Fertility Preservation Guidelines in 2018

Oncofertility Conference
November 14th, 2018

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Disclosures

- Investment in Umotif, PRO platform
  - Not related to any work product
- Will discuss off label use of GnRH analogues for “ovarian suppression”

Objectives

- Describe challenges of guideline formulation
- Review the most recent ASCO and ASRM guidelines
- Consider together a wish list for guidelines

2001

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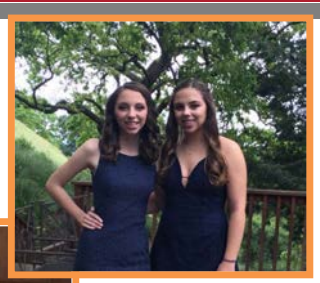


the Oncofertility Consortium

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update

Kutluk Oktay, Brittany E. Harvey, Ann H. Partridge, Gwendolyn P. Quinn, Joyce Reinecke, Hugh S. Taylor, W. Hamish Wallace, Erica T. Wang, and Alison W. Loren

2001

2006

2005

2018

ETHICS COMMITTEE REPORT

Fertility preservation and reproduction in cancer patients

The Ethics Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

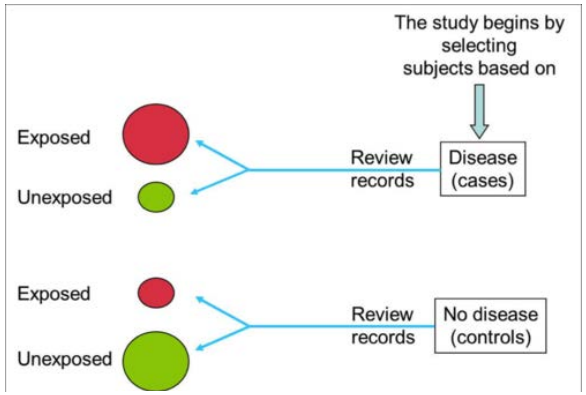
Weill Cornell Medicine

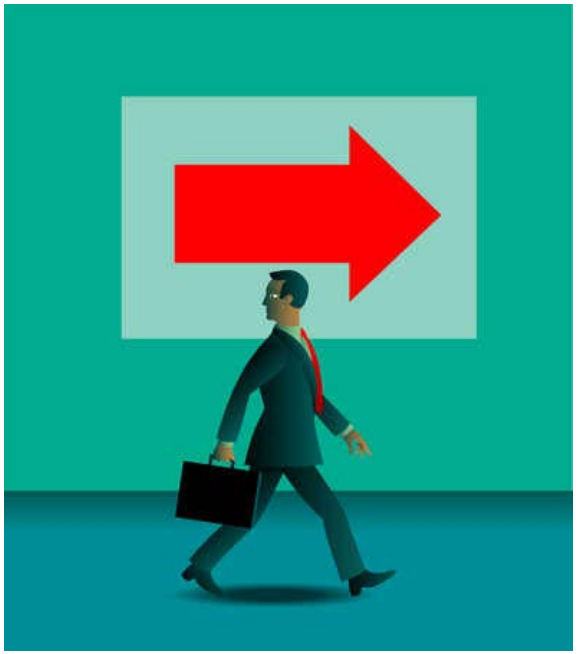
NewYork-Presbyterian

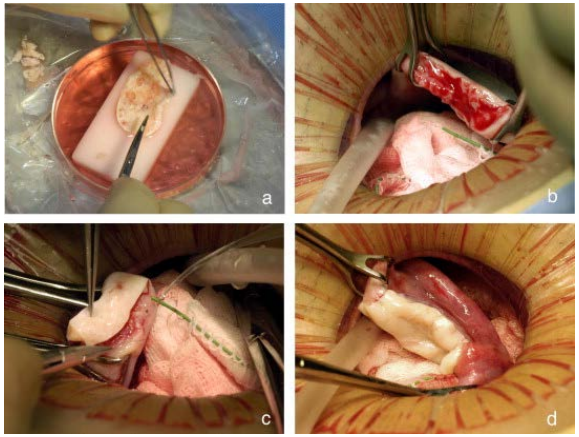
Role of guidelines

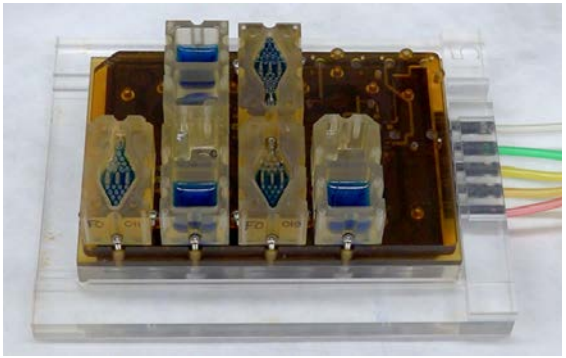
- Disseminate evidence based practices
- Provide expert opinion in the face of inadequate evidence
- Standardize practice across institutions
- Reduce disparities among individuals
- Provide benchmark for insurance coverage

By necessity Guidelines look backwards









Hindsight isn't always 20/20

- Quality of evidence
- Subjectivity in evaluating data in small studies
- Variations in methodology
- Different lens may lead to different focus

International Guideline Harmonization Group

for Late Effects of Childhood Cancer

- establish a common vision and integrated strategy for the surveillance of late effects in CAYA cancer survivors.

