Hereditary Breast Cancer Syndromes: Diagnosis and Management

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DISCLOSURE DECLARATION

HEREDITARY BREAST CANCER SYNDROMES:
Diagnosis and Management

Pavan Kumar Tandra, MBBS
Dr. Tandra has disclosed the following financial relationships:
• Advisory Committee/Board in the area of breast cancer: Puma Biotechnology
The ACTIVITY CODE is: 36127

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Learning Objectives:

• Understanding the Hereditary Breast and/or Ovarian cancer syndromes (HBOCS) - risk assessment, diagnosis and management.

• Understanding the absolute risk of moderate – penetrance germ line mutations and recommendations for screening in the affected families.

• Screening recommendations for individual patients and families harboring cancer causing mutations.

• Prophylactic treatment recommendations for Hereditary Breast/Ovarian cancer Syndromes (HBOS).

• How to utilize the resources available such as genetic counselors, NCCN guidelines etc.
What are germline mutations

- Normally, every cell has 2 copies of each gene: one inherited from the mother and one inherited from the father.
- “Autosomal dominant” means that only one copy of the mutated (altered) gene sufficient to cause the condition.
- “Autosomal recessive” means that a person needs two copies of the mutated gene to have the condition. In this pattern, people with one normal and one mutated gene are called “carriers”. Carriers do not have any signs or symptoms of the condition, but they can still pass on the gene to offspring.

Hereditary cancer syndromes:

classified by mutations associated with an increased risk for certain cancers (high penetrance phenotype) and transmission to offspring through the mother and/or father.

Penetrance refers to the probability of a clinical condition (phenotype) developing in the presence of a specific genotype.

**Known high-penetrance mutations:**
BRCA1/2 (HBOCS), TP53 (LFS) & PTEN (Cowdren syndrome or multiple Hamartoma syndrome)- “Care takers” or Tumor Suppressor Genes.

**Moderate-Penetrance mutations:**
ATM, BRIPT, CDH1, CHEK2, NBN, PALB2, RAD51C, RAD51D, and STK11(PJS).
[Genes that warrant additional screening beyond what is recommended in the general population (ie, those without the specific gene mutation)].

HBOCS: Hereditary Breast and Ovarian Cancer Syndrome.
LFS: Li Fraumeni Syndrome.
PJS: Peutz Jeghers Syndrome.
NCCN Clinical Practice Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

- serves as a resource for healthcare providers to identify individuals who may benefit from cancer risk assessment and genetic counseling.
- Provide genetic counselors with an updated tool for the assessment of individual breast and ovarian cancer risk and to guide decisions related to genetic testing; and
- Facilitate a multidisciplinary approach in the management of individuals at increased risk for hereditary breast and/or ovarian cancer (HBOC).


Hereditary Breast and Ovarian Cancer Syndrome (HBOCS)

The diagnosis of BRCA1 and BRCA2 HBOCS is established in a “proband” by identification of a heterozygous germline pathogenic variant in BRCA1 or BRCA2 on molecular genetic testing.

BRCA1- and BRCA2-associated HBOCS is characterized by an increased risk for female and male breast cancer, ovarian cancer (includes fallopian tube and primary peritoneal cancers), and to a lesser extent other cancers such as prostate cancer, pancreatic cancer, and melanoma primarily in individuals with a BRCA2 pathogenic variant.

The exact cancer risks differ slightly depending on whether HBOCS is caused by a BRCA1 or BRCA2 pathogenic variant.
Inheritance:

- Germline pathogenic variants in *BRCA1* and *BRCA2* are inherited in an autosomal dominant manner, which means the offspring have a 50% chance of inheriting the variant.

- The vast majority of individuals with a *BRCA1* or *BRCA2* pathogenic variant have inherited it from a parent.

- However, because of incomplete penetrance, variable age of cancer development, cancer risk reduction resulting from prophylactic surgery, or early death, not all individuals with a *BRCA1* or *BRCA2* pathogenic variant have a parent affected with cancer.
Patients with h/o Br.Ca- NCCN recommendations for BRCA1/2 testing. At least one criteria.

