

AN EXPLORATION OF FERTILITY PRESERVATION-RELATED DECISION-MAKING IN  
CHILDHOOD CANCER PATIENTS

by

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This thesis was prepared under the direction of the candidate's thesis advisor, Dr. Ashley Kennedy, and has been approved by the members of her supervisory committee. It was submitted to the faculty of The Honors College and was accepted in partial fulfillment of the requirements for the degree of Bachelor of Science in Biological and Physical Sciences.

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## Abstract

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As medical research expands to include a vast variety of new treatments and the world becomes increasingly interconnected, the ethics involving patient care and treatment plan development also become extremely important to consider. One of the most novel and widely unexplored fields of reproductive health is *oncofertility*, a field of medicine that aims to minimize the negative impacts of cancer treatment on fertility. For many childhood cancer patients, cancer treatment involves oncofertility-related discussions that involve their families, physicians, and many other people. This paper serves primarily to evaluate the quality of educational and clinical resources available to childhood cancer patients regarding fertility preservation, the current approach to these cases from an ethical perspective, and to propose a procedure for treatment plan development and decision making that carefully considers the values and beliefs of the patient, his/her family members, physicians, and ethics board members involved with the case to help standardize the process.

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## Introduction

As defined by the National Cancer Institute, “childhood cancer” is “a term used to describe cancers that occur between birth and 15 years of age” (NCI Dictionary of Cancer Terms). While the American population is aware of the significant impact of cancer on children, much of the publicized impact has to do with adulthood cancer and specific types of cancer due to its prevalence. Although childhood cancer makes up less than one percent of all diagnosed cancers in America, over 11,000 children are diagnosed every year and many face years of treatment before they are declared cancer-free ("Key Statistics for Childhood Cancers"). Throughout these years, they face many challenges that impact their lifestyles, both temporarily and permanently, and the solutions to these problems often involve ethically challenging decisions.

Oncofertility is the field of medicine that aims to minimize and compensate for the effects of cancer treatment on the reproductive system ("Oncofertility Medical Definition"). Interventions often includes pre-treatment fertility preservation options as well as post-treatment alternative fertility options for all age groups. Fertility preservation aims to maintain aspects of the reproductive system such as eggs or sperm, either within the body or externally for future use. In patients who are minors, decisions involving fertility preservation are dependent on personal religious and moral values as well as the stage and type of cancer and the patient’s age and gender. Parents and physicians tend to influence the final decision at variable levels depending on the age of the child and alongside physician advice, parents/guardians tend to refer to written materials online or as provided by the physician (Howell 2016).

The resources available to childhood cancer patients and their guardians involved in the decision-making process can be divided into two categories: educational and clinical.

Educational resources tend to make up the bulk of the information covered because of increased accessibility, mainly through the internet and social media. Websites like SaveMyFertility.org are written by physicians and research scientists in the field of oncofertility and are written in layman terms, i.e. are more understandable versions of clinical guidelines ("The Oncofertility Consortium"). These pieces often complement the information given to patients by physicians and therefore enhance the patients' and their guardians' understanding of the options available to them and the reasons to rule out other options that are not viable choices. Other resources about fertility preservation that include forums and personal testimonials offer perspective and advice, but do not provide factual information regarding treatment options or the science behind the cancer. Clinical resources are primarily provided by the physician, where the information is shared verbally during appointments and meetings with the patient and his or her family, but a small part of it comes in the form of handouts or pamphlets that are meant to be read after the direct interaction with the patient (Goetsch 2014). Often, clinical interactions are informative and are intended to be comforting; however, the physician's involvement in educating the patient can result in the physician's injection of personal opinion which will influence the patient's ultimate decision.

The decision-making process regarding fertility preservation in childhood cancer patients not only involves numerous case-related factors, but also the personal preferences of the patient, his or her guardians, and the attending physician. While the patient, if an adolescent, is given a path for input in the outcome, often the guardians of the patient and the physician make the final decision (Goetsch 2014). This decision is dependent on the personal preferences of the family as well as the costs and benefits of each fertility preservation option as determined from educational and clinical resources. To determine the ethics of fertility preservation in child cancer patients,

we must first consider the quality of educational vs. clinical resources available and then examine the impact of the patient's family and physician on a decision that permanently alters the patient's body and their future.

Though it is not the most common category of cancer diagnosed in the general American public, childhood cancer is still newly diagnosed in over 11,000 children annually and countless others continue to battle the illness ("Cancer in Children and Adolescents." National Cancer Institute). As estimated by the National Cancer Institute, of the 11,000 children diagnosed with cancer every year that are ages 0-15, approximately 1,200 will die of the disease. Further, among adolescents (ages 15-19), approximately 600 of the 5,000 diagnosed patients will lose their battle with cancer each year. Cancer is also the leading cause of childhood deaths at a rate of approximately 53% of annual deaths ("Childhood Cancer Deaths Per Year: CureSearch"). Many childhood cancer patients have still-developing immune and biological systems and thus, their chances of ever being declared cancer-free are diminished, especially when comparing pre-pubescent children to adolescents. Of the children diagnosed with cancer, 1 in 8 do not survive and 60% of those who do survive suffer debilitating conditions later in life, including secondary cancers, muscular problems, and fertility-related issues ("Childhood Cancer Deaths Per Year: CureSearch").

Of all cancers occurring in children, the most commonly diagnosed are leukemia and brain and central nervous system cancer, specifically acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) and medulloblastoma (MB), low grade glioma (LGG), neuroblastoma (NB) and Ewing sarcoma (ES) (Saletta, Federica, et al. *Translational Pediatrics*, Apr. 2014.). These cancers also have the most intense impact on the patient because they target two main areas of the body: the brain and the

bloodstream. Due to the biological significance of the involved areas of these commonly occurring cancers, treatment options are limited and must be relatively less harmful to avoid significant damage to a child's developing body. Often, treatment is multimodal, meaning that multiple treatment methods are combined to optimize results, and includes a combination of chemotherapy, radiation, and surgery (Burdach, Stefan E. G., et al. "Precision Medicine in Pediatric Oncology.").

In this thesis, an examination of childhood cancer diagnoses, cancer treatment plans and fertility preservation plans will be discussed, followed by the evaluation of the quality of educational and clinical resources available to childhood cancer patients regarding fertility preservation and the current approach to these cases from an ethical perspective. Based on this evaluation, a procedure for treatment plan development and decision making that carefully considers the values and beliefs of the patient, his/her family members, physicians, and ethics board members involved with the case to help standardize the process will be proposed.

