Hereditary Breast & Ovarian Cancer Syndrome

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Disclosure Information

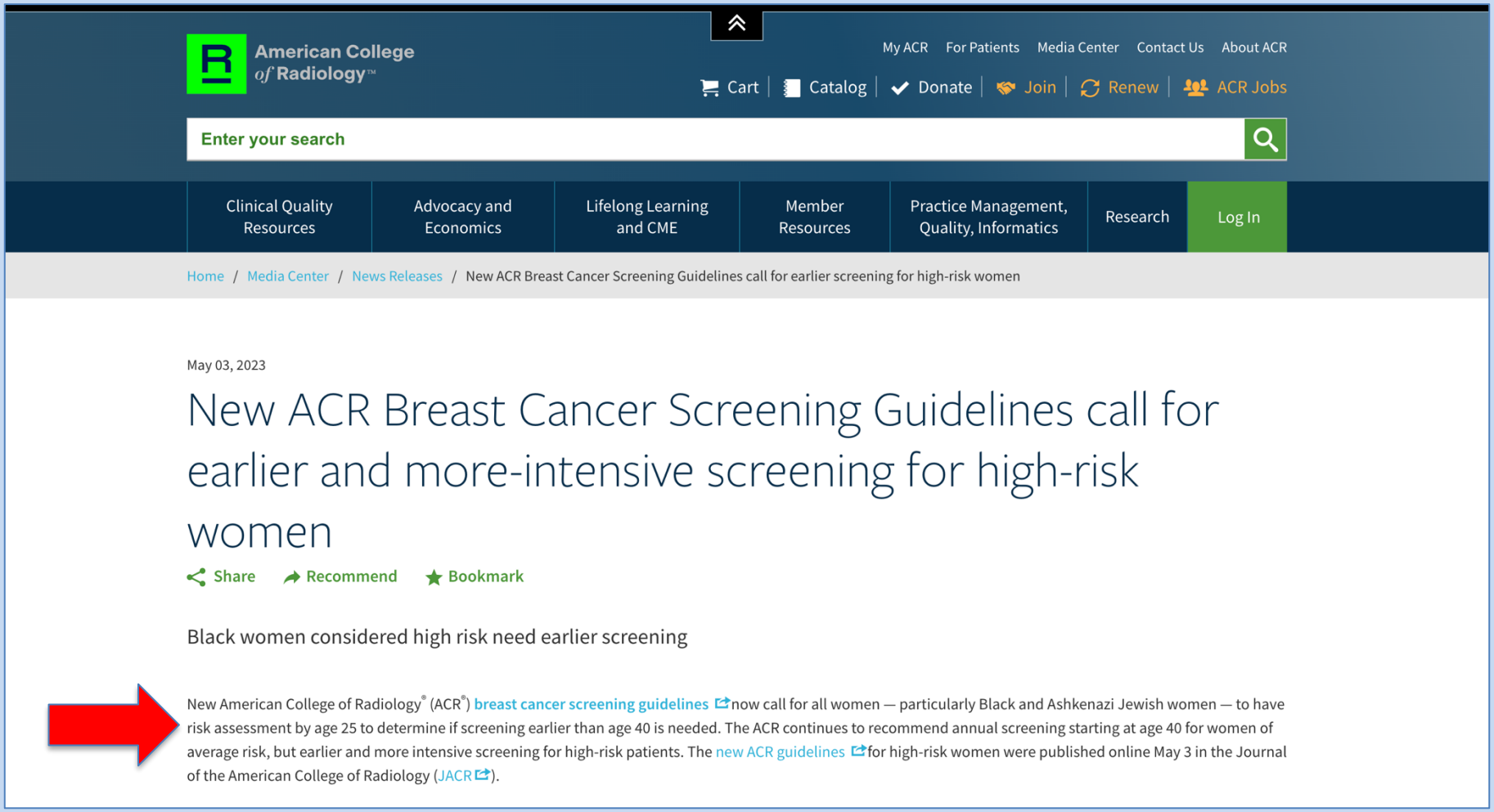
I am the owner of and consultant for Pleasant Consulting LLC.

Client: AtlasMed

Objectives

1. To review the steps in identifying those with HBOC
2. To review the basic clinical management of HBOC
3. To highlight downstream considerations in clinical care

1st Step in Determining Genetic Testing Eligibility= Review personal and family cancer history!



Taken from: https://www.acr.org/Media-Center/ACR-News-Releases/2023/New-ACR-Breast-Cancer-Screening-Guidelines-call-for-earlier-screening-for-high-risk-women#:~:text=New%20American%20College%20of%20Radiology%20%C2%AE%20%28ACR%20%C2%AE%29,if%20screening%20earlier%20than%20age%2040%20is%20needed.

BREAST SCREENING CONSIDERATIONS

General Considerations

- These guidelines are intended for individuals assigned female at birth with residual native breast tissue; however, these guidelines do not provide screening guidance for transgender individuals. Certain organizations have developed consensus-based guidelines for transgender individuals, such as the ACR Appropriateness Criteria. NCCN endorses these criteria. Transgender individuals should consult with their primary care physician to determine when/whether screening would be appropriate.
- Individuals should undergo breast cancer risk assessment by age 25 years and be counseled regarding potential benefits, risks, and limitations of breast screening in the context of their risk stratification.
- Shared decision-making is encouraged based on a patient's values and preferences (Discussion).
- Screening mammography decreases breast cancer mortality. Digital breast tomosynthesis is recommended, when available. Multiple studies show that tomosynthesis can decrease call-back rates and improve cancer detection compared with two-dimensional (2D) mammography alone, though long-term data on incremental mortality reduction have not yet been demonstrated. Radiation exposure may be increased, but remain within FDA guidelines and can be reduced with FDA-approved synthesized 2D reconstruction.
- Current evidence does not support the use of thermography as a screening procedure.

