Reproductive Health: From Diagnosis Through Survivorship – Resources and Perspectives From the Children's Oncology Group

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COG Educational Track at APHON 2020

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1

Disclosure

- Dr. Brooke Cherven and Dr. Barbara Lockart have no industry relationships.
- Off label use will not be discussed.

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Learning Outcomes

- The learner will be able to
  - describe options for preserving fertility prior to gonadotoxic treatment, utilizing risk-based assessment.
  - articulate strategies to promote sexual health among adolescents and young adults during and after cancer treatment.

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Why does this matter?

- Sexuality and reproduction is a normal part of the being human.
- Adults have developmental milestones!

Having cancer does not diminish the normal expression of personhood.

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Why fertility preservation matters

- 75% of young adults who are childless at the time of diagnosis report a desire to parent in the future (Schover, 1999)
- Cancer survivors reports PTSD symptoms related to infertility as long as 10 years post-treatment (Schover, 2009)
- Male survivors report sperm banking helped psychological recovery from cancer. (Saito, Suzuki, Iwasaki, Yumura, Kubota, 2005)

Implications of infertility may be even **more** significant for certain cultural, ethnic or religious groups.

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Is fertility preservation a patient right?

- Justice
- Autonomy
- Beneficence
- Non-maleficence

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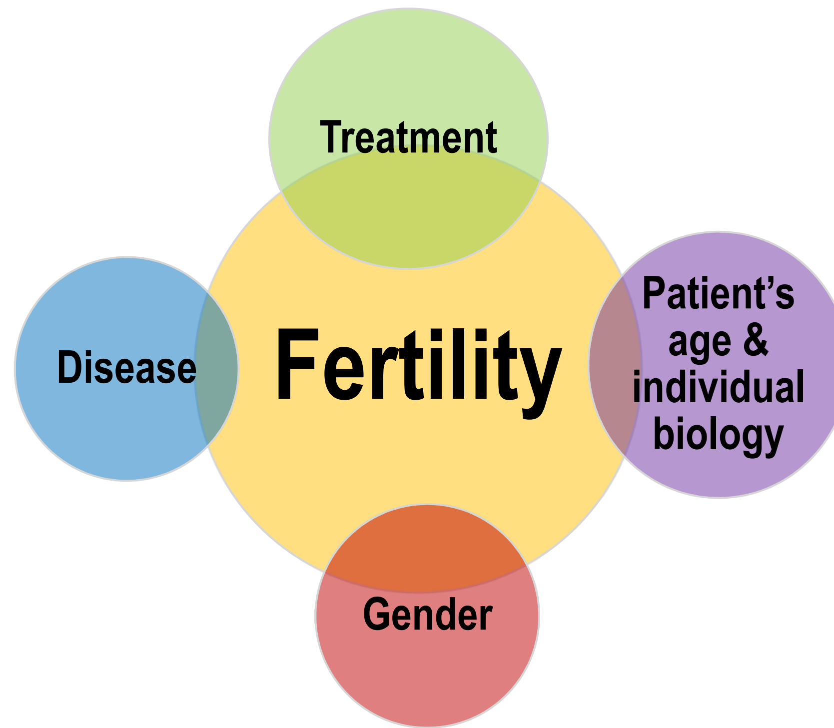
This is what the experts say

Organization	Position Statement
AAP	*"The impact of the treatment on fertility should be discussed."*
ASCO	*"HCPs caring for adult and pediatric patients with cancer…should address the possibility of infertility as early as possible before treatment begins."*
ASRM	*"Children and adolescents represent a special patient group that must be approached thoughtfully…give that this is a particularly vulnerable population, careful counseling and informed consent is especially recommended."*
APHON	*"…discussions regarding fertility preservation and reproductive health should begin before treatment and continue throughout treatment and survivorship in a manner appropriate for the patient's developmental stage."*

Risk for infertility



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When to have the conversation?

- From the time of diagnosis through cancer trajectory
  - Developmentally **and** culturally appropriate language
    - Must be comfortable with "slang"
  - Understanding will change as pt matures
    - Conversations should match current emotional needs
  - Puberty/pre-menopause discussions
    - May not "click' that future fertility may impact
      - Menstruation
      - Sexual function

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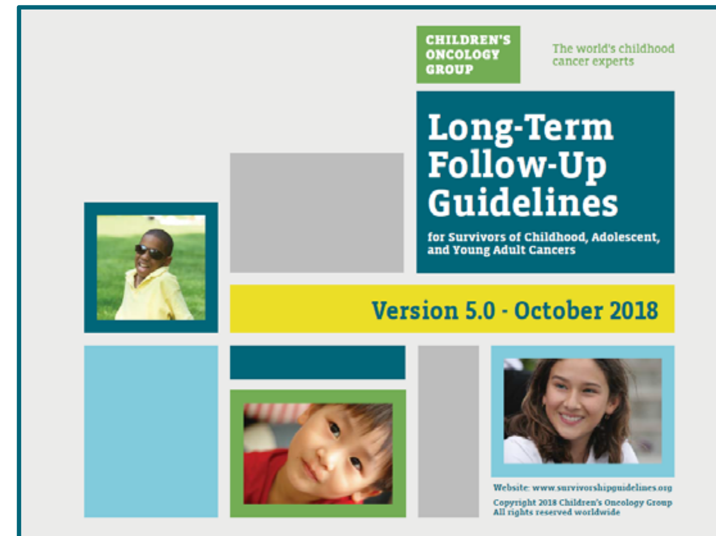
Conversations throughout the cancer care trajectory

- Survivorship
  - COG LTFU Guidelines
- Referrals to
  - Reproductive Medicine
  - Endocrinology for hormone management
- FP choices should not be limited by
  - Gender
  - Sexual orientation/identity
- Plan for disposal of banked tissue if death occurs



