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# Breast and Ovarian Cancer Susceptibility Gene Testing, Prophylactic Mastectomy, and Prophylactic Oophorectomy

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## Policy History

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## Policy

### Scope of Policy

This Clinical Policy Bulletin addresses breast and ovarian cancer susceptibility gene testing, prophylactic mastectomy, and prophylactic oophorectomy.

## Additional Information

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### I. Medical Necessity

#### A. Prophylactic Mastectomy

1. Aetna considers prophylactic mastectomy medically necessary for reduction of risk of breast cancer in any of the following categories of high-risk women:
  - a. Women diagnosed with breast cancer at 45 years of age or younger; or
  - b. Women who are at increased risk for specific mutation(s) due to ethnic background (for instance: Ashkenazi Jewish descent) and who have one or more relatives with breast cancer or epithelial ovarian cancer at any age; or
  - c. Women who carry a germline genetic mutation in the CDH1, TP53, PTEN or PALB2 genes; or
  - d. Women who possess BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing for breast and/or epithelial ovarian cancer; or
  - e. Women who received radiation treatment to the chest between ages of 10 and 30 years, such as for Hodgkin disease; or
  - f. Women with a first- or second-degree male relative with breast cancer (Note: Prophylactic removal of contralateral breast tissue is considered medically necessary in men with breast cancer.); or
  - g. Women with multiple primary or bilateral breast cancers in a first- or second-degree blood relative; or
  - h. Women with multiple primary or bilateral breast cancers; or
  - i. Women with one or more cases of epithelial ovarian cancer and one or more

- first- or second-degree blood relatives on the same side of the family with breast cancer; or
- j. Women with three or more affected first- or second-degree blood relatives on the same side of the family, irrespective of age at diagnosis; or
  - k. Women with atypical hyperplasia of lobular or ductal origin and/or lobular carcinoma in situ (LCIS) confirmed on biopsy with dense, fibronodular breasts that are mammographically or clinically difficult to evaluate.
2. A skin-sparing mastectomy is considered an acceptable alternative method of performing a medically necessary prophylactic mastectomy where there is no cancer involving the skin.
  3. A nipple-sparing mastectomy is considered an acceptable alternative of performing a medically necessary prophylactic mastectomy where there is no cancer involving the nipple-areola complex.
  4. Performance of a prophylactic mastectomy as a two-stage procedure, with an oncoplastic breast reduction followed by a prophylactic mastectomy and breast reconstruction, is considered an equally acceptable alternative to a single stage prophylactic mastectomy for women with large breasts who meet medical necessity criteria for a prophylactic mastectomy.

Aetna considers prophylactic mastectomy experimental, investigational, or unproven for all other indications (e.g., diabetic mastopathy, fibrocystic breast disease, pseudo-angiomatous stromal hyperplasia (PASH)) because its effectiveness for indications other than the ones listed above has not been established.

#### B. Prophylactic Bilateral Oophorectomy

Aetna considers prophylactic bilateral oophorectomy or salpingo-oophorectomy medically necessary in selected women with risk factors for epithelial ovarian carcinoma - including nulliparity, low parity, infertility, early menarche, late menopause, and late first pregnancy - if they meet any of the following criteria:

1. Women who are beyond child-bearing age (40 years of age or older) who have been diagnosed with an hereditary epithelial ovarian cancer syndrome based on a family pedigree constructed by a genetic counselor or physician competent in determining the presence of an autosomal dominant inheritance pattern; or
2. Women who have two first-degree relatives (e.g., mother, sister, daughter) with a history of epithelial ovarian cancer; or
3. Women with a personal history of breast cancer and at least one first-degree relative (e.g., mother, sister, daughter) with history of epithelial ovarian cancer; or
4. Women with BRCA1 or BRCA2 germline mutations confirmed by molecular susceptibility testing; or
5. Women who carry a germline genetic mutation in the BRIP1, RAD51C, RAD51D, MLH1 or MSH2 genes; or
6. Women with one first-degree relative (e.g., mother, sister, daughter) and one or more second-degree relatives (e.g., maternal or paternal aunt, grandmother, niece) with epithelial ovarian cancer.

Aetna considers prophylactic bilateral oophorectomy or salpingo-oophorectomy experimental, investigational, or unproven for all other indications (e.g., post-menopausal women with breast cancer who do not meet criteria above, regardless of whether they are on tamoxifen or aromatase inhibitors) because its effectiveness for indications other than the ones listed above has not been established.

#### C. Hysterectomy with Prophylactic Oophorectomy

The medical literature suggests that a prophylactic hysterectomy should be performed in conjunction with oophorectomy in women from families with Lynch syndrome I. However, for women from families with breast-ovarian cancer

syndrome, site-specific ovarian cancer syndrome, or a family history of epithelial ovarian cancer who choose to have prophylactic oophorectomy, the choice to have prophylactic hysterectomy in conjunction with oophorectomy depends on the women's attitudes regarding hormone replacement and the potential morbidity from the hysterectomy, either abdominally or vaginally.

D. Multigene Panel Testing for Moderate to High Penetrance Breast and/or Epithelial Ovarian Cancer Susceptibility Genes

Aetna considers germline multigene panel testing for moderate to high-penetrance breast and/or epithelial ovarian cancer susceptibility genes (must include at a minimum the high penetrance susceptibility genes for breast cancer) medically necessary once per lifetime for persons who meet one or more National Comprehensive Cancer Network (NCCN) testing criteria for high-penetrance breast cancer susceptibility genes (CRIT-2,4,5,6). Note: NCCN testing criteria for high-penetrance susceptibility genes are included in [NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Guidelines](#) (<https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1503>) (access to NCCN Guidelines is free with registration).

II. Experimental, Investigational, or Unproven

- Elective salpingectomy for ovarian cancer prevention in low hereditary risk women
- Measurement of blood lead level as marker of increased risk of ovarian cancer in BRCA1 carriers
- Prophylactic mastectomy for men with BRCA mutations or family history of breast cancer
- Prophylactic mastectomy for women with the CHEK2 gene mutation
- Testing for germline FANCG variants for predisposition to breast and ovarian cancer

III. Policy Limitations and Exclusions

A. A unilateral oophorectomy at the time of hysterectomy when both ovaries are in place is considered not medically necessary because this is considered inappropriate under current, generally accepted guidelines.

B. Breast and Ovarian Cancer Susceptibility Gene Testing:

1. Not considered medically necessary for individuals less than 18 years of age.
2. Asymptomatic individuals with a family history that meets criteria for testing, who do not have a causative variant already identified, should not rely solely on BRCA1 or BRCA2 gene testing as the current standard of care includes moderate-high penetrance gene analysis to guide future screening and management recommendations.
3. Aetna does not cover breast and ovarian cancer gene susceptibility testing of Aetna members if testing is performed primarily for the medical management of other family members that are not covered under an Aetna benefit plan. In these circumstances, the benefit plan for the family members who are not covered by Aetna should be contacted regarding coverage of breast and ovarian cancer susceptibility gene mutation analysis and sequencing.
4. Occasionally, tissue samples from other family members who are not covered by Aetna are required to provide the medical information necessary for the proper medical care of an Aetna member. Aetna considers molecular-based testing for breast and ovarian cancer susceptibility genes and other specific heritable disorders in non-Aetna members medically necessary in relation to Aetna members when all of the following conditions are met:
  - a. The information is needed to adequately assess risk in the Aetna member; and
  - b. The information will be used in the immediate care plan of the Aetna

- member; and
- c. The non-Aetna member's benefit plan (if any) will not cover the test. A copy of the denial letter from the non-Aetna member's benefit plan must be provided.
5. Aetna may also request a copy of the certificate of coverage from the non-member's health insurance plan if:

- a. The denial letter from the non-member's insurance carrier fails to specify the basis for non-coverage; or
- b. The denial is based on a specific plan exclusion; or
- c. The genetic test is denied by the non-member's insurance carrier as not medically necessary, and the medical information provided to Aetna does not make clear why testing would not be of significant medical benefit to the non-member.

C. Aetna members may NOT be eligible under the Plan for genetic testing for breast and/or ovarian cancer susceptibility for indications or tests other than those listed above including, but may not be limited to, the following:

1. Any of the following genes BARD1, Mre11 (MRN) complex, and NBN, MUTYH (but see [CPB 140 - Genetic Testing \(./100\\_199/0140.html\)](#), for medical necessity criteria for MUTYH).
2. Overly broad multigene panels that exceed recommended genes in the Gene-A table in NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Guidelines, include RNA analysis, for pan-cancer susceptibility, or polygenic risk scores. This includes, but may not be limited to, the following:
  - a. Color Test
  - b. Invitae Multi-Cancer Panel
  - c. Invitae Multi-Cancer +RNA Panel
  - d. Invitae Hereditary Cancer Panel
  - e. Invitae Common Hereditary Cancers+RNA Panel
  - f. CancerNext
  - g. CancerNext-Expanded
  - h. myRisk Hereditary Cancer Panel
  - i. OvaNext
  - j. Single nucleotide polymorphism (SNP) genotyping tests (eg, BREVAGen, OncoVue).

#### IV. Related Policies

- [CPB 0140 - Genetic Testing \(./100\\_199/0140.html\)](#)
- [CPB 0715 - Pharmacogenetic and Pharmacodynamic Testing \(./700\\_799/0715.html\)](#)

#### Applicable CPT / HCPCS / ICD-10 Codes

CPT codes covered if selection criteria are met:

<b>Code</b>	<b>Code Description</b>
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden [FoundationOne CDx]
0102U	Hereditary breast cancer-related disorders (eg, hereditary breast

	cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication])
+0131U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure)
+0135U	Hereditary gynecological cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure)
0172U	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score
19301	Mastectomy, partial (e.g., lumpectomy, tylectomy, quadrantectomy, segmentectomy)
19303	Mastectomy, simple, complete
58150 - 58294	Hysterectomy procedures
58541 - 58554	Laparoscopy, surgical, with hysterectomy
58661	Laparoscopy surgical; with removal of adnexal structures (partial or total oophorectomy and / or salpingectomy)
58700	Salpingectomy, complete or partial, unilateral or bilateral (separate procedure) [not covered for ovarian cancer prevention in low hereditary risk women]
58720	Salpingo-oophorectomy, complete or partial, unilateral or bilateral (separate procedure)
58940	Oophorectomy, partial or total, unilateral or bilateral
81162	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81212	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer)

## gene analysis; full sequence analysis

81217	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81308	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
81433	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
88271 - 88275	Molecular cytogenetics
CPT codes not covered for indications listed in the CPB:	
0103U	Hereditary ovarian cancer (eg, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], EPCAM [deletion/duplication only])
0129U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
+0132U	Hereditary ovarian cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure)
+0133U	Hereditary prostate cancer-related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure)
+0134U	Hereditary pan cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure)
+0136U	ATM (ataxia telangiectasia mutated) (eg, ataxia telangiectasia) mRNA sequence analysis (List separately in addition to code for primary procedure)
+0137U	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
+0138U	BRCA1(BRCA1, DNA repair associated), BRCA2(BRCA2, DNA repair associated)(eg, hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
81321 - 81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis

81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
81441	Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2
81435	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4 and STK11
83655	Lead
96132 - 96133	Neuropsychological testing evaluation services by physician or other qualified health care professional, including integration of patient data, interpretation of standardized test results and clinical data, clinical decision making, treatment planning and report, and interactive feedback to the patient, family member(s) or caregiver(s), when performed
Other CPT codes related to the CPB:	
58570 - 58573	Laparoscopy, surgical, with total hysterectomy
81201, 81202, 81203	APC (adenomatous polyposis coli) (eg, familial adenomatous polyposis [FAP], attenuated FAP) gene analysis; full gene sequence, known familial variants, or duplication/deletion variants
81206, 81207, 81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative, minor breakpoint, qualitative or quantitative, or other breakpoint, qualitative or quantitative
81209	BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81228	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant

81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81245	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
81261	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)
81264	IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
81279	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81300	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81310	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg,

	hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81342	TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81400	Molecular pathology procedure, Level 1
81401	Molecular pathology procedure, Level 2
81402	Molecular pathology procedure, Level 3
81403	Molecular pathology procedure, Level 4
81404	Molecular pathology procedure, Level 5
81405	Molecular pathology procedure, Level 6
81406	Molecular pathology procedure, Level 7
81407	Molecular pathology procedure, Level 8
81408	Molecular pathology procedure, Level 9
81479	Unlisted molecular pathology procedure

Other HCPCS codes related to the CPB:

Talazoparib (Talzenna), Olaparib (Lynparza), Niraparib (Zejula), Rucaparib (Rubraca) - no specific code:

J9045	Injection, carboplatin, 50 mg
J9060	Injection, cisplatin, powder or solution, 10 mg
J9258	Injection, paclitaxel protein-bound particles (teva) not therapeutically equivalent to j9264, 1 mg
J9259	Injection, paclitaxel protein-bound particles (american regent) not therapeutically equivalent to j9264, 1 mg
J9263	Injection oxaliplatin, 0.5 mg
J9264	Injection, paclitaxel protein-bound particles, 1 mg

ICD-10 codes covered if selection criteria are met:

C25.0 - C25.9	Malignant neoplasm of pancreas
C48.0 - C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C50.011 - C50.929	Malignant neoplasm of breast [male/female]
C56.1 - C56.9	Malignant neoplasm of the ovary [epithelial]
C57.00 - C57.02	Malignant neoplasm of fallopian tube
C61	Malignant neoplasm of prostate
D05.00 - D05.92	Carcinoma in situ, breast [invasive and ductal carcinoma in situ (DCIS) is not included]
D24.1 - D24.9	Benign neoplasm of breast [pseudo-angiomatous stromal hyperplasia (PASH) - not covered for prophylactic mastectomy] [atypical hyperplasia of lobular or ductal origin]
N60.91 - N60.99	Unspecified benign mammary dysplasia [atypical hyperplasia of lobular or ductal origin]
Z15.01	Genetic susceptibility to malignant neoplasm of breast [BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing for breast cancer] [genetic mutation in the TP53 or PTEN genes (Li-Fraumeni syndrome, Cowden syndrome, and Bannayan-Riley-Ruvalcaba syndrome)]
Z15.02	Genetic susceptibility to malignant neoplasm of ovary [BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing for ovarian cancer]

Symptom Summary	
Z40.01	Encounter for prophylactic removal of breast
Z40.02	Encounter for prophylactic removal of ovary(s)
Z80.0	Family history of malignant neoplasm of digestive organs [pancreas]
Z80.3	Family history of malignant neoplasm of breast
Z80.41	Family history of malignant neoplasm of ovary [epithelial]
Z80.42	Family history of malignant neoplasm of prostate
Z84.81	Family history of carrier of genetic disease
Z85.07	Personal history of malignant neoplasm of pancreas

ICD-10 codes not covered for indications listed in the CPB:

C00.1 - C24.9, C26.0 - C47.9, C49.0 - C49.9, C51.0 - C55, C57.10 - C60.9, C62.00 - D09.9	Malignant neoplasms [other than breast, ovary, pancreas, retroperitoneum and peritoneum, breast, ovary, fallopian tube, and carcinoma in situ of breast]
N60.11 - N60.19	Diffuse cystic mastopathy [fibrocystic breast disease - not covered for prophylactic mastectomy]
Z31.448	Encounter for other genetic testing of male for procreative management [not covered without diagnosis of breast or prostate cancer]

Prophylactic breast reconstruction:

CPT codes covered if selection criteria are met:

19350	Nipple/areola reconstruction
19357	Breast reconstruction, immediate or delayed, with tissue expander, including subsequent expansion
19361	Breast reconstruction with latissimus dorsi flap, without prosthetic implant
19364	Breast reconstruction with free flap
19366	Breast reconstruction with other technique
19367	Breast reconstruction with transverse rectus abdominis myocutaneous flap (TRAM), single pedicle, including closure of donor site
19368	Breast reconstruction with transverse rectus abdominis myocutaneous flap (TRAM), single pedicle, including closure of donor site; with microvascular anastomosis (supercharging)
19369	Breast reconstruction with transverse rectus abdominis myocutaneous flap (TRAM), double pedicle, including closure of donor site

Other CPT codes related to the CPB:

0129U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
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ICD-10 codes covered if selection criteria are met:

C50.011 - C50.929	Malignant neoplasm of breast
C79.81	Secondary malignant neoplasm of breast
D05.00 - D05.92	Carcinoma in situ of breast
N60.11 - N60.19	Diffuse cystic mastopathy [severe fibrocystic disease]
Z15.01	Genetic susceptibility to malignant neoplasm of breast [BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing for breast cancer] [genetic mutation in the TP53 or PTEN genes (Li-Fraumeni syndrome, Cowden syndrome, and Bannayan-Riley-Ruvalcaba syndrome)][not covered for CHEK2 gene mutation]

Z80.3	Family history or malignant neoplasm of breast
Z85.3	Personal history of malignant neoplasm of breast
Z90.10 - Z90.13	Acquired absence of breast [following medically necessary mastectomy or lumpectomy resulting in significant deformity]

## Background

### Breast and Ovarian Cancer Susceptibility Gene Testing

#### Breast and Ovarian Cancer Susceptibility Gene Testing Documentation Requirements

An "Aetna Breast and Ovarian Cancer Susceptibility Gene Testing Prior Authorization Form" for Breast and Ovarian Cancer Susceptibility Gene Molecular Testing is to be sent along with the Laboratory's Test Requisition Form to Aetna for precertification. Documentation of specific cancer diagnosis in the proband(s) and pertinent medical records may be required prior to authorization. A summary indicating how this testing will change the immediate medical care of the member must also be included with the Prior Authorization request.