## Cancer Treatments

After years of research, a variety of cancer treatments have been made available to patients seeking care for different childhood cancers. Common cancer treatment methods include surgery, chemotherapy, radiation therapy, immunotherapy, and stem cell transport. Though these treatment plans are developed to suit children's bodies and their specific cancer diagnoses, the procedures often cause considerable damage to a child's developing system, including the reproductive system ("Childhood Cancers" 2019).

### Surgery

Surgery involves the physical removal of a cancerous mass from the affected portion of the patient's body. The two major types of surgery performed are open surgery, in which one

large cut is made to remove the tumor, and minimally invasive surgery, in which the surgeon makes multiple small cuts to insert a laparoscope and laparoscopic surgery tools which can be used to complete the tumor removal and requires less time to recover from ("Surgery for Cancer" 2015). While surgery does not have major effects on fertility unless the tumor is in the reproductive organs, it often does not result with the patient being cancer-free; if one small section of the tumor or a single cell remains in the child after a surgical effort to remove the tumor a relapse could occur. Further, surgery to remove cancer from reproductive organs more than likely involves the removal of parts or an entire organ, therefore affecting reproductive ability for the child in the future.

## Radiation Therapy

Radiation therapy involves using high doses of one of two types of high-energy radiation, external beam or internal, to "kill cancer cells and shrink tumors" ("Radiation Therapy for Cancer 2019). The type of radiation therapy chosen for cancer treatment depends on a variety of factors, especially the type and location of the cancer. External beam therapy aims the radiation directly at the cancer (local therapy) and does not involve machine contact with the body. Internal radiation therapy involves the patient ingesting a source of radiation that over time, travels to and kills the cancer ("Radiation Therapy for Cancer" 2019). Radiation treatments can cause damage to the reproductive organs, specifically if "focused on or near the pelvic area, abdomen, spine, and/or the whole body" and therefore can cause damage to sperm or eggs (Gupta 2016). For growing children, radiation therapy can interrupt menstruation in adolescent girls and impact sperm count and sperm motility in boys – changes that in some situations can be permanent. Children who receive radiation treatment to their brains may also have their fertility impacted because reproductive function is partially controlled by the brain via the hypothalamus,

and the hypothalamus is a key regulator of hormone release ( “The Reproductive System: Loma Linda University Fertility” 2015). Radiation provides some level of effective cancer treatment but can also cause physical harm to the reproductive organs.

## Chemotherapy

Chemotherapy is the use of drugs containing alkylating agents to kill cancer cells and works by stunting the growth of cancer cell masses which contain cells that proliferate quickly through interference with DNA needed for cell division; one of chemotherapy’s most unique properties is that it not only treats the main cancer diagnosed in the patient, but also helps alleviate cancer symptoms caused by other tumors that may be causing pain and other health issues. Often, chemotherapy is part of a multimodal treatment plan (which will be discussed in a later section) where multiple different types of treatments are combined into a regimen that will most effectively kill off the cancer ("Chemotherapy to Treat Cancer" 2015). Some chemotherapy drugs, such as cyclophosphamide, lomustine, and ifosfamide, are more likely to lead to infertility (Gupta 2016) because these chemicals can either cause hormonal imbalances or impact reproductive organ function directly. Although chemotherapy produces promising results in treating cancer, it often negatively impacts reproductive function.

## Immunotherapy

Immunotherapy is a type of cancer treatment that enables the patient’s immune system to fight the cancer and enhances tumor-infiltrating lymphocytes (TILs) to fight off rapidly growing cancer cell populations (“Immunotherapy for Cancer” 2019). Although this form of treatment has been deemed the most ideal, especially in its many different sub forms, it is the least reliable due to cancer cells’ ability to genetically change in their structure, and can affect neighboring healthy cells in a parasitic manner to influence their behavior (“Immunotherapy for Cancer”

2019). Immunotherapy also has some adverse side effects, one of which is that it not only acts against the cancer cells, but may also affect healthy cells and tissues, which weakens the patient (“Immunotherapy for Cancer” 2019). In respect to reproductive health, immunotherapy is also one of the safer treatment methods because it employs methods like checkpoint inhibitor therapy; it is “much safer and a huge improvement over chemotherapies which were cytotoxic and much more toxic to fertility” (Malmo 2019). Immunotherapy appears to be one of the frontrunners for cancer treatment without impacting fertility preservation; however, more fine-tuning is required before the procedure can become a more common treatment method.

## Therapy Summary

Research regarding currently existing methods and those in development continue to reveal more information that balances cancer treatment and its impact on fertility. In summary, though there are a wide variety of cancer treatment options available to children battling cancer, many of these options are accompanied by side effects or conditional outcomes that in general, render none more successful than any other. Depending on the patient and the case, certain treatment methods may be more suitable, but in any situation, it is important for parents and guardians of a child with cancer to be well-educated on all possible options before making a final decision regarding the fate of their healthcare and their future abilities.

## Fertility Preservation

Though a childhood cancer diagnosis and subsequent treatment can take a toll on the fertility of the patient, there are many options available for patients to preserve their fertility during treatment. Some options involve the preservation of reproductive organ tissue while others involve the preservation and storage of reproductive cells (eggs and sperm) (“Fertility Preservation for Children Diagnosed with Cancer”). The type of preservation suggested depends

on a multitude of factors, including the type and location of the cancer, the stage of cancer, the type of treatment being administered, and the patient's age and gender. Before these factors are taken into consideration, the fertility risk is considered ("Fertility Preservation for Children Diagnosed with Cancer"). The patient's and patient's family's interest in fertility preservation is also taken into consideration. In males, the most common types of fertility preservation are sperm cryopreservation and testicular tissue cryopreservation, and in females, the most popular methods are oocyte cryopreservation, embryo cryopreservation, and ovarian tissue cryopreservation ("Fertility Preservation for Children Diagnosed with Cancer").