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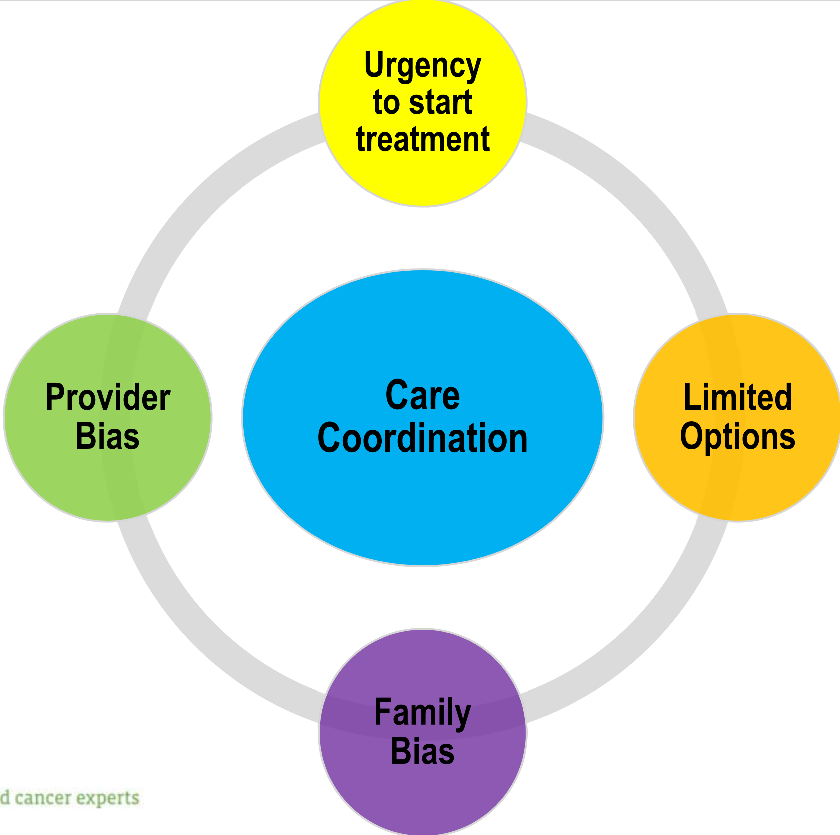
Challenges



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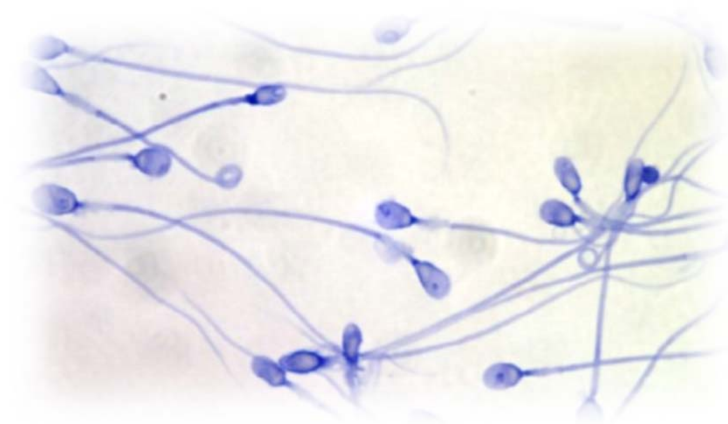
Additional Challenges

- No guarantees of fertility
  - Status at end of treatment
  - That preservation attempts will be successful



Standard fertility preservation for post-pubertal males is *cheaper*, *easier*, **and** *less time consuming* than fertility preservation options available to females!

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Assessing Risk

Therapy	
Chemotherapy	• Alkylator doses are not equivalent • Cyclophosphamide Equivalent Dose (CED) (see Appendix I) • Risk with new agents unclear
Radiation	• Increased dose = increased risk • Younger age protective to females? • Pituitary XRT not associated with infertility • XRT to gonads = high risk of infertility • Proton beam therapy not protective if gonads in field

It takes decades for us to understand infertility risk in pediatric cancer patients!

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Green DM, et al: *Pediatr Blood Cancer 2014*

How do we manage reproductive health?

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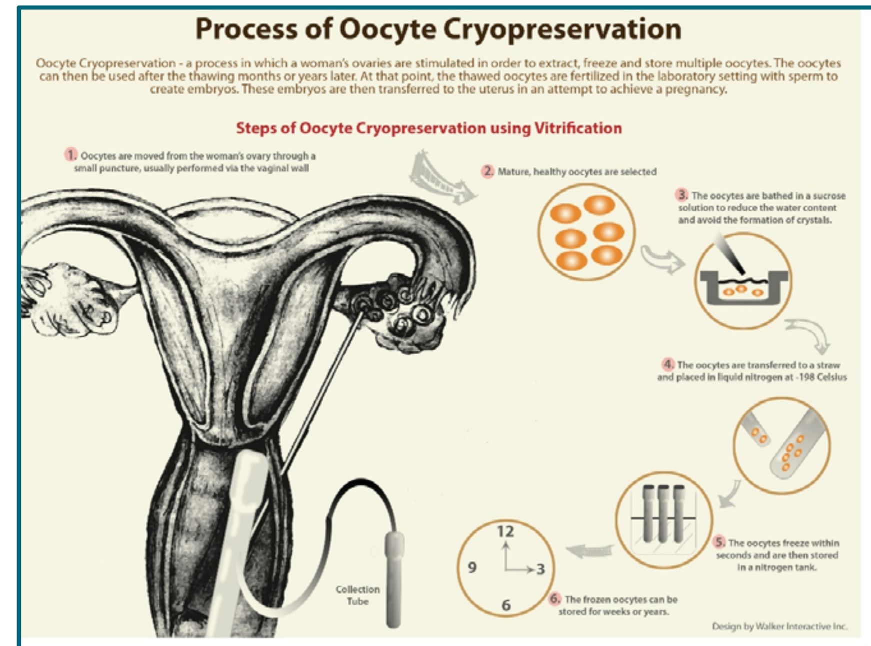
Options - females

- Established – pubertal or older
  - Embryo/oocyte cryopreservation
  - Ovarian transposition
- Investigational – pre or post pubertal
  - Ovarian tissue preservation
- Supportive evidence lacking
  - GnRHa