Note on Breast and Ovarian Cancer Susceptibility Gene Test Authorization Workflow: In order to facilitate proper administrative support for coverage of laboratory testing, the following workflow should be complied with for all breast and ovarian cancer susceptibility gene testing requests:

When a member's physician believes that testing is an integral component for their medical care:

- The member's provider (primary care physician [PCP] -- medical internist, family practitioner, or gynecologist) documents the family history with special attention to breast and ovarian cancer. Generally, information such as prior pathology reports, physicians' notes, and a formal 3-generation pedigree are required to confirm the family history.
- Genetic counseling as to the appropriateness of the testing may be performed by the PCP or the PCP can authorize counseling by an appropriate participating specialist (e.g., medical geneticist).
- When testing is medically indicated, the Aetna Breast and Ovarian Cancer Susceptibility Gene Prior Authorization Form is completed by the provider, confirming the basis for high-risk status (the form can be obtained from Aetna by calling 877-794-8720).
- A copy of the Breast and Ovarian Cancer Susceptibility Gene Prior Authorization Form is then submitted to the requesting Laboratory along with the Laboratory's test requisition form. The blood specimen should not be tested by the Laboratory until confirmation of coverage is received and the test is precertified.
- Both the Laboratory and Aetna will confirm member eligibility and then perform the appropriate testing requested once eligibility is determined.
- If the member does not meet the pre-determined criteria, the member's physician will be contacted with a review of the clinical information provided by the physician.

Post-test results counseling can be authorized by the PCP when appropriate.

Aetna's policy on breast and ovarian cancer susceptibility gene testing of women with breast cancer is based on the guidelines from the National Comprehensive Cancer Network.

Hereditary breast cancer is characterized by multiple family members with a history of pre-menopausal breast cancer. In some families, hereditary breast cancer can be additionally associated with an increased risk for ovarian cancer. Mutations in 2 highly penetrant autosomal dominant genes, BRCA1 and BRCA2 (BRCA stands for BR Breast CAncer), have been identified; these mutations are thought to be responsible for an estimated 5 to 7% of all breast and ovarian cancers. A woman from a high-risk family who inherits a BRCA1 mutation has a greater than 80% lifetime risk of developing breast cancer and an estimated 45% risk of developing ovarian cancer by the age of 70. It is estimated that as many as 1 in 200 women may harbor a BRCA mutation.

Approximately 80% of families with multiple cases of early-onset female breast cancer have the BRCA1 gene mutation. The presence of a BRCA1 mutation is associated with an increased risk of ovarian cancer.

Patients are assigned to categories based upon their pre-test probability of having a BRCA mutation, with a less than 10 % probability considered as low-risk, a 10 to 25 % probability considered as moderate risk, and a greater than 25 % probability being considered as high-risk (USPSTF, 2005). American Society of Clinical Oncology guidelines (2006) state that a woman with greater than 10% likelihood of carrying a deleterious BRCA mutation (based on family history and ethnic background) should be offered genetic testing. BRCA1 and BRCA2 mutation analysis (and, if necessary, gene sequencing) is primarily indicated in women who are at high-risk of hereditary breast or ovarian cancer, including women with a family history of breast or ovarian cancer and women with 1 or more relatives who are known to have a mutation in the BRCA1 or BRCA2 genes.

There is some evidence to suggest that men with BRCA2 mutations are at increased risk of developing cancers of the breast and prostate. It has been estimated that approximately 6 % of men who are positive for BRCA2 will develop breast cancer by the age of 70 (Wolpert et al, 2000). In addition, there is some evidence that suggests that men who are BRCA-positive are at moderately increased risk for prostate cancer. In addition, BRCA testing of a man with breast cancer may be necessary to assess the breast cancer risk of a female blood relative.

Before a physician orders BRCA analysis, it is essential that the patient undergo adequate education and counseling because molecular susceptibility testing raises important medical, psychological, and social issues for patients and their families. The educational process, "genetic counseling", which is a covered benefit in all Aetna products and is often accomplished using trained genetic counselors or medical geneticists, should include the following:

1. Alternatives to molecular susceptibility testing;
2. Clarification of the patient's increased risk status;
3. Counseling regarding therapeutic options; including discussions which address the limitations of these options;
4. Explanation of how genetics affects cancer susceptibility;
5. Limited data regarding efficacy of methods for early detection and prevention;
6. Possible outcomes of testing (e.g., positive, negative, or uncertain test results);
7. Possible psychological and social impact of testing;
8. Potential benefits, risks, alternatives, and limitations of testing.

Performing BRCA screening on an unaffected member in a high-risk family, without knowing the genetic status of the mutation(s) in the family, may sometimes lead to difficulties in interpreting the BRCA screening results. Although a positive test in a high-risk family is usually consistent with increased risk in the individual being screened, a negative test might not necessarily be reassuring. A negative test could be due to lack of inheritance of a BRCA1 or BRCA2 abnormality (true negative), due

to testing an inappropriate gene (false negative). In some cases, false-positive results can arise due to the presence of a clinically insignificant polymorphism in one of the BRCA genes.

The 3 types of clinical testing for BRCA1 and BRCA2 (BRCA1/2) are full gene sequencing, a panel for the founder mutations common in the Ashkenazi Jewish population, and a mutation-specific assay. For persons of Ashkenazi Jewish descent, available guidelines state that the most efficient strategy is to first screen for the 3 common founder mutations, which are present in approximately 3% of the general Ashkenazi Jewish population and account for about 90% of all identified BRCA mutations among Jewish women.

According to established guidelines, if the woman is found to be negative for the founder mutations, then further testing is not considered necessary unless she has other characteristics that place her in a high risk category. If the woman has other characteristics placing her into the high-risk category, she may still carry a rare BRCA mutation that is not detected, so that full gene sequencing is considered necessary to detect a rare BRCA1/2 mutation. By sequencing the entire BRCA1/2 genes, the test is potentially able to identify mutations along the entire length of the gene.

If a specific BRCA mutation is detected in the family member affected by breast cancer (the index case), established guidelines indicate that unaffected family members can be tested for this single mutation using a mutation-specific assay, a highly specific test that only looks for a specific mutation unique to their family.

The U.S. Preventive Services Task Force released a recommendation that primary care physicians should not routinely refer all women for genetic counseling and DNA testing to detect the presence of specific BRCA1 and BRCA2 gene mutations that may be associated with breast or ovarian cancers. However, if a woman has certain specific family history patterns that put her at risk for these gene mutations, her PCP should suggest counseling and possible DNA testing.

Several tools have been developed to guide PCPs in assessing risk and guiding referral: the Family History Risk Assessment Tool (FHAT), the Manchester scoring system, and the Risk Assessment in Genetics (RAGs) tool (USPSTF, 2005; Nelson et al, 2005). The sensitivity and specificity of FHAT for a clinically important BRCA1 or BRCA2 mutation were 94% and 51%, respectively. The Manchester scoring system was developed in the United Kingdom to predict deleterious BRCA1 or BRCA2 mutations at the 10 % likelihood level and had an 87 % sensitivity and a 66% specificity (Evans et al, 2004). The RAGs tool (Emery et al, 1999; Emery et al, 2000), a computer program designed to support assessment and management of family breast and ovarian cancer in primary care settings, is used to assign patients to categories of low-risk (less than 10%), moderate-risk (10 % to 25%), and high-risk (greater than 25%). Primary care clinicians can then manage recommendations of re-assurance, referral to a breast clinic, or referral to a geneticist on the basis of the patient's respective risk categories (USPSTF, 2005).

Guidelines from the U.S. Preventive Services Task Force state that several quantitative tools to predict risk for deleterious BRCA mutations have been developed from data on previously tested women. These risk tools include the Myriad Genetic Laboratories model, the Couch model, BRCAPRO, the Penn Model, the Yale Model, and the Tyrer model (Nelson et al., 2005; Marroni et al, 2004). The USPSTF noted that much of the data used to develop the models are from women with existing cancer, and their applicability to asymptomatic, cancer-free women in the general population is unknown.

Available evidence suggests that current models for predicting BRCA mutation may tend to over-estimate risk when family history is adequate and under-estimate risk when family history is limited. Researchers have speculated that, in young women with limited family structures (e.g., fewer than 2 women who survived past age 45 in either parental lineage), the genetic models that are used to predict carrier status would under-estimate the prevalence of BRCA mutations. Weitzel et al (2007) sought to determine if BRCA gene mutations are more prevalent among single cases of early onset breast cancer in families with limited versus adequate family structure than would be predicted by 3 currently available probability models, the Couch, Myriad, and BRCAPRO models. The investigators studied 306 women who had breast cancer before age 50 years and no 1st- or 2nd-degree relatives with breast or ovarian cancers. The investigators found that about 50% of these women had limited family structure, defined as fewer than 2 1st- or 2nd-degree female relatives surviving beyond age 45 years in either lineage. The mean probability of identifying a BRCA mutation in the study cohort was 20.4% based on the Couch model, 8.0% based on the Myriad model, and 7.3% based on the BRCAPRO model. These probabilities were not dependent on whether participants had limited or adequate family structures. However, when BRCA gene sequences were determined, deleterious mutations were identified in 13% of women with limited family structures versus only 5.2% of women with adequate family structure ( $p = 0.02$ ). Participants with limited family history were 2.8 times more likely to be carriers of BRCA gene mutations than women with adequate family history ( $p = 0.02$ ). These investigators concluded that family structure can affect the accuracy of mutation probability models. These investigators recommended making genetic testing guidelines more inclusive for single cases of breast cancer when the family structure is limited. They stated that probability models need to be created using limited family history as an actual variable.

#### Direct-to-Consumer BRCA Tests

On March 6, 2018, the U.S. Food and Drug Administration authorized 23andMe to market the Personal Genome Service Genetic Health Risk (GHR) Report for BRCA1/BRCA2 (Selected Variants). It is the first direct-to-consumer (DTC) test to report on three specific BRCA1/BRCA2 breast cancer gene mutations that are most common in people of Ashkenazi (Eastern European) Jewish descent. These three mutations, however, are not the most common BRCA1/BRCA2 mutations in the general population. It is important to note that consumers and health care professionals should not use the test results to determine any treatments, including anti-hormone therapies and prophylactic removal of the breasts or ovaries. Such decisions require confirmatory testing and genetic counseling. The test also does not provide information on a person's overall risk of developing any type of cancer. The use of the test carries significant risks if individuals use the test results without consulting a physician or genetic counselor.

The test analyzes DNA collected from a self-collected saliva sample, and the report describes if a woman is at increased risk of developing breast and ovarian cancer, and if a man is at increased risk of developing breast cancer or may be at increased risk of developing prostate cancer. The test only detects three out of more than 1,000 known BRCA mutations. This means a negative result does not rule out the possibility that an individual carries other BRCA mutations that increase cancer risk.

The three BRCA1/BRCA2 hereditary mutations detected by the test are present in about 2 percent of Ashkenazi Jewish women, according to a National Cancer Institute study, but rarely occur (0 percent to 0.1 percent) in other ethnic populations. All individuals, whether they are of Ashkenazi Jewish descent or not, may have other mutations in BRCA1 or BRCA2 genes, or other cancer-related gene mutations that are not detected by this test. For this reason, a negative test result could still mean that a person has an increased risk of cancer due to gene mutations. Additionally, most cases of cancer are not caused by hereditary gene

mutations but are thought to be caused by a wide variety of factors, including smoking, obesity, hormone use and other lifestyle issues. For all of these reasons, it is important for patients to consult their health care professional who can help them understand how these factors impact their individual cancer risk and what they can do to modify that risk.

The FDA's review of the test determined among other things that the company provided sufficient data to show that the test is accurate (i.e., can correctly identify the three genetic variants in saliva samples), and can provide reproducible results. The company submitted data on user comprehension studies, using representative GHR test reports, that showed instructions and reports were generally easy to follow and understood by a consumer. The test report provides information describing what the results might mean, how to interpret results and where additional information about the results may be found.

#### BRCA Testing for Malignant Phyllodes Tumor of the Breast

Rhiem et al (2007) noted that familial breast carcinomas that are attributable to BRCA1 or BRCA2 mutations have characteristic morphologic and immuno-histochemical features. BRCA1-associated carcinomas are poorly differentiated infiltrating ductal carcinomas frequently exhibiting morphologic features of typical or atypical medullary carcinomas such as prominent lymphocytic infiltrate and pushing margins. These investigators reported on 1 patient carrying the deleterious BRCA1 germline mutation R1699W, who presented with a malignant phyllodes tumor of the breast. The re-investigation of archival material by a reference pathologist of the German Consortium for Hereditary Breast and Ovarian Cancer (GCHBOC) revealed BRCA-associated pronounced pushing margins. In a total of 618 unrelated index patients who were registered in the GCHBOC database, no other phyllodes tumor has been described, while 10 carriers of the R1699W mutant had been identified. The authors concluded that the histopathologic appearance of the phyllodes tumor indicated an association with the BRCA1 mutation R1699W although it is a rare event in BRCA-positive families.

An UpToDate review on "Phyllodes tumors of the breast" (Grau et al, 2020) states that "Phyllodes tumors have been associated with Li-Fraumeni syndrome, a rare autosomal dominant condition that is characterized by the development of multiple tumors. No other etiologic or predisposing factors have been linked to phyllodes tumor.

Furthermore, National Comprehensive Cancer Network's clinical practice guideline on "Breast cancer" (Version 1.2021) does not mention BRCA testing for patients with phyllodes tumor.

#### Large Genomic Rearrangements

A clinical study has demonstrated a low overall prevalence of BRCA1/2 large genomic rearrangements in a cohort of patients referred for BRCA testing. Judkins, et al. (2012) reported on the prevalence of BRCA1/2 large genomic rearrangements in 48,456 patients referred for clinical molecular testing for suspicion of hereditary breast and ovarian cancer. Prevalence data were analyzed for patients from different risk and ethnic groups. Patients were designated as "high-risk" if their clinical history predicted a high prior probability, wherein large genomic rearrangement testing was performed automatically in conjunction with sequencing. "Elective" patients did not meet the high-risk criteria, but underwent large genomic rearrangement testing as ordered by the referring health care provider. Among the 25,535 high-risk patients, the prevalence of a full sequence BRCA1/2 mutation was 21.5 percent, and the prevalence of BRCA1/2 large genomic rearrangements was 2.4 percent. Among the 22,921 elective patients, the prevalence of a full sequence BRCA1/2 mutation was 7.8 percent, and the overall prevalence of BRCA1/2 large genomic rearrangements was only 0.48 percent. The

greatest prevalence of BRCA1/2 large genomic rearrangements was in the the high risk group of Latin American/ Caribbean ethnicity, with an overal rate of BRCA1/2 large genomic rearrangements of 6.7 percent. The prevalence of a large genomic rearrangements in the the elective group of Latin American/ Caribbean ethnicity was 1.8 percent. All other ethnicities in the "elective" group had prevalence rates of large genomic rearrangements ranging from 0.0 percent to 0.8 percent.

