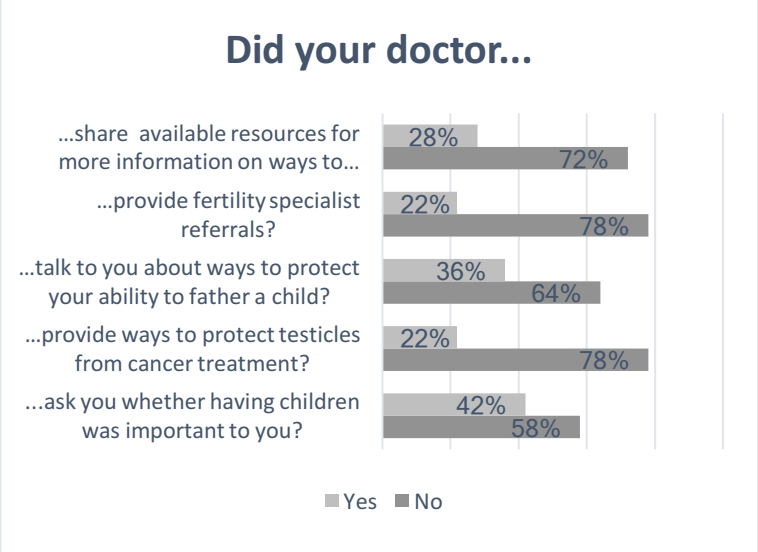


Table 4A. Bivariable comparison of socioeconomic, demographics and clinical characteristics and whether fertility preservation was CONSIDERED				
	Odds ratio	95% CI		P-value
Any barrier experienced	1.21	0.36	4.05	0.76
Race white	0.49	0.15	1.59	0.24
Desire to have a child	16.7	4.17	67	**<0.001**
Previous pregnancies	0.4	0.12	1.29	0.13
Bachelors degree or more	1.78	0.44	7.24	0.42
Income >$100,000	0.35	0.11	1.18	0.09
Full time-employment	0.3	0.09	1.01	0.05
Longterm partnership	0.64	0.2	2.04	0.45
Age at diagnosis (5-year increments)	0.49	0.33	0.72	**<0.001**
Belief that tx may cause infertility	3.67	1.1	12.3	**0.035**
Doctor mentioned risks of TKI on fertility	7.29	2	26.5	**0.003**

Table 4B. Bivariable comparison of socioeconomic, demographics and clinical characteristics and whether fertility preservation was ATTEMPTED				
	Odds ratio	95% CI		P-value
Any barrier experienced	0.26	0.06	1.22	0.09
Race white	0.74	0.16	3.48	0.71
Desire to have a child	24.5	2.74	219	**0.004**
Previous pregnancies	0.46	0.1	2.12	0.32
Bachelors degree or more	1.1	0.2	6.04	0.92
Income >$100,000	0.29	0.05	1.56	0.15
Full time-employment	1	0.18	5.53	1
Longterm partnership	0.51	0.12	2.28	0.38
Age at diagnosis (5-year increments)	0.46	0.27	0.77	**0.003**
Belief that tx may cause infertility	4.3	0.8	23.2	0.09
Doctor mentioned risks of TKI on fertility	5.4	0.99	29.3	0.05

Part I: Ethical, Moral, and Theological Insights into Advances in Male Pediatric and Adolescent Fertility Preservation

Joris Ramstein, BS; Jodi Halpern, MD; Adam Gadzinski, MD; Robert Brannigan, MD; James F. Smith, MD, MS.

Introduction

Cancer treatments in children have improved in the past several decades[1] and survival rates have improved dramatically[2], with the 5-year survival having increased from 58% in 1975-1979 to 83% in 2003-2009 for all cancers, with a range of 67 to 98% across all pediatric cancers[3]. While most children undergoing treatment for cancer can expect to survive, many cancer treatments are associated with impaired fertility potential[4]. In this review, infertility is defined as the inability to conceive naturally in the absence of clinical interventions[5]. While the estimated baseline infertility incidence in the general population is approximately 15%[6 7], decreased fertility following a cancer treatment depends on several variables, including the stage of sexual maturity of the patient[8], the type of therapy used to treat the cancer[9], and the biological sex of the patient[10]. For example, alkylating agents such as procarbazine and cyclophosphamide are associated with a high risk of azoospermia (i.e. sterility) or oligospermia (i.e. impaired sperm quality) in boys[11]. Losing fertility potential can also be dose-dependent: for example, boys treated for Hodgkin's lymphoma became sterile in more than 90% of the cases after undergoing 6 cycles of chemotherapy, 50% following 3 cycles and 33% in alternate yet less effective therapies[12 13]. In light of the increased survival rates combined with the known risks of infertility, guidelines advocating for fertility preservation (FP) [14] have been developed by the American Society of Clinical Oncology (ASCO), the Ethics Committee of the American Society for Reproductive Medicine (ASRM), and the American Academy of Pediatrics' Committee of Bioethics (AAP).

The available FP techniques depend on sexual maturity of the patient, and each technique has its own pros and cons. After puberty, the standard of care involves semen cryopreservation obtained by masturbation or a surgical sperm retrieval for patients unable to produce a semen sample[15]. Before puberty, FP currently available techniques include shielding gonads against radiation[16] and temporary transposition of the gonads[17]. The future may offer novel means of protecting and

restoring fertility; so far, these techniques have only been successful in animal models. The most promising of these experimental techniques begin with a testicular biopsy of a prepubertal boy followed by either *in vitro* expansion of spermatogonial stem cells to sperm or autotransplantation of testicular tissue to allow restoration of spermatogenesis[18]. While there is considerable enthusiasm for these technologies as a solution for iatrogenic prepubertal sterility, success has not yet been demonstrated in humans.

Given this level of uncertainty, the ethical considerations are complex. Relevant factors include: 1. The long-term and short-term potential for benefit and harm of pediatric testicular biopsy are not fully known; 2. Because institutional review board (IRB) approval is technically required to perform the pre-pubertal experimental preservation procedures, access to these FP techniques is limited to the small number of IRB-approved centers. 3. The process of consenting and assenting to these procedures is not fully understood by the pediatric patient, with guidelines only recently discussed by the Practice Committee of American Society for Reproductive Medicine[19] and the Ethics Committee of American Society for Reproductive Medicine [20]. 4. The discussion regarding the use of samples for research and the disposal of samples if the boy were to die following the cancer diagnosis[21] may also need to be addressed differently based on the cultural and religious background of the patient and his guardians. 5. The future ramifications of these novel techniques, such as whether genetic cancer risks would be passed on to offspring, have yet to be fully determined. 6. Finally, the discussion of male cryopreservation therapy in the context of culture and religion has yet to be explored, especially with regard to using assisted reproductive techniques and obtaining sperm or testicular samples[22]; this discussion includes individual religious beliefs around ART, discussing the possibility that the child may grow up to have beliefs that are different from his parents', and the discomfort associated with discussing reproductive health across cultures and religions.