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Simone

- 14-yr-old female
  - Menstruating for 2 years
- Localized pelvic EWS – treated on AEWS0031
  - Chemotherapy
    - Cyclophosphamide equivalency dosing
      - 23.7 gm/m2 = > 80% relative risk of infertility
  - Radiation
    - 55.80 Gy to pelvis
- Options
  - Oocyte harvesting
  - Ovarian tissue cryopreservation

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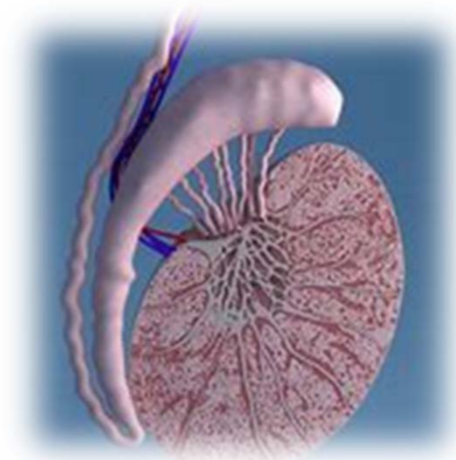
Options - Male

- Established
  - Testicular shielding
  - Orchiopexy
- Investigational
  - Testicular tissue cryopreservation



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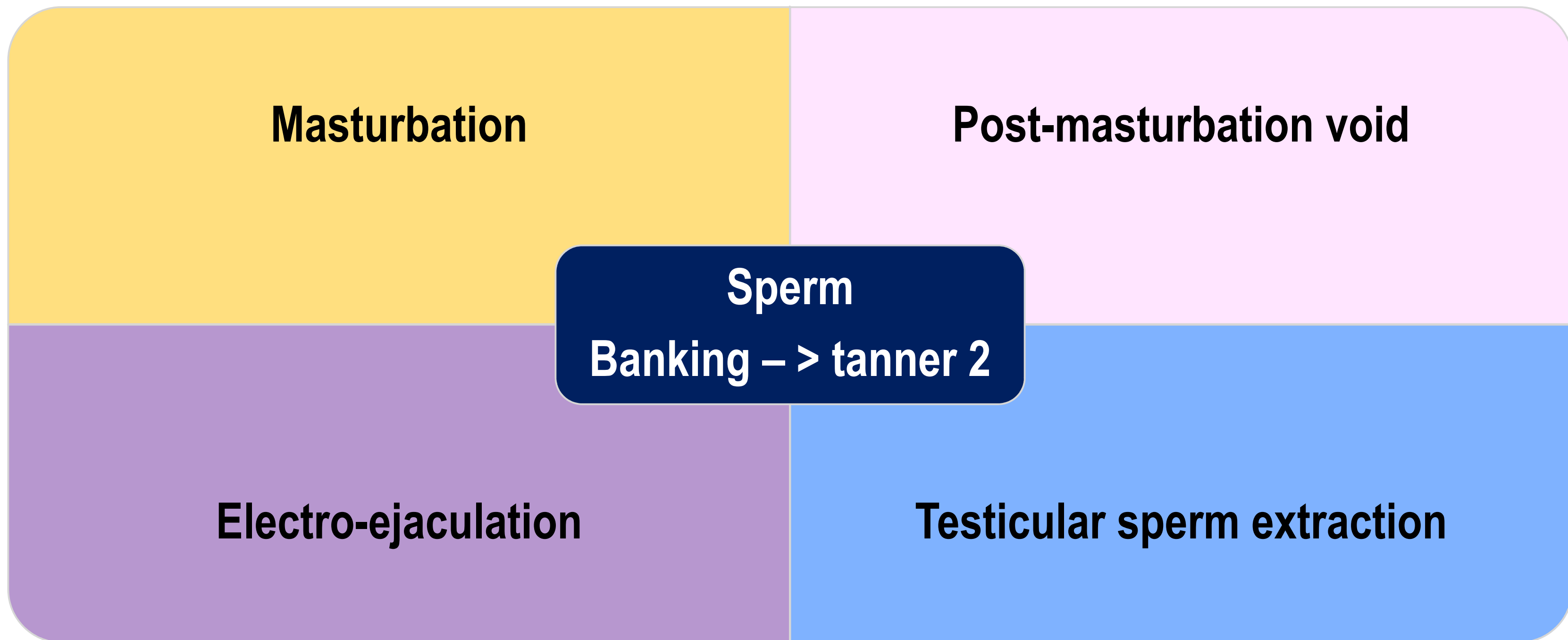
Options - Males
Masturbation
Post-masturbation void
Sperm
Banking – > tanner 2
Electro-ejaculation
Testicular sperm extraction
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Daniel – Initial Diagnosis

- 13-yr-old male,
  - Tanner stage 3
- Metastatic osteosarcoma of the right femur
  - Too numerous to count pulmonary nodules
  - Treated on AOST0031
- Chemotherapy
  - Infertility risk with cisplatin
- Local control
  - Limb salvage and wedge resection
- Family declined sperm banking
  - Did not qualify for testicular tissue cryopreservation

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Daniel-Relapsed

- Pulmonary relapse - 21 months off tx
  - Now age 15-yrs
  - Tanner stage 4
- Chemotherapy
  - Ifosfamide/Etoposide
- Local control
  - Wedge resection
- He wants to sperm banking

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Children's Oncology Group: Focus on Fertility

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COG Supportive Care Endorsed Guidelines

- Fertility preservation
  - Recommend discussion prior to treatment
  - Refer to fertility preservation as request
- Recommendations are not evidence based
- Investigation procedures
  - Testicular/ovarian tissue cryopreservation
  - Should only be provided under clinical trials
- Encourage participation in clinical trials
- Provide psychological support

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Guideline for Fertility Preservation for Patients with Cancer

COG Supportive Care Endorsed Guidelines

Click here to see all the COG Supportive Care Endorsed Guidelines.