- First BrCa diagnosis less than 46 years of age.
- First BrCa diagnosis less than 51 years of age PLUS at least one CBR with BrCa (any age) or PanCa (any age) or PrCa.
- First BrCa at any age with at least one CBR with BrCa diagnosed at 50 years or younger.
- First BrCa at any age with at least two CBRs with BrCa, PanCa or PrCa at ANY age.
- Two BrCa primaries at the same time or at different times (bilateral or two clearly separate breast cancer primaries) if the first event was diagnosed less than 51 years of age.
- Triple negative breast cancer diagnosis less than 61 years of age.
- Family history of male breast cancer at any age or ovarian cancer (including fallopian and primary peritoneal cancers) at any age.

Abbreviations: BrCa: Breast cancer; PanCa: Pancreatic Cancer; PrCa: Prostate Cancer; CBR: Closed blood relatives; 1st degree CBR: parent, sibling or child; 2nd degree CBR: grand parents, grand children, uncles, aunts, nephews, nieces, and half siblings; 3rd degree CBR: great-grand parents, great-grand children, great uncles/aunts, and first cousins.

Patients with NO h/o Br.Ca- NCCN recommendations for BRCA1/2 testing. At least one criteria.

Known high penetrance mutations in family (BRCA1 & 2, TP53 and PTEN) OR

- A Closed Blood Relative with ANY of the following:
  - Any known cancer susceptibility genetic mutation within the family.
  - First- or second-degree relative with BrCa less than 46 years.
  - Two or more BrCa primaries in a single family member
  - Two or more individuals with BrCa primaries on the same side of family with at least one diagnosed less than 51 years.
  - Ovarian/fallopian tube or primary peritoneal cancer or Male BrCa.
  - Family history of three or more of the following (especially if early onset and can include multiple primary cancers in same individual):
    - Breast, Pancreatic cancer, Prostate cancer (Gleason score ≥7), Melanoma, Sarcoma, Adrenocortical carcinoma, Brain tumors, Leukemia, Diffuse gastric cancer, Colon cancer, Endometrial cancer, Thyroid cancer, Kidney cancer, Dermatologic manifestations and/or macrocephaly, Hamartomatous polyps of GI tract.
Start with a “good” family history of cancers.....to identify “at-risk” individuals and families in the community.

Do you have ANY history of cancers in family? (open question)

If the answer is yes, details about the relation- maternal or paternal, first degree, second degree or third degree relative, age of onset of cancer, how it was detected- screening or symptomatic, what symptoms did the patient experience which led to the diagnosis of cancer, primary or metastatic, treatment given (chemotherapy, radiation, surgery or combined), sidedness (example: colon cancer), unilateral or bilateral (ex: breast cancer), synchronous or metachronous, exposure to carcinogens (example: smoking, alcohol, drugs etc), alive or dead and mode of dying- from incurable cancer or from other co-morbidities.

If the answer is No, still ask closed questions to confirm a negative family history of cancers.

Risk assessment using history:

Elements that increase risk:

• Family history, Increasing age & Ethnicity/race (Ashkenazi Jewish)
• Lifestyle factors such as Increased body mass index (BMI), Alcohol consumption, current or prior estrogen and progesterone hormones.
• Reproductive history: Younger age at menarche, Nulliparity/Lower parity, Older age at first live birth & Older age at menopause
• Other : History of lobular carcinoma in situ (LCIS), Atypical hyperplasia (ductal and lobular) or Flat epithelial atypia (FEA). Number of prior breast biopsies, Mammographic breast density & Prior thoracic radiation therapy (RT) <30 y of age

Elements that decrease risk:

• Prior oophorectomy before age 45 years.
• Prior risk-reducing therapy
• Exercise
• Breastfeeding
Additional risk assessment

- The modified Gail Model (NCI Breast Cancer Risk Assessment Tool) is a computer-based version and may be obtained through the NCI website (http://www.cancer.gov/bcrisktool/Default.aspx).

- There are circumstances in which the Gail Model underestimates risk for development of breast cancer, for instance, BRCA1/2 carriers and those with a strong family history of breast cancer or family history of ovarian cancer in the maternal or paternal family lineage or non-white women or women with atypical hyperplasia, making them appear to be ineligible for risk-reducing therapy.

- The Claus, BRCAPRO, Tyrer-Cuzick, and BOADICEA models may be particularly helpful in determining risk for breast cancer in women with a strong family history of breast, ovarian, or other cancers.