Sharifah et al (2010) noted that the incidence of breast cancer has been on the rise in Malaysia. It is suggested that a subset of breast cancer cases were associated with germline mutation in BRCA genes. Most of the BRCA mutations reported in Malaysia were point mutations, small deletions and insertions. These researchers reported the first study of BRCA large genomic re-arrangements (LGRs) in Malaysia. They aimed to detect the presence of LGRs in the BRCA genes of Malaysian patients with breast cancer. Multiplex ligation-dependent probe amplification (MLPA) for BRCA LGRs was carried out on 100 patients (60 were high-risk breast cancer patients previously tested negative/positive for BRCA1 and BRCA2 mutations, and 40 were sporadic breast cancer patients), recruited from 3 major referral centers. Two novel BRCA1 re-arrangements were detected in patients with sporadic breast cancer; both results were confirmed by quantitative PCR. No LGRs were found in patients with high-risk breast cancer. The 2 LGRs detected were genomic amplifications of exon 3 and exon 10. No BRCA2 genomic re-arrangement was found in both high-risk and sporadic breast cancer patients. The authors concluded that these findings will be helpful to understand the mutation spectrum of BRCA1 and BRCA2 genes in Malaysian patients with breast cancer. They stated that further studies involving larger samples are needed to establish a genetic screening strategy for both high-risk and sporadic breast cancer patients.

Ticha and colleagues (2010) noted that LGR represent substantial proportion of pathogenic mutations in the BRCA1 gene, whereas the frequency of re-arrangements in the BRCA2 gene is low in many populations. These investigators screened for LGRs in BRCA1 and BRCA2 genes by MLPA in 521 unrelated patients negative for BRCA1/2 point mutations selected from 655 Czech high-risk breast and/or ovarian cancer patients. Besides long range PCR, a chromosome 17-specific oligonucleotide-based array comparative genomic hybridization (aCGH) was used for accurate location of deletions. They identified 14 patients carrying 8 different LGRs in BRCA1 that accounted for 12.3% of all pathogenic BRCA1 mutations. No LGRs were detected in the BRCA2 gene. In a subgroup of 239 patients from high-risk families, these researchers found 12 LGRs (5.0%), whereas 2 LGRs were revealed in a subgroup of 282 non-familial cancer cases (0.7%). Five LGRs (deletion of exons 1 to 17, 5 to 10, 13 to 19, 18 to 22 and 21 to 24) were novel; 2 LGRs (deletion of exons 5 to 14 and 21 to 22) belong to the already described Czech-specific mutations; 1 LGR (deletion of exons 1 to 2) was reported from several countries. The deletions of exons 1 to 17 and 5 to 14, identified each in 4 families, represented Czech founder mutations. The present study indicates that screening for LGRs in BRCA1 should include patients from breast or ovarian cancer families as well as high-risk patients with non-familial cancer, in particular cases with early-onset breast or ovarian cancer. On the contrary, these analyses do not support the need to screen for LGRs in the BRCA2 gene. Implementation of chromosome-specific aCGH could markedly facilitate the design of primers for amplification and sequence analysis of junction fragments, especially in deletions over-lapping gene boundaries.

Manguoglu and associates (2011) performed the MLPA assay for detection of large re-arrangements of BRCA1 and BRCA2 genes in 16 familial, 29 early onset, 3 male breast cancer, and 2 bilateral breast/ovarian cancer high-risk Turkish index cases. The MLPA assay for all exons of both genes and for 1100delC variant of CHEK2 gene were performed. Analyses, revealed no large genomic re-arrangements in both

genes, and, no 1100del variant in CHEK2 gene. The authors concluded that these data, which represents the first results for Turkish patients, suggest that, the frequency of BRCA1 and BRCA2 genes' large re-arrangements is very low.

#### Prophylactic Mastectomy

Prophylactic total or simple mastectomy, not subcutaneous mastectomy, for patients at high-risk of breast cancer is a difficult issue in that it involves the determination of risk in an individual patient, a separate determination of what level of risk is high enough to justify the extreme choice of prophylactic mastectomy, and assurance from scientific studies in the medical literature that this procedure does result in a reduction of breast cancer occurrence. Even if the risk can be estimated, the decision to proceed with a prophylactic mastectomy will be largely patient driven, dependent on whether the patient feels comfortable living with the estimated risk and how she values the psychosexual function of the breast.

Although the definition of "high-risk" is somewhat arbitrary, the consensus of opinion is that prophylactic mastectomy may be considered only in patients at high-risk of breast cancer with a demonstrated BRCA gene mutation or a life-long risk level in excess of 25 to 30%. The patients described in the above criteria fall into this range.

BRCA1 and BRCA2 may be responsible for only 5% to 10% of all breast cancers and about 20% of breast cancers diagnosed in women under age 45. About 50% to 60% of women with inherited BRCA1 or BRCA2 mutations will develop breast cancer by the age of 70. Provisional recommendations by the Cancer Genetics Studies Consortium for follow-up of individuals with BRCA1 or BRCA2 mutations involve counseling and early breast cancer screening, including annual mammography and clinical breast examination beginning at age 25 to 35 years, and monthly breast self-examination beginning at age 18 to 21 years. A few recent studies have shown that among women who test positive for a BRCA1 or BRCA2 gene mutation, prophylactic surgery at a young age substantially improves survival.

Even among women with breast cancer in their families, the tests for BRCA1 and BRCA2 may be negative 90% of the time, unless a mutation has been previously identified in the family. A negative BRCA1 and BRCA2 test result would mean that a woman still faces the same risk as the general population of developing sporadic, non-inherited breast cancer. However, in such BRCA negative patients, other significant risk factors come into play. A personal history of invasive breast cancer or lobular carcinoma in situ increases the risk of developing a new breast cancer in any remaining breast tissue in either breast by 0.5% to 1.0% per year.

The degree of reduction of risk of breast cancer with prophylactic mastectomy is not well documented in the literature. It is clear that no surgical technique for prophylactic mastectomy removes all breast epithelium. The 2 techniques used are "subcutaneous mastectomy" and "total mastectomy". Subcutaneous mastectomy removes the breast tissue leaving the nipple/areolar complex intact in order to preserve appearance and nipple sensation. Approximately 10 to 20% of the breast epithelium remains under the areola after subcutaneous mastectomy. Because a significant proportion of breast tissue is left with the nipple by subcutaneous mastectomy, the American College of Medical Genetics has concluded that this operation is generally not indicated if mastectomy is to be done for breast cancer prevention (ACMG, 1999). Total mastectomy including nipple removal is necessary to remove the maximum amount of breast tissue (Lopez and Porter, 1996; ACMG, 1999).

Carcinoma of the male breast has many similarities to breast cancer in women, but the diseases have different genetic and pathologic features. Both BRCA1 and BRCA2 mutations can cause breast cancer in women, but only BRCA2 mutations confer a significant risk to men (Giordano et al, 2002). Although older articles have

reported that men with breast cancer have poorer survival rates than women, most recent series show that men and women have equivalent prognoses when matched for age and stage of disease (Giordano et al, 2002). Prophylactic mastectomy of the contralateral breast may be indicated in a man with breast cancer (LeBlond, 1993; Jaiyesimi et al, 1993). However, there is no published clinical data or evidence-based guidelines on prophylactic mastectomy for men with a BRCA2 mutation or a family history of breast cancer. It has been estimated that approximately 6 % of men who are positive for BRCA2 will develop breast cancer by the age of 70 (Wolpert et al, 2000). This is about equal to the risk of breast cancer in average-risk women without BRCA mutations. This difference in risk of breast cancer between BRCA-positive women and men may be due to the fact that men have much less breast tissue and serum estrogen than women.

In a skin-sparing mastectomy, the breast tissue is removed through a conservative incision made around the areola. The increased amount of skin preserved as compared to traditional mastectomy resections serves to facilitate breast reconstruction procedures. Patients with cancers that involve the skin, such as inflammatory cancer, are not candidates for skin-sparing mastectomy. Guidelines on surgery for breast cancer by the British Association for Surgical Oncology and the Royal College of Surgeons (2007) state that skin sparing mastectomy is associated with better cosmetic results. A review article in the *New England Journal of Medicine* (Cordiero, 2008) also notes that a skin sparing mastectomy provided a good cosmetic result.

Nipple-sparing mastectomy is performed in the setting of immediate reconstruction and can achieve good cosmetic results. A Canadian guideline (Alberta Health Services, 2014) concluded that: "Despite these and other studies reporting promising results with nipple-sparing mastectomy, there is currently no published data from a randomized controlled trial, on the oncologic safety of nipple-sparing, as compared to conventional skin-sparing mastectomy. Therefore, nipple-sparing mastectomy is generally not recommended for patients with malignancy but could be considered for carefully selected patients, and in patients undergoing prophylactic mastectomy, when done in conjunction with a separate biopsy of the ductal tissue directly underlying the nipple-areola complex. The decision as to whether to pursue a nipple-sparing procedure requires multidisciplinary input and careful discussion with the patient about potential additional risks associated with this approach."

Yao et al (2015) reported on a case series and a review of the literature on nipple sparing mastectomy in BRCA1/2 mutation carriers. The authors found: "Our study and other series show that nipple-sparing mastectomy (NSM) in BRCA1/2 carriers is associated with low rates of complications and locoregional recurrence that are comparable to results in non-BRCA1/2 carriers. Rates of nipple involvement, nipple recurrence, or development of new cancers in retained nipples are also low with follow-up to date, and comparable to SSMs performed in BRCA1/2 carriers. Longer follow-up of these patients is needed to determine specific locoregional recurrence rates, but results suggest that BRCA1/2 patients are eligible for NSM for both prevention and treatment of breast cancer."

An earlier systematic evidence review of observational studies found no significant differences observed when patients who received nipple-sparing mastectomy were compared to those who received non-skin sparing mastectomy (odds ratios [OR] 0.83, 95% confidence interval [CI]: 0.45 to 1.52; 2 studies, n = 401).

European Society for Medical Oncology guidelines on prophylactic mastectomy (Balmana, et al., 2011) state that "The NSM preserves the skin envelope and the nipple areola complex. Although follow-up on this procedure is still short, preliminary reports show similar failure rates with superior cosmetic results compared with the other mastectomy techniques."

Guidelines from the National Comprehensive Cancer Network (NCCN, 2014) on Breast Cancer Risk Reduction states that nipple sparing mastectomy should be considered for breast cancer risk reduction, and recommends that clinicians " [d]iscuss risks and benefits of nipple-areolar sparing surgery." "Multidisciplinary consultations are recommended prior to surgery, and should include a surgeon familiar with the natural history and therapy of benign and malignant breast disease to enable the woman to become well informed regarding treatment alternatives, the risks and benefits of surgery, nipple-sparing mastectomy, and surgical breast reconstruction options."

Wong and colleagues (2017) updated and examined national temporal trends in contralateral prophylactic mastectomy (CPM) and examined if survival differed for invasive breast cancer patients based on hormone receptor status and age. These investigators identified women diagnosed with unilateral stage I to III breast cancer between 1998 and 2012 within the Surveillance, Epidemiology, and End Results registry. They compared characteristics and temporal trends between patients undergoing breast-conserving surgery, unilateral mastectomy, and CPM. These researchers then performed Cox proportional-hazards regression to examine breast cancer-specific survival (BCSS) and overall survival (OS) in women diagnosed between 1998 and 2007, who underwent breast-conserving surgery with radiation (breast-conserving therapy), unilateral mastectomy, or CPM, with subsequent subgroup analysis stratifying by age and hormone receptor status. Of 496,488 women diagnosed with unilateral invasive breast cancer, 59.6% underwent breast-conserving surgery, 33.4% underwent unilateral mastectomy, and 7.0% underwent CPM. Overall, the proportion of women undergoing CPM increased from 3.9% in 2002 to 12.7% in 2012 ( $p < 0.001$ ). Reconstructive surgery was performed in 48.3% of CPM patients compared with only 16.0% of unilateral mastectomy patients, with rates of reconstruction with CPM rising from 35.3% in 2002 to 55.4% in 2012 ( $p < 0.001$ ). When compared with breast-conserving therapy, these researchers found no significant improvement in BCSS or OS for women undergoing CPM (BCSS: HR 1.08, 95% CI: 1.01 to 1.16; OS: HR 1.08, 95% CI: 1.03 to 1.14), regardless of hormone receptor status or age. The authors concluded that the use of CPM more than tripled during the study period despite evidence suggesting no survival benefit over breast conservation. They stated that further examination on how to optimally counsel women about surgical options is needed.

#### Atypical Ductal Hyperplasia

Prpic et al (1992) stated that the majority of benign breast disorders may be classified as developmental and involutive. Mastalgia and breast nodularity represent the greatest groups of these disorders, while epithelial hyperplasia is a complex benign disorder that is most difficult to be evaluated. A total of 60 women with diagnosis of cyclic mastalgia and 30 with non-cyclic breast pain were followed-up. Patients were administered bromocryptine, danazol or a local progestogel. Better treatment results were achieved in cyclic mastalgia than in women with non-cyclic mastalgia; 145 biopsies of the benign breast tissue were examined histologically. Non-proliferative forms were found in 66.9% of the women, proliferative without atypia in 29.65%, and proliferative with atypia in 3.45% of the patients. The authors concluded that atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) increased 4- to 5-fold the risk for breast cancer. However, they stated that prophylactic subcutaneous or total mastectomy is not as a rule indicated in atypical epithelial hyperplasia, only regular follow-up is required.

Hartmann et al (2015) noted that "NCCN guidelines state that bilateral prophylactic mastectomy should generally be considered only for women who have a genetic predisposition to breast cancer or possibly those who have been treated with thoracic radiation before 30 years of age or who have a history of lobular carcinoma in situ. The Society of Surgical Oncology recognizes atypical hyperplasia as a possible but not routine indication for bilateral prophylactic mastectomy. In one

small, retrospective study, atypical hyperplasia was the indication for the procedure in 11 of 46 patients (24%) who had not undergone BRCA testing and were undergoing risk-reduction surgery. In current practice, with minimal data available on this topic and with chemopreventive agents for risk reduction available, atypical hyperplasia is generally not an indication for prophylactic mastectomy”.

Furthermore, an UpToDate review on “Atypia and lobular carcinoma in situ: High risk lesions of the breast” (Sable and Collins, 2016) states that “Atypical hyperplasia (AH) includes both atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH). ADH is usually found as the target lesion on biopsy of mammographic microcalcifications whereas ALH is usually an incidental finding on breast biopsies performed for other reasons (e.g., abnormal mammogram, breast mass) .... If AH is diagnosed on an excisional biopsy, no additional surgery is indicated. Even if the atypical hyperplasia extends to the margins, as long as the area was adequately sampled, re-excision is not recommended. Instead, attention should be directed towards risk reduction .... Breast cancer surveillance is performed for all women known to be at an increased risk of breast cancer (e.g., positive family history of breast cancer, atypical hyperplasia, LCIS) as well as those at population risk .... Most experts consider prophylactic bilateral mastectomy too drastic for the moderate level of risk associated with LCIS in the absence of other contributory risk factors (e.g., family history premenopausal breast cancer)”. The review does not mention prophylactic mastectomy for atypical ductal hyperplasia.

#### Pseudo-Angiomatous Stromal Hyperplasia (PASH)

An UpToDate review on “Overview of benign breast disease” (Sable, 2016) states that “Pseudoangiomatous stromal hyperplasia -- Pseudoangiomatous stromal hyperplasia (PASH) is a benign stromal proliferation that simulates a vascular lesion. PASH may present as a mass or thickening on physical examination. The most common appearance on mammography and ultrasound is a solid, well-defined, non-calcified mass. The characteristic histologic appearance is a pattern of slit-like spaces in the stroma between glandular units. PASH can be confused with mammary angiosarcoma. If there are any suspicious features on imaging, the diagnosis of PASH on a core biopsy should not be accepted as a final diagnosis, and excisional biopsy should be performed. However, in the absence of suspicious imaging characteristics, a diagnosis of PASH at core biopsy is considered sufficient, and surgical excision is not always necessary. There is no increased risk of subsequent breast cancer associated with PASH”. The review does not mention prophylactic mastectomy as a management option.