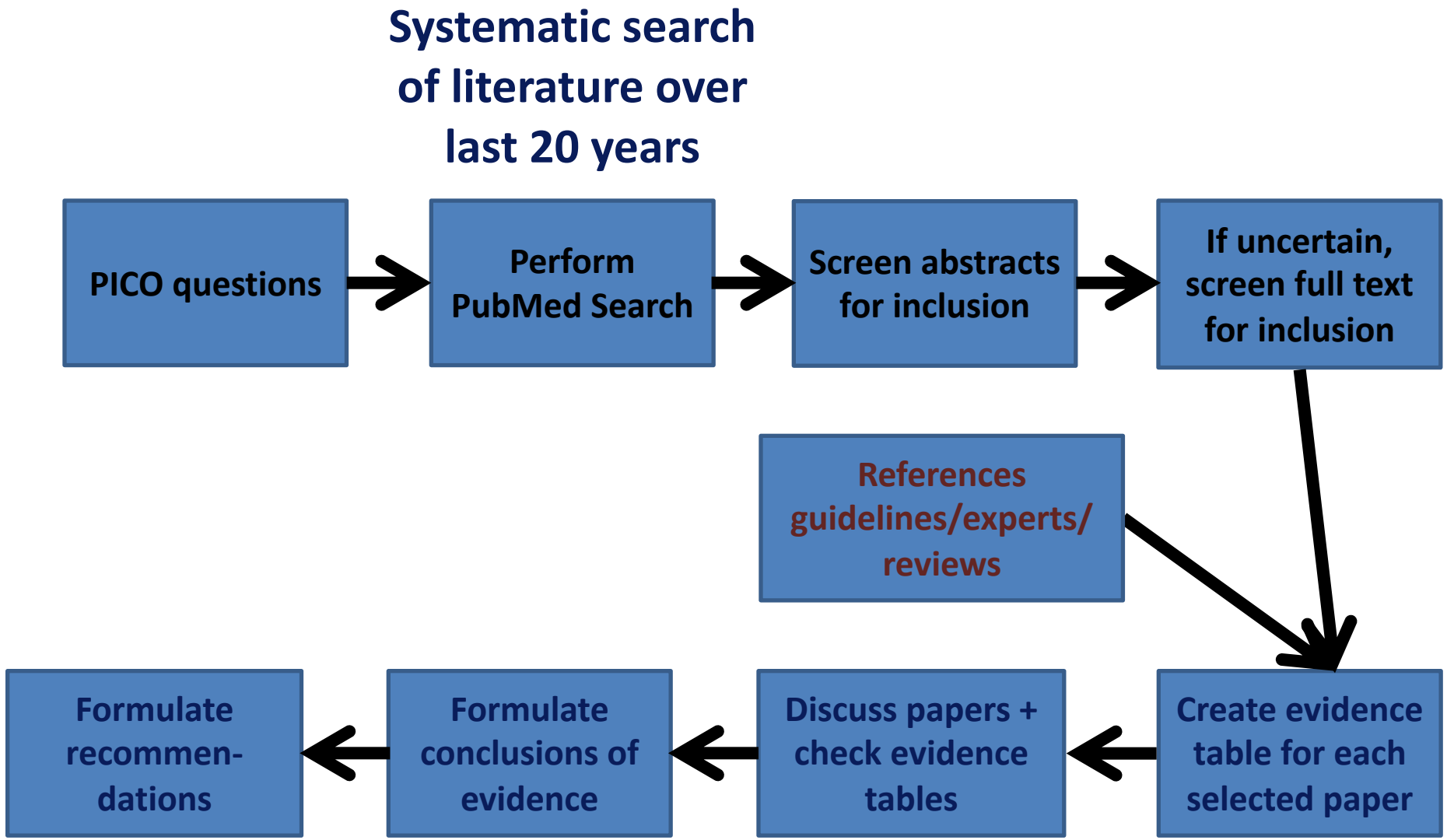
- reduce duplication of effort, optimize the quality of care, and improve quality of life for childhood, adolescent, and young adult cancer survivors.