How to check for BRCA1/2

- Targeted analysis can be considered in individuals of Ashkenazi Jewish ancestry by starting with targeted testing for three BRCA1 and BRCA2 pathogenic founder variants: BRCA1 c.68_69delAG (BIC: 185delAG) BRCA1 c.5266dupC (BIC: 5382insC), and BRCA2 c.5946delT (BIC: 6174delT), which together account for up to 99% of pathogenic variants identified in individuals of Ashkenazi Jewish ancestry.

- If no pathogenic variant is identified by targeted analysis, it may be appropriate to proceed with sequence and deletion/duplication analyses of BRCA1 and BRCA2 or a multi gene panel.
How to check for BRCA1/2 cont…

In a family known to have a BRCA1 or BRCA2 germline pathogenic variant, at-risk adults may be tested for the family-specific germline pathogenic variant. In most cases, relatives at risk need only be tested for the family-specific germline pathogenic variant, except in the following situations:

- Individuals of Ashkenazi Jewish heritage should consider testing for all three founder germline pathogenic variants because of the high population frequency of these founder pathogenic variants as well as reports of the coexistence of more than one founder germline pathogenic variant in some families.
- Individuals with a familial BRCA1 or BRCA2 pathogenic variant on one side of the family and characteristics of HBOC on the other side of the family may consider sequence analysis and deletion/duplication.

Risk Management Recommendations for “High-Penetrance” Genes associated with HBOCS(BRCA1 & 2).
Woman desires risk reducing therapy and Life expectancy ≥10 years:

- Life style modification
- Breast cancer screening (regular): Mammograms and MRI together.
- Tamoxifen (pre and post menopausal)
- Raloxifen (post menopausal only)- long term, less efficacious than Tamoxifen, but still preferred for osteopenic patients.
- Aromatase inhibitors: Anastrozole and Exemestane (not FDA approved)

Risk Reducing mastectomy (RRM) and Risk reducing bilateral salpingo-oophorectomy (RRSO):

- Risk-reducing mastectomy should be considered in women with a genetic mutation conferring a high risk for breast cancer, compelling family history, or possibly with prior thoracic RT at <30 years of age.
- Data have supported a protective effect of bilateral oophorectomy, although NOW there are conflicting reports that challenge that observation.
- Currently, we still recommend evaluation by a gynecologist and consideration of RRSO for BRCA1 &2 young women.

Risk Management Recommendations for “Moderate-Penetrance” Genes associated with HBOCS.

Consideration and adoption of an absolute-risk approach as proposed by Tung et al.

Screening:

- Screening with mammography for moderately penetrant genetic mutations for breast cancer (i.e. ATM, CHEK2 and NBN) should begin when the "estimated 5-year risk of developing breast cancer exceeds 1%", consistent with recommendations for the average-risk population.

- Likewise, breast MRI screening in these carriers should begin when the "estimated 5-year risk of developing breast cancer exceeds 2.2%". It is reasonable to begin MRI and mammographic screening at the same time.

- It is important to note that the age at which breast screening is recommended may be impacted by the presence of risk factors such as family history of breast cancer, especially early-onset breast cancer.
Risk reduction bilateral mastectomy (RRM):

- There is currently insufficient evidence to recommend RRM in carriers of moderately penetrant genetic mutations, although this option may be considered and discussed in the context of a personal or family history of breast cancer.

Risk-reducing Salpingo-oophorectomy (RRSO):

- There is no proven screening modality for ovarian cancer. Obstetricians sometimes consider 6 monthly CA125, ultrasound and pelvic exams for some high-risk patients.
- There is insufficient evidence to recommend a specific age at which RRSO should be considered in carriers of moderately penetrant genetic mutations associated with ovarian cancer (i.e., BRIP1, RAD51C, RAD51D).
- The decision to perform RRSO should NOT be made lightly, given the impact of premature menopause.
- Tung et al. argued that RRSO should NOT be considered until a woman’s “expected lifetime risk of developing ovarian cancer exceeds 2.6%”, which is the expected lifetime risk of a woman with a BRCA-negative family history of ovarian cancer.
- A discussion about risk-reducing surgery may be initiated earlier if there is a family history of early-onset ovarian cancer.
**Risk Management Recommendations for “LOW-Penetrance” Genes associated with HBOCS.**

Consideration and adoption of an absolute-risk approach as proposed by Tung et al.