## Male Fertility Preservation Methods

### Sperm Cryopreservation

Sperm cryopreservation is the most accepted and well-known form of male fertility preservation. A sperm specimen is “typically obtained by masturbation but can also be obtained by penile vibratory stimulation or electroejaculation in patients who cannot perform masturbation” (Burns, Hoefgen, Strine, & Dasgupta 2018). Sperm cryopreservation is recommended for all post-pubescent patients in early stages of cancer and is used primarily by older children diagnosed with early stages of cancer. Of the patients that are aware of sperm cryopreservation and are considering this form of preservation, in approximately eighty percent natural fertility is preserved (Burns, Hoefgen, Strine, & Dasgupta 2018). Sperm cryopreservation can compete with its counterparts because there are no known guidelines for the quality of preserved semen and an associated timeline as well as minimal fetal abnormalities have been associated with this preservation technique (Burns, Hoefgen, Strine, & Dasgupta 2018). Another form of sperm preservation is testicular sperm extraction (TESE), which involves the direct retrieval of sperm from the testis. This method is primarily for patients with azoospermia, “a

condition in which there are no sperm in the semen when a man ejaculates” (“NCI Dictionary of Cancer Terms”). TESE involves finding the source of spermatogenesis and focusing on that area; the technique does not usually result in testicular damage unless the patient receives multiple biopsies in a non-microsurgical method (Burns, Hoefgen, Strine, & Dasgupta 2018).

### Testicular Tissue Cryopreservation (TTC)

The other most common form of fertility preservation available to males, primarily children, is testicular tissue cryopreservation (TTC). This technique “currently has the greatest potential for FP [fertility preservation] in prepubertal children and adolescents” despite its status as experimental (Burns, Hoefgen, Strine, & Dasgupta 2018). TTC involves taking a transscrotal biopsy and harvesting the testicular tissue for cryopreservation. TTC “relies on the future development of experimental techniques for the maturation of spermatogonial stem cells (SSCs) into sperm” (Burns, Hoefgen, Strine, & Dasgupta 2018). Generally, TTC is handled well post-operation and does not cause any delays in cancer treatment. After recovery from cancer, the implantation of mature SSCs in the testis provides the possibility of restoring fertility to its natural potential; however, this must be further investigated before a final statement regarding this therapy method can be made.

TTC is a relatively new technique for male fertility preservation but shows great potential for prepubescent children and adolescents – a quality that no other fertility preservation method shows. The eligibility of a patient for TTC depends mainly on their age: prepubescent children and adolescents that have a high risk of azoospermia, the lack of motile sperm in ejaculate, are considered appropriate subjects of this procedure (“Azoospermia Causes,” Stanford Health Care). With minimal post-procedural morbidity and no delay in therapy initiation, TTC appears to be the best way for pre-pubescent males to have their fertility preserved. However, the long-

term effects of TTC have yet to be studied and potential testicular damage, antisperm antibodies, retrieval of mature sperm, and achievement of pregnancy have yet to be seen (Burns, Hoefgen, Strine, & Dasgupta 2018). Until the long-term effects of TTC are known for sure, it should be recommended that other treatment procedures are considered a first option compared to TTC.

# Female Fertility Preservation Methods

## Cryopreservation

Cryopreservation has been identified as one of the next breakthroughs in the field of fertility preservation. The technology associated with this method has “advanced significantly over the past decade with the successful establishment of vitrification freezing methods” (Waimey et al 2013). Vitrification is the “process of freezing so rapidly that that the water molecules don’t have time to form ice crystals, and instead instantaneously solidify into a glass-like structure” – a flash-freezing technique that has contributed to pregnancy success rates comparable to IVF (Fertility Associates of Memphis 2015). Much of the past research in cryopreservation has been focused on freezing techniques, but scientists aim to focus research in the future on the best thawing practices. Future research will investigate a vertical approach that involves multiple models to identify the best thawing methods and to “understand the implications of vitrification procedures for later translation to human fertility preservation” (Waimey et al 2013).

## In-Vitro Follicle Growth

In-vitro follicle growth of ovarian tissue is an emerging alternative to ovarian tissue transplantation that allows for preserved fertility without the risk of reintroducing cancer to the body via already affected tissue (Marin et al 2018). “Follicle in vitro growth (IVG) has the great potential of restoring fertility by achieving functional oocytes from the most immature stages to maturation” and therefore allowing the reproductive system to effectively start over (Marin et al 2018). By using immature follicles, the patient has a minimized chance of redeveloping cancer and therefore, this method proves to be a superior alternative. In adolescents especially, this method is more feasible and therefore promises better results. Though it does already have

advantages far outweighing the setbacks and the unknown, future research into this specific method will involve better understanding the differences between different types of follicles and optimal growth conditions of frozen and thawed follicles (Waimey et al 2013).

The future for female fertility preservation remains promising and with much room for advancement, but the need to integrate and apply ongoing research has become more evident. While the trend in scientific research is for labs to limit their focus to a few testing models, the collaborative approach “allows researchers to understand differences between species and to develop techniques with an eye toward the common goal of translational application in humans” and thus bring science to life in humans and help cancer patients, especially adolescents, in recovering quickly and achieving their fullest potential later in life (Waimey et al 2013).

In the past decades, strides have been made with regards to the effects of cancer treatment on fertility preservation and with various effective methods of fertility preservation. However, despite the advances made, there is still a long way to go in the field of oncofertility before all patients can be guaranteed full fertility after cancer treatment. While new methods of cancer treatment are in the process of being developed, the field of fertility preservation has much more room for growth and therefore, oncofertility scientists have been focusing their efforts on not only improving existing technology, but also on developing new methods (Waimey et al 2013).

## Ethical Dilemmas Associated with Fertility Preservation

The advances in research and technique development for fertility preservation, especially in cancer patients, has allowed for a vast improvement in medical treatment as well as in the quality of life that cancer patients can achieve in their future. However, the cultural, religious, and age diversity of the average patient population along with the varying levels of invasiveness of these treatments pose many ethical questions. These questions range from how much the patient, if a minor, should be able to influence the decision regarding his/her fertility treatments, to how religiously or culturally permissible a treatment essential to fertility preservation might be. Often, different treatment plans can have different quality of life outcomes and therefore, the conflict between religious and cultural factors and treatment plans can pose a hard decision for both the patient and his/her guardians as well as the physician to make.

