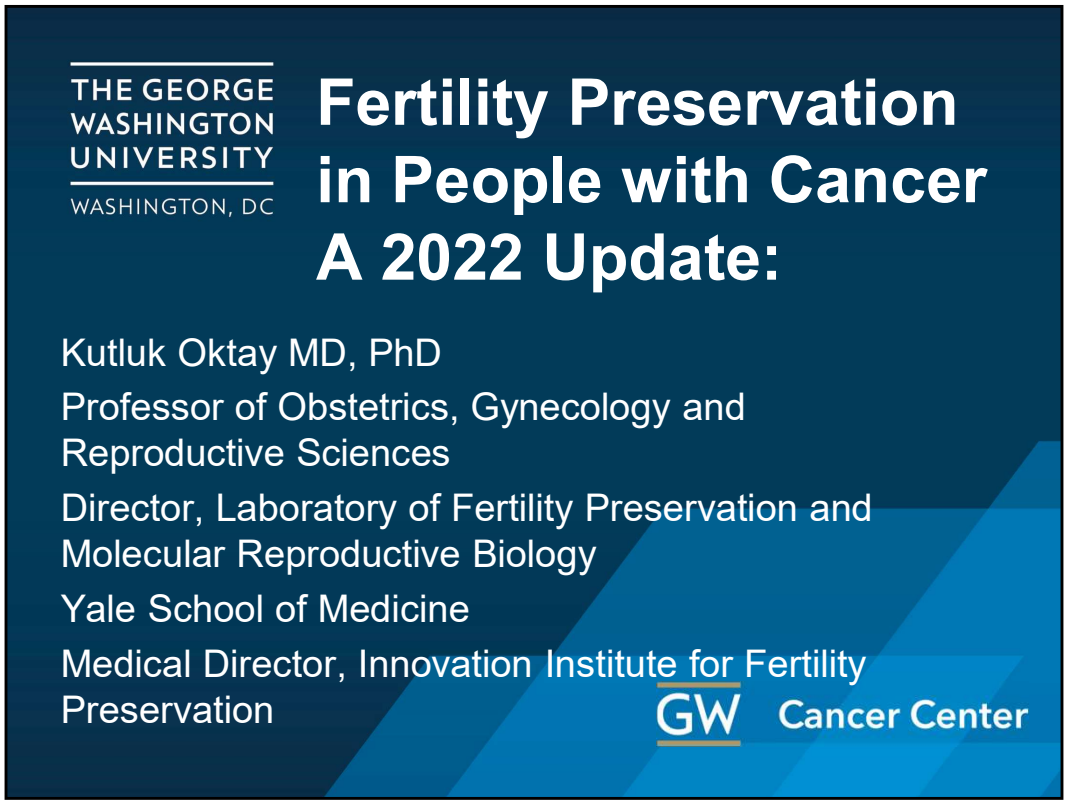
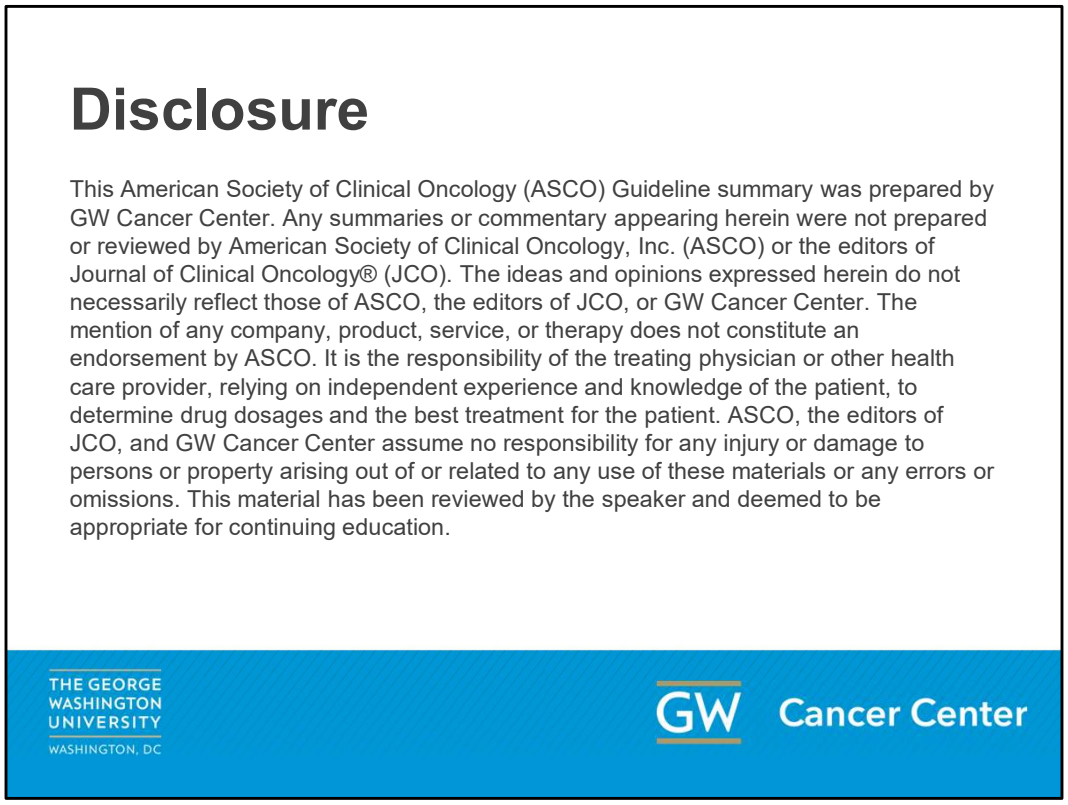
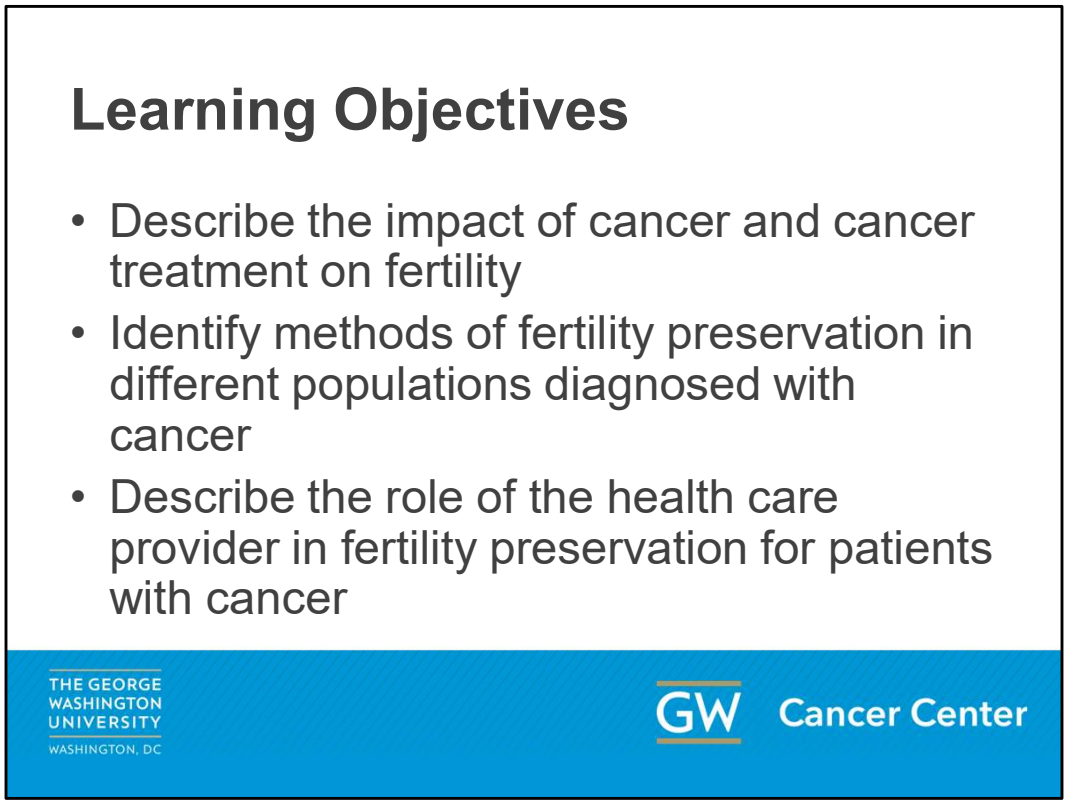


Welcome to this presentation on Fertility Preservation in Patients with Cancer.

My name is Kutluk Oktay, and I am a Professor of Obstetrics, Gynecology and Reproductive Sciences. I also serve as a Director, Laboratory of Fertility Preservation and Molecular Reproductive Biology and the Medical Director of Innovation Institute for Fertility Preservation.



Please note our disclosures. This content was created by a review of ASCO guidelines, and was not prepared by ASCO or JCO. Also, please note that any information provided about fertility and LGBTQ community was not part of the ASCO guidelines. Learners should always seek out the latest information and guidelines before making clinical care decisions.



We will cover three learning objectives in this presentation.

First, we will describe the impact of cancer and cancer treatment on fertility.