Summary of FP and Restoration Options [23] [24]

Advances in cryopreservation techniques, intrauterine insemination (IUI), in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) offer well-established options to post-pubertal male patients who wish to have biological children[25] [26] [27]. Sperm cryopreservation is a process by which mature sperm cells are obtained by masturbation or surgical sperm retrieval procedures and subsequently cooled to subzero temperatures – typically -196°C (the boiling point of liquid nitrogen) – to be preserved indefinitely. At these low temperatures, all biological activities are stopped, including cell death. These sperm can then be recovered for artificial reproductive technologies (ART) including IVF and ICSI. IUI requires a large number of sperm cells (typically at least 10 million moving sperm), while IVF requires retrieval of sperm cells and ova, followed by sperm washing and ovum selection, co-incubation for a few hours, embryo culture, embryo selection, and finally embryo implantation. This technique is generally performed when sperm concentration and quality are normal. ICSI consists of directly inserting a single sperm cell whose tail has been removed into a single ovum using micromanipulation tools and technique. The fertilized embryo is subsequently cultured for 3-5 days before being transferred to the uterus. A pregnancy test is obtained two weeks later.
If the cancer treatment consists of radiation therapy that would affect the genitals, the gonads may be protected against radiation ("shielding")[28], or surgically relocated (i.e "transposed") to a different location in the body[29]. Unfortunately, these methods are experimental and their efficacy has yet to be determined[30].

For boys who have yet to reach spermarche, testicular tissue may offer the hope of reproductive options to those patients when they reach the age of conception. For pediatric patients, testicular tissue cryopreservation consists of obtaining a testicular tissue biopsy under general anesthesia, typically in conjunction with other required procedures (e.g. central line placement, bone marrow biopsy). No significant complications have been reported[31]. The tissue is cryopreserved for long term storage and possible use. Testicular tissue from boys of all ages contains sperm stem cells (SSC) but may not yet contain mature sperm[32]. Only sperm can be used for contemporary fertility techniques.

Future techniques to utilize this tissue include *in vitro* maturation of SSC into mature sperm cells for subsequent use in IVF/ICSI, or germ-cell transplant into native testicular tissue to allow fertility restoration. These techniques have been performed successfully in animal models but never in humans. Testicular biopsy for this indication should only be performed in research centers with IRB approval.

Maturation of SSC followed by IVF/ICSI has been shown to work remarkably well in mouse models[33] and the full differentiation of human SSC into mature sperm cells in vitro was recently demonstrated[34]. However, IVF/ICSI using human (or even primate) mature sperm cells derived from SSC in vitro has not been shown.

Autologous testicular cell transplantation is an exciting potential option that has been used successfully with many animal models since 1994 when Brinster el al first published their work[35]. Most recently, Herman demonstrated the feasibility of testicular cell transplantation for restoring fertility in Rhesus macaque after undergoing bone marrow transplantation[36]. Transplanting germ cells back into the gonads of a human patient after chemotherapy to restore fertility potential has not yet been attempted. Among many technical challenges remaining is the task of purifying SSC populations effectively so that no malignant cells are reintroduced in the process[37].

FP guidelines by AAP, ASCO, ASRM

According to the AAP[38], the counseling guidelines for FP options in children and adolescents with cancer are as follows, *verbatim*:

1. Cryopreservation of sperm should be offered whenever possible to male patients or families of male adolescents.

2. Current fertility-preservation options for female children and adolescents should be considered experimental and are offered only in selected institutions in the setting of a research protocol.

3. In considering actions to preserve a child's fertility, parents should consider a child's assent, the details of the procedure involved, and whether such procedures are of proven utility or experimental in nature. In some cases, after such consideration, acting to preserve a child's fertility may be appropriate.

4. Instructions concerning disposition of stored gametes, embryos, or gonadal tissue in the event of the patient's death, unavailability, or other contingency, should be legally outlined and understood by all parties, including the patient if possible.

5. Concerns about the welfare of a resultant offspring with respect to future cancer risk should not be a cause for denying reproductive assistance to a patient.

The ASCO Clinical Practice Guidelines[39] suggest focusing on three main overarching questions: "are patients interested in interventions to preserve fertility," "what is the quality of evidence supporting current and forthcoming options for preservation of fertility in males," and "what is the role of health care providers in advising patients about FP options." A special consideration should be made when discussing FP techniques with prepubertal male patients since the only preservation options are testicular cryopreservation techniques, which are still in the investigational stage and should only be offered in research facilities where an IRB is in place and overseeing the research progress.

The Ethics Committee of the ASRM[40] also highlights the importance of prioritizing cancer treatment over FP when necessary, and encourages a multidisciplinary approach when addressing issues of FP. In simple terms, ethical

norms require that procedures serve the patient's best interest, and are performed only after receiving their fully informed consent (or assent in the case of adolescent patients). The topic of FP should be discussed with postpubertal minors, both with and without the parents/guardians present, while being mindful of cultural and/or religious values and beliefs. A similar process should be used with prepubescent boys, but because the techniques are still experimental, the site-specific IRB must determine that the expected benefits of the procedure will outweigh the potential risks associated with the procedure.

Key Bioethical Questions for Male Prepubertal Fertility Preservation[41] [42]

1. The potential for benefit and harm of testicular biopsy are not fully known – As emphasized in AAP, ASCO, and ASRM guidelines, all patients about to undergo potentially sterilizing medical or surgical treatment should be informed of the FP techniques available to them. The overarching philosophy when addressing this topic with patients and guardians is that the procedures should always serve the best interests of the patient (beneficence) while providing them enough information to make an informed decision (autonomy). Physicians also try to balance doing the best for their patients (beneficence) while limiting the risk for harm (nonmaleficence). A current highly debated topic between oncologists and fertility specialists is the issue of delaying treatment to allow for FP. Oncologists tend to be concerned that offering FP will delay cancer care and lead to worsened outcomes. In some cases, patients are willing to accept potentially inferior cancer treatments in order to allow FP[43], raising questions of patient autonomy versus beneficence. It is unknown whether a testicular biopsy would negatively impact testosterone production; however, given that FP biopsies are generally smaller than 5% of one testicle, it is doubtful that hypogonadism would be a significant risk above that of the chemotherapy or radiation treatment. In fact, even with extensive testicular dissection, no long-term hypogonadism has been seen, at least not in adults[44]. Such observations have not been made in children.

