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Research Article

Semen Cryopreservation in Men with Cancer: Identifying Patterns and Challenges

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Abstract *Objective.* The aim of this study was to determine the proportion of male cancer patients who undergo semen cryopreservation before chemotherapy after referral was placed, identify factors associated with completing the procedure, and explore reasons for not moving forward with it. *Methods.* The electronic medical records of men with cancer who were referred to a reproductive urologist identified with an ICD-10 code for a fertility preservation procedure (Z31.62, Z31.84) between November 2021 and February 2023 were reviewed. Cancer type, semen cryopreservation rates, and reasons for opting out of the procedure were recorded. *Results.* Of the 128 men diagnosed with cancer who were referred for cryopreservation during the study period, $n = 67$ (52%) underwent semen cryopreservation. Those who did not undergo the procedure tended to be older, with a median age of 38 years compared to those that did it (33 years) ($P = .10$). The most common reasons for non-compliance included financial burden, and lack of interest. *Conclusion.* While it is recommended that patients consider fertility preservation prior to chemotherapy, our findings suggest that only half of male cancer patients completed the procedure despite referral. Further work is needed to determine barriers to access and increase awareness of fertility preservation prior to chemotherapy.

Keywords oncology; cancer; infertility; oncofertility; cryopreservation

1. Introduction

According to data from the Surveillance, Epidemiology, and End Results (SEER) Program at the National Cancer Institute, one out of every two men will be diagnosed with cancer in their lifetimes, and 4% will be diagnosed under the age of 35 [1]. Patients under 15 years of age undergoing cancer treatment are projected to have a 75% five-year cancer survival rate while patients aged 15–44 are projected to have a survival rate of 66% [2,3]. With the increasing survival rates of these patients, fertility potential has emerged as a core survivorship concern. The field of oncofertility aims to optimize fertility preservation before the initiation of gonadotoxic therapies and addresses the interactions between cancer, anti-cancer therapy, fertility, and reproductive health [4].

Cancer treatment is a critical component of cancer care, but it can come with a range of side effects including negative impacts on male fertility. Mainstays of cancer treatment, including chemotherapy and radiation therapy, target cancer cells but other rapidly dividing cells in the body are also at risk for cytotoxicity. These treatments can damage the testicles and reduce sperm production, potentially leading to infertility [5]. In fact, up to 90% of male cancer survivors experience fertility impairment as a result of their cancer treatment [6]. Infertility has a profound impact on quality of life, and patients who become infertile because of treatment may experience distress, depression, and anxiety [7]. As such, fertility preservation has become an essential component of cancer treatment for many male patients [8].

Fortunately, several options are available for male fertility preservation, with sperm freezing being the most common and most effective. The process involves mixing the semen with cryoprotectant, a substance designed to protect and stabilize sperm during freezing, and then storing the specimen in a cryogenic container at a temperature of $-196\,^{\circ}\mathrm{C}$ [9]. The process of cryopreservation helps to maintain the quality of the sperm over an extended period of time (up to 20 years) and can be used as part of assisted reproductive technologies (ART) to allow cancer survivors to have biological children [10]. Cryogenically frozen sperm has been used successfully for many years in fertility clinics and has a high success rate for achieving pregnancy when used for in vitro fertilization (IVF) [11]. Unfortunately, the cost of sperm freezing (and subsequent IVF) can be a financial barrier for some patients, particularly those whose insurance coverage does not include fertility preservation. This can create a significant financial burden, especially in the context of an already costly cancer treatment. Therefore, understanding the barriers that prevent patients from pursuing sperm freezing is an important consideration

in developing improved shared decision-making processes with cancer patients [12].

Given the lack of knowledge in the field, the objective of this study is to investigate the reasons behind the non-completion of sperm freezing among male cancer patients who have been referred to and evaluated by a reproductive urologist. To the best of our knowledge, no previous study has specifically addressed this important aspect of fertility preservation in this patient population. Understanding the underlying reasons for non-completion after patients have received consultation from a reproductive urologist is crucial for developing targeted interventions and support strategies to overcome barriers and improve adherence to fertility preservation protocols. By elucidating these factors, this study aims to fill a critical knowledge gap in the field and provide valuable insights for clinicians, researchers, and policymakers in optimizing the fertility preservation process for men with cancer.