Upper Age Limit for Screening

- Upper age limit for mammographic screening is not yet established.
- Consider severe comorbid conditions limiting life expectancy (eg, ≤10 years) and whether therapeutic interventions would be appropriate and acceptable to the patient.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Genes such as *BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11,* and *TP53*. See GENE-A)[a,g,h,i,j]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - ◊ Treatment indications
      - – To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[k,l] (See NCCN Guidelines for Breast Cancer)
      - – To aid in adjuvant treatment decisions with olaparib for high-risk,[m] HER2-negative breast cancer[j]
    - ◊ Pathology/histology
      - – Triple-negative breast cancer
      - – Multiple primary breast cancers (synchronous or metachronous)[n]
      - – Lobular breast cancer with personal or family history of diffuse gastric cancer (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric)
    - ◊ Male breast cancer
    - ◊ Ancestry: Ashkenazi Jewish
  - Any age (continued):
    - ◊ Family history[o]
      - – ≥1 close blood relative[p] with ANY:
        - breast cancer at age ≤50 y
        - male breast cancer
        - ovarian cancer
        - pancreatic cancer
        - prostate cancer with metastatic,[q] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - – ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer
- Family history criteria: unaffected; or affected but does not meet above criteria
  - Individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[r]
  - Individuals who have a probability >5% of a *BRCA1/2* P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).[s]

Criteria met → GENE-1

If testing criteria not met, consider testing criteria for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

Continued on CRIT-3

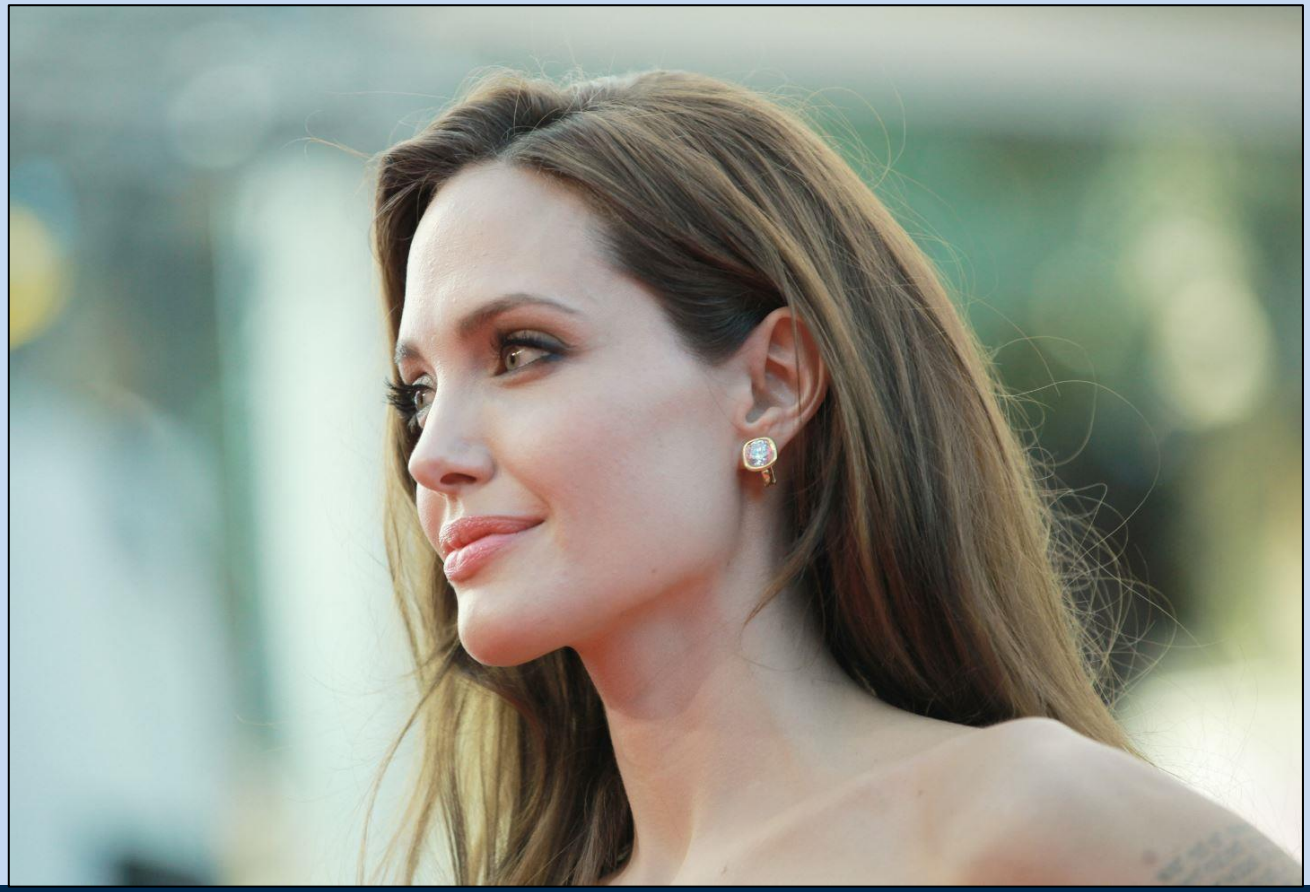
Footnotes on CRIT-2A

Note: All recommendations are category 2A unless otherwise indicated.