GUIDELINE DEVELOPMENT SCHEMA

Step 1: Concordance and discordance among guidelines

Step 2: Clinical Questions

Step 3: Identify and summarize available evidence


Systematic search of literature over last 20 years
PICO questions
Perform PubMed Search
Screen abstracts for inclusion
If uncertain, screen full text for inclusion
References guidelines/experts/ reviews
Create evidence table for each selected paper
Discuss papers + check evidence tables
Formulate conclusions of evidence
Formulate recommen-dations

What female reproductive (preservation) methods could be used?				
Abdel-Hady et al. Fertility sparing surgery for ovarian tumors in children and young adults. Arch Gynecol Obstet 2012; 285:469–471				
Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
1. Study design Prospective case series, single centre 2. Treatment era 2003 - 2009 3. Follow-up: For primary malignant ovarian tumors: Median follow-up 36 months (1-62)	1. Type and Number of Participants 22 patients with malignant and borderline ovarian tumors requiring surgical excision *Original cohort:* 183 patients 2. Diagnoses Ovarian cysts or tumors: 160/183(87%) non-malignant disease 20/183(11%) primary malignant ovarian tumors 2/183(1.2%) borderline tumors 1/183 (1%) metastatic colonic carcinoma 3. Age at diagnosis Median age 17 years (7-20) 4. Age at follow-up NR 5. Controls (if applicable) NA	1. Fertility Preservation method Fertility sparing surgery (ovarian cystectomy/ oophorectomy)	1. Outcome definitions Oncological outcomes? Reproductive outcomes? Preservation of ovary? 2. Results *Live births* 2/2 (100%) pregnant females delivered 2 healthy live births *Oncological outcomes* 2/22 (9.1%) recurrences of disease No mortalities during surgery or follow-up	1. Strengths Large number of patients 2. Limitations - No clear outcome definition - Preservation of ovary only anatomically assessed, not functionally - Preservation of fertility only assessed by using the number of pregnancies 3. Risk of bias *1. Selection bias* Unclear Reason: no inclusion or exclusion criteria are reported, unclear where the 183 patients came from. Could be consecutive but not stated. *2. Attrition bias* High risk Reason: only follow-up for the primary malignant ovarian tumors, so no information on reproductive outcomes in the benign tumors/cysts patients

Original Article

Fertility Preservation in Children, Adolescents, and Young Adults With Cancer: Quality of Clinical Practice Guidelines and Variations in Recommendations

Anna Font-Gonzalez, MSc[1]; Renée L. Mulder, MSc, PhD[1]; Erik A.H. Loeffen, MD[2]; Julianne Byrne, PhD[3]; Eline van Dulmen-den Broeder, PhD[4]; Marry M. van den Heuvel-Eibrink, MD, PhD[5]; Melissa M. Hudson, MD[6]; Lisa B. Kenney, MD, MPH[7]; Jennifer M. Levine, MD, MSW[8]; Wim J.E. Tissing, MD, PhD[2]; Marianne D. van de Wetering, MD, PhD[1]; and Leontien C. M. Kremer, MD, PhD[1]; on behalf of the PanCareLIFE Consortium

APPRAISAL OF GUIDELINES FOR RESEARCH & EVALUATION II

AGREE II

INSTRUMENT

- Scope and Purpose
- Stakeholder Involvement
- Rigor of Development
- Clarity of Presentation
- Applicability
- Editorial Independence

Cancer, July 2016

Weill Cornell Medicine

NewYork-Presbyterian

TABLE 1. Results of AGREE II in 25 Identified Existing CPGs for Fertility Preservation in Children With Cancer, Including 8 High-Quality CPGs

Guideline	Domain 1: Scope and Purpose	Domain 2: Stakeholder Involvement	Domain 3: Rigor of Development	Domain 4: Clarity of Presentation	Domain 5: Applicability	Domain 6: Editorial Independence
High quality[a]						
NVOG 2007[20]	75%	78%	61%	81%	15%	63%
SIGN 2011[21]	92%	89%	79%	97%	69%	54%
Fernbach 2014[22]	89%	53%	66%	97%	15%	63%
ASCO 2013[23]	86%	92%	77%	100%	48%	58%
NICE 2013[24]	94%	83%	98%	94%	83%	71%
SIGN 2013[25]	97%	83%	69%	100%	67%	79%
NCCN 2014[26]	69%	61%	68%	94%	15%	67%
COSA 2011[27]	92%	81%	66%	100%	29%	38%
Overall (mean)	87%	78%	73%	95%	43%	62%
Lower quality						
BFS 2003[28]	53%	44%	13%	72%	21%	0%
EGCCCG 2004[29]	53%	22%	23%	47%	10%	0%
Wallace 2005[30]	39%	8%	16%	39%	4%	29%
RCP 2007[31]	50%	56%	18%	86%	21%	0%
Backhus 2007[32]	42%	22%	4%	31%	4%	8%
AAP 2008[33]	25%	8%	10%	44%	17%	25%
Tangjitgamol 2009[34]	64%	11%	26%	50%	10%	0%
IKNL 2009[35]	61%	53%	33%	58%	6%	38%
Cardoso 2012[36]	58%	31%	35%	75%	8%	25%
Michaeli 2012[37]	47%	17%	8%	50%	0%	0%
ISFP 2012[38]	42%	19%	11%	56%	4%	0%
EAU 2015[39]	42%	47%	55%	89%	29%	92%
ASRM 2013[40]	58%	28%	42%	86%	15%	54%
AHS 2013[41]	86%	28%	53%	89%	23%	71%
BCSH 2014[42]	61%	36%	49%	97%	8%	29%
ISFP 2012[43]	36%	8%	15%	42%	8%	25%
NZ 2014[44]	58%	67%	53%	67%	25%	0%

Key Questions

Who should be advised to receive fertility preservation?