- Lower penetrance genes that may be included as part of multigene testing, but for which there is currently insufficient evidence of an association with breast and/or ovarian cancer, include: BARD1, FANCC, MRE11A, MUTYH heterozygotes, REQL, RAD50, RET1, SLX4, SMARCA4, and XRCC2.

- Risk management recommendations for these genes should take into account family history and other clinical factors.
Specific Gene Mutations and their risk of breast/ovarian/other cancers/other manifestations

ATM (ataxia-telangiectasia mutated ) mutations

- 1% of patients with early stage breast cancer had ATM mutation in a study.
- Estimated relative risk of 2.8 (90% CI, 2.2–3.7; P<.001)
  (based on a meta-analysis of three cohort studies of relatives with ATM)
- A meta-analysis including 5 studies showed that ATM mutation carriers have a 38% lifetime risk of developing breast cancer, with carriers of the c.7271T>G missense mutation having a 69% risk of developing breast cancer by age 70 years.
- An analysis of 27 families in which pathogenic ATM variants were identified showed an association between the c.7271T>G variant and increased risk of breast cancer (hazard ratio [HR], 8.0; 95% CI, 2.3–27.4; P<.001).
NCCN recommendations for ATM:

- Annual mammogram for women with a mutated ATM gene beginning at age 40 years, with consideration of annual breast MRI. RRM may also be considered based on family history.

- Given the association between ATM and development of the autosomal recessive condition ataxia telangiectasia, counseling for carriers of ATM mutations should include a discussion of reproductive options.

- Results of the case-control WECARE study suggested that radiation exposure may be associated with increased risk of contralateral breast cancer in women who are carriers of rare ATM missense variants predicted to be deleterious.

- However, a meta-analysis including five studies showed that radiation therapy (with conventional dosing) is not contraindicated in patients with a heterozygous ATM mutation.

- Therefore, there is currently insufficient evidence to recommend AGAINST radiation therapy in women who are carriers diagnosed with cancer.

BRIP1 (BRCA1 Interacting Protein C-terminal Helicase 1)

- A Fanconi anemia gene that works with BRCA1 to repair damaged DNA.

- 1.4% of patients had a mutation in the BRIP1 (observational study of 1915 unselected ovarian cancer cases)

- UK Ovarian Cancer Screening Study (UKFOCSS) showed that BRIP1 is associated with an increased risk for ovarian cancer (P<.001), with the relative risk (RR) for invasive epithelial ovarian cancer being 11.22 (95% CI, 3.22–34.10; P<.001) and 14.09 for high-grade serous disease (95% CI, 4.04–45.02; P<.001).

- An Icelandic case control study of Icelandic also showed an association between BRIP1 and increased risk of ovarian cancer (odds ratio [OR], 8.13; 95% CI, 4.74–13.95; P<.001).

- The cumulative lifetime risk of developing ovarian cancer by age 80 years in BRIP1 mutation carriers is estimated to be 5.8% (95% CI, 3.6–9.1).
NCCN recommendations for BRIP1 carriers

- Tung et al argued that RRSO should not be considered in these mutation carriers until their cumulative risk exceeds that of a woman with a first-degree relative with a non–BRCA-related ovarian cancer (~2.64%). For BRIP1 mutation carriers, this would be around age 50 to 55 years.

- However, some women may have additive risk factors (e.g., multiple family members with ovarian cancer, lack of parity), and delaying the discussion of RRSO until age 50 years may miss some cases of early-onset ovarian cancer.

NCCN Panel recommendations:

- RRSO in BRIP1 mutation carriers be considered beginning at age 45 to 50 years.
- BRIP1 is not believed to be significantly associated with increased risk of breast cancer.
- BRIP1 is associated with Fanconi anemia, inherited in an autosomal recessive manner. Therefore, counseling for carriers of BRIP1 mutations should include a discussion of reproductive options.