2. Consent, assent and serving the child's best interest – With regards to pediatric patients, the main ethical issue the ASRM raises is the fact that many boys may not be competent to make decisions that would serve their best interest in the future. On the other hand, the parents' decision may also go in a direction that would limit their child's autonomy in the future. This ethical dilemma is an ethical concept commonly known as the child's "rights to an open future", which aim to protect a child against having important life decision made for them before they have the ability to decide for themselves[45]. Opponents to FP may argue that doing the sterilizing cancer treatment without doing a testicular biopsy follows the "natural" course of events and is therefore what truly keeps the rights to an open future intact by avoiding a surgical procedure. On the other hand, proponents of FP may argue that doing the testicular biopsy is precisely what would preserve the boy's rights to an open future by offering him the option to have children in

the future for minimal cost and risk, an option which would otherwise be taken away from him by the cancer treatment. The child's rights to an open future are further discussed in case 1 of the discussion section.

3. The discussion of what to do with the samples in the event of the patient's death – Further consideration must also be placed on discussing the disposal of reproductive samples in the event of a pediatric patient's death. For adult patients, three options are considered ethically appropriate and chosen by each individual prior to cryopreservation: destroy the sample, use the sample for research, or allow the spouse the make the decision. For pediatric patients, generally, IRB committees consider the only ethically appropriate choices to be sample destruction or use for research. This choice is made prior to cryopreservation and can be changed at any point by the parent or guardian. As will be discussed in case 2, certain religious groups don't allow the use of sperm cells for purposes other than reproduction within the boundaries of marriage, and as such may influence the consenting party's decision regarding what to do with the sperm samples.

4. The future ramifications of these novel techniques, such as the risks of cancer relapse and whether genetic cancer risks would be passed on to offspring, have yet to be fully determined – In the case of recovery after chemotherapy, it is also important to think of ways to assist the patient with his future reproductive goals and family planning. Some have suggested that the risks of relapse and possible early death of a parent may be unethical in the context of caring for a future child[46], but the benefits of an offspring being alive have been deemed to outweigh the concerns of losing a parent early. On the other hand, some may worry about the risks of cancer in the offspring. The genetic risks of passing certain genes on to offspring is an appropriate, yet separate discussion that could apply to any couple with a family history of cancer or other genetic defects. When the cancer is not genetic, the risk of neoplasm in the offspring is not significantly increased[47]. Furthermore, contemporary IVF/ICSI techniques allow selection of embryos with specific genetic characteristics.

5. The cultural and religious ramifications of male cryopreservation therapy – The meaning of reproductive health and fertility treatments varies drastically across different cultural and religious backgrounds, and involves complicated views on IVF/ICSI, masturbation, involvement of a sperm/egg/uterus donor and the use of tissue in research.

Case studies and viewpoint of religions

For many people, faith and spirituality provide a foundation for morality and decision-making. When it comes to modern technologies and concepts like oncofertility, the construct is not as simple as saying that all fertility treatments are acceptable or not for a given religion. Generally speaking, no religion has specific guidelines on oncofertility or has yet to deliberate on acceptable guidelines. Furthermore, while most religions possess basic ideologies that can be applied to the fast-paced evolution of technological and biological advances, it is important to keep in mind that even major religions are divided into geographical and cultural subgroups, each containing their own values and ethical standards. In 2010, Zoloth et. al. reviewed the available literature on the topic of religious opinions regarding the ethics of oncofertility[48]. Their findings on Catholicism, evangelical Christianity, Islam, Judaism, Hinduism and Buddhism are summarized below.

Roman Catholic (RC) beliefs on assisted reproduction follow 3 main rules: (1) an embryo possesses the same rights to life and integrity as any human being at the moment of fertilization, (2) a husband and a wife may only procreate with one another, and (3) the procreation must result from the sexual union of a husband and wife. Therefore, any ARTs using donor sperm/egg/embryo, or fertilization outside of sexual intercourse between a married couple (e.g. IVF, ICSI, intrauterine insemination) are not permitted. Masturbation is also deemed morally unacceptable, thus even the collection of sperm is challenging. In the case of sterility within the marriage, medical procedures to restore natural fertility are permitted. For example, in case of fallopian tube blockage, surgical correction is allowed.[49] [50] However, if a couple remains sterile despite such procedures, then adoption is encouraged. The Catholic Church does promote scientific research towards preventing sterility before the act of procreation (i.e. the act of procreation should be left untouched). With regards to boys about to undergo potentially sterilizing chemotherapy treatments, one could conclude that under Catholic doctrine, obtaining testicular sample would be allowed with the hope that testicular tissue transplantation would be an available treatment in the future since this would be the only current FP option that would: (1) remedy infertility directly before the act of procreation, (2) not require IVF, and (3) conserve the act of procreation.

Evangelical Christianity (EC) similarly places high importance on the rights of the embryo from the moment the sperm meets the egg, and on the conception being only in the context of marriage between a man and a woman. The two main branches of evangelical Christianity –the Baptists and Pentecostals - both agree

that conception posthumously is problematic. However, autologous transplantation of testicular tissue may possibly be acceptable pre-conception since the actual act of procreation would be left untouched. Assemblies of God do not support surrogacy and ART, while Southern Baptists allow certain exceptions around this technology; for example, Southern Baptists allow "embryo adoption"[51], because their main issue seems to be around the destruction of embryos. In other words, while this group does not support the practice of IVF/ICSI, they recognize the fact that IVF/ICSI techniques are performed by others and that using an unused embryo is better than to let it be destroyed. For boys about to undergo chemotherapy, testicular tissue transplantation therefore seems to be the only option for Assemblies of God Evangelical Christians. This technique would offer these boys the chance at fertility in heterosexual intercourse.

Islam is a bit different in the sense that IVF and other ART are fully tolerated, as long as the only parties involved are the husband and wife within a marriage[52]. Surrogacy and donor egg/sperm/embryo are considered adulterous and therefore prohibited, while IVF and artificial insemination within the marriage are allowed. Embryo cryopreservation is allowed but should be destroyed if the marriage were to end following divorce or death. These ideas are based on the words of the Prophet Muhammad who said that "for every disease there is a cure". In other words, if infertility is considered a disease, it is acceptable for people to use medical techniques to fix it. For the post-pubertal Muslim boy about to undergo chemotherapy, sperm sample cryopreservation therefore seems to be the easiest, safest and cheapest way to provide procreation options in the future. For the pre-pubertal Muslim boy, testicular biopsy for both later SSC differentiation and IVF/ICSI or for SSC transplantation post chemotherapy would likely be acceptable.

Judaism generally views ARTs favorably. The Halakhah (the body of Jewish rules and laws derived from the Torah) stipulates on the one hand that there is no pressure on infertile couples to procreate. On the other hand, the Torah has been interpreted as saying that procreation is a duty. Furthermore, several scholars note the social pressure placed on Jewish couples to procreate in the aftermath of the genocide that happened during World War II. Also, "healing" is one of the fundamental guiding values when it comes to Jewish reproductive ethics[53], such as restoring lost fertility after cancer treatment. Therefore, oncofertility techniques may arguably be assimilated into Jewish beliefs around healing and procreating. ARTs are generally accepted in the Jewish community, as long as they are used within the context of marriage and that no sperm is wasted in the process. In fact, the "spilling of seed" (i.e. ejaculation outside of the act of procreation) is

admonished in the Hebrew Scriptures. With that being said, many rabbis have argued that masturbation is permissible if the entire sample is used for the purpose of reproduction, for example in IVF or ICSI. While the use of donor sperm, egg or uterus is not prohibited under Jewish doctrine, the identity of the child is determined by genetic heritage and third-party involvement may therefore be problematic. Orthodox and Conservative Judaism differ in their views of who is considered the father and the mother when donors are involved. Testicular biopsy with post-chemotherapy transplantation or SSC differentiation for pre-pubertal boys may thus be acceptable as part of the "healing" process of restoring fertility, as long as all the differentiated sperm cells are used. However, the distinction between how naturally occurring sperm cells and SSC differentiated to mature sperm in cell culture can be used in research remains unclear.