#### Prophylactic Bilateral Oophorectomy

Prophylactic bilateral oophorectomy has been recommended for women at high-risk of ovarian cancer. The term “hereditary ovarian cancer syndrome” refers to 3 rare cancer syndromes, which occurs in approximately 5% of all ovarian cancers. These are: (i) breast-ovarian cancer syndrome, (ii) site-specific cancer syndrome, and (iii) hereditary non-polyposis colorectal cancer syndrome (Lynch syndrome I). Breast-ovarian syndrome occurs in families with clusters of women with ovarian cancer and/or breast cancer. Site-specific ovarian cancer syndrome occurs in families with clusters of ovarian cancer. Lynch syndrome I is a familial cancer syndrome characterized by an inherited predisposition to the development of the early onset (usually ages 40 to 50) of adenocarcinomas of the colon with proximal colonic predominance, ovary, pancreas, breast, bile duct, cervix, endometrium, and of the urologic (most commonly ureter and renal pelvis) and gastrointestinal systems. The lifetime probability of ovarian cancer increases from about 1.6% in a 35-year old woman without a family history of ovarian cancer to about 5% if she has 1 relative and 7% if she has 2 relatives with ovarian cancer. Out of those patients who have a positive family history, 3 to 9% may end up having hereditary cancer syndromes. Epithelial ovarian cancer, the most common histopathologic type, is uncommon in women

before the age of 40. The incidence rates then increase steeply until a woman reaches her 70s, then decrease somewhat. About 7% of women with ovarian cancer report a family history of ovarian cancer, and of these women, over 90% have only 1 relative with ovarian cancer.

There is no patient at greater risk of developing ovarian cancer than a woman in direct genetic lineage of a family with hereditary ovarian cancer syndrome. The probability of a hereditary ovarian cancer syndrome in a family pedigree increases with the number of affected relatives, with the number of affected generations, and with young age of onset of disease. Women suspected of having a hereditary ovarian cancer syndrome should have a family pedigree constructed by a physician or genetic counselor competent in determining the presence of an autosomal dominant inheritance pattern. The number of observed ovarian cancer-affected generations in ovarian cancer syndromes ranges from 2 to 4 per family. The sisters and daughters of a woman from a family with an ovarian cancer syndrome may have a lifetime probability as high as 50% of developing ovarian cancer. The mean age for ovarian cancer onset is 59 years for the general population, while that for various hereditary ovarian cancer syndromes is 52 years for breast-ovary, 49 years for site-specific ovary, and 45 years for Lynch I cases.

Screening for ovarian cancer is notoriously difficult in contrast to the much easier and more proven value of screening for breast cancer. As the lifetime risk of ovarian cancer in patients with hereditary ovarian cancer syndromes is sufficiently high to outweigh any possible morbidity from oophorectomy, early surgical menopause, or hormone replacement therapy, prophylactic (bilateral) oophorectomy is an indicated procedure to all women from these high-risk families after completion of childbearing or the age of 35 to 40 years, at the latest. This recommendation is based also on the reported early disease onset in these patients. It is apparent from the available literature that the younger the age of women undergoing prophylactic oophorectomy, the more beneficial the effects of breast cancer risk reduction.

Observational studies have shown that women who have BRCA1 or BRCA2 mutations have higher risks for both ovarian cancer and breast cancer, and that prophylactic oophorectomy reduces the risk of both types of cancer. In a prospective follow-up study, researchers enrolled 170 eligible women (age of 35 or older) with BRCA mutations who were referred for genetic counseling at Memorial Sloan-Kettering Cancer Center during 6 years. A total of 98 women underwent bilateral prophylactic oophorectomy, and 72 chose surveillance (mean follow-up of 24 months). Among women who selected surveillance, breast cancer was diagnosed in 8, ovarian cancer in 4, and peritoneal cancer in 1. Among women who underwent prophylactic oophorectomy, breast cancer was identified subsequently in 3 and peritoneal cancer in 1; 3 early-stage ovarian cancers were found at surgery. The investigators reported that the hazard ratio (HR) for the development of breast or BRCA-related gynecologic cancer after oophorectomy was 0.25.

In a retrospective multi-center study, 6 of 259 BRCA-positive women were found to have stage I ovarian cancer at the time of prophylactic oophorectomy, and 2 subsequently developed peritoneal carcinomas. Among 292 matched controls who didn't undergo prophylactic surgery, 58 were diagnosed with ovarian cancer during a mean follow-up of 8.8 years. Thus, oophorectomy reduced the subsequent risk for ovarian or peritoneal cancer by 96%. In a subgroup analysis to determine breast-cancer risk, 21 of 99 women who underwent oophorectomy developed breast cancer compared with 60 of 142 controls (risk reduction, 53%).

Prophylactic oophorectomy, as the sole surgical procedure, is not indicated under accepted guidelines for women without a BRCA mutation or a family history of ovarian cancer. However, prophylactic mastectomy may be performed in conjunction with another operative procedure that allows access to the pelvic

organs. The decision on prophylactic oophorectomy as a concurrent procedure remains controversial and should depend on the individual patient and her ability to comply with lifelong estrogen therapy.

Rebbeck et al (2009) stated that risk-reducing salpingo-oophorectomy (RRSO) is widely used by carriers of BRCA1 or BRCA2 (BRCA1/2) mutations to reduce their risks of breast and ovarian cancer. To guide women and their clinicians in optimizing cancer prevention strategies, these investigators summarized the magnitude of the risk reductions in women with BRCA1/2 mutations who have undergone RRSO compared with those who have not. All reports of RRSO and breast and/or ovarian or fallopian tube cancer in BRCA1/2 mutation carriers published between 1999 and 2007 were obtained from a PubMed search. Hazard ratio estimates were identified directly from the original articles. Pooled results were computed from non-overlapping studies by fixed-effects meta-analysis. A total of 10 studies investigated breast or gynecologic cancer outcomes in BRCA1/2 mutation carriers who had undergone RRSO. Breast cancer outcomes were investigated in 3 non-overlapping studies of BRCA1/2 mutation carriers, 4 of BRCA1 mutation carriers, and 3 of BRCA2 mutation carriers. Gynecologic cancer outcomes were investigated in 3 non-overlapping studies of BRCA1/2 mutation carriers and 1 of BRCA1 mutation carriers. Risk-reducing salpingo-oophorectomy was associated with a statistically significant reduction in risk of breast cancer in BRCA1/2 mutation carriers ( $HR = 0.49$ ; 95% confidence interval [CI]: 0.37 to 0.65). Similar risk reductions were observed in BRCA1 mutation carriers ( $HR = 0.47$ ; 95% CI: 0.35 to 0.64) and in BRCA2 mutation carriers ( $HR = 0.47$ ; 95% CI: 0.26 to 0.84). Risk-reducing salpingo-oophorectomy was also associated with a statistically significant reduction in the risk of BRCA1/2-associated ovarian or fallopian tube cancer ( $HR = 0.21$ ; 95% CI: 0.12 to 0.39). Data were insufficient to obtain separate estimates for ovarian or fallopian tube cancer risk reduction with RRSO in BRCA1 or BRCA2 mutation carriers. The authors concluded that the summary estimates presented here indicated that RRSO is strongly associated with reductions in the risk of breast, ovarian, and fallopian tube cancers and should provide guidance to women in planning cancer risk reduction strategies.

Domchek et al (2010) estimated risk and mortality reduction stratified by mutation and prior cancer status. Prospective, multi-center cohort study of 2,482 women with BRCA1 or BRCA2 mutations ascertained between 1974 and 2008 were included in this study, which was conducted at 22 clinical and research genetics centers in Europe and North America to assess the relationship of risk-reducing mastectomy or salpingo-oophorectomy with cancer outcomes. The women were followed-up until the end of 2009. Main outcome measures were breast and ovarian cancer risk, cancer-specific mortality, and overall mortality. No breast cancers were diagnosed in the 247 women with risk-reducing mastectomy compared with 98 women of 1,372 diagnosed with breast cancer who did not have risk-reducing mastectomy. Compared with women who did not undergo RRSO, women who underwent salpingo-oophorectomy had a lower risk of ovarian cancer, including those with prior breast cancer (6% versus 1%, respectively; HR, 0.14; 95% CI: 0.04 to 0.59) and those without prior breast cancer (6% versus 2%; HR, 0.28 [95% CI: 0.12 to 0.69]), and a lower risk of first diagnosis of breast cancer in BRCA1 mutation carriers (20% versus 14%; HR, 0.63 [95% CI: 0.41 to 0.96]) and BRCA2 mutation carriers (23% versus 7%; HR, 0.36 [95% CI: 0.16 to 0.82]). Compared with women who did not undergo RRSO, undergoing salpingo-oophorectomy was associated with lower all-cause mortality (10% versus 3%; HR, 0.40 [95% CI: 0.26 to 0.61]), breast cancer-specific mortality (6% versus 2%; HR, 0.44 [95% CI: 0.26 to 0.76]), and ovarian cancer-specific mortality (3% versus 0.4%; HR, 0.21 [95% CI: 0.06 to 0.80]). The authors concluded that among a cohort of women with BRCA1 and BRCA2 mutations, the use of risk-reducing mastectomy was associated with a lower risk of breast cancer; RRSO was associated with a lower risk of ovarian cancer, first diagnosis of breast cancer, all-cause mortality, breast cancer-specific mortality, and ovarian cancer-specific mortality.

The American College of Obstetricians and Gynecologists' guidelines on "Hereditary breast and ovarian cancer syndrome" (ACOG, 2009) stated that "risk-reducing salpingo-oophorectomy should be offered to women with BRCA1 or BRCA2 mutations by age 40 or after the conclusion of child-bearing".

Also, an UpToDate review on "Risk-reducing bilateral salpingo-oophorectomy in women at high risk of epithelial ovarian and fallopian tubal cancer" (Muto, 2013) states that "For women with BRCA mutations who have completed childbearing, we recommend rrBSO [risk-reducing bilateral salpingo-oophorectomy] rather than ovarian or fallopian tubal cancer screening or chemoprevention. For premenopausal women with Lynch syndrome who have completed childbearing, we suggest rrBSO rather than ovarian cancer screening or chemoprevention. Women who wish to avoid the risks of surgery and premature menopause and who understand the risk of ovarian cancer and the limitations of ovarian cancer screening may reasonable choose ovarian cancer screening. Women with Lynch syndrome should also undergo hysterectomy due to their markedly increased risk of endometrial cancer".

#### **Elective Salpingectomy for Ovarian Cancer Prevention in Low Hereditary Risk Women**

Walker et al (2015) stated that mortality from ovarian cancer may be dramatically reduced with the implementation of attainable prevention strategies. The new understanding of the cells of origin and the molecular etiology of ovarian cancer warrants a strong recommendation to the public and health care providers. These researchers discussed potential prevention strategies, which include: (i) oral contraceptive use, (ii) tubal sterilization, (iii) risk-reducing salpingo-oophorectomy in women at high hereditary risk of breast and ovarian cancer, (iv) genetic counseling and testing for women with ovarian cancer and other high-risk families, and (v) salpingectomy after child-bearing is complete (at the time of elective pelvic surgeries, at the time of hysterectomy, and as an alternative to tubal ligation). The authors stated that the Society of Gynecologic Oncology has determined that recent scientific breakthroughs warranted a new summary of the progress toward the prevention of ovarian cancer. This review was intended to emphasize the importance of the fallopian tubes as a potential source of high-grade serous cancer in women with and without known genetic mutations in addition to the use of oral contraceptive pills to reduce the risk of ovarian cancer.

Furthermore, based on the current understanding of ovarian carcinogenesis and the safety of salpingectomy, the ACOG (2015) supports the following recommendations and conclusions:

- The surgeon and patient should discuss the potential benefits of the removal of the fallopian tubes during a hysterectomy in women at population risk of ovarian cancer who are not having an oophorectomy.
- When counseling women about laparoscopic sterilization methods, clinicians can communicate that bilateral salpingectomy can be considered a method that provides effective contraception.
- Prophylactic salpingectomy may offer clinicians the opportunity to prevent ovarian cancer in their patients.
- Randomized controlled trials are needed to support the validity of this approach to reduce the incidence of ovarian cancer.

An UpToDate review on "Management of patients with hereditary and/or familial breast and ovarian cancer" (Isaaacs and Peshkin, 2016) states that "The only proven risk-reducing procedure for ovarian cancer in BRCA mutation carriers is bilateral salpingo-oophorectomy [BSO]. However, there is controversy about whether it is appropriate to perform a salpingectomy alone for BRCA mutation carriers who wish to defer oophorectomy, based upon a possible fallopian tube origin for some ovarian cancers. The Society of Gynecology Oncology (SGO) Clinical Practice Statement opens with the statement: "Salpingectomy may be appropriate

and feasible as a strategy for ovarian risk reduction". However, the statement and a lengthier explication make clear that this procedure does not eliminate the risk of ovarian cancer, and it does not reduce the risk of breast cancer. Guidelines from the National Comprehensive Cancer Network thus indicate that "salpingectomy alone is not the standard of care and is discouraged outside a clinical trial". Until there are sufficient data from randomized control trials or prospective studies to support salpingectomy as an effective risk-reducing procedure for BRCA mutation carriers, we recommend against salpingectomy without an oophorectomy for these women".

Kapurubandara et al (2015) stated that recent evidence supports the fallopian tube as the site of origin for many pelvic serous cancers (PSC) including epithelial ovarian cancers (EOC). As a result, a change in practice with opportunistic bilateral salpingectomy (OBS) at the time of hysterectomy has been advocated as a preventative strategy for PSC in a low-risk population. These investigators evaluated current clinical practice in Australia with respect to OBS during gynecological surgery for benign indications. An anonymous online survey was sent to all active Royal Australian and New Zealand College of Obstetrics and Gynecology (RANZCOG) Fellows in Australia. Data regarding clinician demographics and the proportion of clinicians offering OBS were collected. Reasons for and against offering or discussing OBS were sought. A descriptive analysis was performed. The response rate was 26% (280/1,490) with 70% of respondents offering or discussing OBS to women undergoing gynecological surgery for benign indications, usually at the time of abdominal (96%) or laparoscopic (76%) hysterectomy. The main reason for offering or discussing OBS was current evidence to suggest the fallopian tubes as the site of origin for most EOC. Main reasons for not offering OBS were insufficient evidence to benefit the woman (36%) or being unaware of recent evidence (33%). The authors concluded that the survey responses indicated that OBS is frequently discussed or offered in Australia, usually at the time of hysterectomy. They stated that given the lack of robust evidence to suggest a benefit at a population-based level, a national registry is recommended to monitor outcomes.

Chene and colleagues (2016) noted that since the recent evidence of a tubal origin of most ovarian cancers, opportunistic salpingectomy could be discussed as a prophylactic strategy in the general population and with hereditary predisposition. These researchers surveyed French gynecological surgeons about their current surgical practice of prophylactic salpingectomy. An anonymous online survey was sent to French obstetrician-gynecologists and gynecological surgeons. There were 13 questions about their current clinical practice and techniques of salpingectomy during a benign hysterectomy or as a tubal sterilization method, salpingectomy versus salpingo-oophorectomy in the population with genetic risk, salpingectomy in relationship with endometriosis and questions including histopathological considerations. Among the 569 respondents, opportunistic salpingectomy was always performed between 42.48% and 43.44% during laparoscopic, laparoscopic-assisted vaginal or laparotomic hysterectomy and only 12.26% in case of vaginal route. In the genetic population, salpingo-oophorectomy was mainly performed. Tubal sterilization was often practiced by the hysteroscopic route. More than 90% of respondents didn't perform salpingectomy in case of endometriosis. There was not any specific tubal histopathological protocol in 71.54% of cases. The authors concluded that salpingectomy may be a preventing strategy in the low- and high-risk population. The survey's responses showed that salpingectomy appeared to be a current practice during benign hysterectomy for more than 40% doctors. However, there was not any change with no more salpingectomy in the population with genetic risk, or in case of endometriosis or tubal sterilization.