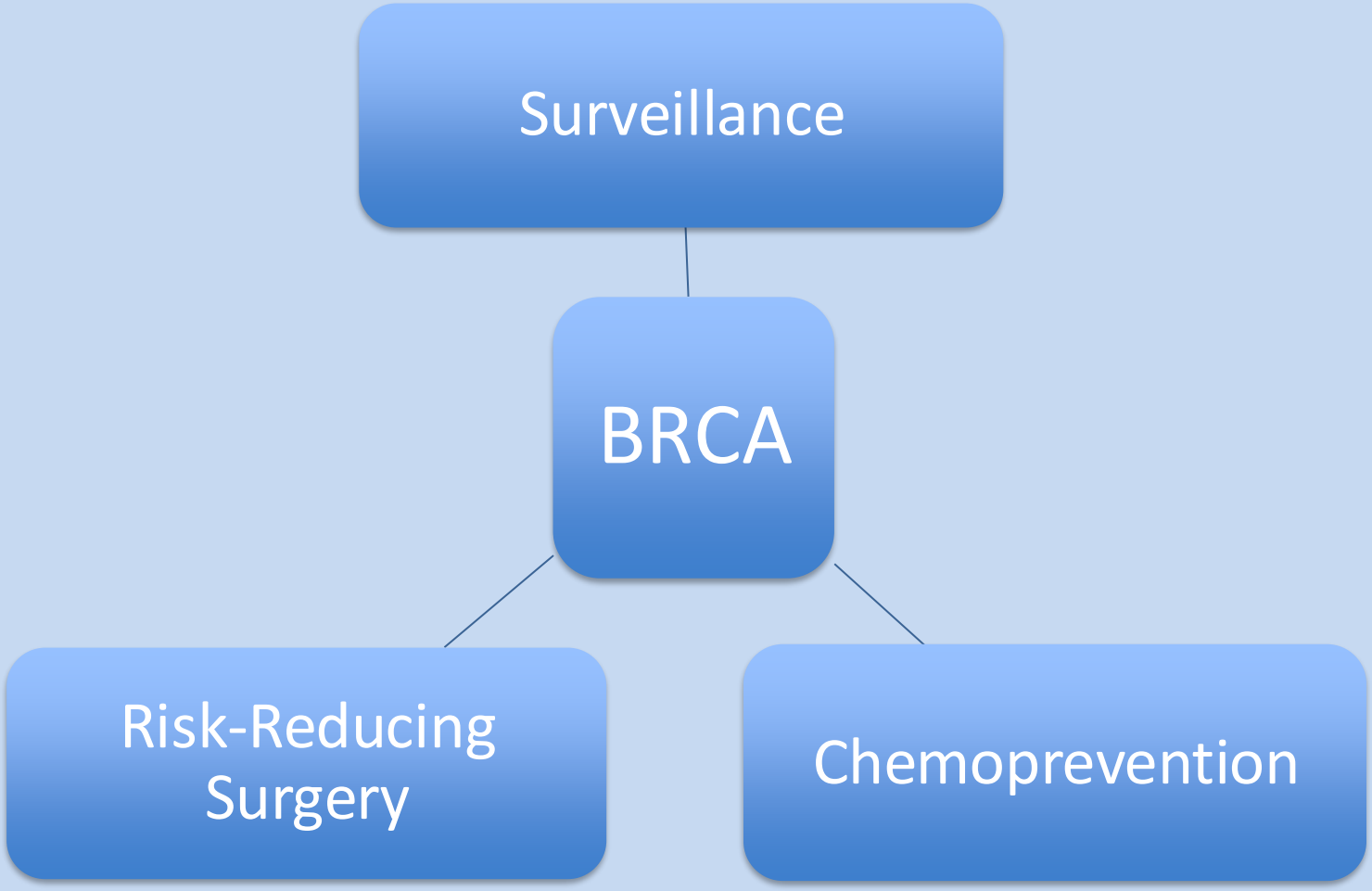
Pathogenic Variant	Breast Cancer Risk	Epithelial Ovarian Cancer Risk
ATM	21-24%	2-3%
BARD1	17-30%	-
BRCA1	60-72%	39-58%
BRCA2	55-69%	13-29%
BRIP1	-	5-15%
CDH1	37-55%	-
CHEK2	23-27%	-
MLH1, MSH2, MSH6, PMS2	<15%	1.3-38%
NF1	20-40%	-
PALB2	32-53%	3-5%
PTEN	40-60%	-
RAD51C	~20%	10-15%
RAD51D	~20%	10-20%
STK11	32-54%	-
TP53	>60%	-

NCCN
1.2026

Review of BRCA Recommendations



Management Options



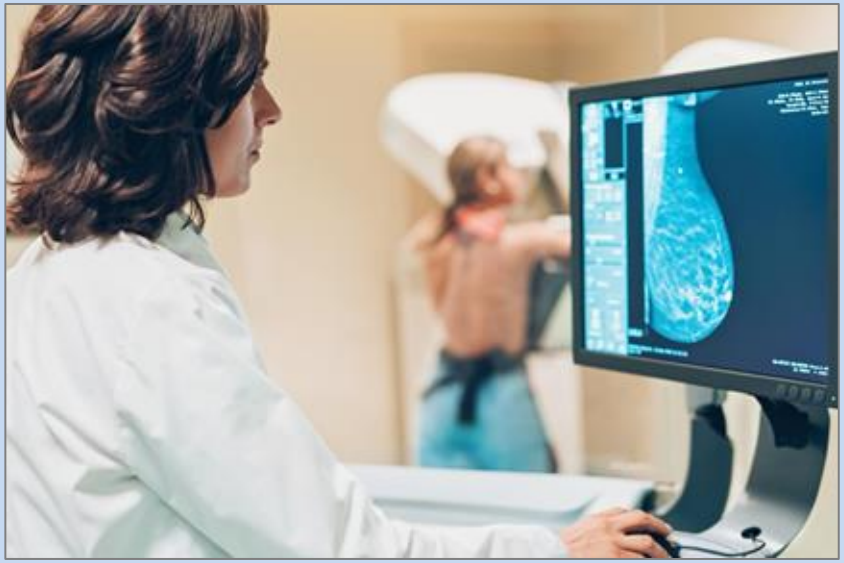
Breast Cancer

Surveillance
Chemoprevention
Risk-Reduction

Breast Surveillance for BRCA

Breast cancer:

- Ages 25-29:
  - Annual breast MRI
  - Clinical breast exam q6-12 months
  - Self breast awareness
- Ages ≥30:
  - Annual MRI + mammogram