What fertility preservation method should be used?

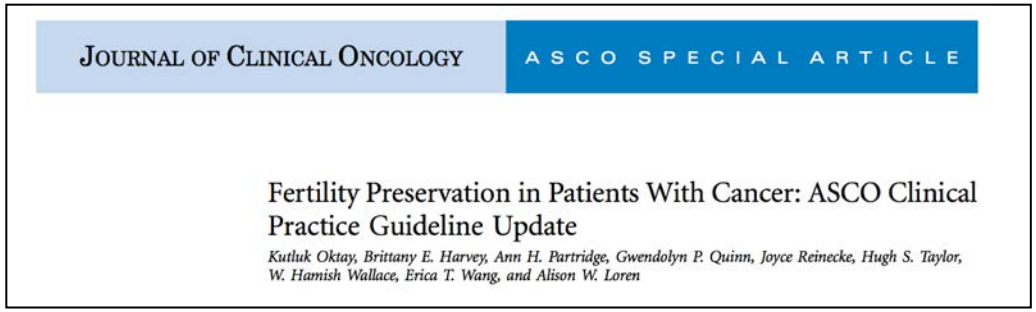
When should fertility preservation be discussed and initiated?

Who should be involved in the counseling and decision making regarding fertility preservation?

What are the ethical and logistical aspects?

Concordance of key questions among high quality guidelines

- Concordance: same recommendation across all guidelines
- Discordance: different recommendations, recommendation not included or only 1 guideline made a specific recommendation
- Large variations were noted between guidelines
  - 12.8% items concordant for females
  - 11.4% items concordant for males



- Who should be advised to receive fertility preservation?
- What fertility preservation method should be used?
- When should fertility preservation be discussed and initiated?
- Who should be involved in the counseling and decision making regarding fertility preservation?
- What are the ethical and logistical aspects?

Key Questions

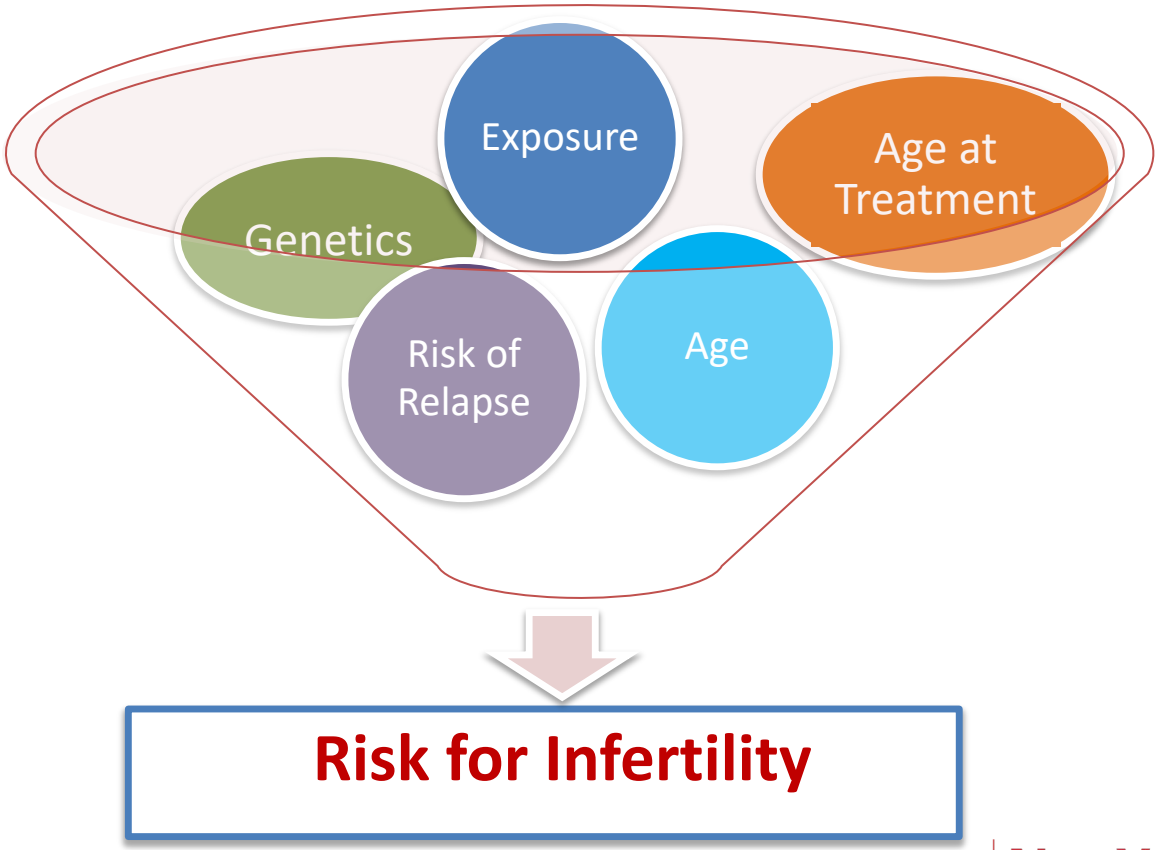
Who should be advised to receive fertility preservation?