Furthermore, National Comprehensive Cancer Network's clinical practice guideline on "Ovarian cancer" (Version 1.2016) stated that "The prevention benefit of salpingectomy alone are not yet proven".

Cancer predisposing genes can be categorized according to their relative risk of a particular type of cancer. High-penetrant genes are associated with a cancer relative risk higher than 5. Low-penetrant genes are presented with relative risk around 1.5, whereas moderate-penetrant genes confer relative cancer risks from 1.5 to 5. Rare moderate-penetrant genes are CHEK2, ATM, BRIP1, and PALB2 (KCE, 2015). Recent data suggest that the penetrance of PALB2 may be higher than reported before and that BRIP may be associated with increased risk of ovarian cancer only. The clinical implications of moderate-risk genes remain unclear. This has been attributed to the fact that moderate risk breast cancer susceptibility genes typically are encountered in a polygenic setting, meaning that several common low-risk breast cancer susceptibility alleles together confer increased breast cancer risks. When they do operate in a monogenic setting, their functional or clinical impact could be low (KCE, 2015).

Aloraifi and colleagues (2015) noted that several "moderate-risk breast cancer susceptibility genes" have been conclusively identified. Pathogenic mutations in these genes are thought to cause a 2- to 5-fold increased risk of breast cancer. In light of the current development and use of multi-gene panel testing, these researchers estimated the cancer risk associated with loss-of-function mutations within these genes. An electronic search was conducted to identify studies that sequenced the full coding regions of ATM, CHEK2, BRIP1, PALB2, NBS1, and RAD50 in a general and gene-targeted approach. Inclusion was restricted to studies that sequenced the germline DNA in both high-risk cases and geographically matched controls. A meta-analysis was then performed on protein-truncating variants (PTVs) identified in the studies for an association with breast cancer risk. A total of 10,209 publications were identified, of which 64 studies comprising a total of 25,418 cases and 52,322 controls in the 6 interrogated genes were eligible under the study's selection criteria. The pooled ORs for PTVs in the susceptibility genes were at least greater than 2.6. Furthermore, mutations in these genes have shown geographic and ethnic variation. The authors concluded that the finding of this comprehensive study emphasized the fact that caution should be taken when identifying certain genes as moderate susceptibility with the lack of sufficient data, especially with regard to the NBS1, RAD50, and BRIP1 genes. They stated that further data from case-control sequencing studies, and especially family studies, are needed.

Winship and Southey (2016) noted that inherited predisposition to breast cancer is explained only in part by mutations in the BRCA1 and BRCA2 genes. Most families with an apparent familial clustering of breast cancer who are investigated through Australia's network of genetic services and familial cancer centers do not have mutations in either of these genes. More recently, additional breast cancer predisposition genes, such as PALB2, have been identified. New genetic technology allows a panel of multiple genes to be tested for mutations in a single test. This enables more women and their families to have risk assessment and risk management, in a preventive approach to predictable breast cancer. Predictive testing for a known family-specific mutation in a breast cancer predisposition gene provides personalized risk assessment and evidence-based risk management.

Breast cancer predisposition gene panel tests have a greater diagnostic yield than conventional testing of only the BRCA1 and BRCA2 genes. However, the clinical validity and utility of some of the putative breast cancer predisposition genes is not yet clear. The authors stated that ethical issues warrant consideration, as multiple gene panel testing has the potential to identify secondary findings not originally sought by the test requested; multiple gene panel tests may provide an affordable and effective way to investigate the heritability of breast cancer.

Thompson and colleagues (2016) stated that gene panel sequencing is revolutionizing germline risk assessment for hereditary breast cancer. Despite scant evidence supporting the role of many of these genes in breast cancer

predisposition, results are often reported to families as the definitive explanation for their family history. These investigators evaluated the frequency of mutations in 18 genes included in hereditary breast cancer panels among index cases from families with breast cancer and matched population controls. Cases (n = 2,000) were predominantly breast cancer-affected women referred to specialized Familial Cancer Centers on the basis of a strong family history of breast cancer and BRCA1 and BRCA2 wild type. Controls (n = 1,997) were cancer-free women from the LifePool study. Sequencing data were filtered for known pathogenic or novel loss-of-function mutations. Excluding 19 mutations identified in BRCA1 and BRCA2 among the cases and controls, a total of 78 cases (3.9%) and 33 controls (1.6%) were found to carry potentially actionable mutations. A significant excess of mutations was only observed for PALB2 (26 cases, 4 controls) and TP53 (5 cases, 0 controls), whereas no mutations were identified in STK11. Among the remaining genes, loss-of-function mutations were rare, with similar frequency between cases and controls. The authors concluded that the frequency of mutations in most breast cancer panel genes among individuals selected for possible hereditary breast cancer is low and, in many cases, similar or even lower than that observed among cancer-free population controls. They noted that although multigene panels can significantly aid in cancer risk management and expedite clinical translation of new genes, they equally have the potential to provide clinical misinformation and harm at the individual level if the data are not interpreted cautiously.

Young and associates (2016) noted that moderate-risk genes have not been extensively studied, and missense substitutions in them are generally returned to patients as variants of uncertain significance lacking clearly defined risk estimates. The fraction of early-onset breast cancer cases carrying moderate-risk genotypes and quantitative methods for flagging variants for further analysis have not been established. These researchers evaluated rare missense substitutions (rMS) identified from a mutation screen of ATM, CHEK2, MRE11A, RAD50, NBN, RAD51, RINT1, XRCC2 and BARD1 in 1,297 cases of early-onset breast cancer and 1,121 controls via scores from Align-Grantham Variation Grantham Deviation (GVGD), combined annotation dependent depletion (CADD), multivariate analysis of protein polymorphism (MAPP) and PolyPhen-2. They also evaluated subjects by polygenotype from 18 breast cancer risk SNPs. From these analyses, these investigators estimated the fraction of cases and controls that reach a breast cancer OR of greater than or equal to 2.5 threshold. Analysis of mutation screening data from the 9 genes revealed that 7.5% of cases and 2.4% of controls were carriers of at least 1 rare variant with an average OR of greater than or equal to 2.5. 2.1% of cases and 1.2% of controls had a polygenotype with an average OR of greater than or equal to 2.5. The authors concluded that among early-onset breast cancer cases, 9.6% had a genotype associated with an increased risk sufficient to affect clinical management recommendations. Over 2/3 of variants conferring this level of risk were rMS in moderate-risk genes. Placement in the estimated OR of greater than or equal to 2.5 group by at least 2 of these missense analysis programs should be used to prioritize variants for further study; panel testing often creates more heat than light; quantitative approaches to variant prioritization and classification may facilitate more efficient clinical classification of variants.

The authors also stated that "Our analysis raised additional questions regarding standard clinical genetic testing practices using panel tests. For the established moderate-risk genes ATM, CHEK2 and NBN, the majority of the pathogenic variants that the test can actually detect are rMS, likely to be reported to patients as variants of uncertain significance (VUS), and likely to be normalized during counselling. In this circumstance, how does one answer the clinical validity question, "Are the variants the test is intended to identify associated with disease risk, and are these risks well quantified?" What is the impact on studies intended to explore the penetrance and tumor spectrum of pathogenic variants in these genes if the studies focus on T+SJVs even though these may represent a minority of the pathogenic variants? One path forward lies in a more nuanced use of the IARC 5-

class system for variant classification and reporting to incorporate more data from ongoing research on missense substitution evaluation. From work that defined the sequence analysis-based prior probabilities of pathogenicity for rMS in BRCA1, BRCA2 and the mismatch repair genes, one can clearly define subsets of rMS that have relatively high probabilities of pathogenicity. A straightforward approach for clinicians could be to make systematic efforts to enroll carriers of high probability of pathogenicity rMS in research studies, such as those coordinated through the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) consortium, while still describing these findings to patients as VUS. For BRCA1, BRCA2 and the mismatch repair genes, these could be defined as rMS with prior probabilities of pathogenicity of  $\geq 0.66$  as defined at the calibrated prior probability of pathogenicity websites ([priori.hci.utah.edu/PRIORS/index.php](http://priori.hci.utah.edu/PRIORS/index.php) and [hci-lovd.hci.utah.edu/home.php](http://lovd.hci.utah.edu/home.php), respectively). rMS from the nine genes examined here that are placed in an OR  $\geq 2.5$  grouping by two or more of the missense analysis programs similarly fall into a relatively high probability of pathogenicity subset. VUS with lower probabilities of pathogenicity could reasonably be normalized since future reclassification to a clearly pathogenic variant is rather unlikely. Such an approach would better prioritize those missense substitutions with high probabilities of pathogenicity, leading to better understanding of these VUS by clinicians and patients. This approach should empower research towards gene validation, penetrance and tumor spectrum and thereby address the question of clinical validity in the future".

Lynce and Isaacs (2016) stated that the traditional model by which an individual was identified as harboring a hereditary susceptibility to cancer was to test for a mutation in a single gene or a finite number of genes associated with a particular syndrome (e.g., BRCA1 and BRCA2 for hereditary breast and ovarian cancer or mismatch repair genes for Lynch syndrome). The decision regarding which gene or genes to test for was based on a review of the patient's personal medical history and their family history. With advances in next-generation DNA sequencing technology, offering simultaneous testing for multiple genes associated with a hereditary susceptibility to cancer is now possible. These panels typically include high-penetrance genes, but they also often include moderate- and low-penetrance genes. A number of the genes included in these panels have not been fully characterized either in terms of their cancer risks or their management options. Another way some patients are unexpectedly identified as carrying a germline mutation in a cancer susceptibility gene is at the time they undergo molecular profiling of their tumor, which typically has been carried out to guide treatment choices for their cancer. The authors focused on the issues that need to be considered when deciding between recommending more targeted testing of a single or a small number of genes associated with a particular syndrome (single/limited gene testing) versus performing a multigene panel. They also reviewed the issues regarding germline risk that occur within the setting of ordering molecular profiling of tumors.

The authors stated that "Although multigene panel testing provides a more comprehensive and efficient approach to testing an individual for a hereditary susceptibility to cancer, the information obtained can be challenging to interpret. Furthermore, many of the genes included in multigene panels have not been fully characterized either in terms of their cancer risks or management strategies. In many cases, single/limited gene testing remains a very appropriate testing option. Presently, we live in an era in which our technical capabilities have outstripped our medical knowledge. A strong and continuous partnership among clinicians, individuals with genetics expertise, and laboratory geneticists is critical to bridge this gap. As to the detection of incidental findings on tumor sequencing, more research is clearly necessary to better clarify how to approach this complex area. Until such time, as stated by ASCO, it is critical that individuals undergoing tumor sequencing be fully apprised of the possibility, benefits, risks, and limitations that such testing could uncover unanticipated mutations in cancer susceptibility genes".

An INESSS assessment (2016) concluded that hereditary cancer panels raises questions about surveillance for carriers of deleterious mutations, the risks of invasive interventions following the incidental discovery of mutations, the lack of recommendations for mutations in certain genes, and an increase in the detection of variants of unknown significance (VUS). The assessment noted that several questions remain regarding the management of patients with certain mutations in genes where the mutation is associated with a moderate or uncertain risk of cancer.

Individuals with a PALB2 mutation have an increased lifetime risk for breast, pancreas, and possibly other cancers. PALB2 mutations are rare intermediate-penetrance genes; women with a PALB2 mutation have a 2-4 fold increased lifetime risk of breast cancer compared to the general population risk of 12% (KCE, 2015). However, risks associated with a PALB2 mutation may be higher in persons with a family history of breast cancer. The PALB2 mutation works in conjunction with other cancer susceptibility genes to modify risk; the exact lifetime cancer risks for individuals with one mutation in this gene are not fully understood. There is a lack of adequate evidence on the clinical utility of testing for PALB2 mutations; it is not known whether enhanced surveillance or preventative measures in persons with PALB2 mutations will lead to improved health outcomes.

#### Testing for BARD1 and RAD51D Mutations for Ovarian Cancer

Loveday et al (2011) stated that recently, RAD51C mutations were identified in families with breast and ovarian cancer. This observation prompted us to investigate the role of RAD51D in cancer susceptibility. These researchers identified 8 inactivating RAD51D mutations in unrelated individuals from 911 breast-ovarian cancer families compared with one inactivating mutation identified in 1,060 controls ( $p = 0.01$ ). The association found here was principally with ovarian cancer, with 3 mutations identified in the 59 pedigrees with 3 or more individuals with ovarian cancer ( $p = 0.0005$ ). The relative risk of ovarian cancer for RAD51D mutation carriers was estimated to be 6.30 (95% confidence interval [CI]: 2.86 to 13.85,  $p = 4.8 \times 10(-6)$ ). By contrast, these investigators estimated the relative risk of breast cancer to be 1.32 (95% CI: 0.59 to 2.96,  $p = 0.50$ ). The authors concluded that these data indicated that RAD51D mutation testing may have clinical utility in individuals with ovarian cancer and their families. Moreover, they showed that cells deficient in RAD51D are sensitive to treatment with a PARP inhibitor, suggesting a possible therapeutic approach for cancers arising in RAD51D mutation carriers.

Ratajska et al (2012) stated that the breast cancer susceptibility gene BARD1 (BRCA1-associated RING domain protein, MIM# 601593) acts with BRCA1 in DNA double-strand break (DSB) repair and also in apoptosis initiation. These researchers screened 109 BRCA1/2 negative high-risk breast and/or ovarian cancer patients from North-Eastern Poland for BARD1 germline mutations using a combination of denaturing high-performance liquid chromatography and direct sequencing. They identified 16 different BARD1 sequence variants, 5 of which are novel. Three of them were suspected to be pathogenic, including a protein truncating nonsense mutation (c.1690C>T, p.Gln564X), a splice mutation (c.1315-2A>G) resulting in exon 5 skipping, and a silent change (c.1977A>G) which alters several exonic splicing enhancer motifs in exon 10 and resulted in a transcript lacking exons 2-9. The authors concluded that these findings suggested that BARD1 mutations may be regarded as cancer risk alleles and warrant further investigation to determine their actual contribution to non-BRCA1/2 breast and ovarian cancer families.

Thompson et al (2013) stated that mutations in RAD51D have been associated with an increased risk of hereditary ovarian cancer and although they have been observed in the context of breast and ovarian cancer families, the association with breast cancer is unclear. These researchers attempted to validate the reported association of RAD51D with ovarian cancer and assessed for an association with breast cancer. They screened for RAD51D mutations in BRCA1/2 mutation-negative

index cases from 1,060 familial breast and/or ovarian cancer families (including 741 affected by breast cancer only) and in 245 unselected ovarian cancer cases. Exons containing novel non-synonymous variants were screened in 466 controls. Two overtly deleterious RAD51D mutations were identified among the unselected ovarian cancers cases (0.82%) but none was detected among the 1,060 families. The authors concluded that these data provided additional evidence that RAD51D mutations are enriched among ovarian cancer patients, but are extremely rare among familial breast cancer patients.

Huang et al (2013) noted that homologous recombination mediates error-free repair of DNA double-strand breaks (DSB). RAD51 is an essential protein for catalyzing homologous recombination and its recruitment to DSBs is mediated by many factors including RAD51, its paralogs, and breast/ovarian cancer susceptibility gene products BRCA1/2. Deregulation of these factors leads to impaired DNA repair, genomic instability, and cellular sensitivity to chemotherapeutics such as cisplatin and PARP inhibitors. MicroRNAs (miRNA) are short, non-coding RNAs that post-transcriptionally regulate gene expression; however, the contribution of miRNAs in the regulation of homologous recombination is not well understood. To address this, a library of human miRNA mimics was systematically screened to pinpoint several miRNAs that significantly reduce RAD51 foci formation in response to ionizing radiation in human osteosarcoma cells. Subsequent study focused on 2 of the strongest candidates, miR-103 and miR-107, as they are frequently deregulated in cancer. Consistent with the inhibition of RAD51 foci formation, miR-103 and miR-107 reduced homology-directed repair and sensitized cells to various DNA-damaging agents, including cisplatin and a PARP inhibitor. Mechanistic analyses revealed that both miR-103 and miR-107 directly target and regulate RAD51 and RAD51D, which is critical for miR-103/107-mediated chemo-sensitization. Furthermore, endogenous regulation of RAD51D by miR-103/107 was observed in several tumor subtypes. The authors concluded that taken together, these data showed that miR-103 and miR-107 over-expression promoted genomic instability and may be used therapeutically to chemo-sensitize tumors.