COG Trials

- ALTE16C1 – Effects of Modern Chemotherapy Regimens on Spermatogenesis and Steroidogenesis in AYA Survivors of Osteosarcoma (open to accrual)
- ALTE11C1 – Longitudinal Assessment of Ovarian Reserve in Adolescents with Lymphoma (closed to accrual)

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ALTE11C1

Activated: 06/17/13 Version Date: 04/06/16
Closed: 03/02/18 Amendment #2

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ALTE11C1

Longitudinal Assessment of Ovarian Reserve in Adolescents with Lymphoma

A Groupwide Non-Therapeutic Protocol

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ALTE16C1

Activated: 10/10/2017 Version Date: 05/03/2019
Closed: Amendment: 2

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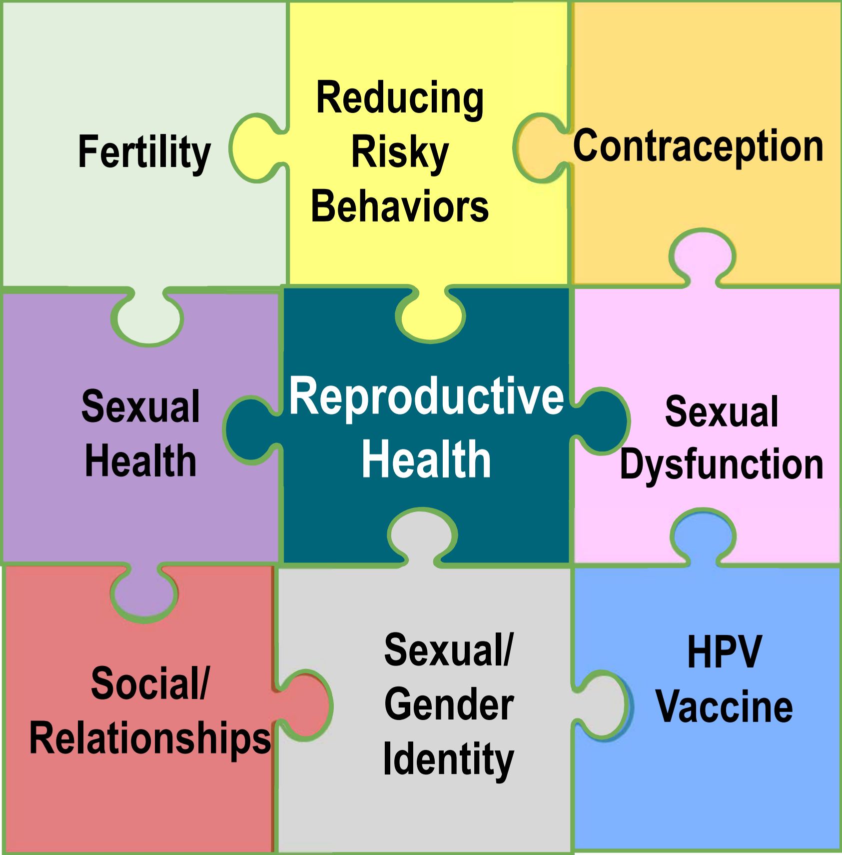
ALTE16C1

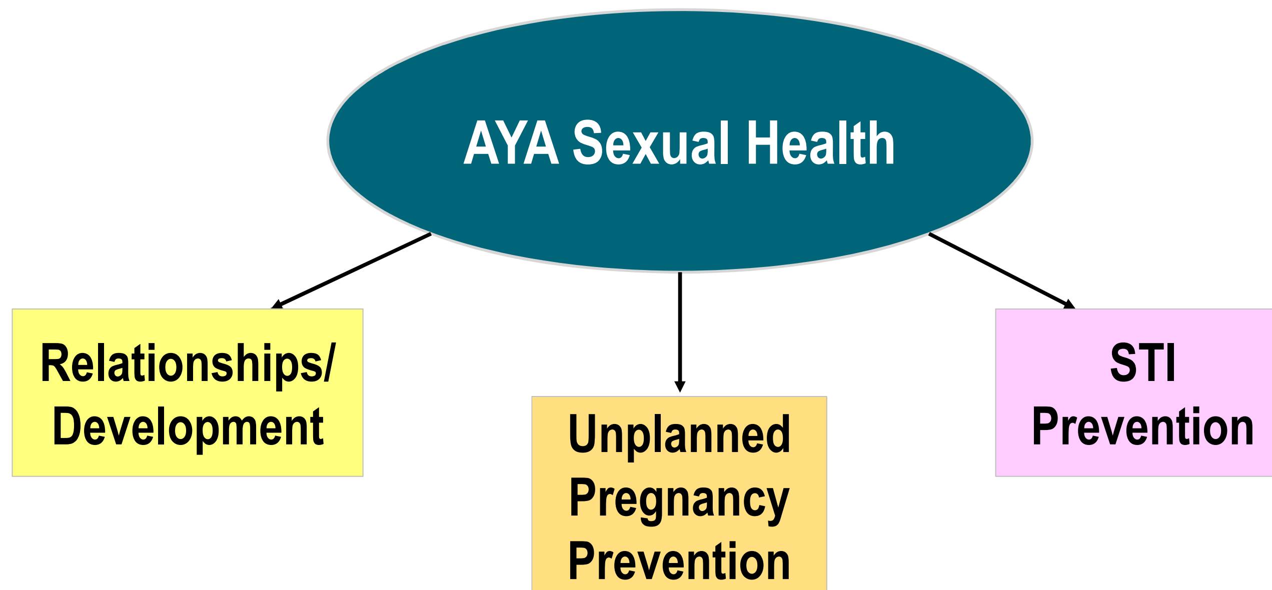
Effects of Modern Chemotherapy Regimens on Spermatogenesis and Steroidogenesis in Adolescent and Young Adult (AYA) Survivors of Osteosarcoma

A Groupwide Non-Therapeutic Study Limited to US and Canada Sites

Reproductive Health Among Survivors of Childhood and Adolescent Cancer



Sexual Health Among Adolescents/Young Adults



Cancer Survivors Report Unmet Sexual Health Needs

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AYA Cancer and Sexual Health

- AYA can experience a delay in sexual milestones compared with peers
  - Challenges with romantic relationships
- AYA with cancer are sexually active
  - One-third of AYA patients sexually active during treatment
- AYA cancer survivors participate in risky sexual behaviors
  - Increasing their risk for STIs and unplanned pregnancy
- AYA cancer survivors experience sexual dysfunction
  - 20-60% of AYA survivors report sexual dysfunction

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Rosenberg et al.; *J Adolesc Health* 2017; 60:93–99; Klosky et al.; *Health Psychol* 2014; 33:868-77; van Dijk et al.; *Psychooncology* 2008; 17:506–511; Frederick et al.; *Pediatr Blood Cancer* 2018; 63:1622–1628.