Source: ACOG Practice Bulletin 182

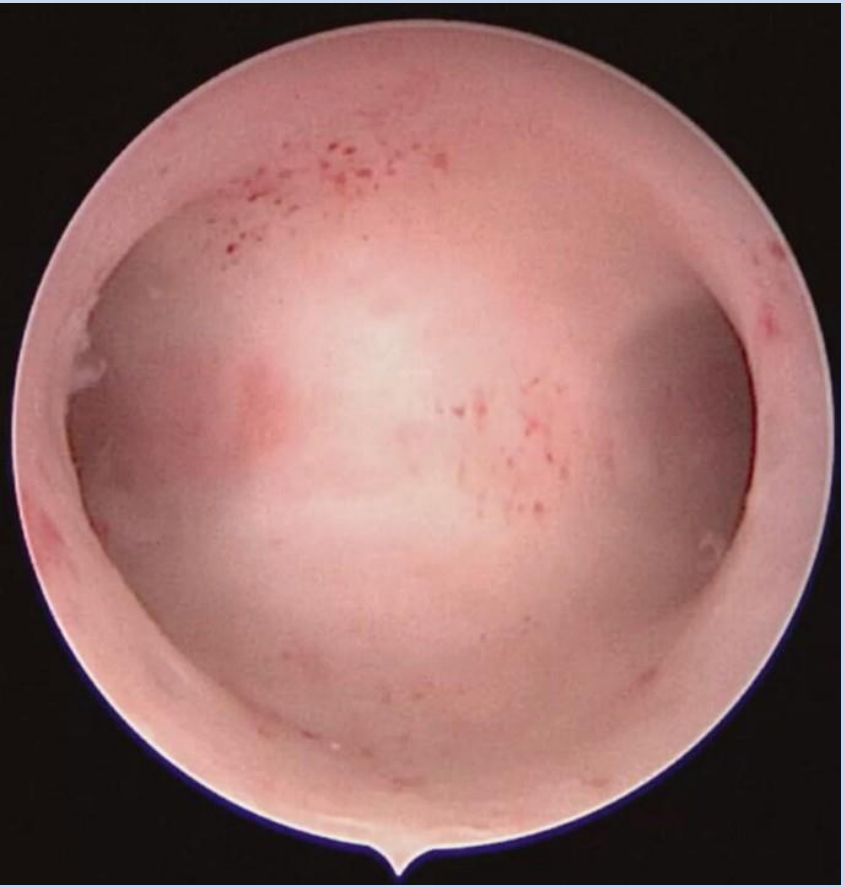
Tamoxifen

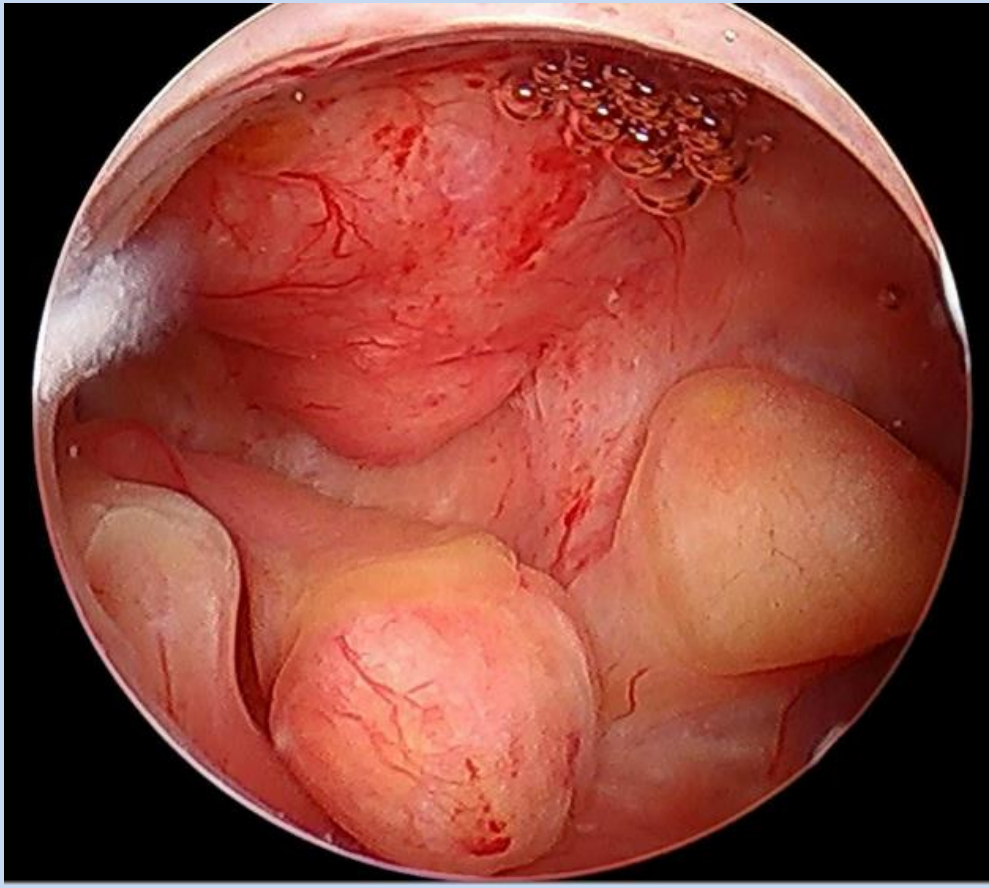
- Decreases breast CA risk ≥45%

- Considerations:
  - BRCA1 vs. BRCA2
  - Future fertility & reliable contraception
  - s/p bilateral mastectomies

- **No routine screening!**→ causes subepithelial stromal hypertrophy of uterine lining→ possible false positives

- SE: Hot flashes, VTE, stroke, cataracts, vaginal discharge, ovarian cysts, AUB, uterine polyps, **endometrial cancer in postmenopausal**