The Church of Latter Day Saints' (LDS) stance on ART provides moral guidance but leaves specific decisions up to the married couple. Like the other religions discussed, fertility restoration treatments are encouraged. Testicular tissue transplantation for fertility restoration would fall under this category. Furthermore, techniques like artificial insemination, IVF and ICSI are all allowed[54]. The church's stance on masturbation is a debated topic, but masturbation for the purpose of medical interventions is generally accepted[55]. In terms of using donor sperm, "the Church strongly discourages artificial insemination/in vitro fertilization using semen from anyone but the husband. However, this is a personal matter that ultimately must be left to the judgment of the husband and wife. Responsibility for the decision rests solely upon them" (taken directly from the LDS handbook on Policies on Moral Issues, chapter 21.4).

Hinduism is complex to discuss as a whole, mostly because "Hinduism" is a colonial simplification of thousands of smaller region-specific religions[56]. As such, it is extremely difficult to describe the bioethics of oncofertility within the context of Hinduism. However, the Hindu tradition is understood to place special importance on family planning, childbearing and having children, especially having boys. One important point to note is that children need not be genetically related to the father to become his heir. One analysis of Hindu practices thus suggests not only that ARTs may be allowed, but actually encouraged. In Bhattacharrya's analysis and review of Hindu bioethical views of assisted reproductive technology, ARTs are accepted and approved techniques for family building. Sperm donation, adoption, surrogacy and "paternal surrogacy" (where a third party man impregnates the woman if the husband is himself infertile) have all been identified in the Hindu narratives[57]. With that being said, while those

narratives suggest that some alternative fertility practices are allowed, it is impossible to draw conclusion without doing further empirical research.

Buddhism, like Hinduism, doesn't have specific rules on assisted reproductive technologies; rather, one may derive interpretations from the Buddhist tradition. The Buddhist tradition includes 5 precepts (sikkhàpada) by which practicing Buddhists live their lives, similar to the 10 commandments: (1) not to harm living beings, (2) not to steal, (3) not to engage in wrong sexual behaviors, (4) not to lie and (5) not to take alcohol or intoxicating drugs. Regarding the 3rd precept, Buddha said that "wrong sexual behavior" consisted of sex with 1) underage persons, 2) persons who had taken a vow of celibacy (nuns/monks), 3) married persons, 4) prisoners, and 5) persons engaged to be married. Sexual practices such as sex before marriage, masturbation, homosexuality, sex with people of other races and non-monogamy are not technically condemned by Buddhism. Another aspect of the Buddhist tradition that some scholars stress is the alleviation of suffering. Some may therefore argue that as long as the fertility technologies being used don't bring harm to any parties involved, ARTs may be allowed and encouraged as a way to alleviate the suffering of not being able to conceive[58]. On the other hand, certain Buddhist texts like the Vinaya Pitaka – which regulates the life of Buddhist monks – consider the desire for a child to be similar to the desire for wealth and economic security, both of which may lead humans away from the path to Enlightenment. Furthermore, while masturbation is not condemned by the Buddhist faith, it is believed that life begins at the moment of conception according to the *Mahātahāsakhaya Sutta*[59]. The creation/destruction of embryos by IVF and other similar procedures may thus be problematic. The decision to undergo oncofertility treatments of any kind may therefore be conflicting for individuals belonging to the Buddhist faith and ultimately based on personal interpretation of Buddhist principles and philosophies. As such, the discussion of Buddhism in the context of ARTs would also require more systematic empirical research, and thus will not be examined further in this article.

Discussion: How can we provide guidance to patients and providers into the moral and theological implications of their decisions?

There are many variables to consider when thinking of the best approach to male pediatric oncofertility counseling, some of which include: the risk of death from the cancer, the risk of sterility, the age of the patient, whether the patient is pre- or post-pubertal, whether the patient understands reproduction, and the patient and his guardians' values around ART and cutting edge FP technologies. When religious ideologies too are taken into account, conflicts can emerge as in the following cases:

Case 1: A 4-year-old male with benign disease requires bone marrow transplant (BMT) with whole body irradiation. The risk of sterility is very high and the risk of death from disease is low. Should he receive a testicular biopsy? (Issues raised: consent and pediatric testicular biopsy).

In many situations, ethical concerns and questions are interwoven with cultural, moral, and religious ones. In this case, the patient is too young to even give assent to the procedure. In fact, in order to assent, an individual must be able to comprehend, retain and weigh the information given to him sufficiently to make a decision that in some way reflects his preferences, even if he is not yet capable of exercising autonomy[60]. Thus with such a young child, rather than any exercise of partial autonomy through assent, the way to respect autonomy is to respect the young child's right to an open future. In 1992, Joel Feinberg[61] described 4 different kinds of rights: rights that children and parents both have (e.g. right not to be killed), rights only adults have (e.g. the right to reject or join a religion), rights only children and dependents have (e.g. shelter and protection), and rights that should be saved until a child becomes an adult. He penned the term "a child's right to an open future" to describe the latter, a child's right to have their autonomy preserved until they are able to make important personal decisions on their own. Children do not yet have the ability to exercise these rights, but these rights can also be 'violated "in advance" before the child is even in a position to exercise them'. In 2001, Dena Davis[62] mentioned the example of the right to reproduce, which a child is not yet able to act upon, but that will become their right in adulthood. Therefore, a child has the right not to be sterilized so that he can exercise that right as an adult. It is a parent's duty to preserve their child's "baseline" state of health, one that is not necessarily enhanced but at least not diminished from an expected standard (e.g. a parent is expected to provide enough food for the child to grow normally, but not necessarily expected to provide more food than required for

normal growth). Simply put, parents are "guardians" of their children's future autonomy while the child's autonomy remains "dormant".
As far as religious ideologies are concerned, testicular biopsy with testicular tissue transplantation and subsequent fertility restoration would be allowed in Catholicism, Evangelical Christianity, Islam, Judaism, Church of Latter-Day Saints and Hinduism. In fact, these religions all seem to agree on one particular point: treatments that have the potential to preserve and/or restore fertility and make the natural act of procreation successful are not only allowed, but encouraged.
The other experimental option with testicular biopsy is *ex vivo* SSC differentiation into mature sperm cells for future IVF/ICSI. IVF/ICSI is forbidden by the Catholic and Evangelical Christian teachings. Islam, Judaism, Mormonism and Hinduism do not seem to condemn the practice. For Islam, this is true as long as it is done within the context of marriage without a third party involved. Orthodox Jewish doctrine accepts it as long as no sperm is wasted in the process (see case 3, below), and Latter-Day Saints only discourage the use of a third-party donors (and even then, the practice is not totally forbidden).