2. Methods

The present study aimed to estimate the number of men with cancer referred for fertility preservation and the proportion of those patients who underwent sperm cryopreservation within the Sylvester Cancer Center/University of Miami Health System in South Florida. The study employed a retrospective analysis of electronic medical records of male patients diagnosed with cancer at our institution between November 2021 and February 2023. The search was conducted using International Classification of Diseases-10 (ICD-10) codes Z31.62 and Z31.84, which correspond to fertility preservation procedures. Furthermore, all identified patient charts were manually reviewed by two reviewers (BL and KC) to identify the type of cancer and the reasons for not continuing with cryopreservation. Patients whose chart did not include a note explaining why cryopreservation was not performed were individually contacted via phone call. For each patient, three attempts were made via phone call. Patients who had previously listed "not interested" as a reason were also contacted to know why the lack of interest.

The appointments were categorized into Completed, Canceled, and No-show types for New Patient Fertility Preservation (NP FERT PRES [100201]), Semen Cryopreservation (CRYOPRES SA [100905]), and Telehealth New Patient Fertility Preservation (TELENPFERT [100742]). The visits were also subcategorized by the provider.

In order to estimate costs associated with cryopreservation, laboratory processing fees as well as long-term cryostorage facility fees (ReproTech) were calculated. In addition, to estimate the costs associated with semen cryopreservation, we contacted the Director of Health System Pricing at the UHealth Reimbursement Department at the University of Miami to obtain prices (in US dollars) for the provider and the laboratory fees for sperm cryopreservation, as well as the infectious disease panel, which is mandatory for cryopreservation as an addendum procedure. We also contacted ReproTech, the long-term cryostorage facility partnered with the University of Miami to offer long-term storage to IVF centers and oncology professionals, to obtain yearly cost estimates.

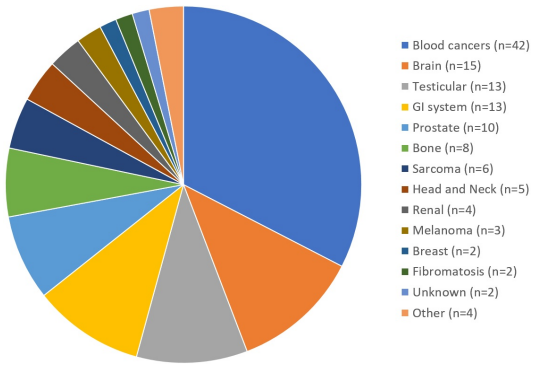

Figure 1: Distribution of cancer types amongst those referred for fertility preservation at the University of Miami during the period 11/2021–2/2023.

3. Results

During the study period, 128 men diagnosed with cancer were referred to the Male Infertility/Andrology clinic for fertility cryopreservation before chemotherapy. At our health system, this signifies a visit to the Male Infertility/Andrology clinic and semen cryopreservation consultation. The median age was 34 years with an interquartile range (IQR) of 16.5 years. The study population exhibited diverse demographic characteristics. The median age of the cohort was 37 years (IQR 21). The most prevalent self-identified racial category was "White," comprising 74 individuals (67.3%), followed by "Black or African American," reported by 40 individuals (36.4%). "Asian" category was reported by 4 participants (3.6%) and "Native Hawaiian or Other Pacific Islander" was reported by 1 participant (0.9%). There were also 5 individuals (4.5%) where race information was "Unknown or Not Reported," and 4 (3.6%) who had previously declined to disclose their race. At the time of initial consultation, 34 patients (26.6%) reported that they had at least one child and 94 patients (73.4%) responded that they did not have any children.

The distribution of cancer diagnoses is presented in Figure 1. The most common type of cancer was blood cancers (including leukemias, lymphomas, and myelomas) with 41 patients (31.7%), followed by brain cancers with 16 patients (12.4%), and testicular cancer with 13 patients (10.1%). Those in the other cancer type section consisted of one of each of the following: lung, pineal gland, spinal cord, thymus.