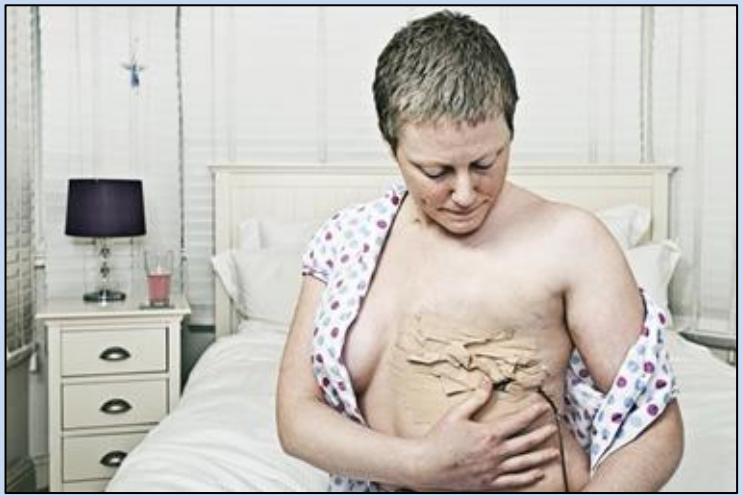


https://link.springer.com/chapter/10.1007/978-981-15-2505-6_8

Risk-Reducing Mastectomy

Pros

- Significant decrease in breast cancer risk
- No screening imaging
- Chest wall exam 1x/year



Cons

- Major surgery
- ≥1 surgeries
- Cannot breast/chest feed
- Impact on body image & sexuality
- **No mortality benefit**

Ovarian Cancer

Surveillance
Chemoprevention
Risk-Reduction

Ovarian Cancer Screening

<u>Pelvic Ultrasound & Cancer Antigen 125 (CA 125):</u>

- High incidence of false positives
- Not specific for ovarian cancer
- **No decrease in ovarian cancer mortality**

Remember:

- *CA 125 <u>not always</u> elevated in ovarian cancer*
- *Can be elevated in other benign and malignant processes*

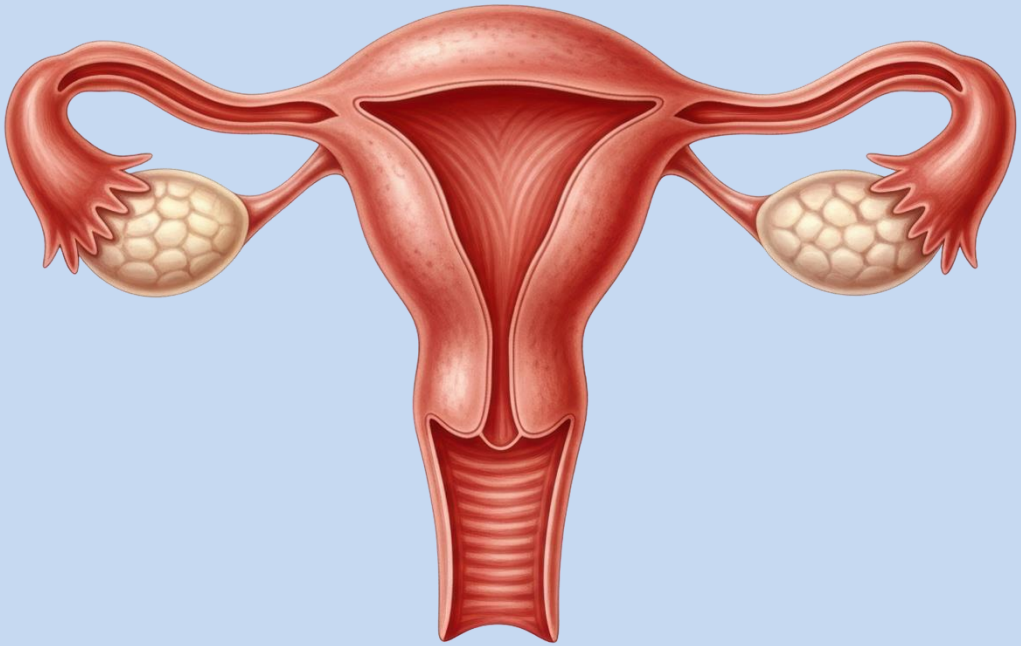
Oral Contraceptive Pill (OCP)

- Breast cancer risk:
  - Mixed data but considered overall acceptable; need to counsel on risk
- Ovarian cancer risk:
  - 45-50% ovarian cancer reduction in BRCA1
  - 60% ovarian cancer reduction in BRCA2

-McLaughlin et al., 2007; Narod et al., 1998.

Surgical Risk Reduction

- **Bilateral salpingo-oophorectomy (BSO):**
  - BRCA 1: recommended ages 35-40
  - BRCA 2: recommended ages 40-45



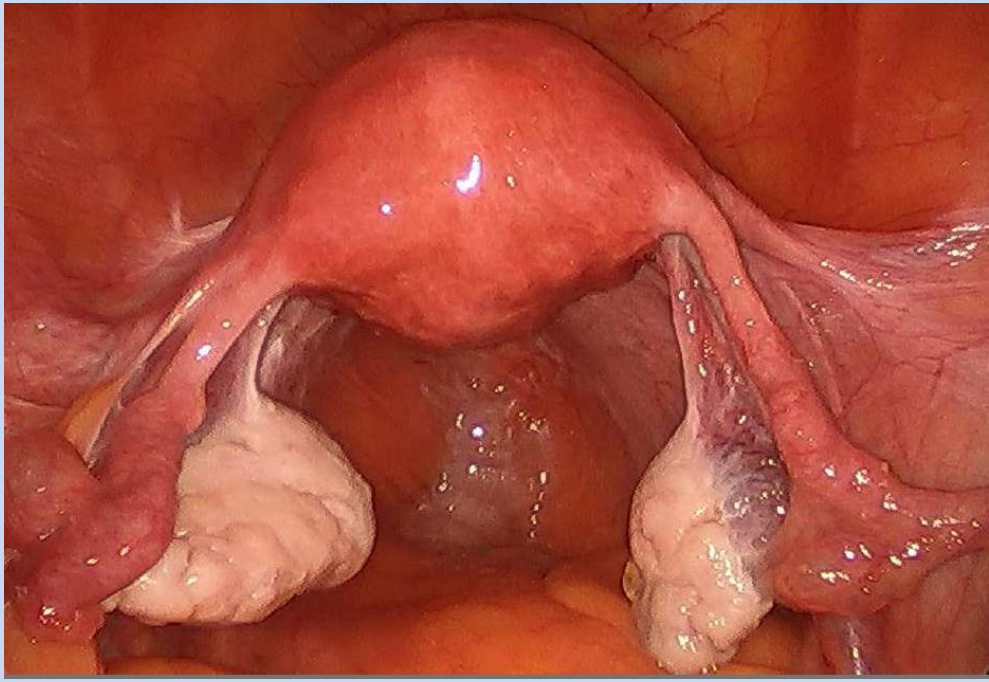
Source: ACOG Practice Bulletin 182.