ASCO: Being at risk for infertility due to anticancer treatment

ASRM: Males: Exposure to toxic effects of RT and chemotherapy at all stages of life.
Females: Surgery, chemotherapy (dependent on drug, dose and age of treatment). TBI, Abd RT, Pelvic RT may cause ovarian and uterine damage and are also dose and age dependent.

EM: Should all patients be referred to a fertility unit before initiating anticancer treatments?

Short answer: No, referrals should be individualized



EM: Should all patients be referred to a fertility unit before initiating anticancer treatments?

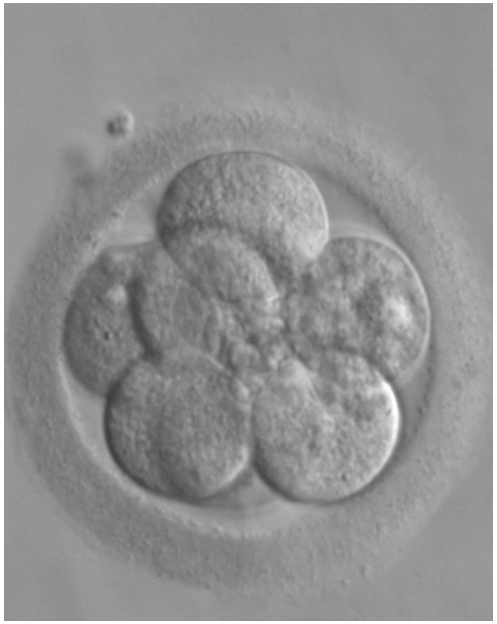
Short answer: No, referrals should be individualized

"providers should not overestimate the risk of treatment-related infertility… and some of them (e.g. very young patients undergoing treatment at low risk of infertility) can be reassured that they will not likely require the help of a fertility clinic after treatment"

"the perception of a high risk for infertility is individual and the patients' own wishes should be taken into account"

Key Questions

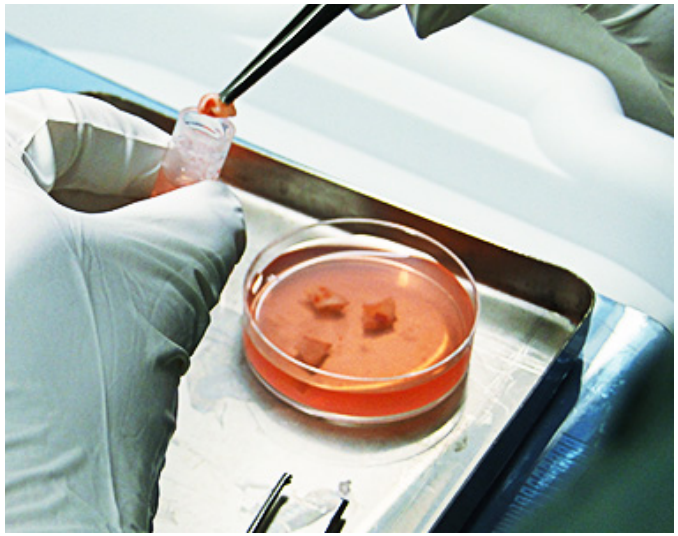
What fertility preservation method should be used?



Non-Experimental

ASCO: aromatase inhibitor based stimulation may ameliorate concern of cancer recurrence from stimulation and subsequent pregnancy.