One main question that has been posed involves the morality of suggesting fertility preservation options for which efficacy has not been proven for prepubescent childhood cancer patients (McDougall 2018). While it is easy to say that administering the procedure and hoping for the best would be better than simply not trying to preserve fertility at all, some physicians and researchers coming from an evidence-based medicine perspective argue that administering such “experimental” procedures is not ethical (McDougall 2018). The same professionals also go on to say that offering any kind of surgical fertility preservation options are not ethically justifiable because the invasive procedures pose some health risk to the patient, rather than avoiding any invasive procedure, which though it may result in lost fertility, poses no additional health risks for the patient (McDougall 2018). However, by not considering alternative invasive and noninvasive options to preserve fertility of a child cancer patient, the physician may risk permanently depriving the patient of fertility abilities and the best quality of life possible.

Though there is a risk posed by preservation procedure options, the risk is not significant enough to cause any permanent harm to the overall health of the patient; the risk may only be more significant in patient whose cancer is near reproductive organs or face hormonal fluctuations (McDougall 2018). In an effort to standardized the process of selecting ovarian tissue cryopreservation as an offered option to female patients, especially prepubescent patients, Wallace and colleagues developed the *Edinburgh selection criteria*, a set of criteria that considered risk of infertility, history of gonadotoxic therapy, and other factors to determine whether a given patient should be offered ovarian tissue cryopreservation as a fertility preservation option. Aside from these criteria, there are few other known standardized rules that are followed to determine a set of options or a treatment plan for any patient, whether they are prepubescent, cancer patients, or fall into any other specific subcategory. While it can be assumed that weighing benefits and risks for specific procedures makes a treatment plan easy to determine, the number of factors that such plans can impact highlights the need for more standardized protocols such as *Edinburgh selection criteria* to identify the best treatment options for any patients seeking fertility preservation treatment, especially childhood cancer patients.

Another major ethical concern related to the preservation of fertility in childhood cancer patients is the involvement of parents and family in the decisions regarding the treatment of the cancer as well as the decision-making regarding fertility preservation. As previously mentioned, childhood cancer encompasses all cancer cases in patients of 0-18 years of age. Currently a “minor” is legally defined as a person under the age of 18, and therefore parents are involved in all medical decisions. This could potentially lead to the problem of teenage cancer patients having to abide by their parents’ decisions regarding their health, even if they want something different for themselves (Romao & Lorenzo 2017). A contributing barrier related to the

discussion of fertility preservation between a physician and the family members of a child with cancer involves the comfort and ease with which this topic can be discussed. Some of the factors that play into this include “knowledge gaps on fertility, lack of educational materials, [and] a sense of embarrassment and/or discomfort discussing the topic in view of specific patient-related factors,” as well as the main decision of how much influence the patient should have on the decision relative to his/her guardians (Romao & Lorenzo 2017).

The amount influence on the childhood cancer patient from his/her guardians varies in each individual case depending on both the age of the patient as well as the personal beliefs of the parents (McDougall, Gillam, Delany, & Jayasinghe 2017). Parents of teenage cancer patients who have given their children independence may allow them to make the final decision regarding fertility preservation. While this does allow the patient to have autonomy over their own health, and it can be said to guarantee that the physician is not blamed in the future, should the patient wish they had picked an alternative treatment plan. Additionally, allowing the teenage/minor cancer patient autonomy of their treatment decisions may increase the threat of the patient making a misinformed and potentially impulsive decision, which can be considered more dangerous than a temporary quarrel between the patient and his/her guardians over the power to decide (McDougall, Gillam, Delany, & Jayasinghe 2017).

The extent to which a childhood cancer patient’s parents should influence the final decision being made regarding fertility preservation not only depends on the patient’s age and the extent to which his/her beliefs differ from theirs, but also the options given to the patient and their family by the attending physicians. Often, when considering a childhood cancer case in which the likelihood for retaining patient fertility following cancer treatment is low, the physicians attending to the case weigh the risks and benefits for the case, develop several

different cancer treatment plans that also include fertility preservation procedures, and present the most feasible options to the patient and his/her family.

In low-benefit low-risk cases, “parents may justifiably choose either to pursue or to decline the procedure” (McDougall, Gillam, Delany, & Jayasinghe 2017). For example, consider the hypothetical case of a 5-year old girl diagnosed with brain cancer whose physicians propose a treatment with a 70% chance of survival but will lose her fertility almost completely. The recommended fertility preservation treatment can be administered at the same time as the procedure to treat her cancer but does not guarantee maintained fertility since the child is prepubescent. The parents understand the situation and the “lack of proven efficacy” of the fertility preservation procedure as well as the rule that should their daughter not survive her fight with cancer the isolated tissue from the child’s reproductive system will be destroyed. They consent to administering the full treatment plan for their child. In this case, the parents fully understand that the child has a low chance of preserving full fertility but choose to take the chance knowing it comes at little additional cost to their daughter’s health and future. Whereas, if the child were to be in the same situation but would have to undergo the fertility preservation treatment separately from her cancer treatment, coupled with her pre-existing discomfort with hospitals, insisting on the fertility preservation treatment would be unethical. In situations where the treatment plans are low-risk and low benefit and patients are not at an age where they can make decisions for themselves, considering the patient’s emotions and mental health are the best way for physicians to recommend certain treatment plans and for parents to accept the recommendations provided.

Ultimately, decisions regarding fertility preservation must take into account the individual case details and personal background of the individual childhood cancer patient.

Factors such as socioeconomic status, religious and cultural beliefs, parental influence and involvement, and patient mental health are especially important and should be considered because, if dismissed, they can cause emotional harm and pose problems while administering treatment and during recovery.

To ensure that childhood cancer patients and their parents/guardians receive all the available options and resources in development of their cancer treatment and fertility preservation plans, hospitals and medical institutions should implement a standardized set of criteria that dictate the procedure by which the treatment plans are produced and introduced to the patient and their family. The criteria should include a standardized timeline for discussing the patient's case, possible treatment options, mental and emotional health, familial and socioeconomic background, and various combinations of cancer and fertility preservation treatments that would be most effectively resolve the patient of their existing health conditions and the associated side effects. Discussing the patient's background and residential environment are vital for physicians to suggest the best treatment plan that can be the most effective given the patient's living space and most attainable for the parents and guardians financially.