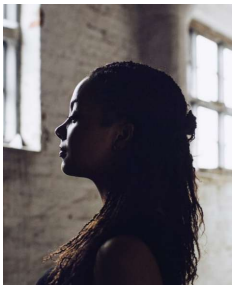
Next, we will identify methods of fertility preservation in different target populations diagnosed with cancer

And lastly, will describe the role of the health care provider in fertility preservation for patients with cancer

Infertility and Patients with Cancer

Males

Females



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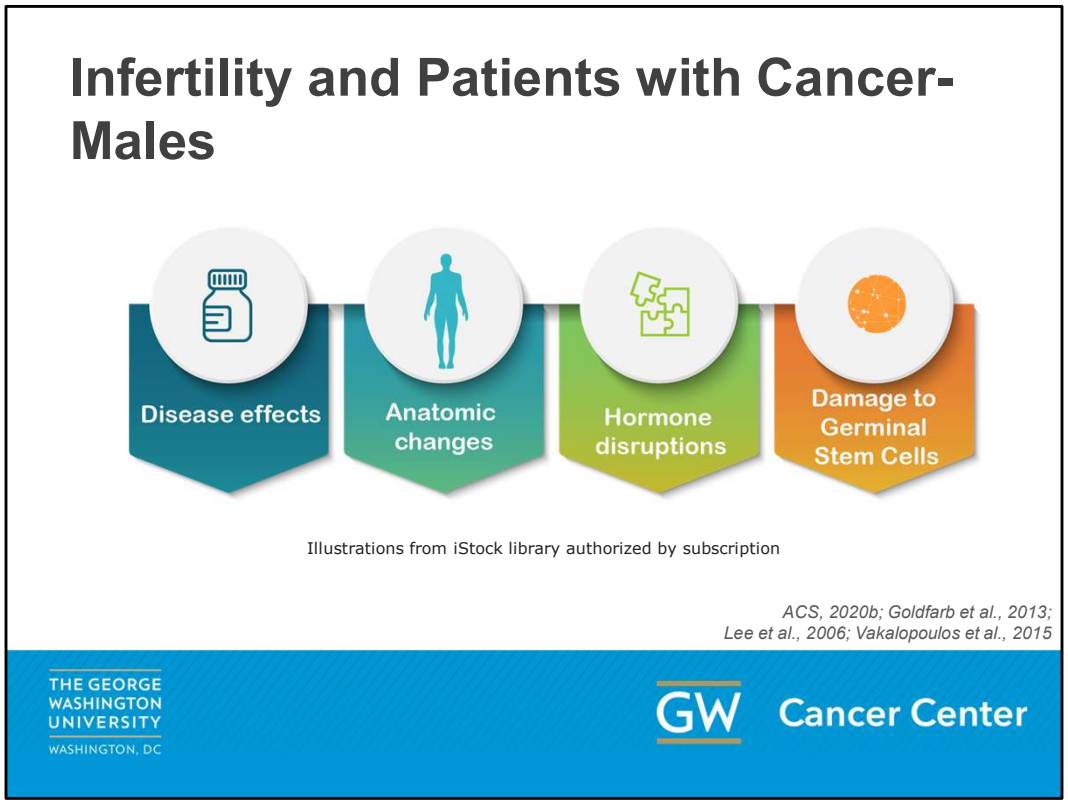
Cancer-related infertility can affect both male and female patients.

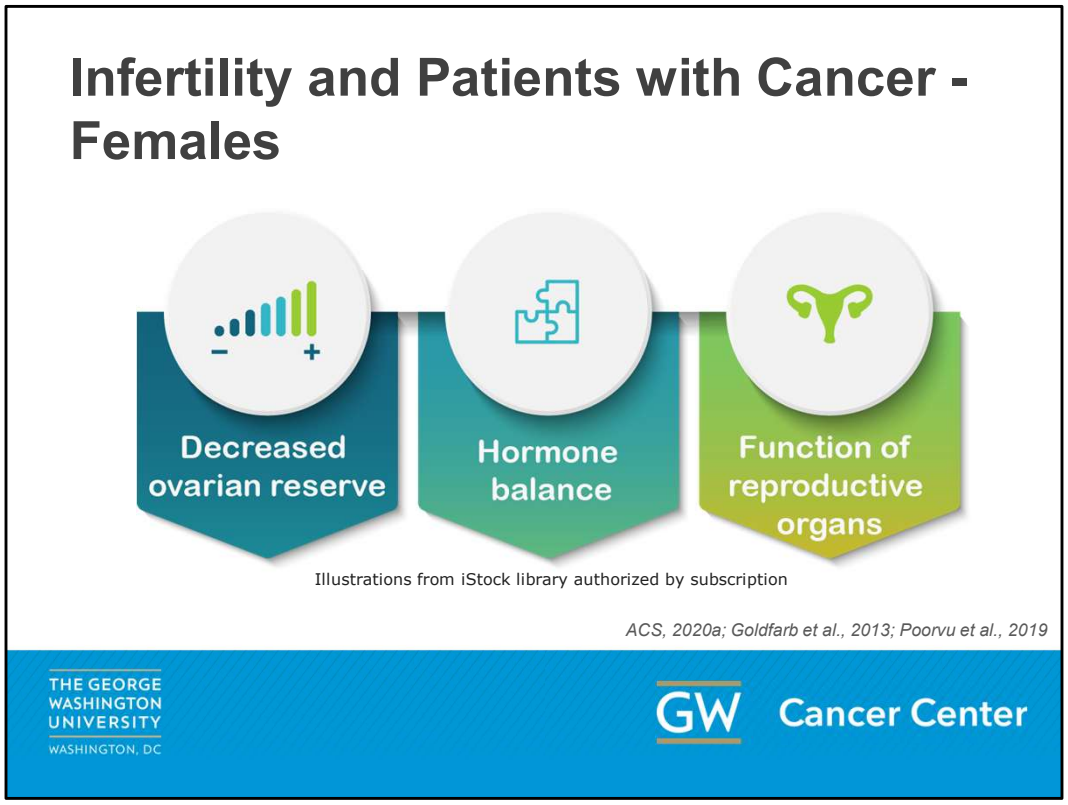


Some causes of infertility in male patients with cancer include:

- Effects of the cancer itself, such as impaired spermatogenesis
- Anatomic changes, such as prostate removal, arterial injury during surgery, gonadal damage, or structural changes in erectile tissue
- Primary or secondary hormone disruptions, due to either the cancer itself or associated treatments, including the chemotherapy drugs used
- Damage or depletion of germinal stem cells from chemotherapy or radiation treatments, which may affect sperm quality and quantity

The impact of chemotherapy on male fertility can be observed and measured by compromised sperm number, motility or morphology, and DNA integrity

For prostate cancer survivors, post-operative erectile dysfunction and other sexual side effects are common.



In female patients with cancer, causes of infertility may include:

- Decreased ovarian reserve from damage to the follicles, in excess of natural depletion from age
- Effects on hormone production though these can be easily overcome by hormonal treatments if there is no damage to ovarian reserve.
- Changes in the anatomy or function of the ovaries, fallopian tubes, uterus, or cervix, which may prevent natural conception or successful pregnancy, necessitating assisted reproductive technology treatments.

Cancer surgery, chemotherapy or radiotherapy can have more severe effects on the reproduction process than the cancer process itself.
Surgery: Removal of tumor in or near another reproductive organ/pelvic or abdominal organs or near the nervous system may affect a woman's fertility
Radiation therapy: Aimed at or around a woman's reproductive organs can affect fertility
Chemotherapy: commonly used cancer drugs deplete ovarian reserve and may affect fertility and potentially lead to premature or early menopause. Higher doses are more likely to cause imminent fertility changes and drug combinations may have even a greater effect

Cancer Treatment and Fertility

- Cancer treatment can cause infertility through cellular damage or removal of gonadal organs
- Treatment effects on fertility depend on the drug, size/location of radiation field, age, sex, and pretreatment fertility of the patient

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Goldfarb et al., 2013; Oktay et al., 2018

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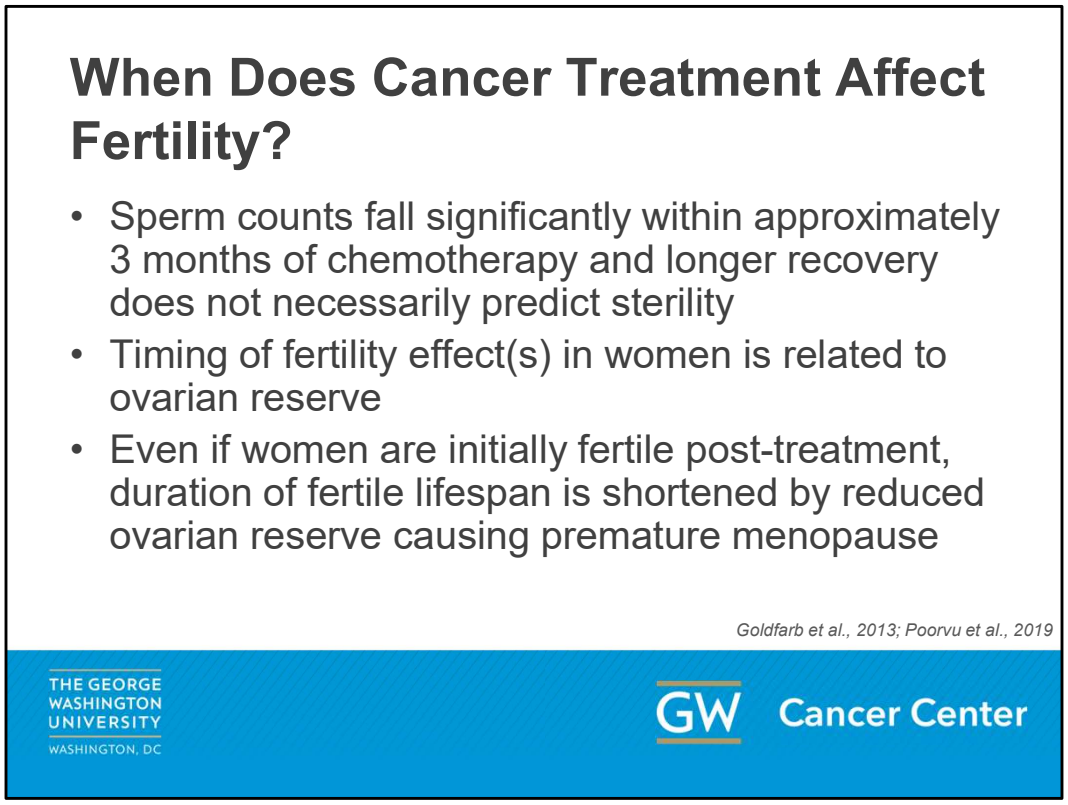
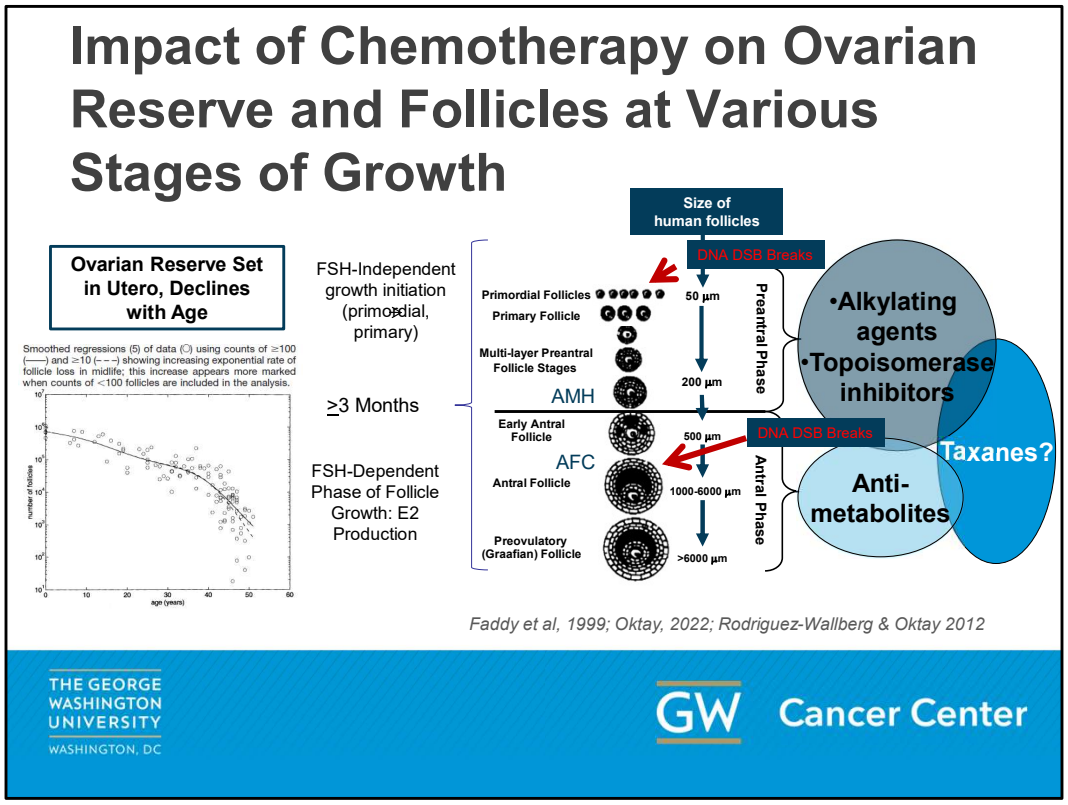
Cancer treatment can cause infertility through cellular damage or removal of gonadal organs
The specific treatment effects may vary depending on the drug used, the size or location of the radiation field, and patient characteristics, such as age, sex, or pretreatment fertility status.