Risk-reducing BSO

- **Decreased ovarian cancer mortality (≥80%)**
- Minimally invasive surgery with good recovery

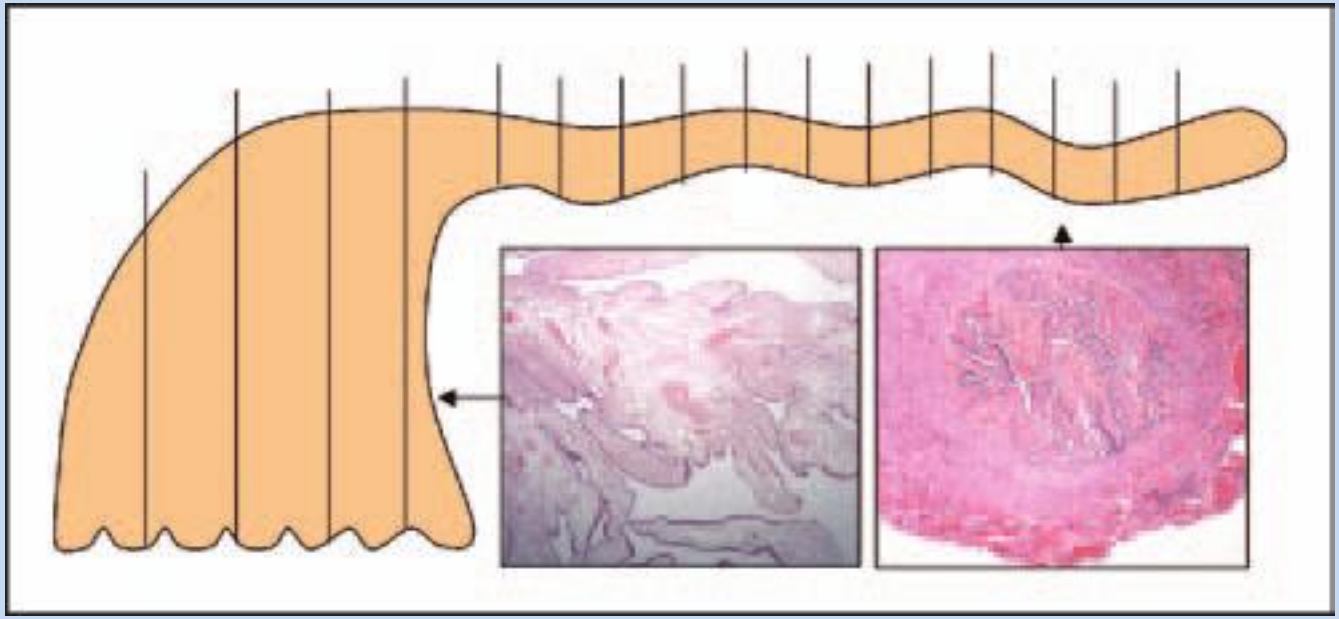
Intra-Op Considerations

1. Survey of abdomen
2. Pelvic washings
3. 2cm pedicle
4. Use endoscopic bag



SEE-FIM

Sectioning and **E**xtensively **E**xamining the **FIM**briated end



researchgate.net

Other BRCA Considerations

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2026
***BRCA*-Pathogenic/Likely Pathogenic Variant - Positive Management**

NCCN Guidelines Index
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Discussion