For parents or guardians to be able to make an informed and ethically sound decision, they should take into consideration all available resources regarding their child's cancer and the fertility preservation options recommended by the doctor. Some of these resources should be provided by the physician so as to make clear what each procedure entails, and additional resources should be identified from reliable sources. Physicians should also facilitate discussion with the patient and his/her family while not involving personal opinion too much so that ultimately, the decision made is the patient and his/her family's own.

Every case has details that could potentially greatly impact the patient's immediate future as well as their long-term health, and these details often influence the treatment plans that a physician proposes to a childhood cancer patient and his/her guardians. To ensure that an educated decision regarding the patient's fertility is made, the physician should suggest all feasible fertility preservation options, regardless of the patient's cultural and religious beliefs. While this may seem impersonal to the patient and his/her family, it allows the parents to consider all possible options - if they feel that fertility can be prioritized over a possible violation of a religious belief, the family or child can choose the best treatment option.

## Educational and Clinical Resources

Existing fertility preservation is a relatively novel option and continue to be researched and promoted where appropriate. The information and educational resources available to both physicians and patients have also expanded. For physicians, more clinical studies become available, allowing them to better understand possible treatments and accurately suggest treatment plans. For patients and their families, more online resources regarding existing/practiced and novel treatments become available, and thus patients can make a more informed decision on treatment plans.

While the educational resources and information available are mostly focused on description of different treatment types, it is important to also consider the quality of these resources to ensure that they influence patients' decisions in an ethical manner. The quality of the educational resources depends on a variety of factors, including the source of the information, the method by which it is conveyed, the accuracy of the information, the objectiveness of the information, and the simplicity of the information with regards to understanding. The variety of research and medical literature available to physicians, specifically literature regarding proper methods to develop and suggest treatment plans to patients, can also have a vast impact on the ethicality of fertility preservation treatments for cancer patients, specifically children.

### Online Resources

Of all the various types of educational and clinical resources available to both patients and physicians, online websites and resources have the most variety ("The Oncofertility Consortium"). This category includes websites and webpages created specifically in order to help patients understand and navigate their diagnosis and possible courses of treatment as well as to

help physicians develop treatment plans that correspond with the patient's health. Often, the online resources are assembled by researchers and medical professionals working through a university lab or hospital researching oncology or oncofertility and are aimed to raise awareness about a specific fertility preservation or cancer treatment that may not be suggested immediately by doctors ("The Oncofertility Consortium").

The availability of online resources to childhood cancer patients and their families allows them to access information at any time and therefore seemingly allows them to be well-informed regarding possible treatment. However, because the internet is not filtered for inaccurate information and is open to anyone to publish material, avoiding the misinformation of patients and their families is extremely difficult to monitor. Many websites are created by research professionals, hospitals, and cancer treatment centers and can be referred to patients after consultations with their physicians. Because these websites are written by health professionals, it can be assumed that they provide all the necessary information for both physicians and patients and their families; however, these websites do not discuss accommodations that can be made for various socioeconomic and cultural restrictions or, for physicians, the ethical concerns that may be associated with various treatments. As part of their work to better educate on and publicize fertility preservation options to cancer patients, the Oncofertility Consortium, a network developed by Dr. Teresa K. Woodruff's lab at Northwestern University, developed SaveMyFertility.Org. This website is described as "an authoritative resource for adult cancer patients and the parents of children with cancer who want to learn more about preserving their fertility before and during cancer treatment" ("About SaveMyFertility 2015). While the website does detail the general procedure to obtain information about fertility preservation, the names of various preservation treatments, and summarizes the procedure in an easy-to-understand

flowchart, it does not explain what each treatment is or what the advantages and disadvantages of each treatment are from both a medical and a socioeconomic standpoint. This website may serve as a good starting point for anyone seeking fertility preservation as part of their cancer treatment but cannot become the only resource to rely on.

The Dana-Farber Cancer Institute at the Boston Children's Cancer and Blood Disorders Center has developed its own pediatric fertility preservation webpage to supplement their pediatric fertility preservation program. This webpage promises a fertility consult to all cancer patients that includes "information on the financial implications of [the] interventions," details several fertility preservation options available to pediatric cancer patients, and provides videos that summarize male and female fertility preservation in childhood cancer patients (Dana-Farber Cancer Institute 2020). While this website does provide valuable information regarding the treatments and the hospital promises financial information during consults, it would be more beneficial not only to the patients of this hospital, but to all childhood cancer patients and their families, to have general financial information or associated resources (i.e. insurance provider contact information) available on the webpage. Though the ultimate goal of medicine is to preserve the health of as many patients as possible through whatever the necessary means, socioeconomic status and other personal factors are also important to consider (Institute of Medicine (US) Committee on Guidance for Designing a National Healthcare Disparities Report 1970).

Many online resources dedicated to fertility preservation, specifically in childhood cancer patients, are informative and convenient for those looking for more information about the treatment options and plan development. These professionally written and factually accurate resources are extremely valuable as additional sources of information to supplement physicians'

advice. Alongside these resources, there are also many webpages and online sites that are written by former patients and their families, or by the general public. The firsthand experience sources, which can include blogs or “vlogs” (video logs), can be incredibly helpful for patients and families who may be apprehensive about fertility preservation treatment in addition to cancer treatment (“Blog: Fertility Preservation.”). However, some of these *firsthand experience sources* may contain misleading or incorrect information and therefore introduce the risk of patients and families being misinformed. Due to this potential for misinformation, patients and families may, yet again, be given a false sense of hope and would have to endure more emotional stress than previously encountered.

Online resources, though they pose a possible risk of misinformation and further emotional stress for the patients and their families, remain extremely valuable sources of additional information to supplement physician advice. They offer an expansion on suggested treatment plans and can often provide emotional support and reassurance through firsthand encounters with patients and their families that have gone through the process of considering and constructing fertility treatment plans.

## Medical Research and Literature

One of the main sources of information for physicians and scientists alike to stay up to date on clinical research developments is medical literature and research publications. These resources focus mainly on the scientific advancements in fertility preservation treatment as well as in cancer treatment that avoid impacting fertility and can therefore provide physicians with more treatment options to offer patients. Some publications are reviews or summaries of existing treatment plans or upcoming options and these publications not only help physicians but can also be an expansion of information for patients and their families. The research published in these

journals is conducted primarily by physician researchers and scientific researchers with contributions of a research team of all educational classifications (undergraduate, graduate, postdoctoral, etc.) and are peer-reviewed by authorities in the field.