For example, high doses of pelvic radiation may affect uterine anatomy, cause endometrial damage, and other changes that may impair embryo implantation or fetal growth. After pelvic radiation, patients are at increased risk of miscarriage, preterm birth, and low birth weight.



Following cancer treatment, patients may experience infertility transiently or permanently. An example of a transient effect is decreased sperm count within approximately 3 months of chemotherapy. Sperm are highly sensitive to chemotherapy and radiation because of their continuous development status. If the spermatogonial stem cells are not affected, new sperm can be formed in about 3 months and sperm counts may recover after months or years. However, if high dose alkylating agents are used, the spermatogonial stem cells are damaged and sperm count may never recover.

In female patients, some chemotherapy agents cause DNA damage and death to ovarian reserve eggs called primordial follicles. Once these cells are lost they cannot be replaced and this would result in premature menopause. On the other hand, damage to developing follicles from chemotherapy, through the same mechanism, can cause amenorrhea. However, if any primordial follicles are left, new developing follicles will form, produce hormones and restore menstruation. Hence, Even in the presence of regular menstruation, patients and providers should not assume that fertility is uncompromised. Both the treatment toxicity and patient's age can affect their ovarian reserve. A decreased reserve will lead to early menopause and age-related infertility.



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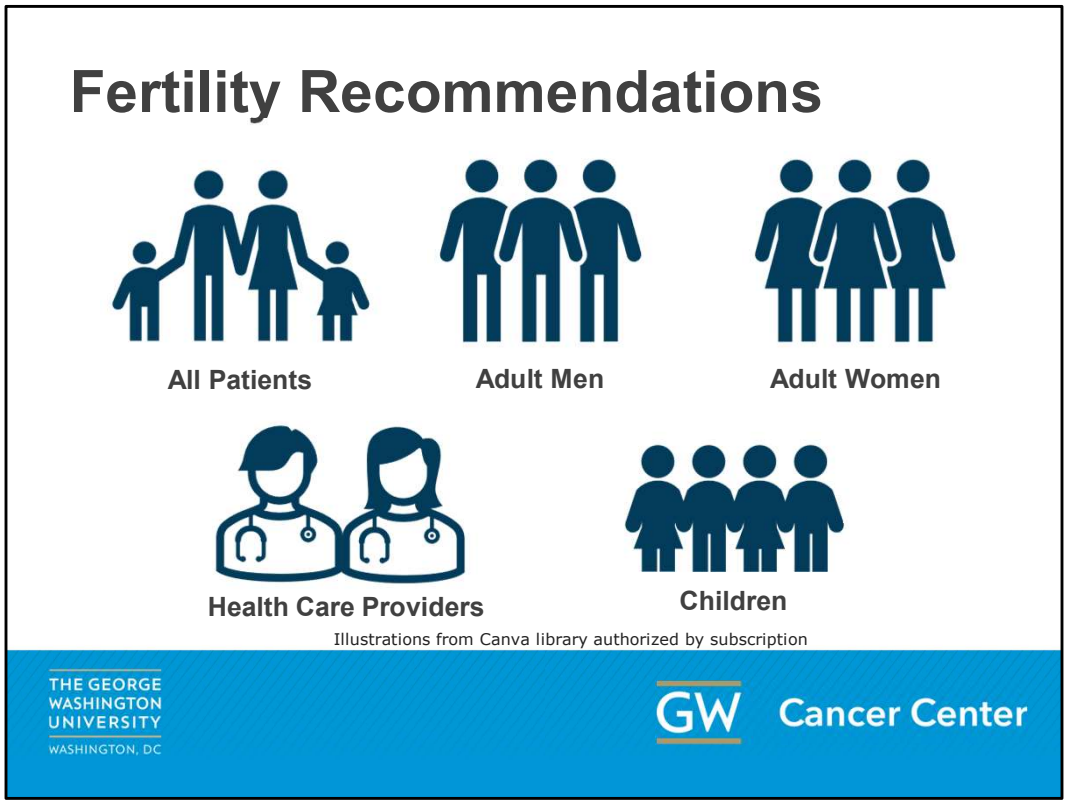
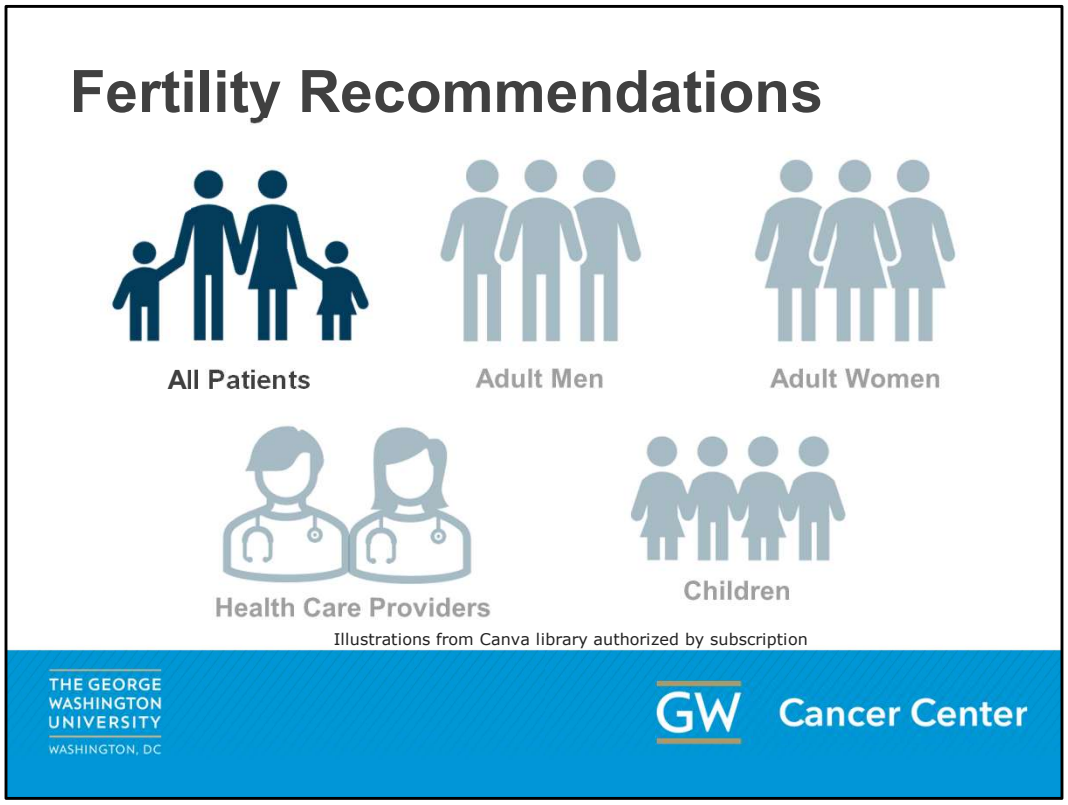


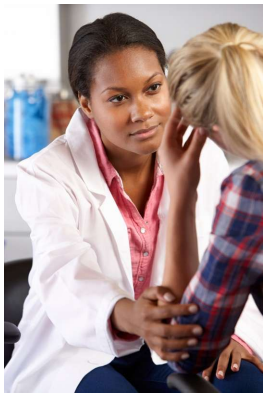
The American Society of Clinical Oncology (ASCO) guidelines for fertility in patients with cancer discuss 4 recommendations for specific target populations of cancer patients and 1 recommendation for health care providers.



We will start with recommendations relevant to all patients with cancer

Timing on Communication on Fertility

- Health care providers caring for adult and adolescent patients with cancer should:
  - Discuss the possibility of infertility
  - Refer interested patients to reproductive specialists



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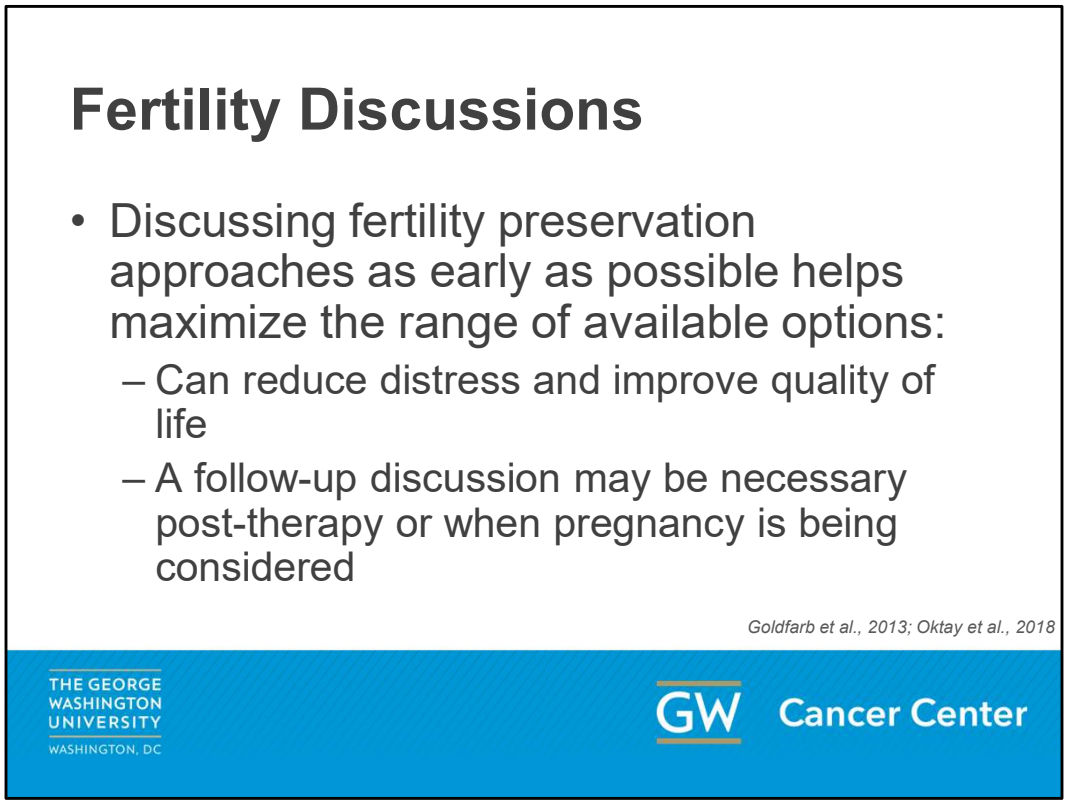
ASCO recommends that health care providers treating any patient with cancer, whether adult or adolescent, discuss the possibility of infertility as soon as possible and before treatment starts.