CDH1 (Cadherin 1) Mutations

For CDH1 gene carriers, lifetime risk for Hereditary Diffuse Gastric Cancer (HDGC) is estimated to be 67% to 70% for men and 56% to 83% for women by age 80. A cumulative lifetime risk for lobular breast cancer is 39% to 52% by age 80.

Current NCCN recommendations:

- Given the considerable risk for lobular breast cancer in women with a CDH1 mutation, the panel recommends screening with annual mammogram (or consideration of breast MRI) beginning at age 30 years.
- Screening may be considered earlier in patients with a family history of early-onset breast cancer.
- The option of RRM should be discussed for these carriers.
- Surgical resection of stomach. If patients refuse, consider annual endoscopy with multiple (more than 30) mucosal biopsies.
CHEK2 (cell cycle checkpoint kinase 2) Mutations:

- In a study of BRCA-negative patients with breast cancer, who have a strong family history of breast or ovarian cancer, a CHEK2 mutation was detected in 8%. Higher frequency in Northern and Eastern European countries.

- The cumulative lifetime risk for breast cancer in women with CHEK2 mutations and familial breast cancer has been estimated to range from approximately 28% to 37%.

- Studies investigating the association between breast cancer risk and specific CHEK2 variants have primarily been based on the truncating variant 1100delC (Copenhagen General Population Study, The CHEK2 Breast Cancer Case-Control Consortium of Europe and Australia).

- Results from a meta-analysis including 18 case-control studies (26,336 cases and 44,219 controls) showed that the missense variant I157T is associated with increased risk of breast cancer (OR, 1.58; 95% CI, 1.42–1.75; \( P \)<.001).

NCCN recommendations:

- The panel recommends annual mammogram beginning at age 40 years for women with a mutated CHEK2 gene, with consideration of annual breast MRI.

- Forty years was chosen by the panel based on risk data that only takes into account frameshift mutations such as 1100delC.

- There are no data on the benefit of RRM for women with CHEK2 mutations, but this procedure may be considered based on family history.
**NBN (Nibrin gene) Mutations**

- Women with heterozygous *NBN* mutations are at increased risk of developing breast cancer (OR, 3.1, 95% CI, 1.4–6.6; *P*=.004).

- A meta-analysis including 7 studies showed a significant association between the variant 657del5 and breast cancer risk (OR, 2.42; 95% CI, 1.54–3.80).

- An analysis of women with breast cancer in Poland (N=562) showed that this founder mutation is associated with early-onset breast cancer (OR, 8.36; 95% CI, 2.57–27.27; *P*<.001).

**NCCN recommendations:**

- The panel recommends annual mammogram for women with a mutated *NBN* gene beginning at age 40 years, with consideration of annual breast MRI.

- This recommendation is based primarily on data derived from the Slavic truncating mutation 657del5.

- There are no data on the benefit of RRM for women with *NBN* mutations, but this procedure may be considered based on family history.

- The *NBN* gene is associated with development of the autosomal recessive condition “Nijmegen breakage syndrome”. Therefore, counselling for carriers of *NBN* mutations should include a discussion of reproductive options.
NF1 (Neurofibromatosis 1) Mutations

Autosomal Dominant. Increased risk of malignant peripheral nerve sheath tumors (PNST), other central nervous system tumors, and gastrointestinal stromal tumors (GIST).

- **Finland population study of 1,404 patients with NF1:**
  An estimated lifetime cancer risk of 59.6% and a significant association between NF1 and an increased risk of breast cancer (standardized incidence ratio [SIR], 3.04; 95% CI, 2.06–4.31; \( P < .001 \)).
  Excess incidence was highest in women younger than age 40 years (SIR, 11.10; 95% CI, 5.56–19.50; \( P < .001 \)).

- **English population based study of 848 patients with NF1:**
  An increased risk of breast cancer (SIR, 3.5; 95% CI, 1.9–5.9), especially among women younger than 50 years (SIR, 4.9; 95% CI, 2.4–8.8) and cumulative lifetime risk of developing breast cancer by age 50 years was 8.4% in this sample.