27

Sexual Health Priorities During Cancer Treatment

- Abstain from sex during times of neutropenia/thrombocytopenia
- Reduce risk for sexually transmitted infections
  - Abstinence
  - Condoms
- Reduce risk for pregnancy
  - Abstinence
  - Contraception
- Screen for sexual dysfunction

Promote a safe and open environment to discuss sexual health with providers

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COG Long-Term Follow-Up Guidelines

Sexual Dysfunction	
Males	• Erectile dysfunction
Females	• Pain or vaginal dryness
Both	• Decreased interest, arousal, satisfaction

Chemotherapy Classification	HCT	XRT Field	Surgery
Alkylating Agents Heavy Metals	Hx of cGVHD (females)	TBI Pelvis Spine Testes Head/Brain	Cystectomy Spinal cord Pelvic surgery Hysterectomy Oophorectomy/Orchiectomy

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HPV in Cancer Survivors

HPV most common STI in US: ↑prevalence in 20-24 yr olds

>30,000 HPV-related Cancers Annually

Cancer Survivors ↑ risk for HPV-related subsequent cancers

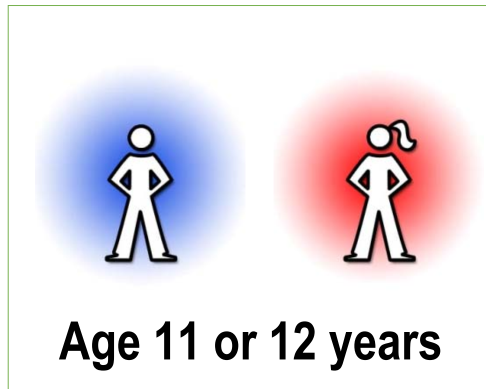
Females: 40% excess
Males: 150% excess

HPV Vaccine protects against 7 oncogenic HPV types

75% HPV-related cancers

Ojha et al.; *Plos One* 2013. 8(8); e70349

HPV Vaccine for Cancer Survivors



Age 11 or 12 years

<u>Cancer Survivors</u>:
Recommended vaccination
9 to 26 years
Consider vaccination up to age 45

3 Doses

6 Months

Illustrations by Sam Phang, 2007

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Petrosky et al.; *MMWR* 2015; 64: 300-304;
Meites et al., *MMWR* 2019;68: 698–702

31

COG Long-Term Follow-Up Guidelines: HPV Vaccination

- Counsel on the importance of HPV Vaccination
- Screen for HPV Vaccination

GENERAL HEALTH SCREENING

HEMATOPOIETIC CELL TRANSPLANT (CONT)

CANCER SCREENING GUIDELINES — CERVICAL CANCER

CANCER SCREENING GUIDELINES — ORAL CANCER

Sec #	Organ	Standard Risk Parameters and Screening Guidelines	Highest Risk Parameters and Screening Guidelines	Health Counseling/ Further Considerations
161	Oral	STANDARD RISK PARAMETERS	HIGHEST RISK PARAMETERS	COUNSELING

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Children's Oncology Group Sexual Health Task Force

Task Force Within COG AYA Committee

Vision: To improve sexual health for adolescents and young adults with cancer.

Mission: to explore the feasibility of a sexual health research initiative, advise on compelling research questions, deliver these within COG cooperative group setting.

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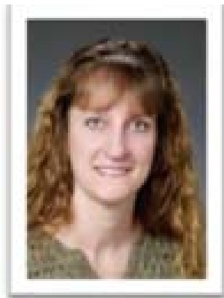
Children's Oncology Group AYA Sexual Health Task Force



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Pediatric Psychologist
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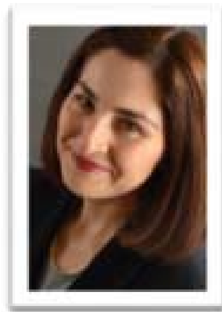

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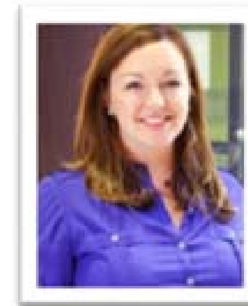

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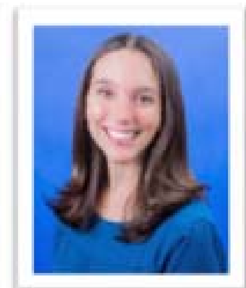

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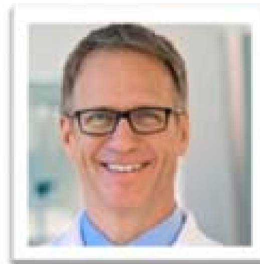

David Freyer, DO
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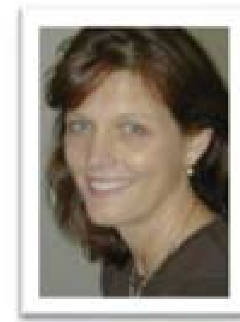