If the patient expresses interest in fertility preservation, or is ambivalent, the health care provider should refer this patient to reproductive specialists.

Of course, fertility preservation conversations should be age-appropriate for adolescent patients.

Guidance on fertility options and communication for prepubescent pediatric patients will be cover later in the module

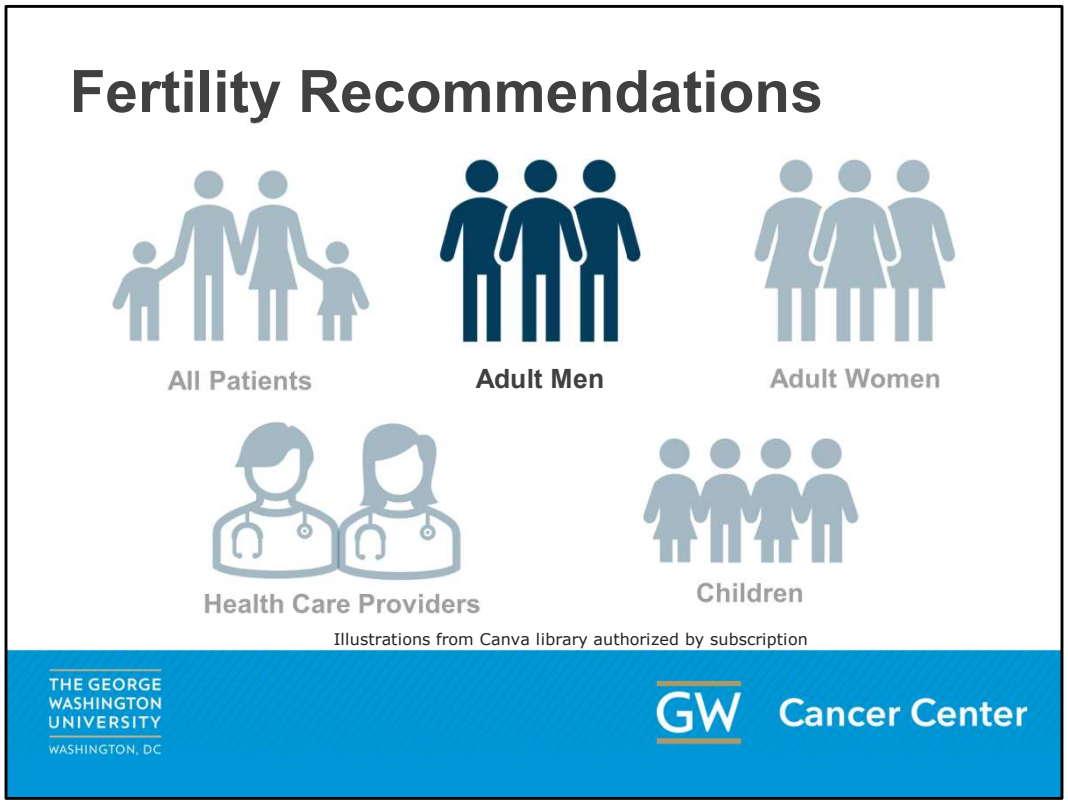


By discussing fertility preservation as soon as possible, the health care provider can help maximize the range of options available to the patient.

Many survivors, especially young survivors (< 40 years old), want to become parents after treatment and are distressed by the possibility of infertility. Addressing and discussing this possibility early in diagnosis can reduce distress and, long-term, improve quality of life for survivors.

Providers should also be prepared to have follow-up discussions after treatment is completed or when the patient is contemplating pregnancy.

Every fertility-related discussion should be documented in the patient's medical record.



Next, we will discuss fertility preservation recommendations for use in adult men with cancer. Please note that these guidelines were written with cisgender men in mind. Cisgender men are those whose gender aligns with their sex assigned at birth. We will talk about transgender patient needs later in the module.

Fertility Preservation in Men with Cancer

- Sperm cryopreservation is an effective method of fertility preservation in adult men
- Hormonal therapy does NOT successfully preserve fertility in men

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Sperm cryopreservation is considered an effective method of fertility preservation for adult men diagnosed with cancer, and sperm banking should be discussed with post pubertal men who will receive cancer treatment.

Importantly, hormonal therapy is not a successful fertility preservation method in men and is not recommended by ASCO.

Experimental Methods in Men with Cancer

- Testicular tissue cryopreservation with the intent of reimplantation (grafting)

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There are other methods of fertility preservation available for use in adult men diagnosed with cancer, but they should only be used as part of a clinical trial or experimental protocol. These methods include testicular tissue cryopreservation, with the intent of reimplantation or grafting of human testicular tissue.

Fertility Preservation in Transgender Men with Cancer

- Embryo and Oocyte cryopreservation available for post pubertal transmen before and after the initiation of gender affirming hormonal therapy (GAHT)

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Sterling & Garcia, 2020

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Transgender persons have the same interests as other persons in having children and in accessing fertility services for [fertility preservation] and reproduction
For all transgender individual's fertility options are categorized into three groups, options available before initiation of gender affirming hormonal therapy, options after initiation and experimental options that can be done concurrently with genital gender affirming surgery.

A transman diagnosed with cancer can pursue fertility preservation via the same options as cisgender women - that is through oocytes or embryo cryopreservation BEFORE and AFTER the initiation of GAHT
However, this method has several additional considerations for transgender men. Transmen will need to undergo the following during preparation for and completion of pregnancy.

a) Routine transvaginal ultrasound examinations
b) Ovarian stimulation
c) Invasive transvaginal procedure to harvest oocytes and to access embryo uterine health ..

Some or most of these can be distressing

Note: This is not part of the ASCO Guidelines, but our discussion here aligns with the health equity focus of the GW Cancer Center

Male Fertility after Chemotherapy

- Advise men of the high risk of genetic damage in sperm if collected after initiation of therapy
- Strongly recommend sperm collection prior to treatment initiation:
  - Intracytoplasmic sperm injection allows future use of even limited number of sperm

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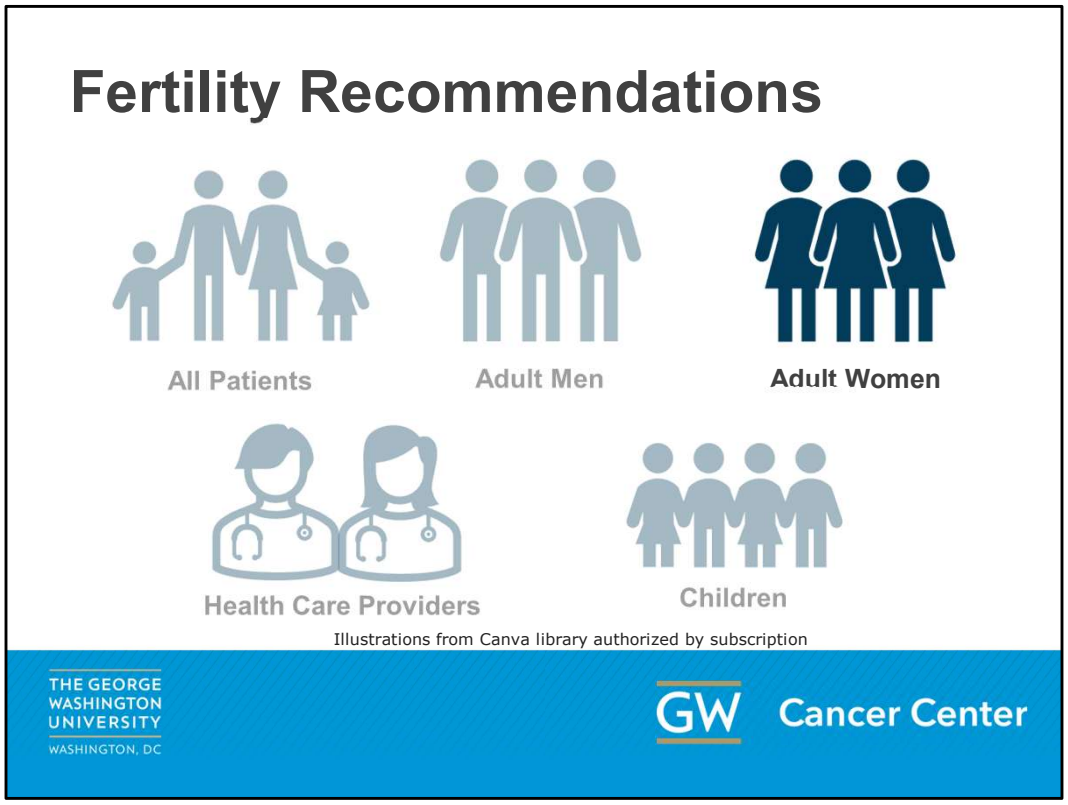
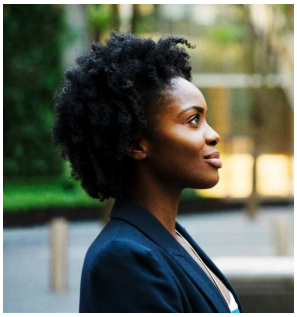
Men should be advised that there may be a higher risk of genetic damage to any sperm collected after chemotherapy is initiated. After even a single treatment, the quality of the sperm DNA and sperm functions may be compromised. Sperm collection prior to the start of treatment is strongly recommended. Patients should not be dissuaded from banking sperm, even if quick initiation of therapy is required and there is limited time to collect an optimal number of sperm specimens. In these compromised situation, intracytoplasmic sperm injection allows for the future use of a very limited amount of sperm, and fertility may still be preserved.