Case 2: an 8-year-old boy with severe malignant disease will be requiring time-sensitive treatment with a high risk of sterility, and a high risk of death from the disease. A testicular biopsy is performed. (Issues raised: delaying cancer treatment and use of testicular tissue for research)
In this case, the initial conversation between the parents and the providers may include the risks of delaying cancer treatment, the meaning of preserving sperm for the child and parents given possible death of this child, and the potential financial burden linked to the procedure. Saving the life of the boy is obviously the most important element of his medical care. Now, let's imagine that the child will survive the treatment whether he starts now or in one week. The caveat is that if he starts in one week, we can save his fertility, but he will also need to be on chemotherapy for an extra 10 days. How exactly does one quantify the importance of fertility preservation, and how much positive outcome from the cancer treatment is worth sacrificing for it? The question of priority between fertility preservation and time sensitivity of cancer treatment is an area of active research and discussion.
Regarding the testicular sample: SSC differentiation *ex vivo* and testicular tissue re-implantation do not yet work in humans, and as such more research must be conducted. What is the stance of different religions on experiments conducted on SSC, which are adult stem cells? Certain religions may allow testicular tissue to be used for one kind of reproductive health research but not for another, depending on the level of maturity the SSC reach, the environment in which they are tested, and whether fertilization and embryo experiments are involved. For example,

Catholicism forbids research on embryonic stem cells (ESC), specifically ESC research that destroys the embryo. By contrast, adult stem cell research is allowed under Catholic doctrine because no embryo is harmed in the process. That being said, research currently being done on *ex vivo* SSC differentiation is a debated topic and has yet to be fully determined. In fact, the Catholic church's stand on sperm cells that were differentiated *ex vivo* versus "naturally differentiated" sperm cells found in semen is unclear. Likewise, Jewish scriptures condemn the "spilling of seeds" if the purpose is not to procreate, whether or not it is in the context of coitus, but it is also unclear whether that includes sperm cells differentiated *ex vivo*. While the Muslim stance on the actual act of sperm sample production is debatable, there is no restriction on how terminally differentiated sperm cells should be used except that they cannot be used to fertilize an egg other than the egg of the sperm donor's wife.

Case 3: A 15-year-old post-pubertal boy with malignancy is about to undergo chemotherapy that may sterilize him and the chance of survival is high. He is able to produce a semen sample but his religion may not permit retrieving the sample. (Issues raised: masturbation and other sperm sample-retrieving techniques)
For post-pubertal boys, masturbation and production of a semen sample for cryopreservation is the standard of care. This sample could be used for IUI, IVF, or ICSI. If masturbation is not possible or allowed, surgical sperm retrieval is a standard technique. Sperm obtained from this approach, however, can only be used for IVF/ICSI. Catholicism and Evangelical Christianity both forbid IVF/ICSI, so even sperm aspiration, sperm retrieval from urine and electro-stimulation under anesthesia as alternatives to masturbation may not be available options for the patient. For the post-pubertal patient unable to produce a semen sample or able to consider IVF/ICSI, the only possible experimental procedure for this patient would be one that restores his fertility after chemotherapy. Currently, the only option would be to consider a testicular biopsy and possible future testicular tissue transplantation. Jewish tradition technically does not allow "seed spilling", but producing sperm samples for the purpose of procreation is arguably acceptable, as long as no semen is wasted. In other words, the act of masturbation itself is not condemned as much as the act of "wasting" semen. Islam's stance on masturbation is not clear. Some Sunni Islamic scholars argue that any sexual act outside of marriage is forbidden from the following quote: *"And those who guard their private parts -- Except from their wives or that their right hands possess (i.e. slaves), -- for them, they are free from blame. But whoever seeks beyond that, then those are the transgressors."* [Qur'an, 23.5-7][63]. However, others argue that while coitus outside of marriage is clearly prohibited, it isn't clear whether or not those forbidden sexual acts include masturbation. If a patient and guardians are

concerned that masturbation may be an issue, alternative sperm-retrieval techniques may be used instead without going against Muslim beliefs. The LDS church's stance on masturbation is similarly debated, but masturbation in the context of a medical procedure (e.g. IVF) is tolerated. Overall, regardless of the religion's stance on masturbation, doing invasive techniques where masturbation is possible may be problematic for the medical professional commitment to doing the least harmful procedure, which again is an ethical conversation around having the child's best interest in mind.

Summary and Conclusions

The wide breadth of religious ideologies around the topic of reproductive health is challenging to navigate, and a "one-rule-fits-all" does not exist for most cases of male pediatric iatrogenic infertility. This is in part due to the fact that many religious beliefs are based on texts that have been interpreted differently by different scholars through the years, and also due to the fast pace of scientific discoveries and technological advances. Generally speaking, most of the religions explored in this review seem to agree that procedures that could restore fertility (such as testicular tissue transplantation) are allowed and encouraged, because the actual event of procreation and fertilization itself is left untouched. Unfortunately, this technique is still in the experimental stage: successful in many animal species and used widely for more than 20 years, but not yet in humans.

Religious doctrines start diverging when SSCs are involved. It isn't clear whether sperm cells differentiated from SSC *ex vivo* are considered to be on the same level as sperm cells found in semen for any of the religions discussed, and should be the topic of further research. With regards to naturally occurring sperm cells, religions like Catholicism, Evangelical Christianity and Judaism condemn the wasting of semen for purposes other than reproduction. The topic of masturbation is debated among Muslim and LDS scholars, and in case of uncertainty alternative techniques to retrieve sperm cells may be used.

Ex vivo ARTs like IVF and ICSI are prohibited under Catholic and many other Christian teachings because fertilization must happen during coitus between two married, opposite-sex individuals. Judaism tends to allow ARTs as long as no semen is wasted in the process, and also because procreation within the Jewish community has been historically encouraged following events like World War II. Islam allows ARTs as long as the only parties involved are a married man and woman.

The involvement of a third-party member is forbidden or at least strongly discouraged by almost all religions across the board. Under Christian, Catholic and Muslim doctrine, the use of a sperm or egg donor is prohibited because the embryo involves someone outside of the marriage. Surrogacy is prohibited under Catholicism and Evangelical Christianity for the same reason, with the exception of Southern Baptist Christians which may allow "embryo adoption". Judaism and LDS strongly discourage the use of sperm, egg and uterus donors, but generally do not condemn it if it is a couple's only choice.