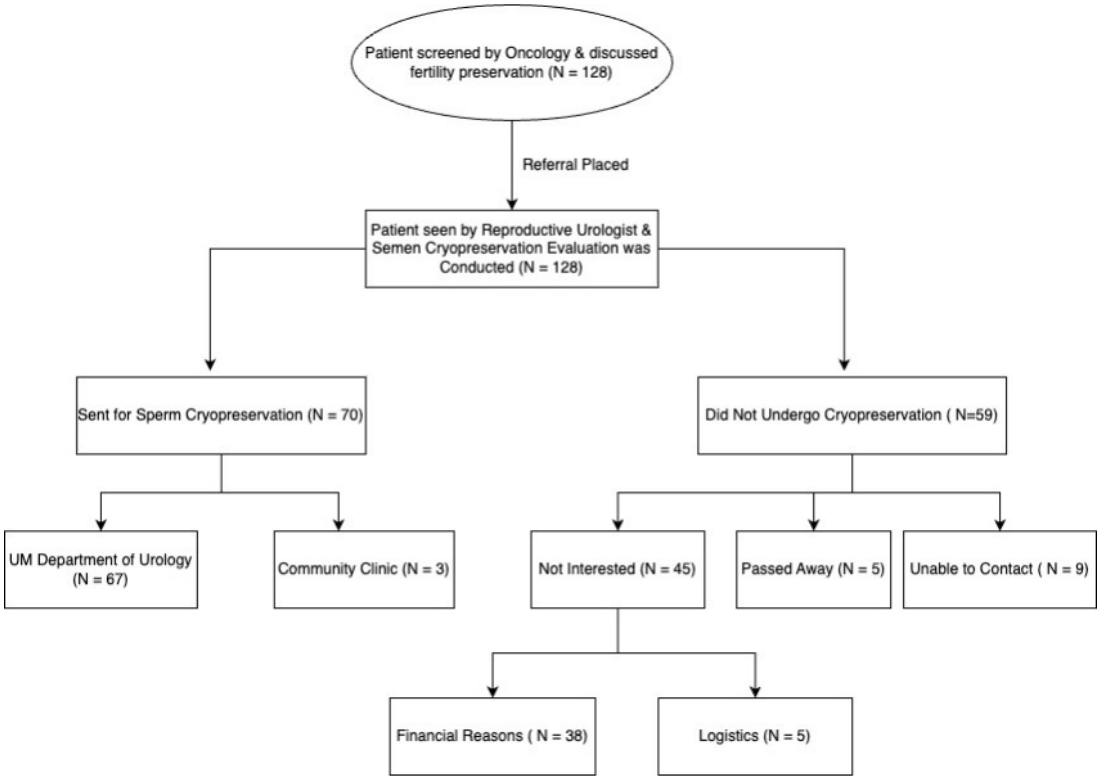

Figure 2: Outcomes of male cancer patients referred for cryopreservation at the University of Miami during the period 11/2021–2/2023 based on chart review.

Table 1: Outcomes of all patients referred for cryopreservation at the University of Miami during the period 11/2021–2/2023 based on billing code for "completed" versus "canceled" and "no-show" appointment types.

Row labels	Count of appointment status
Completed	**67**
NP FERT PRES [100201]	**67**
Canceled	**51**
CRYOPRES SA [100905]	**5**
NP FERT PRES [100201]	**46**
No show	**10**
NP FERT PRES [100201]	**9**
TELENPFERT [100742]	**1**
Grand total	128

Of the referred men, 67 patients (52.3%) underwent evaluation and semen cryopreservation within our department while 5 patients (3.9%) were scheduled for cryopreservation but canceled (Table 1). An additional 3 patients (2.3%) reported that they were undergoing sperm cryopreservation at a "community facility," and the remaining 59 patients (46.1%) did not undergo fertility preservation (Figure 2). Those who did not undergo cryopreservation tended to be older with a median age of 38 years (IQR 14) compared to 33 years (IQR 15) in the group that elected to undergo cryopreservation ($P = .10$).

Table 2: Reasons why men interested in fertility preservation chose not to undergo sperm cryopreservation after diagnosis with cancer at the University of Miami during the period 11/2021–2/2023 based on direct conversation via telephone call.

Reason for not proceeding with sperm cryopreservation	Count
Financial	**7**
Logistics	**4**
Elsewhere	**3**
Azoospermic	**3**
Already started tx	**3**

Of the 59 who chose not to undergo cryopreservation, twenty-four patients' charts contained a note describing why they elected not to proceed with sperm cryopreservation obtained at the time an attempt was made to schedule the appointment. Of these, the most common reasons were "not interested" (15), followed by "provided information but never called back" or "left voicemail" (6) and "already started treatment" (3). Those who were not interested and who did not have reasoning documented in the chart were contacted via telephone. Only 20 patients responded to phone calls and provided reasoning for not completing cryopreservation. The most common reason was financial by 7 patients followed by logistical reasons from 4 patients (Table 2).