Now, we will discuss fertility preservation in adult women with cancer. The ASCO guidelines were written with cisgender women in mind. We will get to transgender patient needs later.

Fertility Preservation Options in Women with Cancer

- Embryo cryopreservation:
  - Has a partner/using donor sperm
- Oocyte cryopreservation:
  - Without a male partner
  - Who do not wish to use donor sperm
  - Who have practical/religious/ethical objections to embryo freezing



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Embryo cryopreservation is routinely used to store surplus embryos after IVF and is a well-established method of preserving fertility in women diagnosed with cancer.

Cryopreservation of unfertilized embryos is also an available option. As of October 2012, experts considered cryopreservation of oocytes an effective method to help preserve fertility.

Cryopreservation of unfertilized oocytes may be well suited for certain women, including those who don't have a male partner, don't want to use donor sperm, and those with practical, religious or ethical objections to freezing fertilized embryos.

Fertility preservation, especially cryopreservation of unfertilized oocytes, should be performed in a facility with necessary expertise.

In most cases, newer protocols for ovarian stimulation are cycle-day-independent, called random start, and can be started more quickly than older methods, which relied on timing with the menstrual cycle.

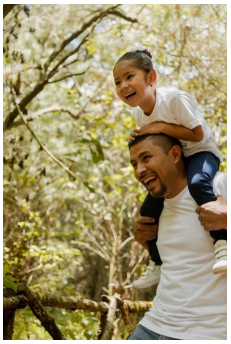
For patients with estrogen-sensitive breast cancer or gynecologic malignancies, there may be concern that fertility preservation or subsequent pregnancy could increase the risk of cancer recurrence. Aromatase inhibitor-based protocols may address these concerns and studies have not found evidence that fertility preservation or pregnancy

increases cancer recurrence risk.

Ovarian Tissue Cryopreservation for Auto-Transplantation (Updated 2022)

Benefits:

- Can be performed with short notice
- Does not require ovarian stimulation
- Does not rely on sexual maturity and may be the only method available in children
- Can restore natural hormone production and fertility after transplantation
- No longer experimental (2019, ASRM Practice Committee)



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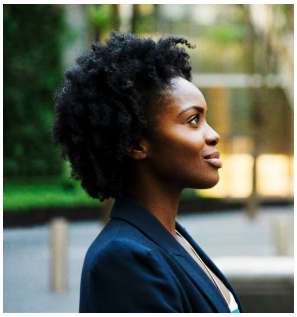
The recommendation regarding use of ovarian tissue cryopreservation and transplantation was also updated in 2018. Benefits of this method include that it can be performed immediately for future transplantation, may restore global ovarian function, and does not require ovarian stimulation. Ovarian tissue cryopreservation and transplantation also does not rely on sexual maturity and may be the only method available in children. It is no longer experimental in the US, Europe, Japan other localities.

Special Case of Fertility Preservation in Women with Breast Cancer

- Aromatase Inhibitor protocols can be used to reduce estrogen exposure and safely perform ovarian stimulation for oocyte/embryo cryopreservation
- Women with BRCA mutations may have lower ovarian reserve and may lose more of their ovarian reserve after chemotherapy



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Oktay et al 2005; Oktay et al., 2018; Oktay et al 2020

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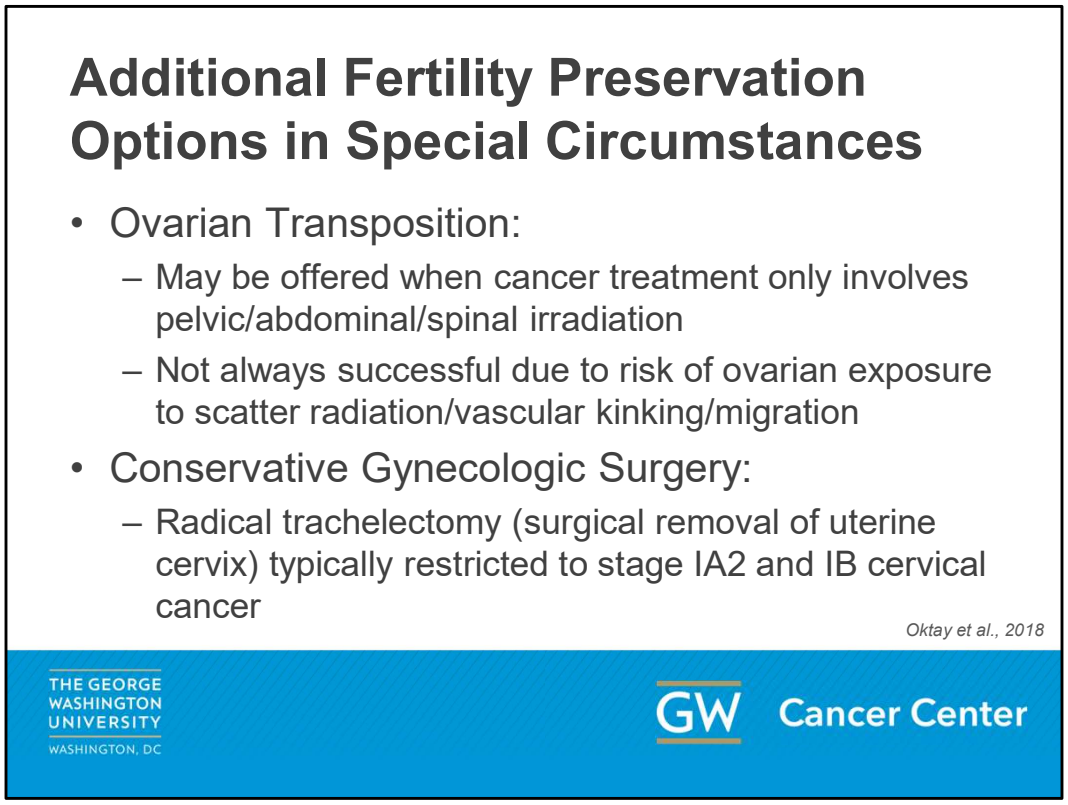
For patients with estrogen-sensitive breast cancer or gynecologic malignancies, there may be concern that fertility preservation or subsequent pregnancy could increase the risk of cancer recurrence. Aromatase inhibitor-based protocols may address these concerns and studies have not found evidence that fertility preservation or pregnancy increases cancer recurrence risk.

Women with BRCA mutations may have lower ovarian reserve and may lose more of their ovarian reserve after chemotherapy



Some other available methods for use in women include ovarian transposition and conservative gynecologic surgery. Ovarian transposition may be offered when cancer treatment includes pelvic irradiation, but patients should be made aware that this method isn't always successful, and the ovaries may be exposed to some scatter radiation. There is also a risk that the ovaries will migrate back to their original position, so if this method is selected, the procedure should be performed as close to the time of radiation treatment as possible.

In general, surgical fertility preservation interventions focus on sparing the reproductive organs as much as possible. Ovarian cystectomy can be performed for early-stage ovarian cancer. In cervical cancer, surgical removal of the uterine cervix is also a possibility but is typically restricted to stage IA2 and IB cervical cancer with < 2 cm diameter and < 10 mm invasion.

Ovarian Suppression (Updated 2022)

- In young women with breast cancer, GnRHa suppression should not be used as a method of fertility preservation
- Some suggested its use for reducing amenorrhea risk in women with breast cancer aged<40 years but this is not proven and unlikely to be effective

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The recommendation about ovarian suppression was updated in 2018. The evidence behind use of GnRHa (Gonadotropin-releasing hormone agonist) and other ovarian suppression methods for fertility preservation is conflicting. This method should NEVER be offered as a fertility preservation method.. In young woman with breast cancer, when other proven methods of preservation are not feasible, some suggest GnRHa may be offered with the aim of reducing amenorrhea risk, but this is doubtful.

Fertility Preservation in Transgender Women with Cancer

- Sperm cryopreservation available for post pubertal transwomen before and after the initiation of gender affirming hormonal therapy (GAHT)