UpToDate reviews on "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Clinical features and diagnosis" (Chen and Berek, 2016), "Neoadjuvant chemotherapy for newly diagnosed advanced ovarian cancer" (Konstantinopoulos and Bristow, 2016) do not mention the use of BARD1 and RAD51D mutation testing.

The National Comprehensive Cancer Network's clinical practice guideline on "Ovarian cancer" (Version 2.2015) does not mention the use of BARD1 and RAD51D mutation testing.

#### CHEK2 Mutation Testing

Myszka and associates (2011) noted that CHEK2 gene encodes cell cycle checkpoint kinase 2 that participates in the DNA repair pathway, cell cycle regulation and apoptosis. Mutations in CHEK2 gene may result in kinase inactivation or reduce both catalytic activity and capability of binding other proteins. Some studies indicated that alterations in CHEK2 gene confers increase the risk of breast cancer and some other malignancies, while the results of other studies are inconclusive. Thus, the significance of CHEK2 mutations in etiology of breast cancer is still debatable. These researchers evaluated the relationship between the breast/ovarian cancer and CHEK2 variants by: (i) the analysis of the frequency of selected CHEK2 variants in breast and ovarian cancer patients compared to the controls; and (ii) evaluation of relationships between the certain CHEK2 variants and clinicopathological and pedigree data. The study was performed on 284 breast cancer patients, 113 ovarian cancer patients, and 287 healthy women. These investigators revealed the presence of 430T > C, del5395 and IVS2 + 1G > A variants; but not 1100delC in individuals from both study and control groups. The authors did not observe significant differences between cancer patients and controls neither in

regard to the frequency nor to the type of CHEK2 variants.

Liu and colleagues (2012) stated that CHEK2 gene I157T variant may be associated with an increased risk of breast cancer, but it is unclear if the evidence is sufficient to recommend testing for the mutation in clinical practice. In a systematic review, these investigators systematically searched PubMed, Embase, Elsevier and Springer for relevant articles published before November 2011. Summary OR and 95% CI incidence rates were calculated using a random-effects model with STATA (version 10.0) software. A total of 15 case-control studies, including 19,621 cases and 27,001 controls based on the search criteria, were included for analysis. A significant association was found between carrying the CHEK2 I157T variant and increased risk of unselected breast cancer (OR = 1.48, 95% CI: 1.31 to 1.66, p < 0.0001), familial breast cancer (OR = 1.48, 95% CI: 1.16 to 1.89, p < 0.0001), and early-onset breast cancer (OR = 1.47, 95% CI: 1.29 to 1.66, p < 0.0001). These researchers found an even stronger significant association between the CHEK2 I157T C variant and increased risk of lobular type breast tumors (OR = 4.17, 95% CI: 2.89 to 6.03, p < 0.0001). The authors concluded that their research indicated that the CHEK2 I157T variant may be another important genetic mutation which increases risk of breast cancer, especially the lobular type. The methodological quality of this systematic review/meta-analysis was limited; the evidence was not quality appraised for risk of bias.

Young and co-workers (2012) noted that links between the CHEK2 1100delC heterozygote and breast cancer risk have been extensively explored. However, both positive and negative associations with this variant have been reported in individual studies. For a detailed assessment of the CHEK2 1100delC heterozygote and breast cancer risk, relevant studies published as recently as May 2012 were identified using PubMed and Embase and selected using a priori defined criteria. The strength of the relationship between the CHEK2 1100delC variant and breast cancer risks was assessed by ORs under the fixed effects model. A total of 29,154 cases and 37,064 controls from 25 case-control studies were identified in this meta-analysis. The CHEK2 1100delC heterozygote was more frequently detected in cases than in controls (1.34% versus 0.44%). A significant association was found between CHEK2 1100delC heterozygote and breast cancer risk (OR = 2.75, 95% CI: 2.25 to 3.36). The ORs and CIs were 2.33 (95% CI: 1.79 to 3.05), 3.72 (95% CI: 2.61 to 5.31) and 2.78 (95% CI: 2.28 to 3.39), respectively in unselected, family, early-onset breast cancer subgroups. The authors concluded that the CHEK2 1100delC variant could be a potential factor for increased breast cancer risk in Caucasians. However, more consideration is needed in order to apply it to allele screening or other clinical work.

Huzarski et al (2014) estimated the 10-year survival rates for patients with early onset breast cancer, with and without a CHEK2 mutation and identified prognostic factors among CHEK2-positive breast cancer patients. A total of 3,592 women with stage I to stage III breast cancer, diagnosed at or below age 50, were tested for 4 founder mutations in the CHEK2 gene. Information on tumor characteristics and on treatments received was retrieved from medical records. Dates of death were obtained from the Poland Vital Statistics Registry. Survival curves were generated for the mutation-positive and -negative sub-cohorts. Predictors of survival were determined among CHEK2 carriers using the Cox proportional hazards model. Of the 3,592 patients eligible for the study, 140 (3.9%) carried a CHEK2-truncating mutation and 347 (9.7%) carried a missense mutation. The mean follow-up was 8.9 years. The 10-year survival for all CHEK2 mutation carriers was 78.8% (95% CI: 74.6 to 83.2%) and for non-carriers was 80.1% (95% CI: 78.5 to 81.8%). Among women with a CHEK2-positive breast cancer, the adjusted HR associated with ER-positive status was 0.88 (95% CI: 0.48 to 1.62). Among women with an ER-positive breast cancer, the adjusted HR associated with a CHEK2 mutation was 1.31 (95% CI: 0.97 to 1.77). The survival of women with breast cancer and a CHEK2 mutation is similar to that of patients without a CHEK2 mutation.

In a cross-sectional study, Tung and colleagues (2015) evaluated the frequency of deleterious germline mutations among individuals with breast cancer who were referred for BRCA1/2 gene testing using a panel of 25 genes associated with inherited cancer predisposition. This study utilized next-generation sequencing (NGS) in 2,158 individuals, including 1,781 who were referred for commercial BRCA1/2 gene testing (cohort 1) and 377 who had detailed personal and family history and had previously tested negative for BRCA1/2 mutations (cohort 2). Mutations were identified in 16 genes, most frequently in BRCA1, BRCA2, CHEK2, ATM, and PALB2. Among the participants in cohort 1, 9.3% carried a BRCA1/2 mutation, 3.9% carried a mutation in another breast/ovarian cancer susceptibility gene, and 0.3% carried an incidental mutation in another cancer susceptibility gene unrelated to breast or ovarian cancer. In cohort 2, the frequency of mutations in breast/ovarian-associated genes other than BRCA1/2 was 2.9%, and an additional 0.8% had an incidental mutation (i.e., mutations were identified in additional genes in 14 women, of which CHEK2 was the most frequent ( $n = 5$ ), comprising approximately 33% of mutations identified in mutation-positive, BRCA-negative patients). In cohort 1, Lynch syndrome-related mutations were identified in 7 individuals. In contrast to BRCA1/2 mutations, neither age at breast cancer diagnosis nor family history of ovarian or young breast cancer predicted for other mutations. The frequency of mutations in genes other than BRCA1/2 was lower in Ashkenazi Jews compared with non-Ashkenazi individuals ( $p = 0.026$ ). The authors concluded that using an NGS 25-gene panel, the frequency of mutations in genes other than BRCA1/2 was 4.3%, and most mutations (3.9%) were identified in genes associated with breast/ovarian cancer.

Easton and associates (2015) reported that the magnitude of relative risk of breast cancer associated with CHEK2 truncating mutations is likely to be moderate and unlikely to be high. On the basis of 2 large case-control analyses, these researchers calculated an estimated relative risk of breast cancer associated with CHEK2 mutations of 3.0 (90% CI: 2.6 to 3.5), and an absolute risk of 29% by age 80 years.

Adank et al (2015) stated that in the majority of breast cancer families, DNA testing does not show BRCA1 or BRCA2 mutations and the genetic cause of breast cancer remains unexplained. Routine testing for the CHEK2\*1100delC mutation has recently been introduced in breast cancer families in the Netherlands. The 1100delC mutation in the CHEK2-gene may explain the occurrence of breast cancer in about 5% of non-BRCA1/2 families in the Netherlands. In the general population the CHEK2\*1100delC mutation confers a slightly increased breast cancer risk, but in a familial breast cancer setting this risk is between 35 to 55% for 1st degree female carriers. Female breast cancer patients with the CHEK2\*1100delC mutation are at increased risk of contralateral breast cancer and may have a less favorable prognosis. Female heterozygous CHEK2\*1100delC mutation carriers are offered annual mammography and specialist breast surveillance between the ages of 35 to 60 years. The authors concluded that prospective research in CHEK2-positive families is essential in order to develop more specific treatment and screening strategies.

Palmero et al (2016) stated that in Brazil, breast cancer is a public health care problem due to its high incidence and mortality rates. In this study, these researchers investigated the prevalence of hereditary breast cancer syndromes (HBCS) in a population-based cohort in Brazil's southernmost capital, Porto Alegre. All participants answered a questionnaire about family history (FH) of breast, ovarian and colorectal cancer and those with a positive FH were invited for genetic cancer risk assessment (GCRA). If pedigree analysis was suggestive of HBCS, genetic testing of the BRCA1, BRCA2, TP53, and CHEK2 genes was offered. Of 902 women submitted to GCRA, 214 had pedigrees suggestive of HBCS; 50 of them underwent genetic testing: 18 and 40 for BRCA1/BRCA2 and TP53 mutation screening, respectively, and 7 for CHEK2 1100delC testing. A deleterious BRCA2 mutation was identified in 1 of the HBOC probands and the CHEK2 1100delC

mutation occurred in 1 of the HBCC families. No deleterious germline alterations were identified in BRCA1 or TP53. The authors concluded that although strict inclusion criteria and a comprehensive testing approach were used, the suspected genetic risk in these families remains unexplained. They stated that further studies in a larger cohort are needed to better understand the genetic component of hereditary breast cancer in Southern Brazil.

Furthermore, it has been reported that CHEK2 mutations do not contribute substantially to hereditary breast cancer in various ethnic populations such as Greeks (Apostolou et al, 2015), Malaysians (Mohamad et al, 2015), and Moroccans (Marouf et al, 2015).

Available evidence has demonstrated that a CHEK2 mutation is of moderate-penetrance and confers a risk of breast cancer of 2 to 5 times that of the general population. This risk seems to be higher in individuals who also have a family history of breast and/or ovarian cancer; however, accurate risk estimates are subject to bias and over-estimation. Well-designed studies are needed to examine if some patients with a CHEK2 mutation have a risk that is similar to the risk with a high-penetrance mutation and who would be best managed according to established guidelines for high-risk patients. Clinical management recommendations for inherited conditions associated with moderate-penetrance mutations (e.g., BRIP, CHEK2, NBS1, and RAD50) are not standardized, nor is it known if testing for CHEK2 mutations will result in alterations in the management of patient or improved health outcomes. Thus, the available evidence is insufficient to determine the effects of CHEK2 mutation testing on health outcomes.

#### Prophylactic Mastectomy for Diabetic Mastopathy

Agochukwu and Wong (2017) stated that diabetic mastopathy is a benign condition of the breast that typically manifests in patients with diabetes mellitus. Lymphocytic mastopathy is the term used to describe this condition in patients without diabetes mellitus. Most patients undergo excisional biopsy, but the use of mastectomy, even in cases of diffuse, bilateral disease, is rarely reported. These investigators presented the case of a 32-year old woman with type 1 diabetes and bilateral diabetic mastopathy. Because of pain, and concern for limitations in future cancer detection, she underwent bilateral NSM with immediate direct-to-implant reconstruction. A systematic literature review was performed to examine the therapeutic options for this disease, particularly from a plastic surgery perspective. A total of 60 articles were reviewed that contained information regarding 313 patients. Of these patients, only 4 underwent mastectomy. The authors concluded that this case was the 1st report of bilateral NSM and immediate implant reconstruction for a patient with bilateral, symptomatic diabetic mastopathy.

Furthermore, an UpToDate review on "Overview of benign breast disease" (Sabel, 2017) states that "Diabetic mastopathy, also known as lymphocytic mastitis or lymphocytic mastopathy, is seen occasionally in premenopausal women who have longstanding type 1 diabetes mellitus. The typical presentation is a suspicious breast mass with a dense mammographic pattern. Core biopsy is recommended for diagnostic confirmation. Pathology shows dense keloid-like fibrosis and periductal, lobular, or perivascular lymphocytic infiltration. The pathogenesis is unknown, but it may represent an autoimmune reaction as the histologic features are similar to those seen in other autoimmune diseases. Once the diagnosis is established, excision is not necessary and there is no increased risk of subsequent breast cancer".

#### BRCA Testing in Hereditary Pancreatic Cancer

Pilarski (2019) stated that beyond breast and ovarian cancers, mutations in the BRCA1 and BRCA2 genes increase risks for pancreatic and prostate cancers and contribute to the prevalence of these cancers. Mutations in a number of other

genes have also been shown to increase the risk for these cancers as well. Genetic testing is playing an increasingly important role in the treatment of patients with pancreatic and prostate cancer and is now recommended for all patients with pancreatic or metastatic prostate cancer, as well as patients with high Gleason grade prostate cancer and a remarkable family history. Identification of an inherited mutation can direct evaluation of the patient for other cancer risks as well as identification and management of disease in at-risk relatives. Growing evidence suggested improved responses to PARP inhibitors and other therapies in patients with mutations in the BRCA and other DNA repair genes. Although more work must be carried out to clarify the prevalence and penetrance of mutations in genes other than BRCA1 and BRCA2 in patients with pancreatic and prostate cancer, in most cases, testing is now being done with a panel of multiple genes. Because of the complexities in panel testing and the increased likelihood of finding variants of uncertain significance, pre- and post-test genetic counseling are essential. The author stated that in familial pancreatic cancer, defined as having 2 or more first-degree relatives affected with pancreatic cancer, BRCA2 mutations are found in about 5% to 10% of cases, and BRCA1 mutations, in approximately 1%. Therefore, BRCA1 and BRCA2 are the most common causes of familial pancreatic cancer.

#### BRCA1/2 Mutation for Predicting the Effect of Platinum-Based Chemotherapy in Triple-Negative Breast Cancer

Jia et al (2022) noted that platinum-based chemotherapy (PBC) remains the mainstay of treatments for triple-negative breast cancer (TNBC). TNBC is a heterogeneous group, the issue of whether BRCA1/2 mutation carriers have a particular sensitivity to platinum agents is inconclusive. In a meta-analysis, these investigators examined the relationship between BRCA1/2 mutation and PBC susceptibility in individuals with TNBC, aiming to gain more information on the size of the benefit of PBC in BRCA1/2 mutation carriers. All studies applying PBC with a subgroup of BRCA1/2 status were included. All endpoints, including pathological complete response (pCR) and residual cancer burden (RCB) in the neoadjuvant phase, disease-free survival (DFS) in the adjuvant phase, objective remission rate (ORR), progression-free survival (PFS), and overall survival (OS) in the advanced phase, were assessed using HRs and 95 % CI. From the 22 studies included, there were 2,158 patients with TNBC, with 392 (18 %) bearing the BRCA1/2 gene mutation. Based on 13 studies applying neoadjuvant PBC, these researchers discovered that BRCA1/2 mutation was substantially associated with a 17.6 % increased pCR rate (HR 1.32, 95 % CI: 1.17 to 1.49,  $p < 0.00001$ ;  $I^2 = 51\%$ ). Same result was observed in RCB0/I index (HR 1.38, 95 % CI: 1.08 to 1.76,  $p = 0.009$ ;  $I^2 = 0\%$ ). The meta-analysis of 6 trials addressing advanced therapy revealed that ORR rates were significantly higher in patients with BRCA1/2 mutation (HR 1.91, 95 % CI: 1.48 to 2.47,  $p < 0.00001$ ;  $I^2 = 32\%$ ), as well as PFS (HR 1.13, 95 % CI: 0.81 to 1.57,  $p = 0.47$ ;  $I^2 = 0\%$ ) and OS (HR 1.89, 95 % CI: 1.22 to 2.92,  $p = 0.004$ ;  $I^2 = 0\%$ ). The authors concluded that according to the meta-analysis of 22 trials in TNBC, BRCA1/2 mutation carriers were significantly more sensitive to PBC regimens, especially in neoadjuvant and advanced therapy. Moreover, these investigators stated that other confounding factors need to be addressed in future prospective studies; namely, besides BRCA1/2, other genes involved in homologous recombination repairs, such as ATM, RAD51, and BRIP1 are required to be examined in the future.