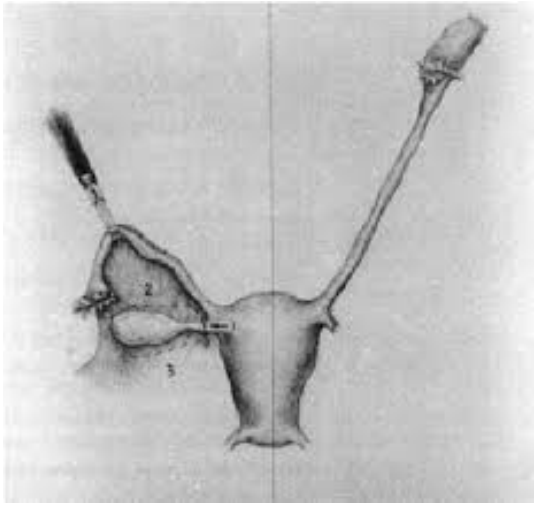
Experimental

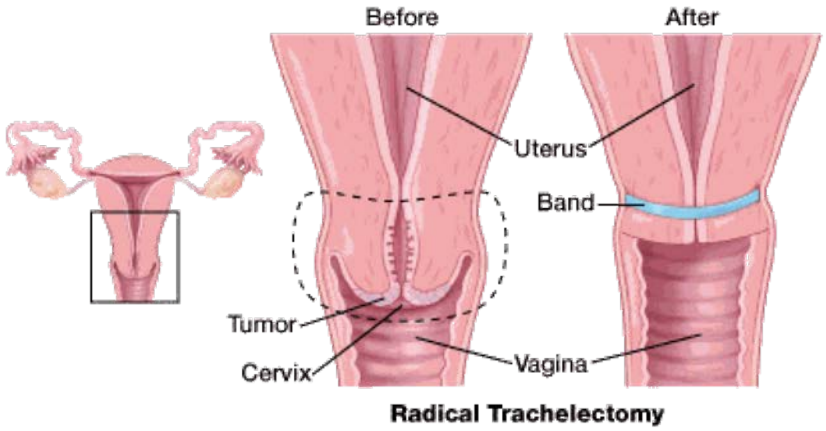


ASCO: needs to be confirmed whether safe in leukemia
Emerging data may prompt reconsideration of the designation of experimental in the future

ASRM: Should only be offered as part of an IRB-approved research protocol

EM: best candidates: pre-pubertal girls, those who cannot delay chemotherapy, patients who have already received chemotherapy. Not recommended in patients over 40 or with reduced ovarian reserve. Concern of reintroducing malignant cells.





ASCO/ASRM

Ovarian transposition should be offered although is not always successful

ASCO/ASRM

Conservative gyn surgery in Stage 1A2 to 1B cervical cancer (radical trachelectomy)

Conflicting Data

ASRM: data conflicting, other FP should be offered in addition to considering GnRH Meta analysis shows efficacy in in breast cancer patients

Did not prevent primary ovarian insufficiency in patients with lymphoma

ASCO: (updated) conflicting evidence

"The panel recognizes that, when proven FP methods (oocyte, embryo, ovarian tissue) are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. However, GnRHa should not be used in place of proven fertility preservation methods."

Table 1. Randomized Controlled Trials

First Author, Year, Trial	No. of Patients		Agents	Disease Sites	Follow-Up (years)	Primary Outcome	No. of Pregnancies (%)	*P*
	Enrolled	Evaluable						
Leonard, 2017, OPTION[9]	106	95	GnRHa	Breast	5.0*	POV	9 (9)	NR
	121	107	Control				6 (6)	
Demeestere, 2016[8]	65	32	GnRHa	Lymphoma	5.33	POF	17 (53.1)	NS
	64	35	Control				15 (42.8)	
Moore, 2015, POEMS[7]	126	105	GnRHa	Breast	4.1	POV	22 (21)	.03
	131	113	Control				12 (11)	
Lambertini, 2015, PROMISE-GIM6[6]	148	148	GnRHa	Breast	7.3	POV	8 (5)	NS
	133	133	Control				3 (2)	
Elgindy, 2013[5]	25	17	GnRHa	Breast	1.0	Resumption of menses	1 (4)	NS
	25	17	Control				1 (4)	
	25	17	GnRHa				1 (4)	NS
	25	17	Control				0 (0)	
Munster, 2012[4]	27	26	GnRHa	Breast	1.6	POV	0 (0)	NS
	22	21	Control				2 (10)	
Gerber, 2011[3]	30	30	GnRHa	Breast	4.0	Resumption of menses	1 (3)	NS
	31	30	Control				1 (3)	

Abbreviations: GnRHa, gonadotrophin-releasing hormone agonist; NR, not reported; NS, not significant; OPTION, Ovarian Protection Trial In Premenopausal Breast Cancer Patients; POEMS, Prevention of Early Menopause Study; POF, premature ovarian failure; POV, preservation of ovarian function; PROMISE-GIM6, Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients—Gruppo Italiano Mammella 6.
*Median not reported.

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*Median not reported.