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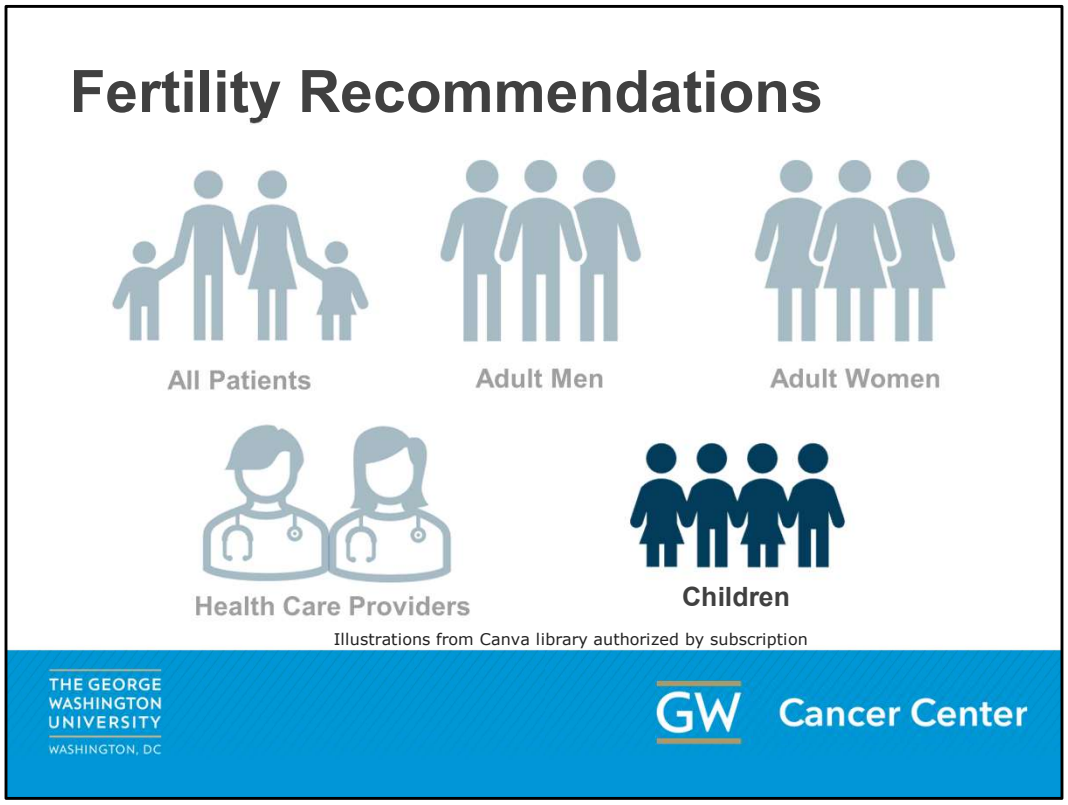
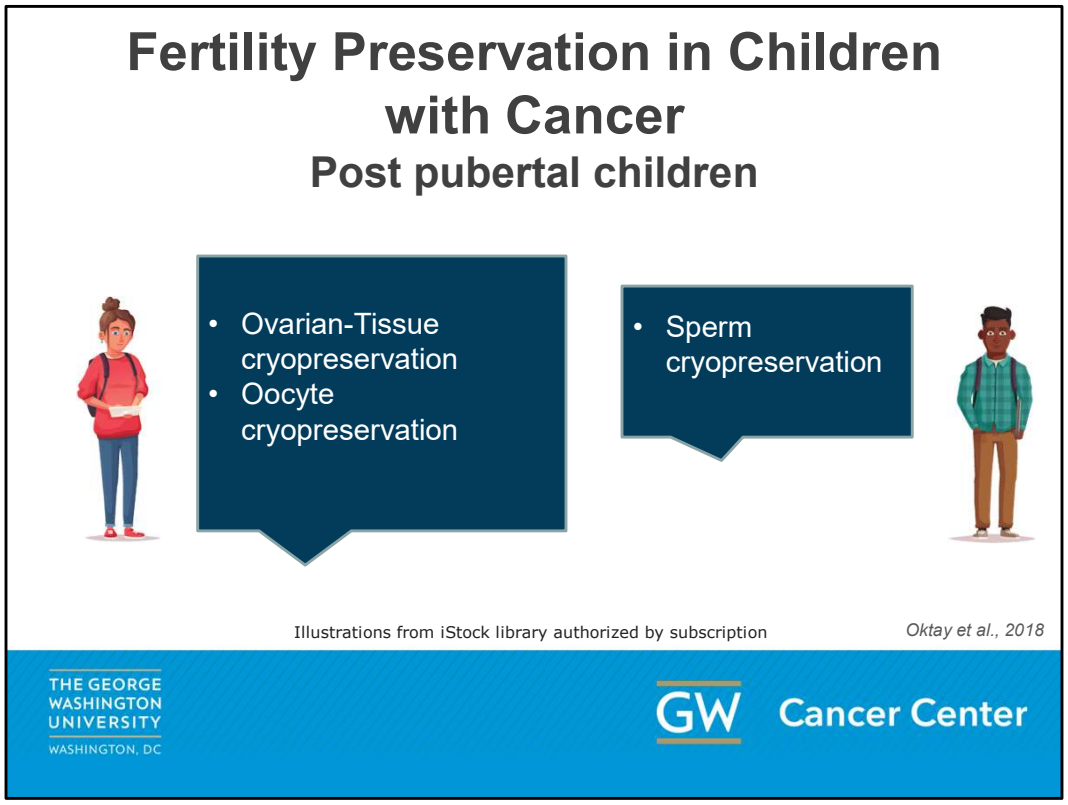
Fertility preservation option for post pubertal transwomen diagnosed with cancer is cryopreservation of ejaculated semen. It is important to consider the focused-use of their genitals to facilitate this process that can lead to gender dysphoria.

Transwomen who find the provision of ejaculated sample uncomfortable may opt for sperm aspiration or microsurgical sperm extraction as alternative methods, however, these options are more invasive and costly.



When working with children, especially prepubertal children, some additional considerations are needed, due to the limited fertility preservation options available for pediatric patients.



When working with post pubertal children with cancer, the established methods of fertility preservation discussed earlier in this presentation are recommended. These are oocyte and ovarian tissue cryopreservation for female children and sperm cryopreservation for male children

Fertility Preservation in Children

Pre pubertal children

- Ovarian (now established) and testicular cryopreservation (investigational) are the only available options
- Immature oocytes may also be obtained from ovarian tissue and cryopreserved after in vitro maturation

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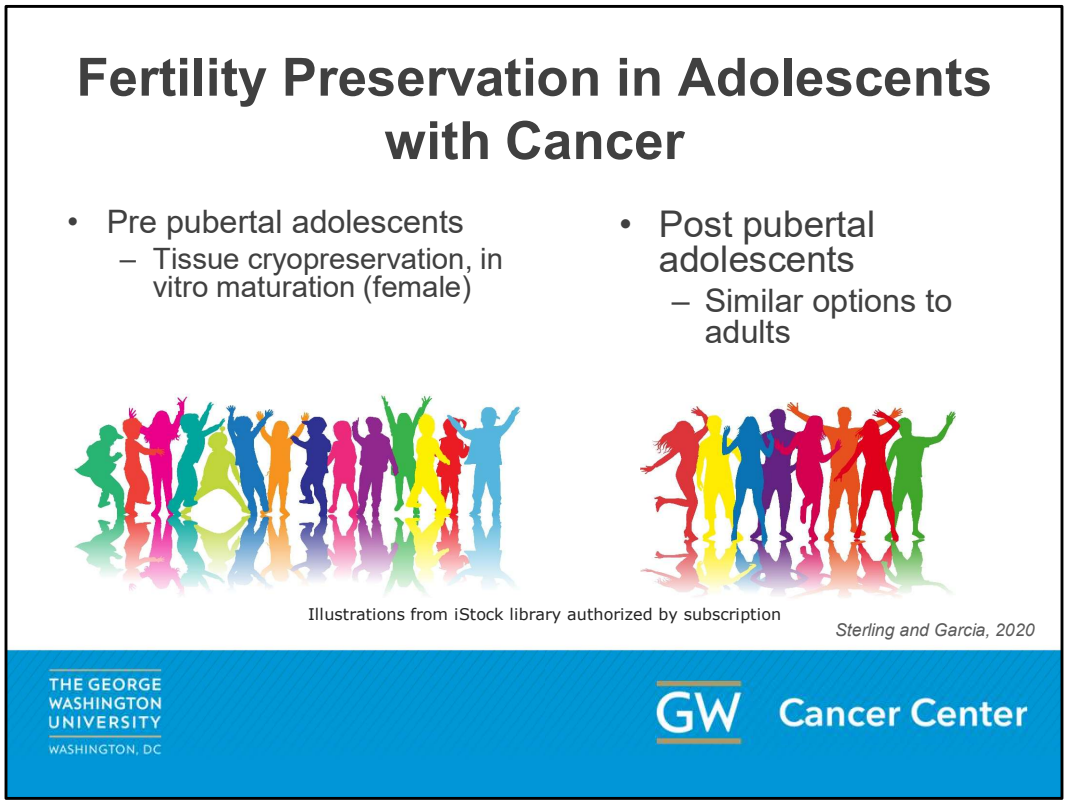
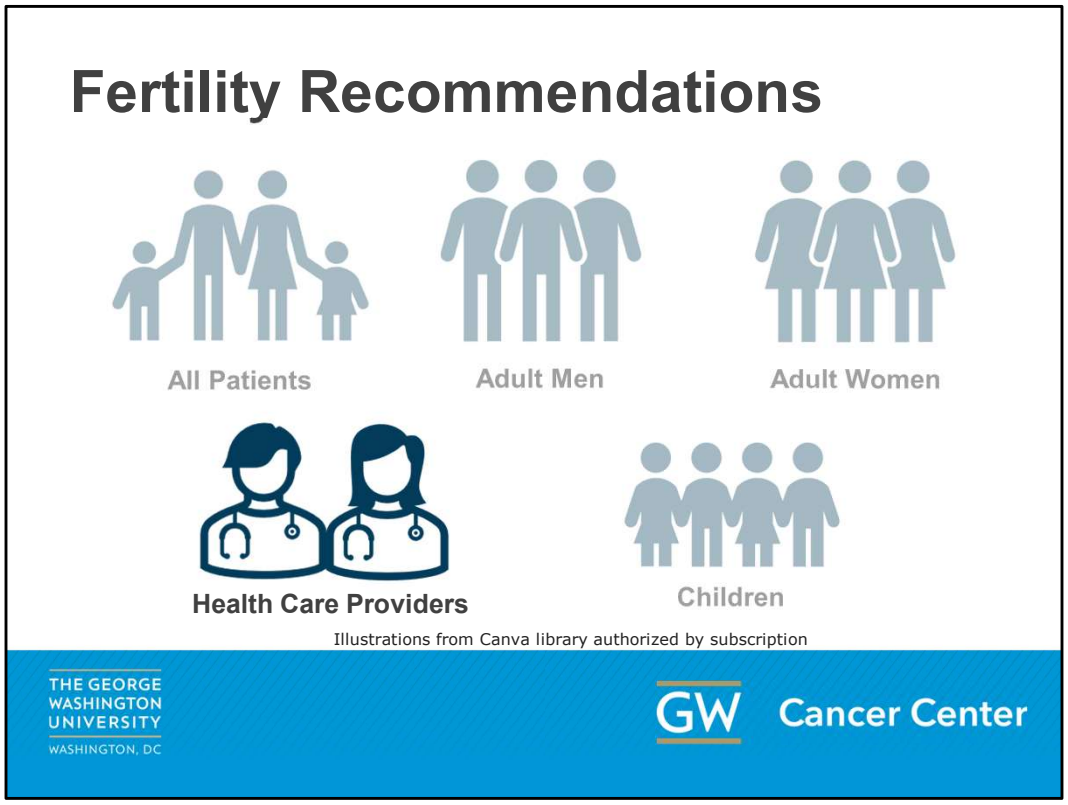
In prepubertal children diagnosed with cancer, there are more limited options for fertility preservation, and some remain under investigation. Only ovarian or testicular cryopreservation are available for use in these patients. Ovarian tissue cryopreservation can be combined with aspiration of immature oocytes from the follicles on the surface of the harvested tissue, followed by in vitro maturation and oocyte cryopreservation. Testicular cryopreservation remains experimental.

In all cases involving minors, consent from the parent or guardian & assent from the child is required.



Fertility preservation discussions with children and adolescents diagnosed with cancer, should include parents but should ensure maintenance of patient's autonomy. It is important to consider that there may be disagreements between adolescents and their parents about the uptake of fertility preservation methods.

- The only option for prepubertal children are ovarian tissue banking with or without oocyte in vitro maturation, and testicular tissue cryopreservation; however, the testicular cryopreservation is in the experimental phase and not available as established techniques
- Post-pubertal children should receive fertility preservation counselling and be offered the same options offered for adults with the exception of embryo freezing.



Next, we'll discuss recommendations regarding the role of the health care provider in fertility preservation.