Table 3: Infectious disease panel fees at the University of Miami health system in US dollars. Source: *Provided by the director of health system pricing at the Health Reimbursement Department at the University of Miami, Mr. Harold Goldsmith.*

CPT code	Qty	Charge code	Charge description	Hospital fee	Professional fee
87340	1	107701439	HCHG HEPATITIS B SURFACE ANTIGEN HA	169	16
86803	1	107701451	HCHG HEPATITIS C AB NON-A NON-B	214	16
87389	1	620739316	HCHG HIV 1/2 AB + T24 AG (4 GENERATION)	63	11
Grand total				**446**	**43**

Table 4: ReproTech fees for 2021–2022 in US dollars. Source: © 2012–2022 ReproTech LLC, https://www.reprotech.com/sperm-storage-costs/.

Sperm storage	Cost
Quarterly	$80
1 year	$300
2 years	$550
3 years	$850
4 years	$1,080
5 years	$1,260

Table 5: Comprehensive cost estimation of cryopreservation procedure, including initial consultation to long-term storage of sperm samples.

Appointment types	Fees in US dollars
New patient level 3 consult	270
Lab visit	550
Long-term storage facility	300/year
Infectious disease panel	487

Of the total 59 patients who did not undergo cryopreservation, between the documented reasoning and phone calls, the most common reasons given for not proceeding with fertility preservation were "not interested" by 45 patients (76%). Of those, who at the time were interested, the most common reason for not proceeding was "financial reasons" by 38 patients (84%) followed by 5 patients (11%) with "logistical reasons." Of note, there were 5 (8%) patients out of the 59 who did not undergo cryopreservation, that were deceased at the time of the analysis and their families were not contacted.

4. Discussion

The present study aimed to address a significant gap in understanding regarding the completion rates of sperm freezing among men with cancer after they have been referred to and seen by a reproductive urologist. The overarching hypothesis guiding this research was that a substantial proportion of male cancer patients do not proceed with sperm cryopreservation due to various factors, including financial constraints. Our main objective was to explore the reasons behind the non-completion of sperm freezing in this population, shedding light on a critical problem that has yet to be comprehensively examined. By investigating this issue, we aimed to make a substantial contribution to the field of fertility preservation in both urology and oncology. Understanding the barriers and challenges that lead to non-completion will not only provide valuable insights for clinicians and researchers but also pave the way for the development of targeted interventions and support strategies. Ultimately, filling this knowledge gap will have a profound impact on improving access to and adherence with fertility preservation protocols for male cancer patients, thereby offering them the opportunity to have biological children in the future.

In our facility, 128 men requested consults for fertility preservation prior to or during oncologic treatment between November 2021 and March 2023. Of these 128 patients, only $n = 67$ (52%) moved forward with sperm cryopreservation. One of the main stated barriers was the economic burden that cryopreservation would represent despite the discount programs, especially considering these patients' existing medical bills resulting from their cancer diagnosis and treatment.

Cryopreservation of sperm is a crucial procedure for male cancer patients who wish to preserve their fertility prior to cancer treatment. However, the cost of the procedure may pose a significant financial burden for patients, and ultimately, only about 50% of male cancer patients proceeded with sperm cryopreservation in our series. Additionally, usage of cryopreserved sperm requires IVF which can pose a significant cost burden on those seeking fertility. The American Society for Reproductive Medicine estimates the cost of each cycle of IVF to be $19,000 but other estimates of the total cost of IVF, pregnancy, and delivery can be as high as $60,000 [13]. Importantly, some couples may require multiple cycles of IVF to obtain even one viable embryo or live birth therefore further increasing the cost burden.

Traditionally, cost has been a barrier to sperm cryopreservation, thus we performed a cost-analysis to better understand the cost associated with sperm cryopreservation. Initial consultation, infectious disease testing with sperm processing, and storage for 5 years tabulate to around $2,500 (Tables 3–5). This can place a high financial burden on patients, especially in the context of having to fund potentially expensive life-saving cancer therapies.

The male cryopreservation process at our institution begins with an initial consultation with a urologist specializing in male infertility, which is typically covered by insurance. Details regarding this consultation which follows American Urologic Association (AUA) guidelines for the diagnosis and treatment of male infertility can be found in the appendix. However, patients may be required to pay a co-pay of $50 or higher. In cases where the patient does not have insurance, the cost of the consultation is $270. After the initial consultation, patients undergo an Infectious Disease Panel screening, which includes testing for infectious diseases such as HIV, Hepatitis B, and Hepatitis C. The cost includes both hospital and professional fees, for a total of $487 (Table 3). Subsequently, patients are scheduled for a laboratory appointment that includes semen analysis, processing, and cryopreservation, which costs $550. Once the process is finalized, the long-term storage facility is contacted, and the samples are transferred for storage. The cost of storing frozen sperm samples long-term is $300 per year (Table 4). Based on our analysis, the total cost for a 5-year sperm storage time per patient was $2,567 (Table 5).