***BRCA* PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT**

Site		
...neal/ ...rine ...ancers	Salpingectomy	• Salpingectomy reduces the risk of ovarian cancer in the general population and is an option for premenopausal patients with hereditary cancer risk who are not yet ready for oophorectomy.[13,14,15,16] • If patients undergo salpingectomy, completion oophorectomy is recommended as per gene-specific guidelines, unless specified by clinical trial protocol. • SEE-FIM protocol for pathologic assessment and pelvic washings should be performed at salpingectomy or completion oophorectomy. • CA-125 and pelvic ultrasound are recommended for preoperative planning. • Clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. Strong consideration of surgical choice study participation if available[i] • Consider continuation of combination OCP or hormonal IUD for continued ovarian cancer risk reduction while ovaries remain in place. • Salpingectomy is also an option for average or uncertain risk patients if they also desire surgical sterilization.
	Considerations for hysterectomy	• Limited data suggest that there may be a slightly increased risk of serous uterine cancer among individuals with a *BRCA1/2* P/LP variant. The clinical significance of these findings is unclear. Further evaluation of the risk of serous uterine cancer in the *BRCA* population is ongoing. The provider and patient should discuss the risks and benefits of concurrent hysterectomy at the time of RRSO for individuals with a *BRCA1/2* P/LP variant prior to surgery.[17] • Individuals who undergo hysterectomy at the time of RRSO are candidates for estrogen-alone HRT, which is associated with a decreased risk of breast cancer compared to combined estrogen and progesterone, which would be required when the uterus is left in situ.[11,18,19] • Risk of pelvic floor dysfunction or urinary incontinence after hysterectomy is influenced by factors other than hysterectomy alone; if no preceding pelvic organ prolapse, long-term follow up studies indicate risks are <5%.[20,21]
	Hormone replacement options after risk-reducing surgery	• In conjunction with a gynecologist or other qualified health care professional with expertise in menopause management: ▸ HRT recommendations should be tailored depending on each patient's personal history of breast cancer and/or breast cancer risk reduction strategies. ▸ HRT is an important consideration for premenopausal patients who do not carry a diagnosis of breast cancer or do not have other contraindications for HRT. ▸ Premature menopause due to RRSO can cause detriments to bone health, cardiovascular health, psychosocial health, neurologic health, sexual health, and generalized quality-of-life. HRT can reduce these risks. • Studies examining the risk of subsequent breast cancer associated with HRT use after RRSO have primarily focused on average durations of HRT use up to 3–5 years, and the safety of longer-term use remains uncertain. • If uterus is left in place at time of RRSO, consider options for hormone replacement ▸ LNG-IUD for uterine protection with oral or transdermal estrogen. LNG-IUD may have benefits over combined HRT including potential decreased risk for breast cancer.[22] ▸ Combination E/P HRT with counseling regarding bleeding precautions and endometrial cancer risk/awareness. ▸ Combination estrogen with selective estrogen receptor modulator (such as bazedoxifene).[23] ▸ Combination OCPs that can be taken continuously without placebo week.

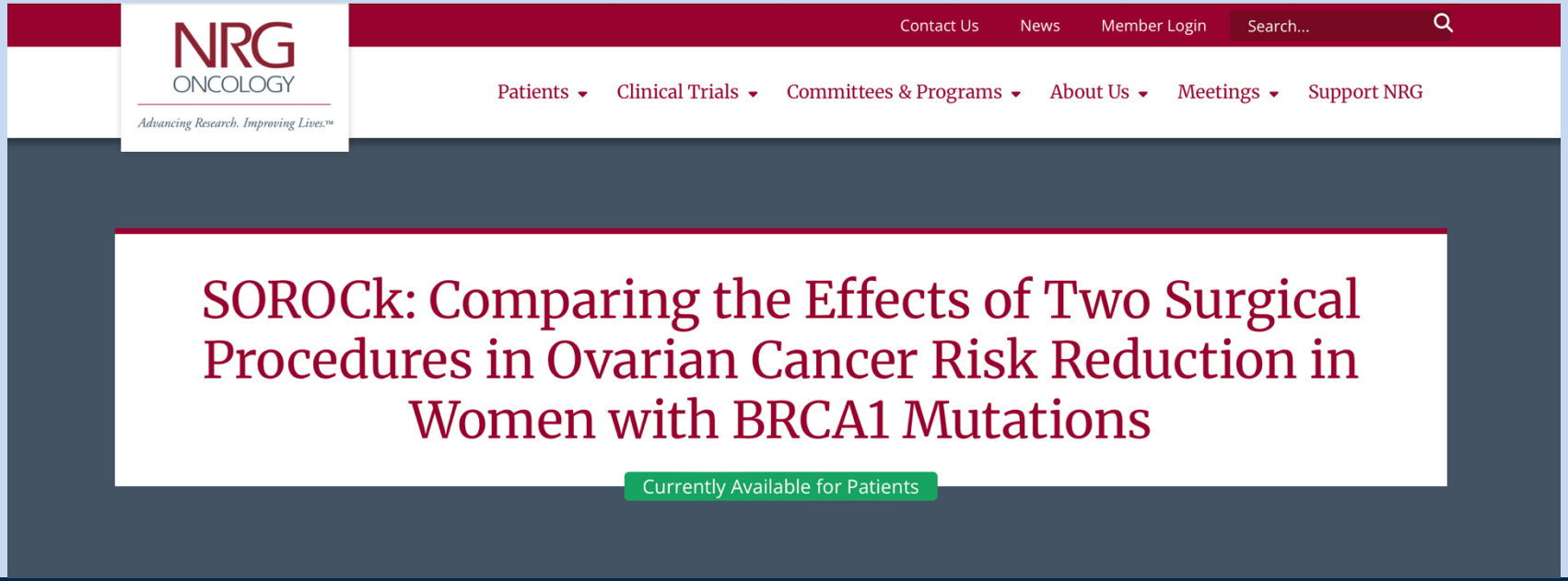
[i] Clinical trials are in progress. See Discussion.

References on BRCA-A 5 of 5

Note: All recommendations are category 2A unless otherwise indicated.

Interval Salpingectomy with Delayed Oophorectomy

- Salpingectomy does reduce risk
- However… interval surgeries still being studied for high risk patients



Uterine Cancer & BRCA

Multicenter cohort study (Jonge et al., 2021):

- 5980 BRCA+ and 8451 BRCA-
- Endometrial CA: 58 BRCA+ and 33 BRCA-
- BRCA1 had increased risk
  - SIR 3.65 overall
  - **SIR 12.64 serous-like EC**
- BRCA2
  - SIR 1.70 overall
  - SIR 5.11 serous-like EC

Take-Away…

- While relative risk is high (~2-3 fold)…
- **Absolute risk is LOW!!!!**
  - **Overall 3.0%**
  - **Serous-like EC 1.1%**

Jonge et al., 2021

Post-Operatively→ Surgical Menopause

Postoperatively

- Hot flashes
- Night sweats
- Reduced sleep quality
- Sexual dysfunction
- Decreased libido
- Dyspareunia
- Vaginal atrophy
- Depression & anxiety
- Weight gain
- Changes in cognition
- Increased bone thinning

Increased Cardiovascular Mortality

- Heart disease= leading cause of death in USA!
  - Oophorectomy <50 years old→ **RR= 4.55**

(Atsma et al., 2006)

Benefits of Hormone Therapy (HT)

- Reduces cardiovascular risk
- Prevents bone loss
- Decreases all cause morality
- Improves vasomotor symptoms
- Better quality of life!!!