The authors stated that this meta-analysis had several drawbacks including the majority of the trials they included were subgroups of larger clinical studies, which might have added bias to the meta-analysis. In addition, the definitions of outcomes, treatment regimens, and assessment criteria were not similar among these included studies, which may have contributed to bias but not considerable variance.

Lau et al (2022) stated that ovarian cancer is the leading cause of death in gynecologic malignancy in the U.S. Some patients affected by ovarian cancers often present genome instability with 1 or more of the defects in DNA repair pathways, especially in homologous recombination (HR), which is strictly linked to mutations in BRCA 1 or BRCA 2. The treatment of ovarian cancer remains a challenge, and the majority of patients with advanced-stage ovarian cancers experience relapse and require additional treatment despite initial therapy, including optimal cyto-reductive surgery (CRS) and PBC. Targeted therapy at DNA repair genes has become a unique strategy to combat HD-deficient (HRD) cancers in recent years. Poly (ADP-ribose) polymerase (PARP), a family of proteins, plays an important role in DNA damage repair, genome stability, and apoptosis of cancer cells, especially in HRD cancers. PARP inhibitors (PARPi) have been reported to be highly effective and low-toxicity drugs that will greatly benefit patients with HRD (i.e., BRCA 1/2 mutated) epithelial ovarian cancer (EOC) by blocking the DNA repair pathways and inducing apoptosis of cancer cells. PARPi compete with NAD<sup>+</sup> at the catalytic domain (CAT) of PARP to block PARP catalytic activity and the formation of PAR polymers. These effects compromise the cellular ability to overcome DNA SSB damage. The process of HR, an essential error-free pathway to repair DNA DSBs during cell replication, will be blocked in the condition of BRCA 1/2 mutations. The PARP-associated HR pathway can also be partially interrupted by using PARPi.

Grossly, PARPi have shown some therapeutic benefits in many randomized phase-II and phase-III clinical trials when combined with the standard CRS for advanced EOCs. However, similar to other chemotherapy agents, PARPi have different clinical indications and toxicity profiles and also face drug resistance, which has become a major challenge. In high-grade EOCs, the cancer cells under hypoxia- or drug-induced stress have the capacity to become polyploid giant cancer cells (PGCCs), which can survive the attack of chemotherapeutic agents and start endo-replication. These stem-like, self-renewing PGCCs generate mutations to change the expression/function of kinases, p53, and stem cell markers, and diploid daughter cells could exhibit drug resistance and facilitate tumor growth and metastasis. The authors discussed the underlying molecular mechanisms of PARPi and the results from the clinical studies that examined the effects of the FDA-approved PARPi olaparib, rucaparib, and niraparib. These researchers also reviewed the current research progress on PARPi, their safety, and their combined usage with anti-angiogenic agents. Nevertheless, many unknown aspects of PARPi, including detailed mechanisms of actions, along with the safety and effectiveness of the treatment of EOCs, warrant further investigation.

#### Penetrance of Male Breast Cancer Susceptibility Genes

Chamseddine et al (2022) noted that several male BC (MBC) susceptibility genes have been identified; however, the MBC risk for individuals with a pathogenic variant in each of these genes (i.e., penetrance) remains unclear. In a systematic review, these investigators examined studies reporting the penetrance of MBC susceptibility genes to better summarize current estimates of penetrance. They developed a search query to identify MBC-related studies indexed in PubMed/Medline. A validated natural language processing method was employed to identify studies reporting penetrance estimates. These penetrance studies' bibliographies were reviewed to ensure comprehensiveness. These investigators accessed the potential ascertainment bias for each enrolled study. A total of 15 penetrance studies were identified from 12,182 abstracts, covering 5 purported MBC susceptibility genes: ATM, BRCA1, BRCA2, CHEK2, and PALB2. Cohort (n = 6, 40 %) and case-control (n = 5, 33 %) studies were the 2 most common study designs, followed by family-based (n = 3, 20 %), and a kin-cohort study (n = 1, 7 %); 7 of the 15 studies (47 %) adjusted for ascertainment adequately; thus, the MBC risks reported by these 7 studies could be considered applicable to the general population. Based on these 7 studies, these researchers found pathogenic variants in ATM, BRCA2, CHEK2 c.1100delC, and PALB2 showed an increased risk for MBC. The association between BRCA1 and MBC was not statistically significant. The

authors concluded that the findings of this study supported the conclusion that pathogenic variants in ATM, BRCA2, CHEK2 c.1100delC, and PALB2 increased the risk of MBC. On the other hand, pathogenic variants in BRCA1 may not be associated with increased MBC risk.

Ionescu et al (2022) stated that MBCs are uncommon, as men account for less than 1 % of all breast carcinomas. Among the predisposing risk factors for MBC, the following appear to be significant: First, breast/chest radiation exposure. Second, estrogen use, diseases associated with hyper-estrogenism, such as cirrhosis or Klinefelter syndrome. Third, family health history. There are clear familial tendencies, with a higher incidence among men who have a large number of female relatives with BC. Fourth, major inheritance susceptibility. Moreover, in families with BRCA mutations, there is an increased risk of MBC, although the risk appeared to be greater with inherited BRCA2 mutations than with inherited BRCA1 mutations. Due to diagnostic delays, MBC is more likely to present at an advanced stage. A core biopsy or a fine needle aspiration must be carried out to confirm suspicious findings. Infiltrating ductal cancer is the most prevalent form of MBC, while invasive lobular carcinoma is extremely uncommon. The authors concluded that MBC is almost always positive for hormone receptors. A worse prognosis is associated with a more advanced stage at diagnosis for men with BC. Moreover, these researchers stated that randomized controlled trials (RCTs) that recruit both female and male patients should be developed in order to gain more consistent data on the optimal clinical approach.

#### Prophylactic Mastectomy for Women with the CHEK2 Gene Mutation

The American College of Medical Genetics and Genomics (ACMG)'s clinical practice statement on "Management of individuals with germline pathogenic/likely pathogenic variants in CHEK2" (Hanson et al, 2023) stated that although CHEK2 is considered a moderate penetrance gene, cancer risks may be considered as a continuous variable, which are influenced by family history and other modifiers. Therefore, early cancer detection and prevention for CHEK2 heterozygotes should be guided by personalized risk estimates. Such estimates may result in both downgrading lifetime breast cancer risks to those similar to the general population or upgrading lifetime risk to a level at which CHEK2 heterozygotes are offered high-risk breast surveillance according to country-specific guidelines. Risk-reducing mastectomy (RRM) should be guided by personalized risk estimates and shared decision-making. Colorectal cancer (CRC) and prostate cancer (PCa) surveillance should be considered based on assessment of family history. For CHEK2 heterozygotes who develop cancer, no specific targeted medical treatment is recommended at this time. The ACMG stated that systematic, prospective data collection is needed to establish the spectrum of CHEK2-associated cancer risks and to determine yet-unanswered questions, such as the outcomes of surveillance, response to cancer treatment, as well as survival following cancer diagnosis.

An UpToDate review on "Overview of hereditary breast and ovarian cancer syndromes" (Peshkin and Isaacs, 2023) states that "Breast cancer risk reduction -- ATM, CHEK2, neurofibromatosis type 1 (NF1), RAD51C and RAD51D carriers are not felt to be at sufficient risk to recommend RRM, although individual women may also consider it based on their personal and family history".

Furthermore, NCCN's clinical practice guideline on "Genetic/familial high-risk assessment: breast, ovarian, and pancreatic" (Version 2.2024) provides the following information: "Risk reduction: Evidence insufficient for RRM, manage based on family history".

#### Contralateral Prophylactic Mastectomies

In a systematic review and meta-analysis, Yao et al examined the evidence of the impact of CPM on survival outcomes in patients with unilateral breast cancer (UBC). These investigators searched PubMed, Embase and Scopus databases for observational studies published up to November 15, 2023. Random-effects model was employed to obtain pooled effect estimates that were reported as HR with 95 % CI. The outcomes of interest were OS, BCSS, recurrence free survival (RFS) and risk of contralateral breast cancer (CBC). A total of 21 studies were included; most of them had a retrospective design. CPM was associated with significant improvement of OS (HR 0.80, 95 % CI: 0.75 to 0.85), BCSS (HR 0.82, 95 % CI: 0.74 to 0.90), RFS (HR 0.72, 95 % CI: 0.60 to 0.86) and significantly reduced risk of CBC (HR 0.05, 95 % CI: 0.03 to 0.09) in patients with UBC. No evidence of publication bias was detected. The authors concluded that the findings of this systematic review and meta-analysis provided strong evidence supporting the positive impact of CPM on survival outcomes in patients with UBC. Moreover, these investigators stated that further research and long-term follow-up studies are needed to validate these findings.

He et al (2024) noted that in 2016, an American Society of Breast Surgeons (ASBrS) statement discouraged CPM in average-risk women with UBC. Despite evidence of no oncologic benefit and related attempts to discourage the practice, CPM remains prevalent. In a retrospective, single-center study, these researchers examined CPM trends post-ASBrS statement and factors associated with these trends. This trial included patients with primary UBC undergoing complete mastectomy at a tertiary center between January 2014 and December 2020. These investigators evaluated the proportion opting for CPM, compared pre- and post-ASBrS statement CPM rates, and examined associated patient and tumor factors. Pearson's Chi-square test, Fisher's exact test, as well as equal variance t-tests were employed to compare subsets who underwent CPM versus those who did not. Of 605 patients, 161 (27 %) underwent CPM during the study period, with the median follow-up time for all patients being 58 months (inter-quartile range [IQR]: 38 to 81). Among all patients, CPM rates ranged from 30 % to 14 % before the ASBrS statement and then declined from 36 % to 19 % after the statement. For average-risk patients (no genetic mutation), these rates ranged from 20.2 % to 10.2 % from 2014 to 2016 and had a steady decline from 23.2 % in 2017 to 13.2 % in 2020. Only 2 cases (1.2 %) had incidental CBC. Patients undergoing CPM tended to be younger, more likely to have a breast cancer gene mutation, pursue reconstruction, and elect for nipple- or skin-sparing mastectomy. Recurrence and mortality events did not differ significantly. Genetic testing and pathogenic variant rates were greater among CPM patients. The authors concluded that after an initial time lag, CPM rates appeared to be decreasing post-ASBrS statement, with ongoing data needed to confirm this trend. CPM rates among breast cancer gene patients aligned appropriately with guidelines catering to this higher risk population. These investigators stated that better educational tools and decision aids may impact CPM trends and facilitate shared decision-making.

Vadlakonda et al (2024) stated that CPM remains a personal decision, influenced by psychosocial factors, including cosmesis and peace of mind. Although use of CPM is disproportionately low among Black patients, the degree to which these disparities are driven by patient-level versus hospital-level factors remains unknown. Patients undergoing mastectomy for non-metastatic ductal or lobular breast cancer were tabulated using the National Cancer Database from 2004 to 2020. The primary endpoint was receipt of CPM. Multi-variable logistic regression models were constructed with interaction terms between Black-serving hospital (BSH) status and patient race to examine associations with CPM. Cox proportional hazard models were employed to assess long-term survival. Of 597,845 women studied, 70,911 (11.9 %) were Black. After multi-variable adjustment, Black race (adjusted OR 0.65, 95 % CI: 0.64 to 0.67) and treatment at BSH (adjusted OR 0.84, 95 % CI: 0.83 to 0.85) were independently linked to lower odds of CPM. Although predicted probability of CPM was universally lower at higher BSH, Black patients faced a

steeper reduction compared with White patients. Receipt of CPM was linked to improved survival (HR 0.84, 95 % CI: 0.83 to 0.86), whereas Black race was associated with a greater HR of 10-year mortality (HR 1.14, 95 % CI: 1.12 to 1.17). The authors concluded that hospitals serving a greater proportion of Black patients were less likely to use CPM, suggestive of disparities in access to CPM at the institutional level. These investigators stated that further research and education are needed to characterize surgeon-specific and institutional practices in patient counseling and shared decision-making that shape disparities in access to CPM.

#### Blood Lead Level as Marker of Increased Risk of Ovarian Cancer in BRCA1 Carriers

Kiljanczyk et al (2024) noted that BRCA1 mutations substantially elevate the risks of breast cancer (BC) and ovarian cancer (OC). Various modifiers, including environmental factors, can influence cancer risk. Lead has been associated with various cancers; however, its impact on BRCA1 carriers remains unexplored. A cohort of 989 BRCA1 mutation carriers underwent genetic testing at the Pomeranian Medical University, Poland. Blood lead levels were measured using inductively coupled plasma mass spectrometry. Each subject was assigned to a category based on their tertile of blood lead level. Cox regression analysis was employed to examine cancer risk associations. Elevated blood lead levels (higher than 13.6 µg/L) were associated with an increased risk of OC (uni-variable: HR = 3.33; 95 % CI: 1.23 to 9.00; p = 0.02; multi-variable: HR = 2.10; 95 % CI: 0.73 to 6.01; p = 0.17). No significant correlation was found with BC risk. The authors concluded that high blood lead levels were associated with increased risk of OC in BRCA1 carriers, suggesting that BRCA1 patients with elevated lead levels should not delay prophylactic oophorectomy. Moreover, these researchers stated that the findings of this trial require validation in other ethnic groups and regions of the world, as well as with mutations in other predisposing genes.

#### Testing for Germline FANCG Variants in Predisposition to Breast and Ovarian Cancer

Soukupova et al (2024) stated that mono-allelic germline pathogenic variants (GPVs) in 5 Fanconi anemia (FA) genes (BRCA1/FANCS, BRCA2/FANCD1, PALB2/FANCN, BRIP1/FANCJ, and RAD51C/FANCO) confer an increased risk of BC and/or OC; however, the role of GPVs in 17 other FA genes remains unclear. These investigators examined the association of germline variants in FANCG/XRCC9 with BC and OC risk. The frequency of truncating GPVs in FANCG did not differ between BC (20/10,204; 0.20 %) and OC (8/2,966; 0.27 %) patients compared to controls (6/3,250; 0.18 %). Furthermore, only 1 out of 5 tumor samples showed loss-of-heterozygosity of the wild-type FANCG allele. Lastly, none of the 9 functionally tested rare recurrent missense FANCG variants impaired DNA repair activities (FANCD2 monoubiquitination and FANCD2 foci formation) upon DNA damage, in contrast to all tested FANCG truncations. The authors concluded that although heterozygous GPVs in 5 FA genes (BRCA1, BRCA2, PALB2, BRIP1, or RAD51C) confer high/moderate BC/OC risk, they found no association between FANCG GPVs and BC/OC risk. Regarding the case-control evidence for OC predisposition, these findings agreed with a previous study by Song et al (2021) who also found no association between GPVs in other FA genes (including FANCG) and OC risk. Specifically, Songs et al identified 11/6,184 (0.17 %) FANCG GPVs carriers in OC patients compared to 8/6,089 (0.13 %) such carriers in controls (OR = 1.4; 95 % CI: 0.5 to 3.4). Furthermore, these researchers detected loss-of-heterozygosity (LOH), an important marker of allelic imbalance indicating the presence of a driver mutation in a tumor suppressor gene, in only 1 of the 5 tumors analyzed. Lastly, the in-vitro functional assays demonstrated that all rare missense variants analyzed did not affect the role of FANCG in DNA repair. These investigators stated that taken together, the findings of this study strongly suggested that heterozygous germline FANCG variants (including GPVs) did not confer an increased risk of BC or OC.