A subcategory of fertility preservation research literature used by physicians to develop personalized and well-fitting treatment plans is primary research articles, which involves the description and discussion of newly discovered fertility preservation treatment methods and cancer treatment methods that are not gonadotoxic. One such publication discussed the cryopreservation of ovarian and testicular tissue, particularly in younger patients likely to lose gonadal function due to cancer treatment, that was a relatively novel treatment option at the time of the paper's publication in 2003 (Hovatta 2003). The publication focuses on cryopreservation techniques as applied in both the research and clinical settings (in animal models and patients) and outlines specific parameters necessary for tissue storage. The paper also provides insight on the experiences of physicians at Huddinge University Hospital using these cryopreservation techniques and the results obtained from these procedures. One example that the paper discussed was the use of ovarian tissue cryopreservation on "31 women/girls with a mean age of 25" all experiencing some type of cancer or autoimmune disorder (that also required chemotherapy) who requested fertility preservation treatment (Hovatta 2003). In addition to success with cancer patients, the hospital's use of the technique revealed that "all young women who are likely to undergo premature ovarian failure because of causes other than chemotherapy may benefit from ovarian tissue cryopreservation" (Hovatta 2003). Publications like these not only provide physicians with factual information, but also with "personal" physician experience that may further solidify their decision to use a specific procedure as part of a current patient's treatment plan.

Another subcategory of fertility preservation literature includes review and summary articles that consist of descriptions of various fertility preservation treatments or focus on the benefits and drawbacks of procedures currently in practice. One such paper about the newest advancements in fertility preservation for childhood cancer patients outlines both the effects of various cancer treatments on reproductive function in children with cancer and then delineates various fertility preservation options for prepubescent and pubescent males and females. While summarizing various treatment options and the corresponding pros and cons, the review paper also discusses factors specific to the patient and his/her family, such as religion, finance, and ethics, that should be taken into consideration before finalizing a treatment plan. Publications like this review allow physicians quick access to this information – access they may need during a consultation or to supplement their comparison of available treatment options when discussing with other health professionals.

Medical literature serves as a valuable and important resource for physicians and researchers to stay up to date on treatment procedures for fertility preservation and allows for some patients' families (especially those with science backgrounds) to be well informed regarding treatment options. However, the vocabulary and terminology used in these publications can be complicated and advanced, and because of this, patients and their families may feel overwhelmed with information or be prone to misinterpretation the information. The possibility of misinformation because of this may result in decisions regarding treatment that are not well informed, and, in the future, patients and their families may experience emotional stress.

## Direct Interactions with Healthcare Professionals

One of the main sources of information regarding both cancer and fertility preservation for childhood cancer patients and their families is the interactions they have with the child's

physician and other healthcare professionals that are part of their healthcare team. The information provided to the patient and his/her family is mostly factual information regarding what various procedures entail and, based on the lifestyle of the patient, tailored in explanation to ensure that patients and their families understand the options (Hambley 2015). However, there are a variety of ethical concerns that accompany this method of information delivery, including the possibility the doctor would withhold information based on his/her own personal beliefs as well as the possibility of not fully explaining the treatment options to the patient and his/her family.

One of the main concerns with a patient's decision-making being heavily reliant on direct encounters with their physician is that the information being given to them is controlled by the physician. One of the key pieces of information that every doctor in training is taught, is that their personal views should never impact the quality of treatment they provide or affect the information being given to a patient with regards to treatment plans (Kennedy 2017). While a physician should always strive to be as personable with a patient as possible, it is not ethical to assume that the physician's personal beliefs will be the same as those of the patient's. For example, a certain childhood cancer patient may only have treatment plans available to them are gonadotoxic. As a result, the attending physician must now develop another treatment plan that focuses specifically on fertility preservation and once these options are gathered, the physician must then present these options to the patient and his/her family. If the physician, however, is firmly against Testicular Tissue Cryopreservation because his/her religious values do not agree with any sort of gonadal modification and it is possible that he or she may exclude this option to the patient and his/her family or express their disagreement to the procedure. Thus, TTC, one of the best fertility preservation treatment options available could be discounted by the patient or

their family and could contribute to the detriment of their treatment plan and therefore, his/her quality of life. The influence of the physician's personal beliefs on the development of a treatment plan could result in the withholding some of the best plans of care from patients and therefore negatively affect their health in the long run (Kennedy 2017).

If a patient and his/her family is too reliant on interactions with healthcare professionals, they may also be subject to misinformation or insufficient information regarding available treatment plans. Because most of these cases are treated over an extended period of time, the physicians are able to provide as much information as possible to the patient and his/her family to use in their decision making. However, when dealing with cases that are time-sensitive, physicians may be forced to summarize what they think is the most important information for the patient to consider and may omit any details they feel are not important. In doing so, the physician takes away the patient and his/her family's ability to fully control the plan of treatment and may cause detriment to the patient's quality of life.

## Pamphlets and Reading Materials

Another common source of information for childhood cancer patients facing potential damage to their reproductive function are the pamphlets and reading materials available to them in their physician's office or provided to them by healthcare professionals. These materials, while valuable and convenient, can also lead to misinformation because, in comparison to online resources, pamphlets and other paper reading materials may not always be completely up to date. If a physician provides a patient and his/her family with these reading materials that are not complete with the newest of information about all available treatment plans for both cancer and fertility preservation, then patient is misinformed. As mentioned previously, this detracts from the patient and his/her family's ability to make an informed decision and therefore, can take

away from the patient's chance to have the best quality of life following cancer treatment and fertility preservation treatment.

## Guidelines for Treatment

To ensure that every childhood cancer patient has the opportunity to obtain the best healthcare, with respect to both cancer treatment and fertility preservation, it is essential to construct a series of standardized guidelines and general procedures for all physicians. Ideally, guidelines would include specifics on who should be involved in making the final decision about a treatment plan, the level to which the patient, patient's family, and physician should be able to influence the decision, and the external factors related to the patient that the physician should consider when providing treatment plans. The use of the guidelines described later in this paper, will help attempt equality in patient treatment and help streamline the treatment plan development and administration for physicians and healthcare professionals.