Despite the critical need for fertility preservation prior to cancer treatment, the significant financial burden associated with the procedure remains a major obstacle for many patients [14]. These high costs can place a significant burden on patients, particularly those without adequate insurance coverage or financial resources [15]. The result is that many patients must choose between undergoing potentially life-saving cancer treatment and preserving their fertility with many opting for cancer treatment over fertility preservation [16].

Furthermore, the financial burden associated with the process widens the disparities in access to care, as patients from lower socioeconomic backgrounds may be unable to afford the procedure. This can result in a further exacerbation of health disparities in the population [17].

It is therefore critical that healthcare providers and policymakers work to address the high costs associated with fertility preservation for cancer patients, in order to ensure that all patients have equal access to this essential aspect of care [17]. This may involve efforts to increase insurance coverage for fertility preservation [18], as well as initiatives to reduce the cost of infectious disease testing and long-term storage.

To address this issue, there are several strategies that can be employed to improve access to sperm freezing for these patients. First, increasing public awareness and education about the importance of fertility preservation can be achieved through targeted outreach campaigns, social media, and educational materials. Second, providing financial assistance to low-income patients can be achieved through charitable organizations, government agencies, or through financial assistance programs offered by healthcare providers. Third, telemedicine and remote consultations can be utilized to increase access to fertility specialists for remote or underserved patients. Finally, fertility preservation discussions should be an integral component to all oncologic treatment plans.

In recent years, a significant development has occurred in the realm of infertility treatment coverage, driven by a wave of state mandates [19]. These mandates have broadened the scope of what insurers are required to cover, specifically pertaining to fertility preservation. Since 2017, a total of 21 states have introduced legislation aiming to mandate coverage for fertility preservation procedures, encompassing the removal and storage of eggs and sperm, prior to radiation and chemotherapy treatment for cancer patients [20]. Notably, five states including Connecticut, Rhode Island, Maryland, Delaware, and Illinois were the first ones to successfully enact such legislations, while many others still have bills pending for consideration. This progressive movement in state mandates represents a significant step towards ensuring that individuals facing cancer treatment have access to vital fertility preservation options, providing them with the opportunity to safeguard their reproductive future.

Incorporating discussions about fertility preservation into routine cancer care and providing comprehensive counseling and support to patients and their families can help ensure that all patients have access to the resources they need to make informed decisions about fertility preservation. By implementing these strategies, healthcare providers can help reduce financial barriers to sperm freezing for low-income patients, thereby improving their chances of having biological children in the future, while at the same time saving them from much more costly and invasive therapies in the future in an attempt to overcome what cancer treatment may have already done to their reproductive organs.

Despite the strengths of our study in identifying ways to optimize fertility preservation in cancer patients, it is not without limitations. One of the main limitations of this study is its retrospective nature. As a result, the study is limited by the quality and completeness of the data available in the medical charts of the patients. Furthermore, the follow-up data is limited to notes in the charts, which may not capture all relevant information. For instance, it is unclear what percentage of patients made an educated decision to not proceed with sperm cryopreservation and what the ultimate reason for not proceeding with cryopreservation was. In addition, the study does not have access to data on patients' financial stability, such as their income or insurance status. This lack of information limits the ability to draw conclusions about the impact of financial constraints on the decision to undergo sperm cryopreservation. Importantly, our center is an academic medical center in the United States,

thus all cost data is based on the American healthcare system and the absence of insurance coverage for many fertility procedures in the United States. In other countries, these procedures and costs may be vastly different or even may be covered by the reimbursement system [21].

On the same note, despite considering financial constraints as a potential barrier to completing sperm freezing, it is important to acknowledge that some patients may be unwilling to disclose their personal financial information. This can introduce a potential bias in the data, as the study relies on patients voluntarily providing information about their financial situations. As a result, the study may not capture the true extent of the financial burden experienced by patients who do not complete sperm cryopreservation. This limitation highlights the need for sensitive and confidential data collection methods to ensure that patients feel comfortable sharing their financial circumstances, while also recognizing that some individuals may still choose to withhold such personal information. It is also important to acknowledge the limitation associated with the sample size of our study. While our data provides insight into the reasons for non-completion of sperm cryopreservation among male cancer patients referred to and seen by a reproductive urologist, the sample size was quite small as these diagnoses and referrals are rare events. This limitation may affect the generalizability of our findings to larger populations and should be considered when interpreting the results. Importantly, our institution is a high-volume center for cancer and reproductive urology, therefore we believe the results could be inferred to another population. Despite this, a larger and more diverse sample would allow for more robust statistical analyses and a more comprehensive exploration of the factors influencing non-compliance with fertility preservation protocols which could potentially be performed through a multi-institutional analysis.