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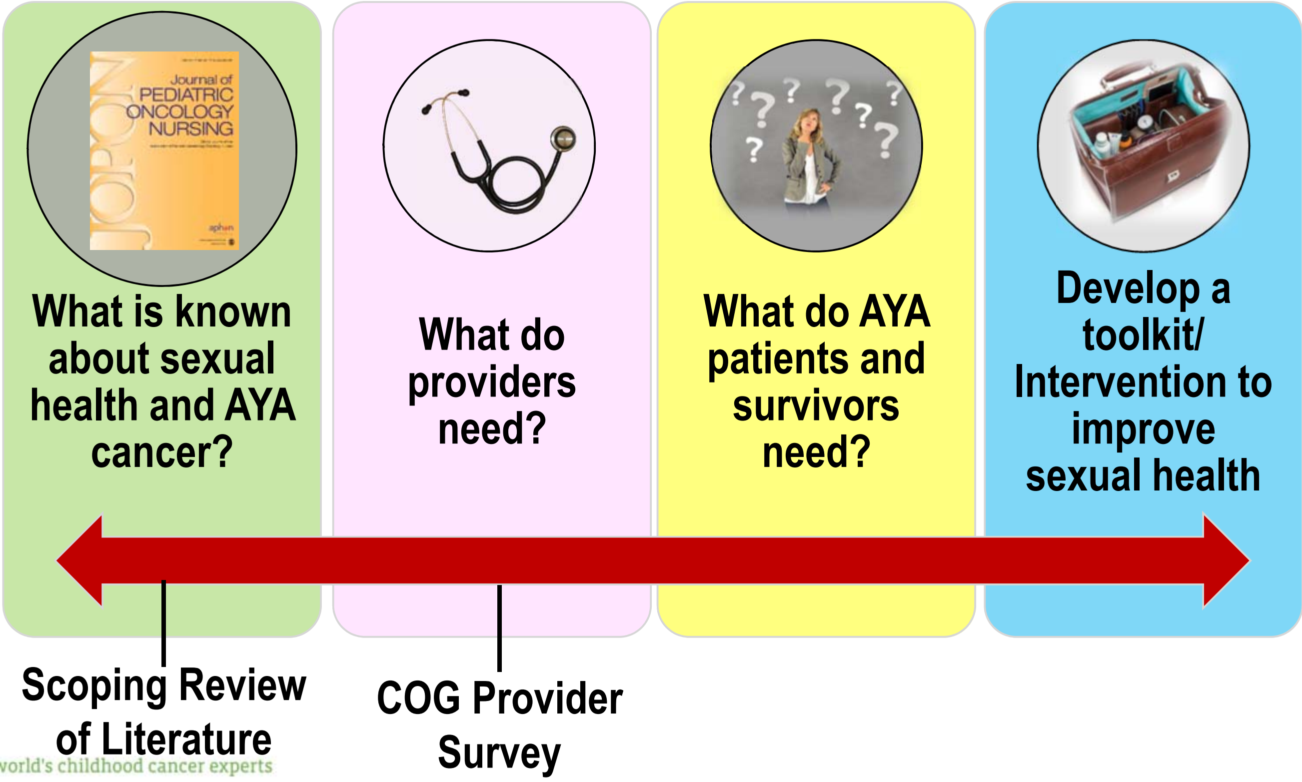
34


COG Sexual Health Task Force
Journal of PEDIATRIC ONCOLOGY NURSING
JOPON
What is known about sexual health and AYA cancer?
What do providers need?
What do AYA patients and survivors need?
Develop a toolkit/ Intervention to improve sexual health
Scoping Review of Literature
COG Provider Survey
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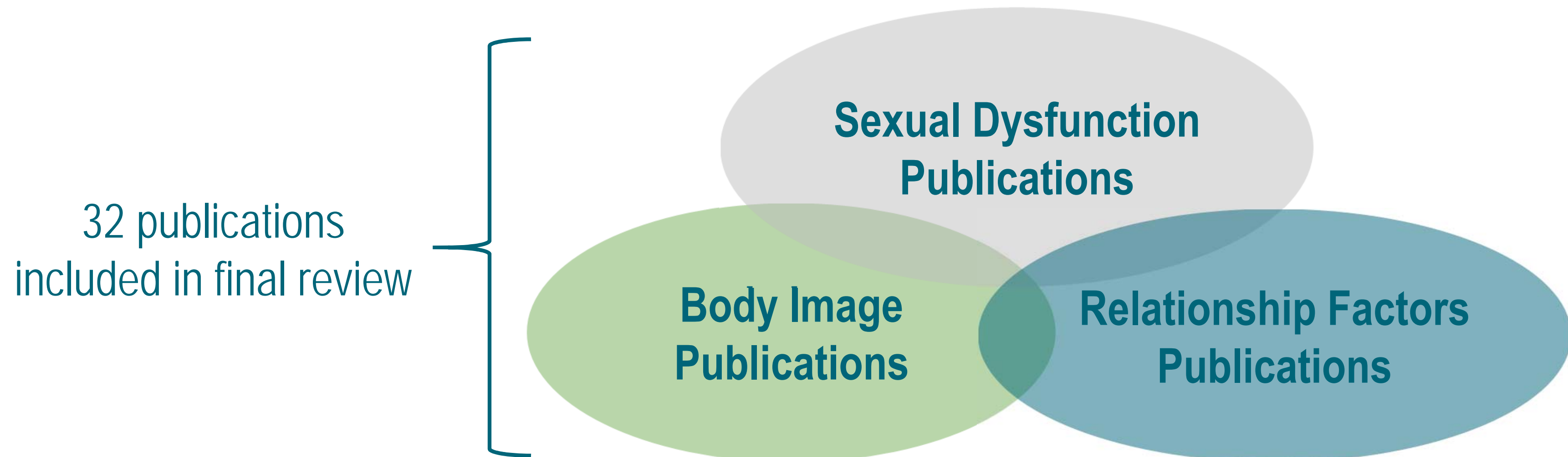
Scoping Review of Literature:

Among cancer survivors, did childhood/AYA cancer impact sexual function?