One of the most important factors in determining the right cancer and fertility preservation treatment plans for childhood cancer patients is determining who should be involved in the decision-making process and treatment plan. In most cases, any cancer patient under the age of 18 is accompanied by his/her parents or guardians for legal reasons as well as to ensure that the treatment plan chosen can be supported financially and logistically by the patient's caregivers. Cancer treatment itself is an extremely difficult process for the patient to handle physically and emotionally and having a reliable support system is extremely important to ensure the patient's wellbeing and the effectivity of the treatment. Fertility preservation is also a decision that has a long-term impact and must be taken with care to ensure that the patient's quality of life remains at its best. The involvement of a team of healthcare professionals, namely physicians, in the treatment plan selection process is also extremely important to ensure that all possible options are considered, carefully explored, and explained well to the patient and his/her family. While it is at the patient and his/her family's discretion to involve others in the decision-

making process, the people that should be the most involved are the patient, his/her parents or guardians, and a well-equipped, well-rounded healthcare team.

The direct involvement and level of influence of a patient in determining the cancer treatment plan and fertility preservation plan that they will follow is directly correlated to their age (Howell 2016). For patients who are pre-pubescent and do not have a full understanding of their reproductive health, it is best for the patient's parents or guardians to be in control of the decision. Often times, parents are uncomfortable with explaining to their young, pre-pubescent children how the reproductive system functions because the children have not reached that level of maturity. While the health and wishes of the patient are important to consider, the involvement of the family in these cases is vital to ensure that the decision made does not defy any personal values or beliefs and that the treatment plan can be fully effective and followed by the caregivers. The main ethical concerns with the involvement of parents and guardians in the decision-making process involves cases where patients are experiencing or have experienced puberty, specifically in the range of 12 to 17 years old. While all patients in this age range are undergoing or have undergone bodily changes due to puberty, the difference is the level of maturity at which the patient is. The easiest solution for these cases is to determine age ranges at which patients can have more influence on the decision rather than their parents or guardians. In cases of patients living in America, the best indicator of maturity levels of children is their schooling level. The difference between the average 12-year-old in middle school and 17-year-old that is nearing the end of high school is evident: the 12-year-old is still dependent on his/her guardians for most day-to-day tasks while the 17-year-old can obtain a driving license, may be preparing for college, and may be more independent. The 17-year-old has a certain concept of his/her personal preferences and the future he/she desires, and for parents or guardians with

potentially differing values and beliefs to influence most of the decision would be detracting from the patient's quality of life. Therefore, the best way to distinguish the level to which a childhood cancer patient should be able to influence the final decision made regarding his/her treatment plan for cancer and fertility preservation should be determined by age ranges. For patients of ages 0-12, the parents or guardians should make the decision they think best and should consult the child regarding personal preferences regarding procedures (i.e. surgery); from the age of 13 onwards, the parents/guardians and patient should have a relatively equal say in what cancer and fertility preservation treatment plans will be selected. The role of the physician in any case should be restricted mainly to provide information and options for the patient.

When determining the best cancer and fertility treatment plans for childhood cancer patients, physicians must also consider a variety of external factors associated with the patient that can impact the effectivity of the treatment. The physician and other healthcare professionals working on a case have all the information regarding treatment plans and thus are in a powerful position in terms of potential influence on the patient's final decision. While it may seem easiest to omit treatment options and plans that conflict with the patient's lifestyle, doing so can take away from the patient's chance at the best quality of life. All possible treatment options, regardless of whether they conflict with socioeconomic status, personal beliefs, and other factors, should be provided to allow the patient and his/her family select the option they see best. For some cases, an option that a physician may disregard due to conflict with the patient's situation or beliefs could easily become the treatment plan should the patient and his/her family choose to work around these conflicts to achieve the best health. The duty of healthcare professionals dealing with such cases is to inform the patient and his/her guardians of all possible options and

the influence of such external factors should be at the discretion of the patient and his/her guardians.

## Summary

Childhood cancer, defined as any case of cancer occurring through the age of 15, makes up less than one percent of all diagnosed cancer cases, but impacts 11,000 children every year ("Key Statistics for Childhood Cancers"). While many advancements to find cures and new treatment options have been made in the research field, the side effects that go along with cancer treatment continue to cripple pediatric cancer patients. The impact of various forms of cancer treatment on the reproductive abilities of childhood cancer survivors is one of the less discussed side effects. With the new and widely unexplored field of oncofertility to provide cancer patients and survivors with a variety of fertility preservation options, there are also ethical concerns that have been raised regarding fertility preservation treatments and the process by which treatment plans are selected for childhood cancer patients. The impact of available resources online and clinically as well as the patient, the patient's parents or guardians, and the healthcare professionals involved in the case on the selection of a treatment plan for both the cancer and fertility are essential in determining the quality of life that the patient has during and following cancer treatment.

The most common cancer treatment methods include surgery, radiation therapy, chemotherapy, immunotherapy, and hormone therapy. Surgery is an invasive method by which a tumor or cancerous mass can be removed. Radiation therapy involves the administration of high energy radiation to the part of the body that the cancer has impacted. Chemotherapy involves the administration of chemical drugs that target the source of the cancer cells and aim to kill off all cancer cells. Immunotherapy involves enabling the patient's immune system to fight the cancer and enhances the tumor-infiltrating lymphocytes (TILs) to help fight off the rapidly growing

cancer cell population. Hormone and drug therapies involve administering drugs or additional doses of hormones to train specific parts of the body to fight off and kill cancer cells.

A wide variety of fertility preservation procedures are available to pediatric cancer patients who are both pre and post-pubertal. For pre-pubertal males, Testicular Tissue Cryopreservation (TTC), which involves obtaining and preserving a testicular tissue sample, is the most common procedure. For post-pubertal males, Sperm Cryopreservation, which involves obtaining and preserving sperm samples, is the most common procedure. For pre-pubertal females, cryopreservation, which involves obtaining and preserving ovarian tissue samples, is the most common procedure. For pre- and post-pubertal females, In-Vitro Follicle Growth (IVG), which involves obtaining and reintroducing immature follicles to the female's reproductive system, is the most common procedure. Ultimately, with each of these procedures, there are a variety of risks and benefits associated, and the selection of the procedure is dependent on the patient's case specifics.