**NCCN recommendations:**

- Given the increased risk of early-onset breast cancer in these mutation carriers, annual breast screening with mammography should begin at age 30 years.
- Screening with breast MRI could also be considered. A prospective United Kingdom study showed that breast cancer risk in these mutation carriers is not significantly increased at age 50 years and beyond.
- Case-control analyses revealed that relative risk (RR) estimates for women aged 30 to 39 years was 6.5 (95% CI, 2.6–13.5);
  aged 40 to 49 years, it was 4.4 (95% CI, 2.5–7.0). RR estimates then decrease for women aged 50 to 59 years (RR, 2.6; 95% CI, 1.5–4.2), and continue to decrease as age increases (RR, 1.9; 95% CI, 1.0–3.3 for age 60–69 years, and RR, 0.8; 95% CI, 0.2–2.2 for age 70–79 years).
- Therefore, breast MRI screening in patients with NF1 may be discontinued at age 50 years.
- There are no data regarding the benefit of RRM. Therefore, RRM is not recommended in these patients, but this procedure may be considered based on family history.
**PALB2 Mutations**

- **PALB2** (partner and localizer of **BRCA2**) is a Fanconi anemia gene. 1% to 3% of women with Br Ca harbor a pathogenic **PALB2** mutation.

- Relative risk of 5.3 (90% CI, 3.0–9.4) (based on a meta-analysis of 3 studies).

- Br Ca **risk increases with age**, with 14% lifetime risk by age 50 years and a 35% lifetime risk by age 70 years.

- **Risk also increases with increasing number of relatives affected.** (No first-degree relative: 33% BrCa risk by age 70 years Vs 58% in those with 2 first-degree relatives)

- **Contralateral Br Ca was reported in 10% of **PALB2** carriers** (Polish study of patients with Br Ca). This study also showed that the 10-year survival rate among **PALB2** carriers with breast cancer was 48%, compared with 72% in **BRCA1** mutation carriers and 76% in non-carriers (P<.001). Further, 10-year survival among those with tumors ≥2 cm was substantially worse (32.4%) than those with tumors <2 cm (82.4%; HR, 7.04; 95% CI, 2.47–20.07; P<.001).

**NCCN recommendations:**

- The panel recommends annual mammogram for **PALB2** mutation carriers **beginning at age 30 years**, because this is the age when the average 5-year risk of breast cancer in these mutation carriers exceeds 1%.

- Breast MRI screening may also be considered, as well as RRM.

- Though some studies suggest that there may be an association between **PALB2** and increased ovarian cancer risk, there is currently insufficient evidence to consider RRSO in these mutation carriers.

- **PALB2** is associated with Fanconi anemia, inherited in an autosomal recessive manner. Therefore, counseling for carriers of **PALB2** mutations should include a discussion of reproductive options.
**RAD51C and RAD51D Mutations:**

- Genes in the RAD51 protein family are involved in homologous recombination and DNA repair. RAD51C and RAD51D have been shown to be associated with an increased risk of ovarian cancer.

- The cumulative risk of developing ovarian cancer in carriers of a **RAD51C mutation does not approach 2.6%** (ie, the expected lifetime risk of a woman with a first-degree relative with ovarian cancer) until age 60 to 64 years, with a cumulative risk of 1.5% between the ages of 55 and 59 years. In carriers of a **RAD51D mutation**, the cumulative risk approaches 2.6% around age 50 to 54 years.

**NCCN recommendations:**

- The panel recommends that RRSO in RAD51C and RAD51D mutation carriers be considered beginning at age 45 to 50 years. As with BRIP1 mutations, large prospective trials are needed to make a firm age recommendation regarding when a discussion about RRSO should begin in RAD51C and RAD51D mutation carriers.

- There is currently insufficient evidence that mutations in RAD51C and RAD51D are associated with increased risk of breast cancer. Therefore, carriers of these gene mutations are advised to follow guidelines for women at average risk of developing breast cancer.

- RAD51C is associated with Fanconi anemia, inherited in an autosomal recessive manner. Therefore, counseling for carriers of RAD51C mutations should include a discussion of reproductive options.
MLH1, MSH2, MSH6, PMS2, and EPCAM Mutations (Lynch Syndrome)

- Women with Lynch syndrome are at increased risk of endometrial and ovarian cancers (up to 60% and 24%, respectively). Total abdominal hysterectomy and/or bilateral salpingo-oophorectomy are options that may be considered for risk reduction in women who have completed childbearing and carry a MLH1, MSH2, MSH6, PMS2, or EPCAM mutation.