Findings:

- Wide variation in definition and measurement of sexual dysfunction
- Substantial sexual dysfunction among AYA cancer survivors
- Survivors desire education, resources, and clinical support

COG Sexual Health Provider Survey

Aims:

- Determine current pediatric oncology clinician practices around sexual health communication.
- Identify clinician-reported facilitators of and barriers to sexual health communication
- Identify clinician preferred education and resource needs to help improve sexual health communication with AYA patients

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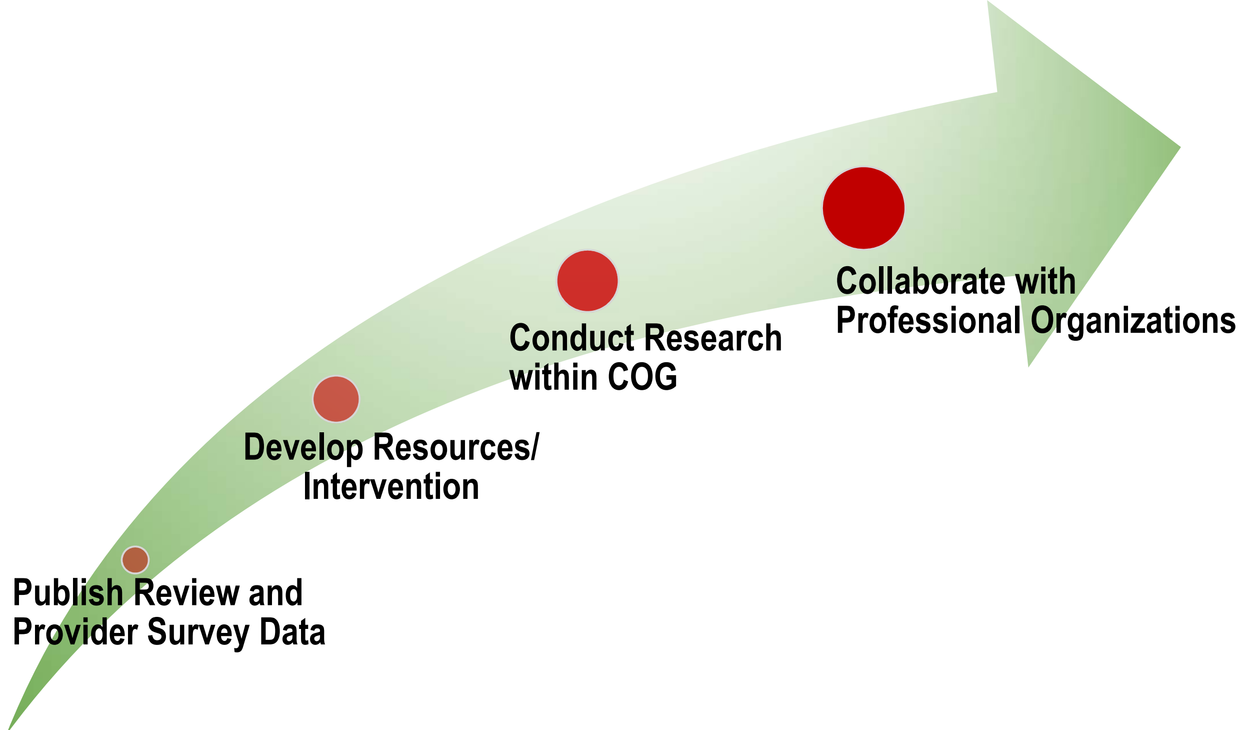
COG Sexual Health Task Force: Next Steps



38

Communication and Considerations for Sexual Health Discussions

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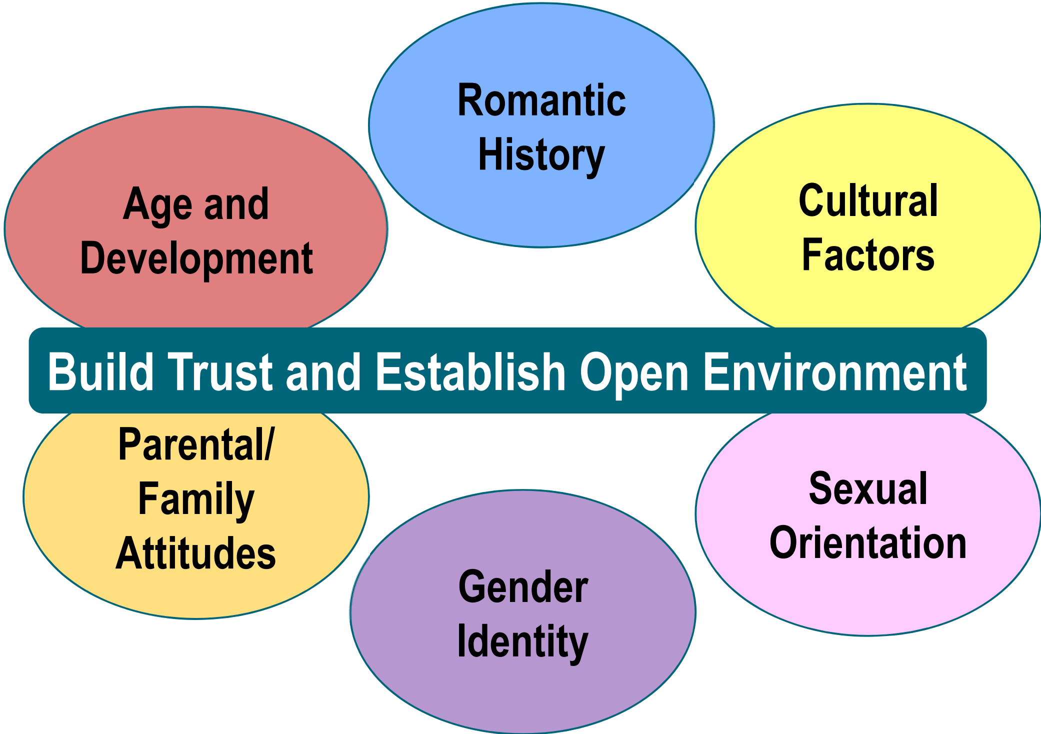
Considerations for Discussions of Sexual Health
Romantic History
Age and Development
Cultural Factors
Build Trust and Establish Open Environment
Parental/ Family Attitudes
Sexual Orientation
Gender Identity
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Audience Response

Association of Clinical Oncology Guideline:
It is recommended that there be a discussion with the patient,
initiated by a member of the health-care team,
regarding sexual health and dysfunction resulting from cancer or its treatment

- Conversations regarding sexual health should begin at diagnosis and continue through survivorship
- Identify resources for referral (e.g., urology, OB/GYN, psychology) for patients who report problems

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Sexual Health Discussions

- Set the stage
  - Private setting
  - Parents/family members and other leave the room
  - Discuss confidentiality at start of the conversation