To conclude, studies have shown that fear of inability to produce biologic children after treatment adds significant feelings of anguish in patients [22]. The hope of raising a child after a cancer diagnosis can contribute to better acceptance of oncologic treatment and its adverse effects [23]. Research studies have already shown that patients have positive feelings about preserving their fertility; unfortunately, the number of patients who reach fertility preservation therapies is still exceedingly small compared with the number diagnosed with cancer [24]. Currently, the technologies available for oncological treatment are advanced and contribute to higher life expectancy and a greater chance of cure, making it possible for cancer survivors to form their own biological families [25]. Given the current analysis conducted, and a report that almost 50% of patients requiring preservation of their reproductive functions are not able to undergo the process due to their current financial situation, action must be taken to ensure patients that they do not have to choose between foregoing their future life plans in order to save their lives at the moment. This situation supports the need for providers and institutions to provide the means necessary for all patients, regardless of socioeconomic status, to preserve their reproductive function, and thus contributing to a higher quality of life, and encouraging positive thinking regarding cancer treatment.

5. Conclusion

In conclusion, oncofertility represents an important component of oncologic care and current evidence suggests that discussion of fertility preservation strategies prior to initiating chemotherapy are substandard. This study represents the first systematic analysis of the reasons behind the non-completion of sperm freezing among male cancer patients who have been referred to and seen by a reproductive urologist. Previous studies have primarily focused on examining the overall rates of fertility preservation utilization or identifying factors associated with patients' decision-making regarding fertility preservation. However, there has been a notable gap in understanding the specific reasons why patients, despite having received consultation from a reproductive urologist, do not proceed with sperm cryopreservation. By addressing this critical knowledge gap, our study provides valuable insights into the barriers and challenges that contribute to non-compliance with fertility preservation protocols in this specific context. These findings complement existing research efforts and contribute to a more comprehensive understanding of the factors influencing male cancer patients' decision-making regarding fertility preservation. Such insights can inform the development of targeted interventions and support strategies aimed at improving completion rates and facilitating access to fertility preservation options for this patient population.

Appendix

Details of initial consultation for oncofertility patients.

(1) Comprehensive history and physical exam including the genitalia.
   (a) The history should include a reproductive history and identify other medical causes of reproductive impairment such as prior abdominopelvic surgery, cryptorchidism, or usage of spermatotoxic medications.
   (b) The physical exam should identify concomitant etiologies of reproductive impairment as outlined in the AUA guidelines including obesity, virilization, gynecomastia, past scars that may have involved the genitourinary system, presence of bilateral vas deferens, and shape/size of the testes.

(2) Thorough discussion of the risk of azoospermia during and after treatment with chemotherapeutic medications.
(3) All patients will be offered sperm cryopreservation which will include a discussion of the financial aspects of the cryopreservation outlined above as well as approximate cost of IVF which would be necessary with the cryopreserved sperm.
   (a) If facilities are available on the day of consultation, a semen analysis may be able to be performed on the day of their initial consultation. They will receive the results of the semen analysis on the same day and sperm will be frozen.
   (b) If facilities are unavailable or the patient prefers to provide the sample on another day, that will be scheduled at the patient's convenience.
(4) All efforts will be made to not delay cancer treatment due to cryopreservation delay, as semen analysis and cryopreservation is available during multiple days of the week at our center. At most, we anticipate a patient may wait from Thursday until the following Monday to provide a sample, and then could start chemotherapy the same day as their cryopreservation.

Authors' contributions B. Ledesma, E. Ibrahim, and R. Ramasamy designed research; B. Ledesma, K. Campbell, and A. Muthigi performed research; B. Ledesma, K. Campbell, V. Ila, E. Ibrahim, and R. Ramasamy analyzed data; and B. Ledesma, K. Campbell, A. Muthigi, and R. Ramasamy wrote the manuscript.

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Conflict of interest The authors declare that they have no conflict of interest.

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