Many questions remain for religious leaders and scholars around the topic of reproductive health and fertility treatments. The topic of testicular tissue biopsy and transplantation has been discussed as being generally acceptable across most religions, because the act of procreation remains untouched within the boundaries of a marriage. How about receiving a SSC transplant from a donor? None of the religions discussed are against organ transplant, the act of coitus would be maintained between husband and wife, no *in vitro* experiments are involved for the fertilization, and the sperm cell final differentiation happens *in vivo*. What are the religious arguments in favor, and what are the religious arguments against this example? This example is clearly ethically problematic for genetic reasons, and is only meant to emphasize the fact that the discussion around fertility and reproductive health can get tricky when so many variables – including an individual's faith – are part of the equation being considered. Similarly, it isn't clear which research procedures are tolerated under which religion, especially when it comes to undifferentiated spermatogonial stem cells.

This review has been mostly focused on the restrictive nature of religious doctrines, and didn't explore other factors that may influence a male pediatric patient and his guardians' decision to proceed with oncofertility treatments. Regardless of religious affiliation, these techniques are still experimental and should only be allowed in institutions where IRB approval has been obtained. Considering the likelihood that the experimental testicular biopsy procedures may be functional in less than 20 years, what are the ethical obligations of providers who have the ability to offer these services? Considering most people do not have easy access to a hospital that provides these procedures, what are our obligations as a society to expand these services to those who could benefit from them?

Finally – and most importantly – this review did not discuss the opinion of the individual who is directly affected by the cancer treatment. Everyone is entitled to their freedom of choice, and someone's decision regarding their care may ultimately go against what their faith would deem acceptable. What are the factors that would influence a family to pick a religious belief over a treatment, or a treatment over a religious belief?

The topic of experimental fertility therapies brings up more questions than answers at this time, both because technologies in the field are evolving at an incredibly fast pace and because we are entering uncharted ethical territory. Some religions have fairly specific guidelines around fertility treatments, while others will require more empirical research to answer these questions. Qualitative-based research directly

asking members and leaders of these religions questions about their interpretation of their respective faith around reproductive and fertility care should serve as a starting point, followed by more targeted questions around the topic of fertility preservation.

Part II: Access to Fertility Preservation for Cancer Patients on Tyrosine Kinase Inhibitors

Introduction & Background

In 2017, almost 1.7 million new cancer cases and more than 600,000 cancer deaths are projected to occur in the United States[64]. The risk of infertility caused by cancer treatments is a primary concern for many of the male survivors of these malignancies[65]. Among existing cancer treatments, tyrosine kinase inhibitors (TKIs) are a relatively new class of targeted therapy that have been shown to treat a growing number of malignancies with fewer side-effects than many of their chemotherapeutic counterparts.[66] [67] [68] [69] [70] The use of TKIs is expected to increase as a direct result in the years to come.

Many traditional cancer therapies, including chemotherapies and radiation, are known to cause infertility[71] [72]. Alkylating agents such as cyclophosphamide and procarbazine have been shown to cause oligospermia, azoospermia, and impaired fertility[73]. Other non-alkylating therapies including methotrexate[74], doxorubicin[75] and taxanes have also been shown to negatively affect spermatogenesis[76]. For many newer (and a number of older) cancer therapies, there is a dearth of clinical research exploring their potential toxic effect. For TKI's two case reports suggest that TKIs may result in low sperm concentration[77] [78]. Interestingly, several different tyrosine kinases are critical for spermatogenesis, sperm motility, and egg fertilization. As such, TKIs have been hypothesized to impair these processes. In fact, recent results[79] [80] [81] [82] [83] [84] [85] suggest that "imatinib crosses the blood-testis barrier and reduces sperm density, sperm count, survival rates, and activity in CML-CP patients". Other preliminary results suggest that capacitation – the process by which spermatozoon become phosphorylated by specific tyrosine kinases in the environment of the female reproductive tract, leading to hyperactivation and the subsequent acrosome reaction essential to fertilization of the egg by the sperm cell – may be inhibited by some TKIs[86].

The majority of men undergoing potentially sterilizing treatments report never having been told about such effects. Zebrack et. al found that 59% of survivors were unsure of the status of their fertility, and half of them could not remember whether anyone had talked to them about the risks of the cancer treatment on their fertility[87]. Since TKIs do not target rapidly dividing cells like many common cancer treatments do, healthcare professionals may be even less likely to suspect that their patient's fertility may be affected. This has not been studied before.

Paradoxically, the American Society of Clinical Oncology, American Academy of Pediatrics, the American Society of Reproductive Medicine as well as other groups recommend counseling for all reproductive aged men and women about the potential reproductive effects of cancer therapies and recommend referral to fertility specialists for interested patients[88].

In this study, we sought to better quantify the barriers to accessing oncofertility care, including but not limited to patient knowledge, financial, geographical and cultural barriers to fertility preservation among men utilizing TKIs.

Materials and Methods

Cohort Description:
Participants were recruited into the cohort from UCSF oncology clinics, primarily Mt. Zion and Mission Bay clinics. The inclusion criteria for the study were defined as age 18-65, male sex, and use of TKIs. Exclusion criteria were defined as: female sex, people who have not been on TKI. Of the 79 men who enrolled in the study, 67 (85%) agreed to fill out the survey. The participants completed the survey on paper, on a tablet, or online (REDCAP). The institutional Committee on Human Research approved this protocol and all subjects provided consent.

Outcome Variables:
Participants were asked whether they had considered fertility preservation and whether they had attempted fertility preservation after learning of their cancer diagnosis.

Potential predictors of access to fertility preservation:
Cancer diagnosis, type of TKI and other cancer treatments, age at diagnosis, desire to have children at the time of therapy, race, education, employment and income, marital status, knowledge of and desires for fertility preservation, discussion with their healthcare providers about fertility preservation, and barriers to fertility preservation access were determined through answers to the questionnaires completed by the participants. For education, income and race, categories were dichotomized due to small sample size. Education was categorized into “some college or less” (including "Less than 8 years of school", "8-12 years, without high school graduation", "High school graduation or GED (high school equivalency)", "Vocational or technical school", "Some college or university/ Associate of Arts (AA) degree"), Bachelor’s degree, and Graduate/professional school and dichotomized to Bachelor’s degree or less than Bachelor’s degree. Household income was categorized as less than $40,000 per year, $40,000-100,000 per year, $100,000 or more per year, and was dichotomized as less than $100,000 or more than $100,000 for the bivariate analysis. Employment status was reported as full-time employment, part time employment, retired, student, unemployed, and dichotomized as full-time employment or not. Race was determined by self-report and categorized to White, Black or African American, American Indian or Alaska Native, Asian, and other/mixed, according to guidelines utilized by the NIH, and dichotomized as white or non-white. In contrast to our outcome variables, participants were also asked what specific information they were provided by their doctors. Regarding the conversation with their doctors, participants were asked whether their doctor had i) asked about their desire to have children in the future,

ii) discussed ways to protect their testicles and their ability to have children from the cancer treatment, iii) provided referrals to fertility specialists and iv) provided resources for more information on ways to preserve fertility.