Role of the Health Care Provider

- All oncology health care providers should:
  - Encourage interested patients to participate in registries/clinical studies
  - Refer patients to reproductive specialists
  - Refer distressed patients to psychosocial providers

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Ethics Committee of the American Society for Reproductive Medicine, 2021; Fantus et al, 2015

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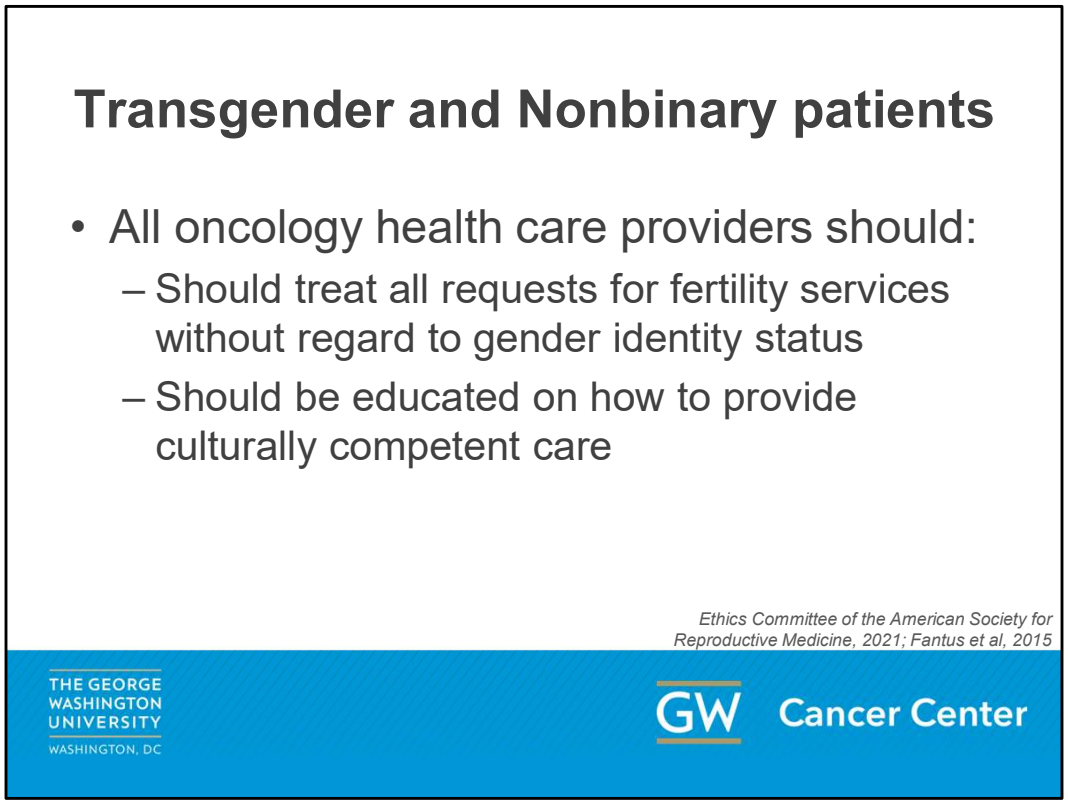
All providers working with oncology patients should actively facilitate and ask patients about their interest in parenthood and fertility preservation. Patients may not be thinking about fertility given everything else they are processing. Providers should be prepared to discuss infertility as a possible effect of cancer treatment. The provider should encourage patients to participate in available cancer registries and clinical studies where appropriate. These are important tools for understanding the safety and effectiveness of fertility preservation strategies in patients with cancer. Further, the provider should refer any patient who is interested in, and those who are either ambivalent or hesitant about, fertility preservation to specialists as soon as possible. The potential of infertility may also cause distress in some patients, and these patients should be referred to mental health professionals for guidance and support.



For Transgender and Non-Binary persons:
Research shown recurring patterns of negative clinical experiences which symbolize healthcare providers' discriminating attitudes and assumptions of heterosexuality.
Health care providers;

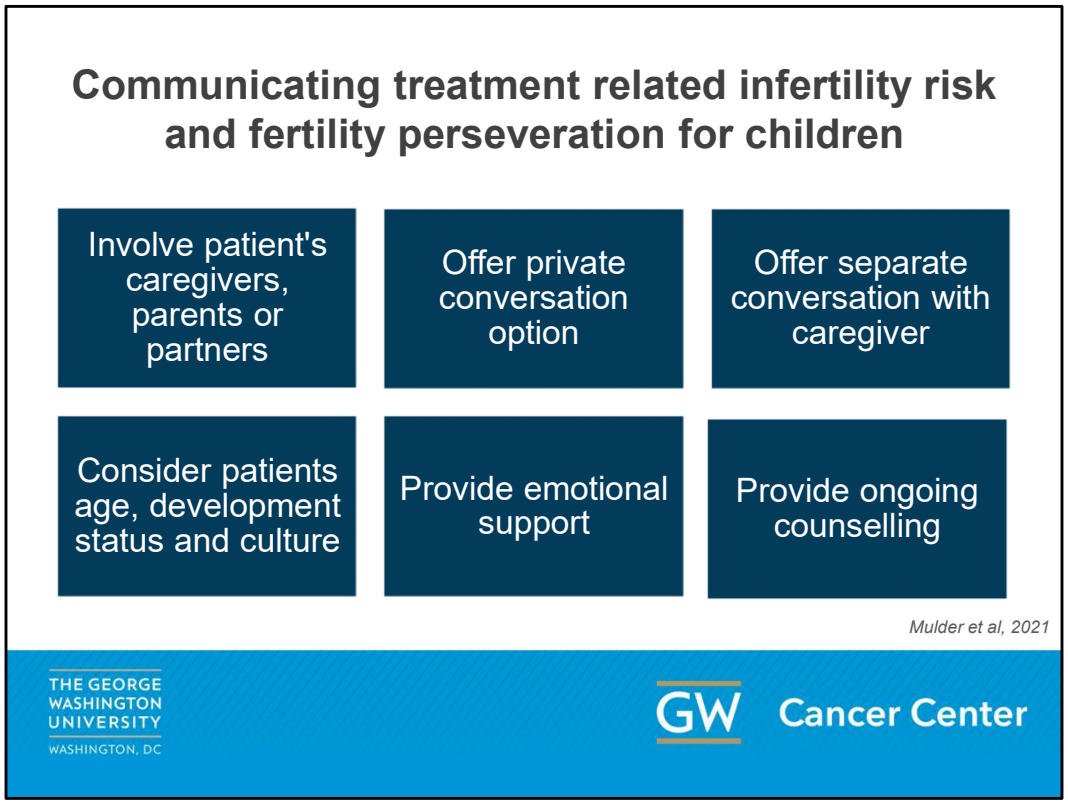
- Should treat all requests for fertility services without regard to gender identity status
- Should be educated on how to provide culturally competent care
- Should offer FP counseling to individuals before gender transition
- Should ensure that transgender patients who seek fertility services are informed about any distinctive medical risks and the lack of data about long-term outcomes for patients and their offspring.
- Should treat all requests for assisted reproduction without regard to gender identity status.

Organizations without sufficient resources to offer care have an ethical duty to assist in referral to providers equipped to manage such patients.

For adolescent and young adults
Addressing fertility preservation may be difficult as patients may not be willing to disclose their sexual orientation. It is thus important to integrate FP options that are considerate of sexual diversity as routine practice.

- Health care providers should aim to obtain training on sexual diversity which may help identify personal biases, heteronormative assumptions and homophobic attitudes that may impact service provision

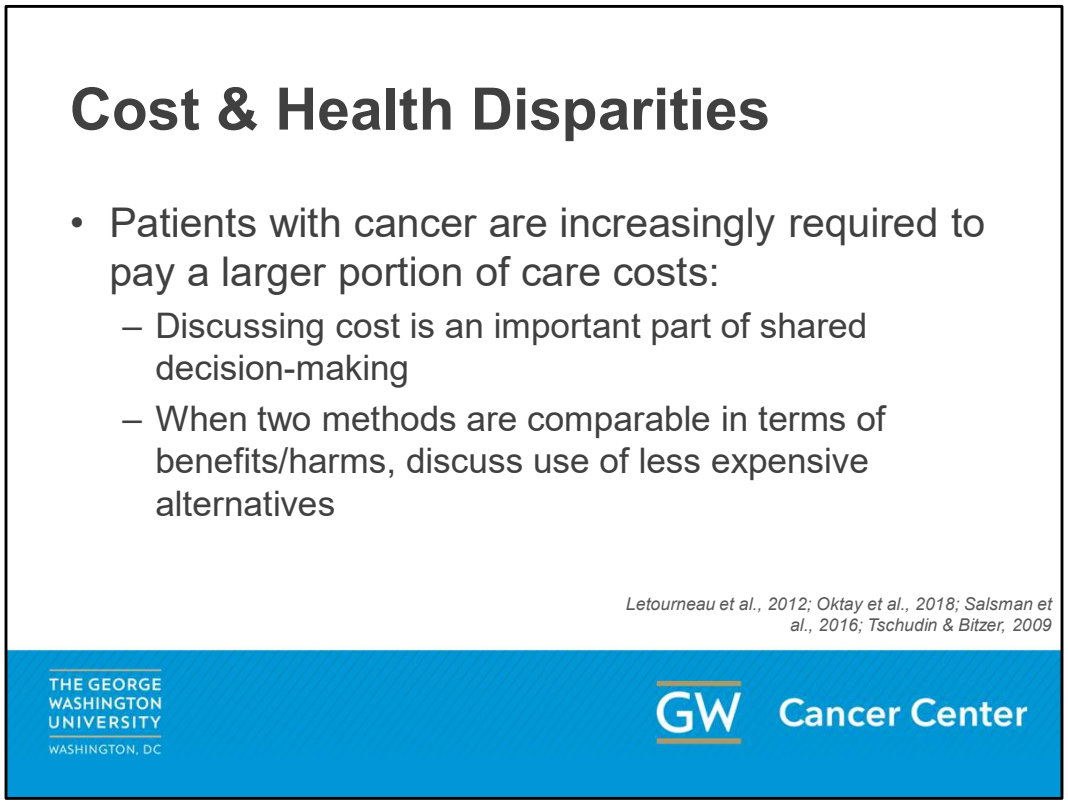
- Health care providers should be familiar with resources, referrals and support services for LGB adolescents who may be interested in fertility preservation and parenthood



Communication and ethical considerations for fertility preservation for patients with childhood, adolescent, and young adult cancer:

- Involve patients or their parents, caregivers, or partners, or both
- Offer a private conversation with the patient depending on age
- Offer a separate conversation with parents, caregivers, or partners after consent or assent of the patient
- Consider the patient's age, developmental status, and the family's cultural and religious beliefs
- Provide emotional support to patients and their parents, caregivers, or partners during counselling about treatment-related infertility risk and fertility preservation and prompt psychosocial specialist referrals as and when appropriate
- Initiate counselling as early as possible after a cancer diagnosis and a treatment plan have been established, or when a change in disease status occurs that requires treatment intensification with gonadotoxic agents or methods
- Offer counselling on an ongoing basis during treatment and throughout survivorship because the infertility risk or patient's ideas might change

These recommendations are from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group



Cancer treatment and fertility preservation can be expensive, and patients are increasingly required to pay a larger portion of their care costs through deductibles and coinsurance. The costs may vary by insurance coverage type. Discussing cost is an important part of shared decision-making between the patient and provider. In cases when there are two practical, feasible methods that are comparable in terms of the harms and benefits, the provider should discuss the availability of alternative, less expensive methods.