Table 3. Guidelines

Guideline	Recommendation
NCCN Breast Cancer 2017[21]	Randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. Smaller historical experiences in patients with ER-positive disease have reported conflicting results with regard to the protective effect of GnRH agonist therapy on fertility.
NCCN AYA Oncology 2017[20]	Some data suggest that menstrual suppression with GnRH agonists may protect ovarian function. However, evidence that menstrual suppression with GnRH agonists protects ovarian function is insufficient, so this procedure is not currently recommended as an option for fertility preservation.
AIOM 2016[15]	Temporary ovarian suppression with LHRHa during chemotherapy should be recommended to all premenopausal patients with breast cancer undergoing chemotherapy who are interested in ovarian function and/or fertility preservation.
SEOM 2016[16]	The use of GnRHa could be an option to discuss with patients with early-stage receptor-negative breast cancer if embryo or oocyte cryopreservation not feasible. The use of GnRHa to preserve fertility in women with other cancer should not be recommended.
BCY2 2016[17]	The most recent data suggested a protective ovarian effect of LHRHa in both patients with hormone receptor–positive and –negative disease with no signal for harm from a breast cancer recurrence standpoint. The BCY2 Panel therefore agreed this strategy can be discussed with patients interested in potentially preserving fertility and/or ovarian function.
St Gallen 2015[18]	LHRH agonist therapy during chemotherapy proved effective to protect against premature ovarian failure and preserve fertility in young women with ER-negative breast cancer undergoing chemotherapy.
ESMO 2013[19]	The use of GnRH analogs concomitantly with chemotherapy should not be regarded as a reliable means of preserving fertility. Data on long-term ovarian function and pregnancy rates in these cohorts are warranted.

Abbreviations: AIOM, Italian Association of Medicine; AYA, Adolescent and Young Adult; BCY2, International Consensus Conference for Breast Cancer in Young Women; ER, estrogen receptor; ESMO, European Society for Medical Oncology; GnRHa, gonadotrophin-releasing hormone agonist; LHRH, luteinizing hormone-releasing hormone; LHRHa, luteinizing hormone-releasing hormone agonists; NCCN, National Comprehensive Cancer Network; SEOM, Sociedad Española de Oncología Médica.

EM: Ovarian Suppression with the use of LHRHa during chemotherapy should be considered a reliable strategy to preserve ovarian function and fertility, at least in breast cancer patients, given the availability of new data suggesting both the safety and efficacy of the procedure”

(but four of the experts disagreed with the statement and still consider the strategy experimental)

Key Questions

When should fertility preservation be discussed and initiated?

All Recommend

ASCO: Sperm collected after the initiation of therapy has a potentially higher risk of DNA damage

EM: Ovarian Tissue Cryopreservation

ASCO: fertility preservation

ASRM: using the preserved gametes or providing other assisted reproduction

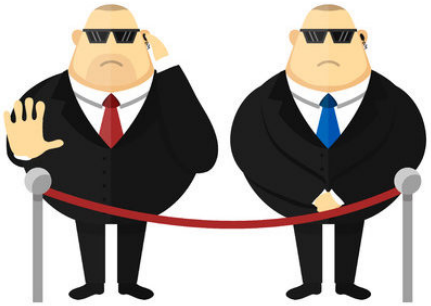
Key Questions

Who should be involved in the counseling and decision making regarding fertility preservation?

Oncology Health Care Providers

ASCO: all oncologic health care providers should be prepared to discuss infertility as a potential risk of therapy.

ASRM: all oncologists should be aware of the adverse effects of treatment on fertility and of ways to minimize those effects



Reproductive Health Care Providers

ASCO: Patients who express an interest (or ambivalence or uncertainty) should be referred to reproductive specialists

ASRM: Main role is in counseling and providing preservation

Psychosocial Team Members

ASCO: Refer to psychosocial providers when distressed about potential infertility

ASRM: A collaborative multidisciplinary team approach is encouraged.

Key Questions

What are the ethical and logistical aspects?

Disposition of Stored Gametes, Embryos and Gonadal Tissue

Instructions should be specified about the disposition of stored gametes, embryos or gonadal tissue in the event of the patient's death, unavailability or other contingency. Minors should update directions when they reach age of majority.

Minors with Cancer

Parents may act to preserve the fertility of cancer patients who are minors and when the intervention is likely to provide potential benefits to the child.

Assent of the child should be obtained if possible

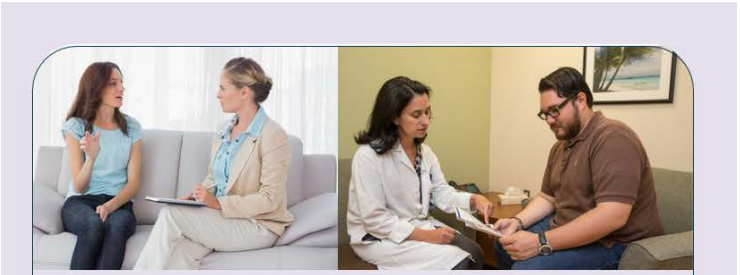
Unless written instructions state otherwise, gametes should be discarded if the child does not survive to adulthood.

The discussions should be documented in the medical chart. (ASCO)

Moving Forward: Guidelines 2023?