What about breast cancer risk with HT???

Breast CA Risk After BO

- International case-control study
- After oophorectomy:
  - **56% reduction in breast cancer in BRCA1**
  - **46% reduction in breast cancer in BRCA2**
  - Risk reduction greater <40 than >40 (OR 0.36 vs 0.53)
  - Protective 15 yrs after oophorectomy

– Eisen et al., 2016

Study Authors	Design	Results
Domchek et al., 2011	Prospective cohort 321 BRCA s/p rrBSO Followed 5.4 yrs	HT not associated with breast CA risk
Kotsopoulous et al., 2016	432 match case-control BRCA1 4.42 years	No ↑ breast CA risk on HT
Kotsopoulos et al., 2018	872 BRCA1 s/p BSO	No ↑ breast CA risk on HT 10 yr f/u→ breast CA reduction with ET **Non-significant <u>increase</u> with EPT**
Michaelson-Cohen et al., 2021	Retrospective cohort 306 BRCA1/2 s/p BSO Followed 7.26 yrs	<45 y/o: HT did not ↑ odds of breast CA >45 y/o: HT **<u>did</u>** ↑ odds of breast CA

Bottom line

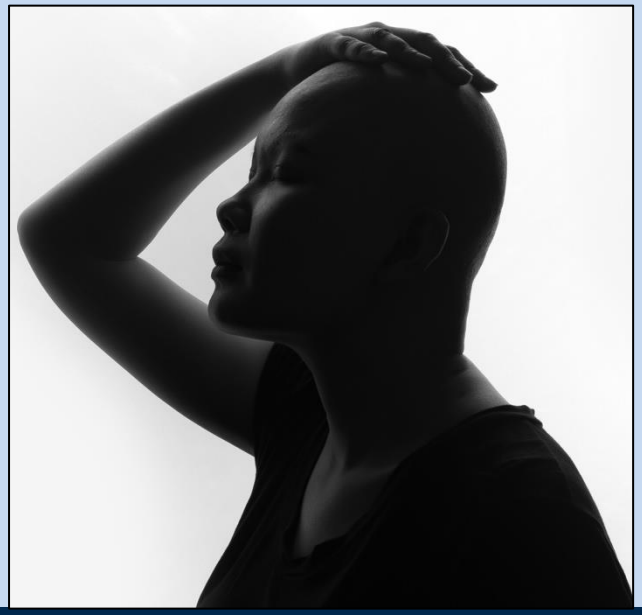
HT is acceptable for BRCA carriers without breast cancer s/p BSO until the age of 51-52 (natural menopause)

Preimplantation Genetic Testing (PGT)

- Genetic testing on embryos prior to transfer
- Costs $$ thousands; **not covered by insurance**
- Racial and socioeconomic disparities
- Ethical debate

Breast Cancer in Black Communities

- **Higher mortality (38%)**
- More likely to have triple-negative cancer, early onset, more advanced disease
- Mixed data on BRCA prevalence



Perspective Article

Universal Genetic Counseling and Testing for Black Women: A Risk-Stratified Approach to Addressing Breast Cancer Disparities

Versha A. Pleasant,[1] Sofia D. Merajver[2]

Abstract

Black women experience disproportionate breast cancer-related mortality, with similar overall incidence to White women. Approaches to address these racial health disparities should be multifaceted. Universal genetic counseling and testing for Black women could represent one dimension of a comprehensive approach in guiding early identification of those more likely to experience higher breast cancer-related mortality. The increased risk of triple-negative breast cancer and greater likelihood of early-onset breast cancer among Black women are 2 major justifications, given that these elements are already preexisting testing criteria per the National Comprehensive Cancer Network. Increasing assessment of breast cancer-related risk in the Black community through universal genetic counseling and testing should be considered to focus enhanced screening and preventive measures in a tailored risk-appropriate context.

Clinical Breast Cancer, Vol. 25, No. 3, 193–197 © 2024 The Authors. Published by Elsevier Inc.

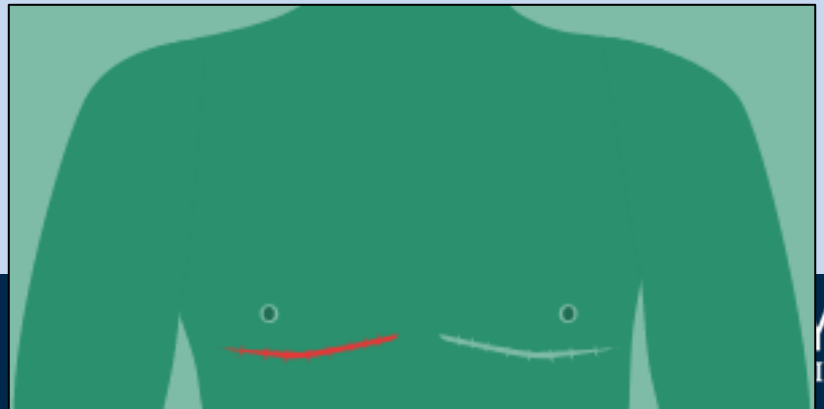
Keywords: Genetic testing, Genetics, Health disparities, Black, Breast cancer

Breast Cancer among Transgender People

- >1.5 million identify as transgender in USA
- Lack of data quantifying differences in breast cancer incidence and outcomes
- No consensus for breast cancer screening

Considerations

- “Top” surgery ≠ prophylactic mastectomy
- Oophorectomy for risk-reduction vs gender affirmation
- Long term effect of testosterone on breast cancer risk unknown
- Unknown risk of prolonged exposure to estrogen



Conclusions

Conclusions

- Screen for HBOC by 25 (but continuously)
- Cancer risk is important but not the only consideration
- Patients must be treated holistically (they are not just BRCA!)

Thank you!

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