Infertility & Education

- Among 1,041 women ages 18-40 with cancer, those with less than a bachelor's degree, previous children, and those older than 35 were less likely to receive fertility counseling
- In young adults with cancer, females were significantly more likely to receive fertility information

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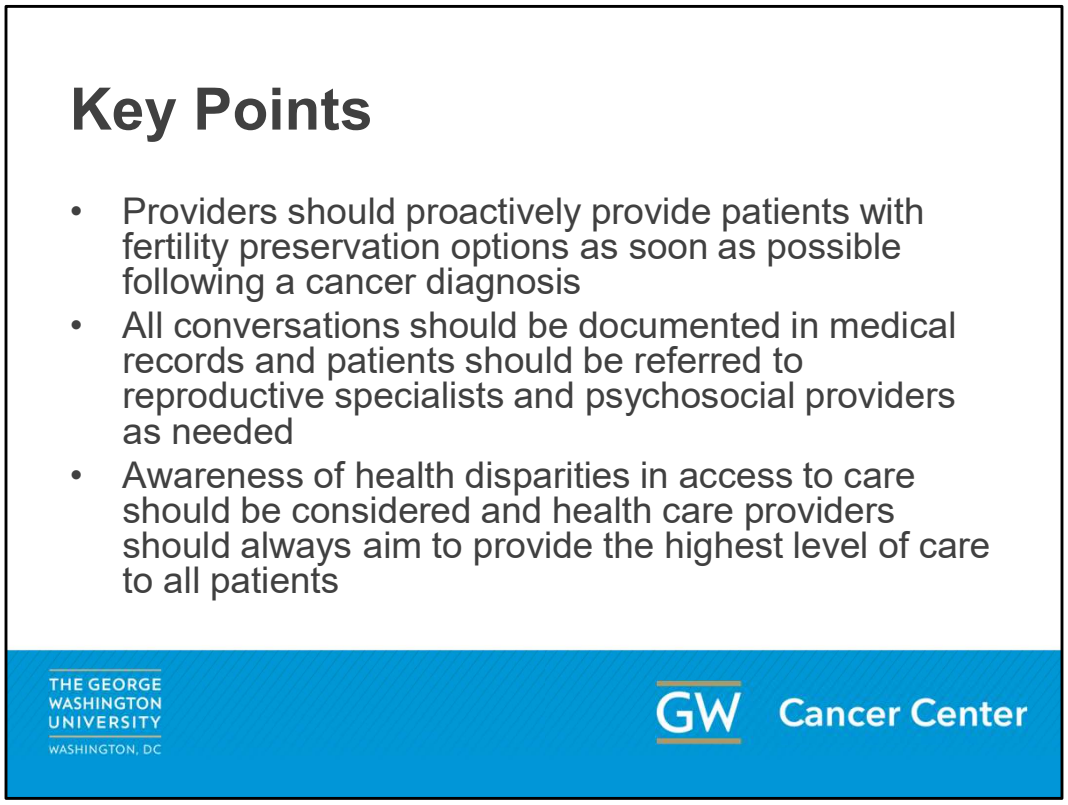
Although infertility can affect any patient with cancer, studies have found that female patients with lower education levels, those who have had prior children, and those older than 35 were less likely to receive fertility counseling.

Among young adults, despite both males and females expressing the importance of their ability to have children after treatment, females were significantly more likely to receive fertility information.

Providers should be aware of these disparities and work to ensure all patients interested in, ambivalent about, or hesitant about fertility preservation receive a counseling referral prior to initiation of treatment.

Counselling on fertility preservation should be universal.

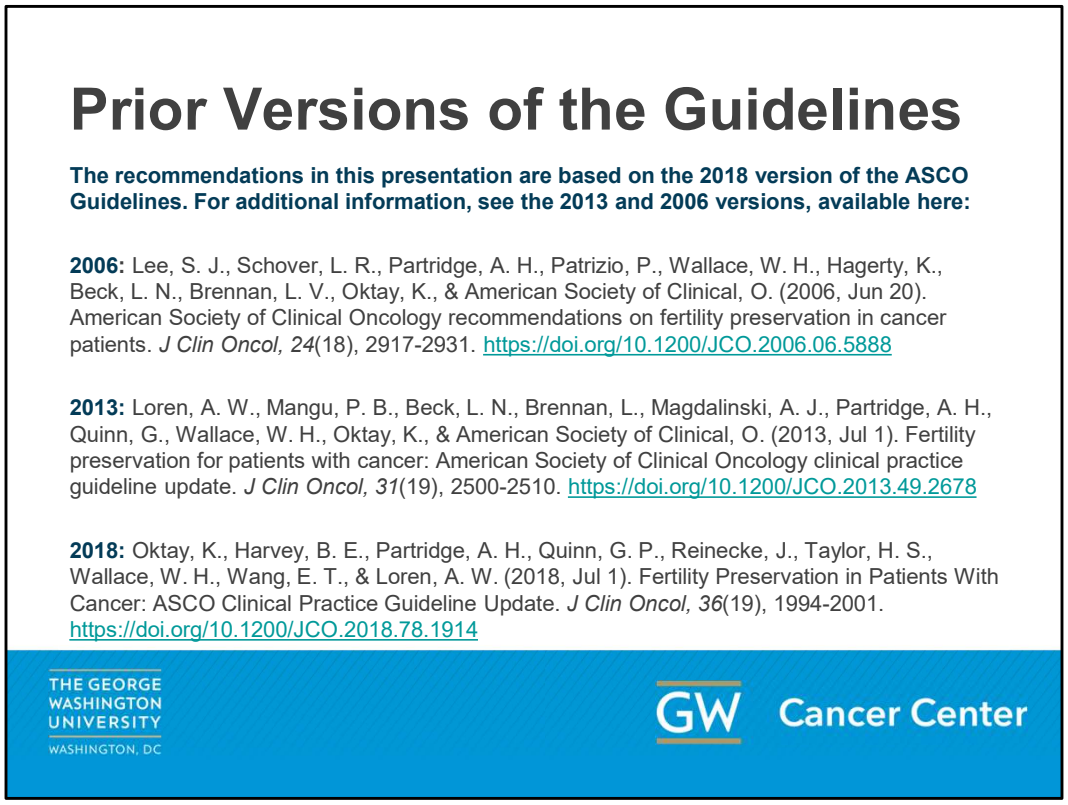


To recap, here are some key takeaways from this presentation.

1) Providers should be ready to discuss fertility preservation with their patients as soon as possible after cancer diagnosis

2) Providers should document all fertility-related conversations in the patient's medical record and refer the patient to reproductive specialists and psychosocial providers, as needed

3) Providers should be aware of health disparities in access to care and aim to provide the highest level of care, especially to vulnerable populations i.e.
   -Providers should increase their knowledge base and strive to provide highest level of care to vulnerable populations that may be prone to disparities in access to care



The recommendations presented here are based on the 2018 ASCO guidelines. For additional information, including a more in-depth discussion of the evidence, the 2018, 2013 and 2006 versions are available through these links.

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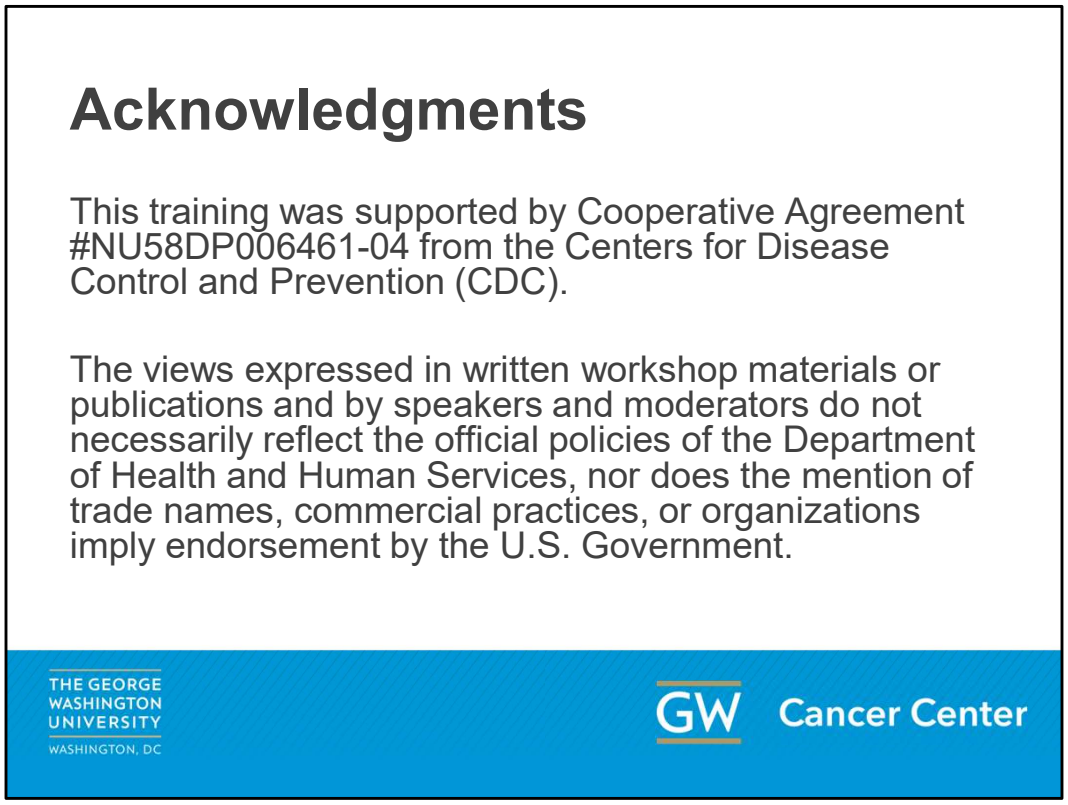

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