Barriers to Fertility Preservation:
Participants were asked to consider several scenarios, and whether those had prevented them from seeking fertility preservation. Financial barrier was considered to be experienced by the participants if the "it was too expensive" and/or "my insurance did not cover fertility preservation" option were selected. Geographic barrier was based on "the fertility clinic was too far away". Language barrier was based on "the fertility doctor did not speak my preferred language". Knowledge barrier was based on "I did not understand that my cancer treatment may affect my fertility", "I did not know that preserving my fertility may help preserve my fertility", and/or "I thought that based on my or my partner's age I may not qualify". Other barriers included "I did not have a partner at the time" and "other".

Statistical Analysis:
Descriptive statistics were used to characterize the study population. Chi-square tests were used for categorical variables and ANOVA for continuous variables. We report Odds Ratios (OR) and their 95% confidence intervals to estimate the association between subject characteristics and whether they had considered and/or attempted fertility preservation following a cancer diagnosis. STATA 15 (Statacorp, College Station, TX, USA) was used for all analyses.

Results

A total of 67 participants completed the survey with a mean age of 48 years old (range: 21-72; SD: 13), 43% were 18 to 45. Importantly, all participants who were interested in having children were 55 years old or less (Table 1). 66% of the participants identified as White or Caucasian, 17% as Asian, 8% Black or African American, and 9% in the other categories, including mixed race. Regarding salary, employment and education, 40% of the participants reported a household income greater than $100,000, 73% reported having a Bachelor's or Graduate degree, and 82% reported being employed full-time. In terms of relationships, 66% had a partner, and 53% reported having achieved at least one pregnancy with a partner previously. Note that 21 of the 67 participants (32%) reported wanting to have children in the future.

The majority (54%) of participants had a diagnosis of CML. The other 46% had cancers which included renal cell carcinoma, gastrointestinal stromal tumors, hepatocellular carcinoma and pancreatic neuroendocrine tumors. 34% were taking Dasatinib at the time of the survey, 27% Imatinib, and 39% were taking other TKIs including but not limited to Sunitinib, Pazopanib, Nilotinib, Bosutinib, Sorafenib, and Everolimus.

When asked about knowledge around TKIs and their impact on fertility potential, 57% reported not being provided with information about the risks of cancer treatment to fertility and ability to father a child by anyone on the medical team, 54% believed that the treatment might affect their fertility, and 58% were concerned about becoming infertile as a result of cancer treatment (Table 2). A quarter (25%) of the participants considered fertility preservation and 12% attempted fertility preservation after learning they had cancer, while 58% reported that their doctor had not asked them whether having children was important to them (Table 3). When asked about the services provided specifically by their doctor at the time of diagnosis, 78% reported that their doctor did not discuss possible ways to protect their testicles from the effects of cancer treatment, 64% reported that their doctor did not discuss possible ways to protect their ability to father a child, 78% reported that their doctor did not suggest they seek consultation with a fertility specialist, and 72% reported that their doctor did not provide available resources for more information regarding ways to preserve fertility (Table 3).

In terms of the challenges associated with fertility preservation access, 45 participants (67%) reported experiencing at least one barrier to fertility

preservation. Of those who reported experiencing barriers, 7% reported financial barriers. 49% encountered knowledge barriers. 24% were not provided a referral to a fertility specialist. Geographical and language barriers were reported in 2% and 2% of the participants, respectively, and 47% reported other unspecified barriers.

Exposure variables, which included barriers experienced, race, desire to have a child, previous pregnancies, education, income, employment, partnership status, age at diagnosis, receiving treatment(s) other than TKI, and belief that treatment may cause infertility were evaluated in bivariate models with outcome variables defined as "FP considered" and "FP attempted" (results reported in Table 4A and Table 4B, respectively).

Bivariate analyses demonstrated that men who wished to have a child in the future were much more likely to consider FP (OR 16.7, $p<0.001$) and to attempt FP (OR 24.5, $p=0.004$) than those who did not. Men who believed that the treatment may cause infertility were almost 4 times as likely to consider FP (OR 3.67, $p=0.035$) and to attempt FP (OR 4.3, $p=0.09$) compared to those who did not. Each 5-year increase in a participant's age was associated with a 51% decrease in considering FP (OR 0.49, $p<0.001$), and a 54% decrease in attempting FP (OR 0.46, $p=0.003$). Those who were provided information about the risks of cancer treatment to their fertility by a medical team member were 7.3 times more likely to consider FP (OR 7.3, $p=0.003$) and 5.4 times more likely to attempt FP (OR 5.4, $p=0.05$) than those who were not. Note that each 5-year increase in age was associated with a 37% decrease in likelihood of being provided information about the risks of cancer therapy on fetility by a member of the medical team (OR 0.63, $p<0.001$). While not achieving statistical significance at the $p<0.05$ level, those who had achieved previous pregnancies were 60% less likely to consider FP (OR 0.4, $p=0.13$) than those who did not; those who made more than $100,000 per year were 65% less likely to consider FP (OR 0.35, $p=0.09$) and 71% less likely to attempt FP (OR 0.29, $p=0.15$) than those who made less than $100,000; those who were employed full-time were 70% less likely to consider FP (OR 0.3, $p=0.05$) than those who were not; finally, those who reported experiencing barriers to fertility preservation were 74% less likely to attempt FP (OR 0.26, $p=0.09$), but 21% more likely to consider FP (OR 1.21, $p=0.76$) than those who did not report barriers.

Discussion

The reasons patients receiving TKIs are not preserving fertility are often complex and multifactorial. Our findings suggest the main barrier to male fertility care is the lack of awareness of the possibility that cancer therapies can cause infertility and/or that this may be prevented through fertility care[89]. Even though a 32% of participants in our cohort reported wanting children in the future, most doctors did not tell their patients of the potential risks of TKI cancer treatments on their ability to father a child, nor did they ask them whether they wanted to have children. Importantly, more than half of all the participants were not asked whether having children was important to them by their doctor at all or that preservation techniques might help save their fertility.

Schover et. al. (2002) demonstrated that only 60% of men remembered being told that infertility was a risk of cancer treatment and 51% had been offered the option to bank sperm. Those who discussed infertility with their physicians had higher knowledge about cancer-related infertility and were significantly more likely to bank sperm[90]. Our study reiterates this lack of knowledge and discussion with this relatively new catergory of cancer drug, despite previous concerns and ASCO recommendations.