- No clear evidence supports routine screening for gynecologic cancers in these mutation carriers. Annual endometrial sampling and routine transvaginal ultrasound plus serum CA-125 testing are not endorsed because they have not been shown to be sufficiently sensitive or specific, but there may be circumstances in which these tests may be helpful.

- Some studies have suggested that female MLH1 mutation carriers may be at increased risk for breast cancer, with one study estimating an 18.6% cumulative risk to age 70 years (95% CI, 11.3–25.9). However, not enough evidence currently exists for the panel to recommend breast screening for women with Lynch syndrome beyond that which is recommended for the average-risk population.

STK11 Mutations

- Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder characterized by gastrointestinal polyps, mucocutaneous pigmentation, and elevated risk for gastrointestinal cancers as well as breast or non-epithelial ovarian cancers.

- Breast cancer risk in women with Peutz-Jeghers syndrome is 8% at age 40 years, 13% at age 50 years, 31% at age 60 years, and 45% at age 70 years.

NCCN recommendations:

- There are no data on the benefit of RRM for women with STK11 mutations. Therefore, RRM is not recommended in these patients, but this procedure may be considered based on family history.
**BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS**

The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
</table>
| ATM  | Increased risk of BC  
Screening: Annual mammogram and consider breast MRI with contrast starting at age 40 y  
RMM: Counsel based on family history | No increased risk of OC | Unknown or insufficient evidence for pancreas or prostate cancer |
| BRCA1 | Increased risk of BC  
Screening: No increased risk of OC | No increased risk of OC | Considered for risk of autosomal recessive condition in offspring. |
| BRCA2 | Increased risk of BC  
Screening: No increased risk of OC | No increased risk of OC | Considered for risk of autosomal recessive condition in offspring. |
| BRIP1 | Increased risk of BC  
Screening: No increased risk of OC | No increased risk of OC | Considered for risk of autosomal recessive condition in offspring. |
| CHEH | Increased risk of BC  
Screening: No increased risk of OC | No increased risk of OC | Considered for risk of autosomal recessive condition in offspring. |
| BCR1 | Increased risk of BC  
Screening: No increased risk of OC | No increased risk of OC | Considered for risk of autosomal recessive condition in offspring. |

**continued**

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</table>
| PALB2 | Increased risk of BC  
Screening: Annual mammogram and consider breast MRI with contrast at age 30 y  
RMM: Counsel based on family history | Unknown or insufficient evidence for OC risk | Unknown or insufficient evidence |
| PTEN | Increased risk of BC  
Screening: No increased risk of OC | No increased risk of OC | Considered for breast MRI at age 30 y  
RMM: Counsel based on family history |
| RAD51C | Increased risk of BC  
Screening: No increased risk of OC | No increased risk of OC | Considered for breast MRI at age 30 y  
RMM: Counsel based on family history |
| RAD50 | Increased risk of BC  
Screening: No increased risk of OC | No increased risk of OC | Considered for breast MRI at age 30 y  
RMM: Counsel based on family history |
| STK11 | Increased risk of BC  
Screening: GCN Guidelines for Genetic/Familial High-Risk Assessment  
Colon/Rectum | Increased risk of non-penetrant OC  
Screening: GCN Guidelines for Genetic/Familial High-Risk Assessment  
Colon/Rectum | Considered for breast MRI at age 30 y  
RMM: Counsel based on family history |
| TP53 | Increased risk of BC  
Screening: No increased risk of OC | No increased risk of OC | Considered for breast MRI at age 30 y  
RMM: Counsel based on family history |

**continued**
Summary:

- Taking a good history, risk assessment using available tools and identifying "at risk individuals in the clinic" is essential.
- Risk reduction strategy (either medical or surgical) is very important to reduce the risk of patients and families.
- Counseling and drawing pedigree charts by genetic counselors to identify "other" hereditary cancer syndromes is important before offering the "right" multi gene testing.
- The evidence supporting risk management recommendations for mutations in genes of moderate, low, and uncertain penetrance is continuing to evolve, and it is important for these recommendations to reflect the current evidence base.

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If you have questions, please contact Sara Weber.
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www.unmc.edu/cce/outreach