There are many resources available to childhood cancer patients that may need to undergo fertility preservation procedures and these resources include websites and other educational sources online, firsthand experiences documented online, medical and research literature, pamphlets and physical reading materials, and direct interactions with healthcare professionals. Each type of resource has its own benefits and drawbacks that make it comparatively better or worse than another, but the most important factor to consider is whether there is a risk for misinformation or misinterpretation by the patient. The best way to stay well-informed using these resources is to use reliable sources, for professionals to combine reliable sources to create a database for cancer patients seeking information, and for patients to continue to consult their physicians regarding any questions before making the final decision.

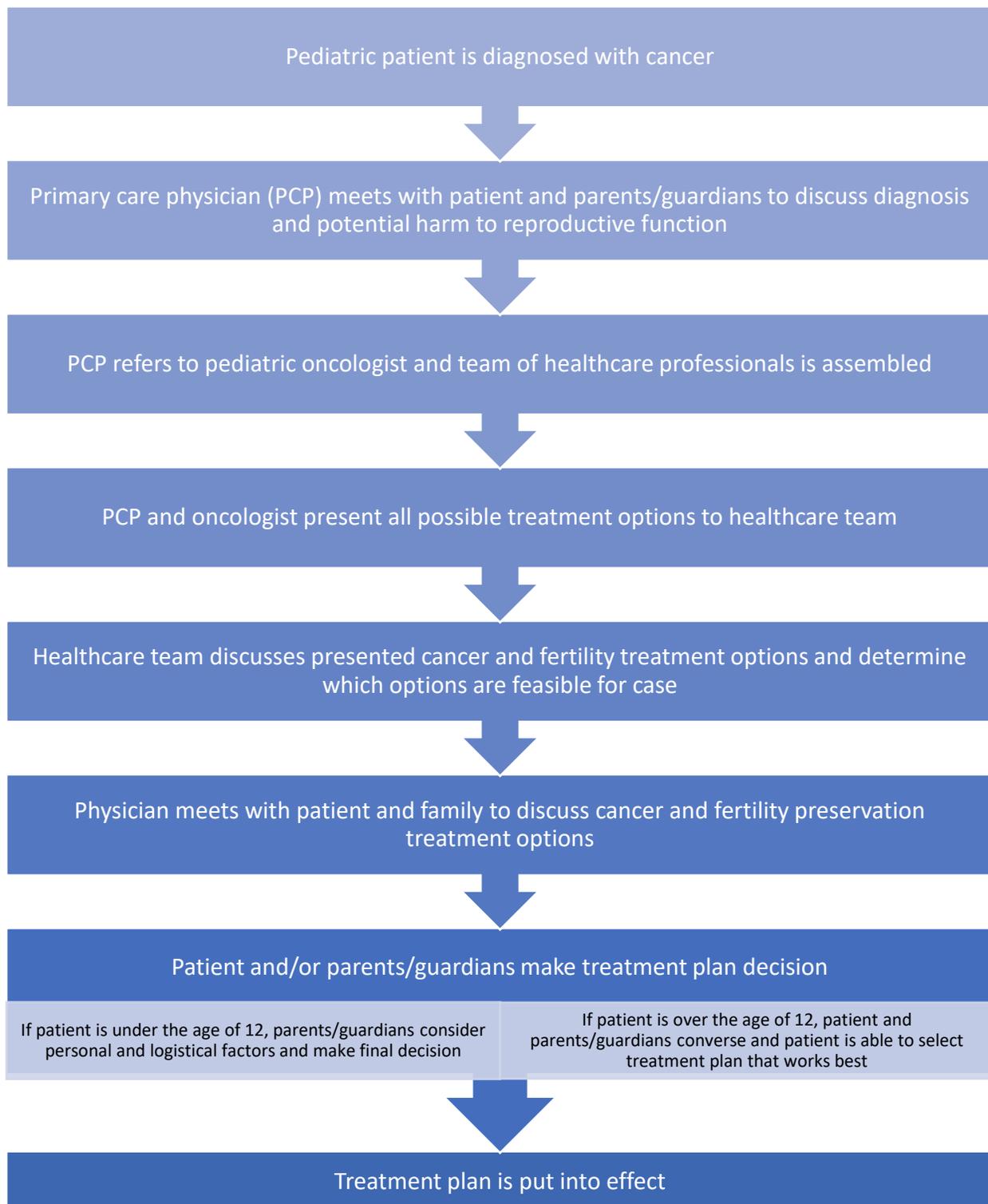
The three main factors to consider when examining the ethicality of the decision-making process associated with pediatric cancer treatment and fertility preservation treatment plans are the people involved in the decision, the level to which these people influence the final decision, and other external factors that may impact the treatment plan chosen and to what extent it can be effective. The main people involved in such decisions include the patient, his/her parents or guardians that act as caretakers and a support system during treatment, and the physicians and other healthcare professionals involved with the case and treatment plans. The level to which the patient influences the decision depends mainly on the patient's age and understanding of his/her health and his/her own personal beliefs. If the patient is under the age of 12, the parents or guardians should have majority of the influence on the decision because the patient is not yet at an age to fully understand his/her health or be independent in his/her decision making. Any patients above the age of 12 should have an equal chance to influence the final decision as do their parents and guardians since they are at the stage to understand reproductive health and to begin making decisions independently. The role of the physician and other healthcare professionals is solely to inform the patient of all possible options. External factors such as socioeconomic status, personal preferences, and religious beliefs are important for the patient and his/her family to consider, but should not be taken into consideration when determining possible treatment plans because the patient or his/her guardians may choose to proceed with a specific treatment regardless of these conflicts; without the additional options that would otherwise be omitted due to these conflicts, the patient may not have a chance at the best possible quality of life.

## Conclusion

Ultimately, a multitude of factors impact the treatment plan for both cancer and fertility preservation that is chosen by a childhood cancer patient. There is currently no standardized procedure that physicians can follow when dealing with pediatric cancer patients, more specifically cases where fertility could be compromised. By ensuring that the resources and information provided to patients and their families are relatively standardized and encompass as much information as possible while avoiding the application of personal beliefs and biases, physicians can ensure that their patients are able to make a decision regarding treatment that will impact their future positively and give them a chance at the best quality of life post-treatment. Oncofertility is an ethically and scientifically novel and complex field but holds a world of possibilities – success for physicians, happiness for families, and positive and healthy futures for those who have suffered or are battling childhood cancers.

## Appendix A

Figure 1: Proposed Childhood Cancer and Fertility Preservation Treatment Process Summary



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