This knowledge barrier can also originate from the provider: for example, 91% of the oncologists surveyed in one study agreed that patients at risk for infertility should be offered sperm banking. Of those, 48% responded that they discussed the option with less than 25% of male patients who are actually eligible[91]. One reason for these relatively infrequent discussions by oncologists may be due to limits in oncologist knowledge on the topic. Tournaye et al (2004)[92] found that 74% of responding oncologists reported not being aware of advances in available reproductive technologies[93]. Add to this a multitude of other social and economic reasons, including cost, stigma, religious beliefs, and cultural values. Men are less likely to inquire about fertility care than women[94 95], and there are perhaps differing public perceptions about whether fertility care is a luxury rather than a medical necessity.

Furthermore, almost 4 out of 5 people reported not being offered any alternatives or fertility referrals at all. This large discrepancy between fertility desires and knowledge around the risks of TKI cancer treatments on one's fertility is clearly problematic. This is potentially infringing on a patient's right to autonomous decision-making around their care, which is an important ethical issue. While many could argue that cancer treatment should be prioritized over fertility care if

one had to be chosen over the other, this is a decision that ultimately belongs to the patient. The question should not be whether or not to discuss fertility preservation with a patient about to undergo potentially sterilizing treatments, but rather, how to discuss the sensitive topic of fertility in conjunction with a diagnosis as difficult as cancer. A relative limitation of our study is that we evaluated patient perspective only and did not ask about provider knowledge of TKI drug effect on fertility to study the disconnect. However, we suspect the result would be similar to the previous studies with more well known fertility damaging cancer drugs.

Moreover, 7% of the respondents who experienced barriers to care expressed a financial barrier to fertility preservation. Though not a particularly high percentage, it is important to keep in mind that this was a relatively affluent group of patients, with 40% earning more than $100,000 annually. In spite of infertility being recognized as a disease by the American Society of Reproductive Medicine (ASRM) in 2008, only 6 states in the US have laws that require insurers to cover male infertility[96], regardless of the cause of infertility. In fact, men undergoing sterilizing cancer therapy will often not be covered by their insurance to preserve their fertility. Further investigation should be performed in a more financially heterogeneous cohort of men to determine the financial burden of FP as it relates to desires around oncofertility care in the general population.

When looking at the bivariate analyses of barriers subcategories (knowledge, referral, financial, geographic, language, other) compared to whether FP was considered or attempted, a clear relationship was observed; however, given the relatively small sample size in this cohort, these associations did not achieve statistical significance. It is interesting to note that the odds ratios for every single barrier subcategory were >1 when compared to FP consideration, and all were <1 when compared to FP attempt. In other words, those who experienced barriers were more likely to have considered FP, but less likely to attempt it than those who did not experience barriers. Possibly, these patients came up against unsurmountable obstacles and were unable to proceed further down the fertility preservation pathway.

In the bivariate analyses, desire to have a child was strongly associated with both FP consideration and attempt. In other words, a positive answer to the question “do you wish to have children in the future?” may be enough to predict whether a male cancer patient would consider and attempt fertility preservation. This presents a simple question that clinicians caring for these patients can add to their evaluation and treatment consultations. Furthermore, a patient’s belief that the treatment may cause infertility was also associated with considering and attempting FP, consistent

with the idea that those who knew the potential risks of infertility were more likely to consider and attempt FP than those who didn't. Oncologists may not be providing patients with these potential risks because they themselves do not know the potential reproductive risk TKI therapies may cause.

Increasing age at diagnosis was associated with a decrease in both FP consideration and FP attempt, meaning that interest in FP decreased with age. This may be because men who were older were more likely to have already had children (OR 1.22; 95%CI 0.99-1.50) , and less interested in having children (OR 0.38; 95%CI 0.23-0.62). Similarly, participants who had achieved previous pregnancies with a partner were associated with lower FP consideration (OR 0.42, p=0.15) and attempt (OR 0.48, p=0.35), consistent with the idea that people who already have children are less interested in having more in the future than those who don't.

Meanwhile, surprising results included a decreasing interest in FP in those with higher incomes. Similarly, those who were employed full-time were less likely to consider FP. One possible hypothesis for these results is that wealthier people tend to be older, have less time, already have children, are less interested in having more children. The results for both income and employment were not statistically significant, and a larger cohort would be required to further investigate these results.

It is also important to note certain limitations of the cohort studied. The population was predominantly white (66%), wealthy (40% made >$100,000/year), and educated (73% bachelor's or more). With that being said, these elements may arguably further reinforce the reality of such barriers, considering the fact that a significant proportion of this wealthy, educated cohort reported experiencing them. A larger sample size may also reveal more statistically significant trends observed in this preliminary analysis. Future studies of clinical importance should therefore be performed in more heterogeneously diverse populations, including people who do not necessarily have access to the UCSF oncology clinics, in order to shed more light on the seemingly unequal distribution of fertility preservation services among cancer patients. Follow-up studies should also further explore the barriers to fertility care experienced by cancer patients, inparticular those who selected the "other" option, in more qualitative studies.

This is the first study of its kind to look at issues of access to care in patients on TKI therapy. These are novel findings related to questions that have never been explored before, in the largest cohort that has looked at access to care in these patients. Previous work has hypothesized that a number of barriers can affect

access to fertility preservation care[97]. This is the first study not only to define and classify such barriers, but also to investigate their prevalence and relative consequences in this vulnerable population.

In summary, not only were almost half of the patients surveyed worried about the risks of cancer treatment on their fertility, more than half felt like they had not received the adequate amount of information about the risks of infertility linked to cancer therapy. Furthermore, the high number of participants that expressed experiencing barriers to oncofertility preservation shows the need for more comprehensive and available information when making difficult decisions related to fertility around cancer care.

Limitations notwithstanding, these findings have important implications for clinicians, patients, and policymakers. Clinicians need additional education around the fertility risks associated with TKI and training about fertility preservation counseling. A simple question such as "do you wish to have children in the future?" can help establish a plan for the patient that will meet his needs moving forward. For patients, the fact that the majority of respondents reported a lack of knowledge around the risks of their cancer treatment on their fertility begs a broader question around informed consent and whether patients truly understand the stakes and risks associated with such potent treatments, especially following a traumatizing diagnosis. Policymaker need to consider these findings when drafting new laws around cancer survivorship and fertility preservation.

Conclusions

Considering the advances in cancer treatments and increasing survival rates, it will be important to obtain more information related to desires around life after cancer beyond desires around fertility and family planning. Moving forward, we will need a larger sample size in order to determine how to provide fertility care to those at risk in a sensitive way, including but not limited to determining the most appropriate timing to have these conversation (i.e. either at the same time as cancer diagnosis or at a later date; possibly even prophylactically before confirmation of cancer diagnosis), cultural preferences around fertility care, ways to break down barriers to accessing such services, and studying why knowledge around onfertility preservation is not more readily available not only to patients but also to their physician and care team. In the future, these results may pave the way for more comprehensive screening tools when caring for cancer patients, such as including a question as simple as "do you wish to have children in the future?" to be prompted on the electronic medical record screen while discussing cancer treatment, and moving towards a model that breaks down more barriers experienced by cancer patients.

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