- Ask Permission
  - "*"Many AYAs worry about how cancer will affect dating and relationships. I would like to take some time today to talk about this. Is this okay with you?"*

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Discussing Sex with AYA Patients: *Diagnosis and During Treatment*

5 P's (Sexual Health History)

- Previous **P**artners
- Sexual **P**ractices
- **P**rotection from STIs
- **P**rior History of STIs
- Prevention of **P**regnancy

- **Focus on building trust/open relationships**
- **Identify and address risky behaviors**
- **Counsel regarding safe sex practices during cancer treatment**
- **Continue discussions throughout treatment**

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CDC, 2015 STD Guidelines

43

Examples

- *I am going to ask you a few questions about your sexual health and sexual practices. I understand that these questions are very personal, but they are important for your overall health."*
- *Some of my patients your age have started having sex. Have you been sexually active? What kind of sexual contact do you have or have you had?*
- *What kinds of protection do you use to prevent sexually transmitted infections and pregnancy?*

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Discussing Sex with AYA Patients: *After Treatment/Survivorship*

PLISSIT

- **P**ermission
- **L**imited **I**nformation
- **S**pecific **S**uggestions
- **I**ntensive **T**herapy

5 A's

Ask
Advise
Assess
Assist
Arrange Follow-Up

- Screen for sexual dysfunction
- Counsel on safe sex practices
- Refer for sexual therapy, psychology as appropriate

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Park et al.; *Cancer* 2009; 15:74-77

45

Examples

- *Do you have any questions about sexual health or is there anything that you are worried about that you'd like to ask me?*
- *"Many cancer survivors have concerns about changes in sexual function; do you have any questions or concerns you would like to ask me about?"*
  - *Can give examples if needed: pain with intercourse, decreased lubrication (females), or problems getting or maintaining an erection (males), decreased desire for sex.*
- What other things about your sexual health and sexual practices should we discuss to help ensure your good health?

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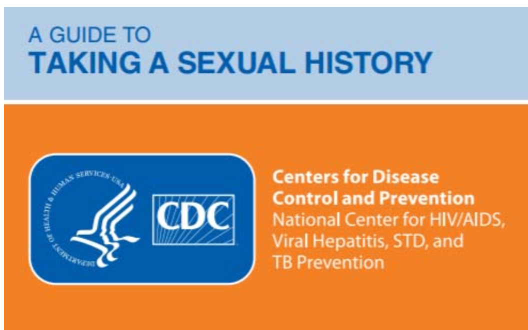
Resources

CDC Sexual Health Assessment Guide



Project ECHO
Virtual Course in Reproductive and Sexual Health for Oncology Healthcare Providers

What is ECHO?
Enriching Communication Skills for Health Professionals in Oncofertility (ECHO) is a web-based training program focusing on building communication skills

Training Topics
- Risk of infertility
- Fertility preservation
- Sexual functioning
- Body image
- Family planning
- Contraception
- Ethical, social, and cultural considerations

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Appendix I - Cyclophosphamide Equivalent Dose

- All the listed agents mg/m2 dose are = to 100 mg/m2 of CPM
  - e.g.: BCNU 6.7 mg/m2 = CPM 100 mg/m2
- To calculate CED multiply the cumulative dose of the agent by the multiplier
  - e.g.: if cumulative dose of BCNU was 220 then CED is 220 x 15 = equivalent to 3300 mg/mg CPM
  - You may also use a CED calculator such as the one found at https://fertilitypreservationpittsburgh.org/fertility-resources/fertility-risk-calculator/
- CED of ≥7500 mg/m2 = is a significant risk of loss of reproductive potential

Agent	Multiplier	CED Dose
Cyclophosphamide	1	100 mg/m2
BCNU	15	6.7mg/m^2
Busulfan	8.823	11.3mg/m^2
CCNU	16	6.3 mg/m^2
Chlorambucil	14.286	7 mg/m^2
Ifosfamide	0.244	409 mg/m^2
Melphalan	40	2.5 mg/m^2
Nitrogen mustard	100	1 mg/m^2
Procarbazine	0.857	117 mg/m^2
Thiotepa	50	2 mg/m^2

48

Appendix I – using CED female case study EWS0031

Agent	Dose
Cyclophosphamide	100 mg/m^2
Ifosfamide	409 mg/m^2

- CPM 1200 mg/m2 X 7 cycles = 8400 mg/m2 total CPM = **CED** 8400 mg/m2
- IFOS1800 mg/m2 X 5 days X 7 cycles = 63000 mg/m2 cumulative IFOS dose
- IFOS **CED** obtained by multiplying 63000 x 0.244 = 15,372 mg/m2
- CPM **CED** 8400 mg/m2 + IFOS **CED** 15,372 mg/m2 = **CED** 23,772 mg/m2, which is considered to be a significant fertility risk for this patient

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UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM Knowledge that will change your world

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Abbreviations

FULL TERM	ABBREVIATION
Adolescent and young adult	AYA
American Academy of Pediatircs	AAP
American Society for Clinical Oncology	ASCO
American Society for Reproductive Medicine	ASRM
Association Pediatric Hematology Oncology Nurses	APHON
Carmustine	BCNU
Children's Oncology Group	COG
Chronic graft versus host disease	cGVHD
Cyclophosphamide	CPM
Cyclophosphamide Equivalent Dose	CED
Ewing's Sarcoma	EWS
Fertility preservation	FP

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50

Abbreviations

FULL TERM	ABBREVIATION
Gonadotropin-releasing hormone agonist	GnRHa
Gram	gm
Gray	Gy
History	HX
Human Papilloma Virus	HPV
Ifosfamide	Ifos
Lomustine	CCNU
Long-Term Follow-Up	LTFU
Meter square	m2
Number	N or n
Osteosarcoma	osteo or OST
Patient(s)	pt(s)

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Abbreviations

FULL TERM	ABBREVIATION
Post traumatic stress disorder	PTSD
Radiation therapy	XRT
Sexually Transmitted Infection(s)	STI(s)
Total Body Irradiation	TBI
Treatment	Tx
Year(s)	yr(s)

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