- Is it important to clarify risk of AOF vs. POI?
- What are the genetic factors in infertility risk?
- What is the utility of GnRHa in populations other than early stage breast cancer?
- To whom and when should gonadal tissue cryopreservation be offered? Will it lose the experimental label?
- Importance of a navigator

www.echo.rhoinstitute.org



Are you:

- **A psychologist or counselor, social worker, nurse, or APP who works with cancer patients ages 15-45?**
- **Interested in learning about fertility preservation, sexual health, contraception, and psychosocial issues?**

What is ECHO?
Enriching **C**ommunication Skills for **H**ealth Professionals in **O**ncofertility (ECHO) is a web-based training program focusing on building communication skills

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

Why participate?
- 17.75 FREE continuing education credits from APA, ASWB, ANCC, and AAPA
- Free educational materials
- Training facilitated by a national team of experts
- Certificate of completion

Apply Today!
Interested learners should submit their application on www.echo.rhoinstitute.org.
Deadline to apply is November 25, 2018.

Contact Information
For additional information or questions, please contact us at:
Phone: (813)745-6941
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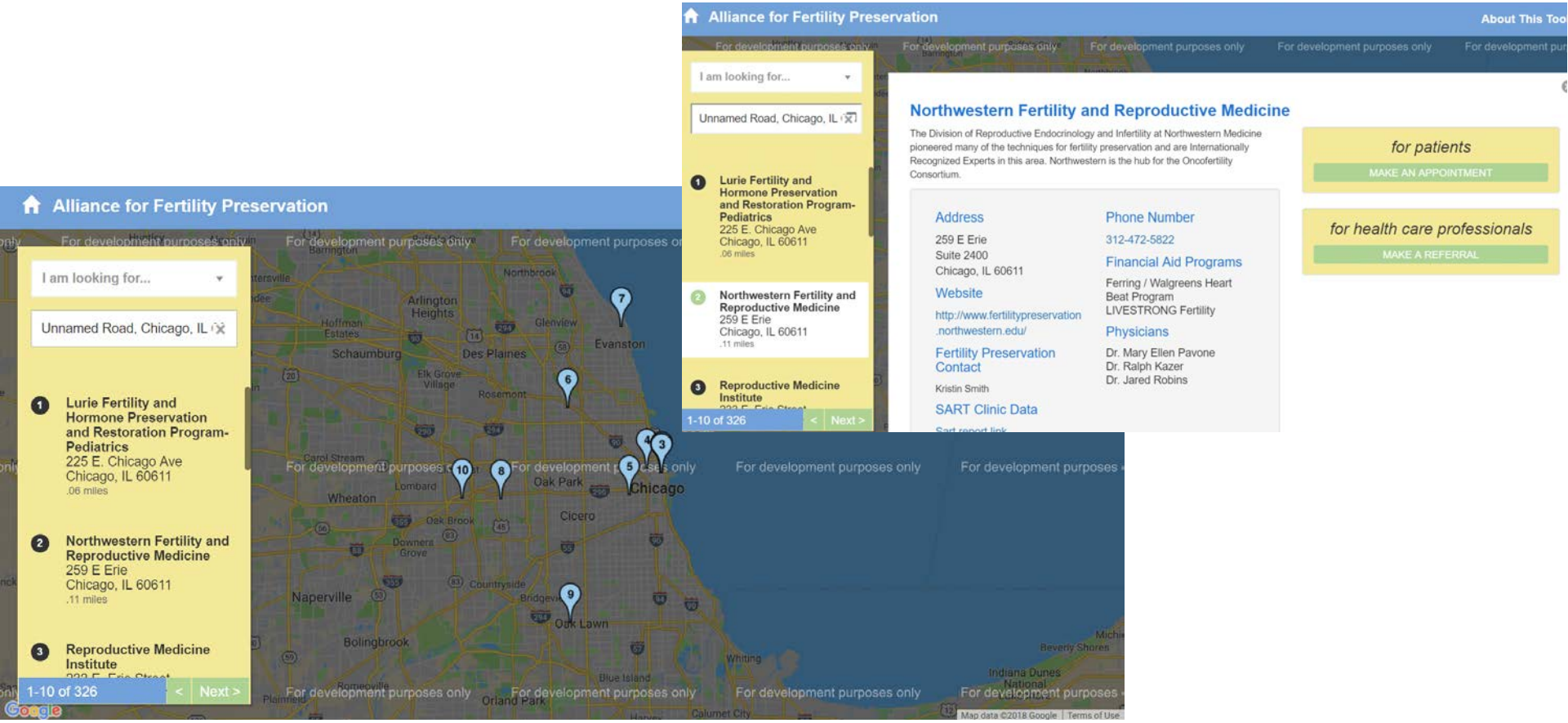
Web: www.echo.rhoinstitute.org

ECHO is funded by a National Cancer Institute R25 Training Grant:5R25CA142519-02

www.allianceforfertilitypreservation.org



Weill Cornell Medicine

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Thank you!