## Glossary of Terms

Term	Definition
Close Blood Relative	First-degree relatives (e.g., mother, sister, daughter), second-degree relatives (e.g., aunt, grandmother, niece) and third degree relatives (e.g., first cousins, great grandparents and great grandchildren), all of whom are on the same side of the family. For purposes of BRCA testing criteria, half-siblings would be considered first-degree relatives.
Triple-Negative Breast Cancer	The individual's breast cancer cells test negative for estrogen receptors (ER negative), progesterone receptors (PR negative) and human epidermal growth factor receptors (HER2 negative).

## References

The above policy is based on the following references:

### BRCA Testing

1. Alberta Heritage Foundation for Medical Research (AHFMR). BRACAnalysis genetic test. Techscan. Edmonton, AB: AHFMR; November 1999.
2. American College of Medical Genetics (ACMG). Genetic susceptibility to breast and ovarian cancer: Assessment, counseling and testing guidelines. Bethesda, MD: ACMG; 1999.
3. American College of Medical Genetics (ACMG). Statement on population screening for BRCA-1 mutation in Ashkenazi Jewish women. Bethesda, MD: ACMG; 1996.
4. American College of Medical Genetics Foundation. Genetic susceptibility to breast and ovarian cancer: assessment, counseling, and testing guidelines. Albany, NY: State of New York; 1999.
5. American College of Obstetricians and Gynecologists (ACOG). Breast-ovarian cancer screening. ACOG Committee Opinion Number 176. Washington, DC: ACOG; October 1996.
6. American College of Obstetricians and Gynecologists (ACOG). Breast cancer screening. Washington, DC: American College of Obstetricians and Gynecologists (ACOG); August 2011.
7. American College of Obstetricians and Gynecologists (ACOG). Hereditary breast and ovarian cancer syndrome. ACOG Practice Bulletin No. 103. *Obstet Gynecol*. 2009;113(4):957-966.
8. American Medical Association (AMA). The role of genetic susceptibility testing for breast & ovarian cancer. Continuing Medical Education Monograph. Chicago, IL: AMA; 1999.
9. American Society of Clinical Oncology Statement of the American Society of Clinical Oncology: Genetic testing for cancer susceptibility. *J Clin Oncol*. 1996;14:1730-1736.
10. American Society of Human Genetics Ad Hoc Committee on Breast and Ovarian Cancer Screening. Statement of the American Society of Human Genetics on genetic testing for breast and ovarian cancer predisposition. *Am J Hum Genet*. 1994;55:ii-iv.
11. Bansal A, Critchfield GC, Frank TS, et al. The predictive value of BRCA1 and BRCA2 mutation testing. *Genet Test*. 2000;4(1):45-48.
12. Bayraktar S, Elsayegh N, Gutierrez Barrera AM, et al. Predictive factors for BRCA1/BRCA2 mutations in women with ductal carcinoma in situ. *Cancer*. 2012;118(6):1515-1522.
13. Bellosillo B, Tusquets I. Pitfalls and caveats in BRCA sequencing. *Ultrastruct Pathol*. 2006;30(3):229-235.

14. Berchuck A, Cirisano F, Lancaster JM. Role of BRCA1 mutation screening in the management of familial ovarian cancer. *Am J Obstet Gynecol*. 1996;175:738-746.
15. Biesecker BB, Boehnke M, Calzone K, et al. Genetic counseling for families with inherited susceptibility to breast and ovarian cancer. *JAMA*. 1993;269:170-174.
16. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Genetic testing for inherited BRCA1 or BRCA2 mutations. TEC Assessment Program. Chicago, IL: BCBSA; 1997;12(4).
17. Brigham and Women's Hospital. Breast disease. Guide to prevention, diagnosis and treatment. Boston, MA: Brigham and Women's Hospital; 2001.
18. Brozek I, Ochman K, Debniaak J, et al. High frequency of BRCA1/2 germline mutations in consecutive ovarian cancer patients in Poland. *Gynecol Oncol*. 2008;108(2):433-437.
19. Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. *JAMA*. 1997;277:997-1003.
20. Castilla LH, Couch FJ, Erdos MR, et al. Mutations in the BRCA1 gene in families with early-onset breast and ovarian cancer. *Nature Genetics*. 1994;8:387-391.
21. Chamseddine RS, Wang C, Yin K, et al. Penetrance of male breast cancer susceptibility genes: A systematic review. *Breast Cancer Res Treat*. 2022;191(1):31-38.
22. Clark BA. Cancer genetics for the clinician: recommendations on screening for BRCA1 and BRCA2 mutations. *Cleve Clin J Med*. 2000;67(6):408-415.
23. Couch FJ, DeShano ML, Blackwood MA, et al. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. *N Engl J Med*. 1997;336(20):1409-1415.
24. Cowgill SM, Muscarella P. The genetics of pancreatic cancer. *Am J Surg*. 2003;186(3):279-286.
25. Drucker L, Stackievitz R, Shpitz B, Yarkoni S. Incidence of BRCA1 and BRCA2 mutations in Ashkenazi colorectal cancer patients: Preliminary study. *Anticancer Res*. 2000;20(1B):559-561.
26. Emery J, Walton R, Coulson A, et al. Computer support for recording and interpreting family histories of breast and ovarian cancer in primary care (RAGs): Qualitative evaluation with simulated patients. *BMJ*. 1999;319:32-36.
27. Emery J, Walton R, Murphy M, et al. Computer support for interpreting family histories of breast and ovarian cancer in primary care: Comparative study with simulated cases. *BMJ*. 2000;321:28-32.
28. Evans DG, Gaarenstroom KN, Stirling D, et al. Screening for familial ovarian cancer: Poor survival of BRCA1/2 related cancers. *J Med Genet*. 2009;46(9):593-597.
29. Fasouliotis SJ, Schenker JG. BRCA1 and BRCA2 gene mutations: Decision-making dilemmas concerning testing and management. *Obstet Gynecol Surv*. 2000;55(6):373-384.
30. Fitzgerald MG, MacDonald DJ, Krainer M, et al. Germ-line BRCA1 mutations in Jewish and non Jewish women with early onset breast cancer. *N Engl J Med*. 1996;334:143-149.
31. Ford D, Easton DF, Stratton M, et al. (1998): Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. *Am J Hum Genet*. 1998;62:676-689.
32. Grau AM, Chakravarthy AB, Chugh R. Phyllodes tumors of the breast. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2020.
33. Healy B. BRCA genes: Bookmarking, fortune telling, and medical care. *NEJM*. 1997;336:1448-1449.
34. Heinig J, Jackisch C, Rody A, et al. Clinical management of breast cancer in males: A report of four cases. *Eur J Obstet Gynecol Reprod Biol*. 2002;102(1):67-73.
35. Heisey RE, Carroll JC, Warner E, et al. Hereditary breast cancer. Identifying and managing BRCA1 and BRCA2 carriers. *Can Fam Physician*. 1999;45:114-124.
36. Ionescu S, Nicolescu AC, Marincas M, et al. An update on the general features of breast cancer in male patients -- A literature review. *Diagnostics (Basel)*. 2022;12(7):1554.
37. Jia X, Wang K, Xu L, et al. A systematic review and meta-analysis of BRCA1/2 mutation for predicting the effect of platinum-based chemotherapy in triple-negative breast cancer. *Breast*. 2022;66:31-39.
38. Kauff ND, Offit K. Modeling genetic risk of breast cancer. *JAMA*. 2007;297(23):2637-2639.

39. Kirchhoff T, Satagopan JM, Kauff ND, et al. Frequency of BRCA1 and BRCA2 mutations in unselected Ashkenazi Jewish patients with colorectal cancer. *J Natl Cancer Inst.* 2004;96(1):68-70.
40. Krainer M, Silva-Arrieta S, FitzGerald MG, et al. Differential contributions of BRCA1 and BRCA2 to early-onset breast cancer. *N Engl J Med.* 1997;336:1416-1421.
41. Langston AA, Malone KE, Thompson JD, et al. BRCA-1 mutations in a population-based sample of young women with breast cancer. *N Engl J Med.* 1996;334:137-142.
42. Lau C-H, Seow K-M, Chen K-H, et al. The molecular mechanisms of actions, effects, and clinical implications of PARP inhibitors in epithelial ovarian cancers: A systematic review. *Int J Mol Sci.* 2022;23(15):8125.
43. Liede A, Metcalfe K, Hanna D, et al. Evaluation of the needs of male carriers of mutations in BRCA1 or BRCA2 who have undergone genetic counseling. *Am J Hum Genet.* 2000;67(6):1494-1504.
44. Malander S, Ridderheim M, Måsbäck A, et al. One in 10 ovarian cancer patients carry germ line BRCA1 or BRCA2 mutations: Results of a prospective study in Southern Sweden. *Eur J Cancer.* 2004;40(3):422-428.
45. Marroni F, Aretini P, D'Andrea E, et al. Evaluation of widely used models for predicting BRCA1 and BRCA2 mutations. *J Med Genet.* 2004;41(4):278-285.
46. McGahan L, Kakuma R, Ho C, et al. A clinical systematic review of BRCA1 and BRCA2 genetic testing for breast and ovarian cancers. Technology Overview No. 20. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); March 31, 2006.
47. McGahan L, Kakuma R, Ho C, et al. BRCA1 and BRCA2 predictive genetic testing for breast and ovarian cancers: A systematic review of clinical evidence. Technology Report No. 66. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); March 31, 2006.
48. McIntosh A, Shaw C, Evans G, et al. Clinical guidelines and evidence review for the classification and care of women at risk of familial breast cancer. London; UK: National Collaborating Centre for Primary Care/ University of Sheffield; May 2004.
49. Moyer VA. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med.* 2014;160(4):271-281.
50. Myers ER, Havrilesky LJ, Kulasingam SL, et al. Genomic tests for ovarian cancer detection and management. Evidence Report/Technology Assessment 145. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2006.
51. National Comprehensive Cancer Network. Breast cancer. NCCN Clinical Practice Guidelines in Oncology, Version 1.2021. Fort Washington, PA: NCCN; 2021.
52. National Institute for Clinical Excellence (NICE). Familial breast cancer. The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. Update Clinical Guideline 14. London, UK: NICE; July 2006.
53. Nelson HD, Huffman LH, Fu R, Harris EL; U.S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: Systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2005;143(5):362-379.
54. Niell BL, Rennert G, Bonner JD, et al. BRCA1 and BRCA2 founder mutations and the risk of colorectal cancer. *J Natl Cancer Inst.* 2004;96(1):15-21.
55. Noorani H Z, McGahan L. Predictive genetic testing for breast and prostate cancer. Technology Report. Issue 4. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1999.
56. Nusbaum R, Isaacs C. Management updates for women with a BRCA1 or BRCA2 mutation. *Mol Diagn Ther.* 2007;11(3):133-144.
57. Pal T, Permuth-Wey J, Betts JA, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. *Cancer.* 2005;104(12):2807-2916.
58. Pilarski R. The role of BRCA testing in hereditary pancreatic and prostate cancer families. *Am Soc Clin Oncol Educ Book.* 2019;39:79-86.
59. Preisler-Adams S, Schonbuchner I, Fiebig B, et al. Gross rearrangements in BRCA1 but not BRCA2 play a notable role in predisposition to breast and ovarian cancer in high-risk families of German origin. *Cancer Genet Cytogenet.* 2006;168(1):44-49.
60. Puget N, Sinilnikova OM, Stoppa-Lyonnet D, et al. An Alu-mediated 6-kb duplication in

- the BRCA1 gene: A new founder mutation. *Am J Hum Genet.* 1999;64:300-302.
61. Rhiem K, Flucke U, Engel C, et al. Association of the BRCA1 missense variant R1699W with a malignant phyllodes tumor of the breast. *Cancer Genet Cytogenet.* 2007;176(1):76-79.
  62. Sivell S, Iredale R, Gray J, Coles B. Cancer genetic risk assessment for individuals at risk of familial breast cancer. *Cochrane Database Syst Rev.* 2007;(2):CD003721.
  63. Smirnova TY, Pospekhova NI, Lyubchenko LN, et al. High incidence of mutations in BRCA1 and BRCA2 genes in ovarian cancer. *Bull Exp Biol Med.* 2007;144(1):83-85.
  64. Sogaard M, Kjaer SK, Gayther S. Ovarian cancer and genetic susceptibility in relation to the BRCA1 and BRCA2 genes. Occurrence, clinical importance and intervention. *Acta Obstet Gynecol Scand.* 2006;85(1):93-105.
  65. Solomon JS, Brunicardi CF, Friedman JD. Evaluation and treatment of BRCA-positive patients. *Plast Reconstr Surg.* 2000;105(2):714-719.
  66. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med.* 1997;336:1401-1408.
  67. Swedish Council on Technology Assessment in Health Care (SBU). Presymptomatic diagnosis of hereditary breast cancer - early assessment briefs (ALERT). Stockholm, Sweden: SBU; 2000.
  68. Szabo CI, King MC. Inherited breast and ovarian cancer. *Hum Mol Genet.* 1995;4 Spec No:1811-1817.
  69. Tranchemontagne J, Boothroyd L, Blancquaert I. Contribution of BRCA1/2 mutation testing to risk assessment for susceptibility to breast and ovarian cancer. Summary Report. AETMIS 06-02a. Montreal, QC: Agence D'Évaluation des Technologies et des Modes D'Intervention en Santé (AETMIS); March 2006.
  70. S. Food and Drug Administration (FDA). FDA authorizes, with special controls, direct-to-consumer test that reports three mutations in the BRCA breast cancer genes. News. Silver Spring, MD: FDA; March 6, 2018.
  71. S. Food and Drug Administration (FDA). FoundationFocus CDxBRCA next generation sequencing oncology panel, somatic or germline variant detection system. PMA No. P160018. Silver Spring, MD: FDA; December 19, 2016.
  72. S. Preventive Services Task Force. Task force recommends against routine testing for genetic risk of breast or ovarian cancer in the general population. Press Release. Rockville, MD: Agency for Healthcare Research and Quality; September 5, 2005.
  73. Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. *JAMA.* 2006;295(12):1379-1388.
  74. Weber B. Breast cancer susceptibility genes: Current challenges and future promises. *Ann Int Med.* 1996;124:1088-1090.
  75. Weitzel JN, Lagos VI, Cullinane CA, et al. Limited family structure and BRCA gene mutation status in single cases of breast cancer. *JAMA.* 2007;297(23):2587-2595.
  76. Wolpert N, Warner E, Seminsky MF, et al. Prevalence of BRCA1 and BRCA2 mutations in male breast cancer patients in Canada. *Clin Breast Cancer.* 2000;1(1):57-65.

#### CHEK2 Mutation Testing

1. Adank MA, Hes FJ, van Zelst-Stams WA, et al. CHEK2-mutation in Dutch breast cancer families: Expanding genetic testing for breast cancer. *Ned Tijdschr Geneeskde.* 2015;159:A8910.
2. Apostolou P, Fostira F, Papamantzelopoulou M, et al. CHEK2 c.1100delC allele is rarely identified in Greek breast cancer cases. *Cancer Genet.* 2015;208(4):129-134.
3. Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med.* 2015;372(23):2243-2257.
4. Huzarski T, Cybulski C, Wokolorczyk D, et al. Survival from breast cancer in patients with CHEK2 mutations. *Breast Cancer Res Treat.* 2014;144(2):397-403.
5. Liu C, Wang Y, Wang QS, Wang YJ. The CHEK2 I157T variant and breast cancer susceptibility: A systematic review and meta-analysis. *Asian Pac J Cancer Prev.* 2012;13(4):1355-1360.
6. Marouf C, Hajji O, Diakite B, et al. The CHEK2 1100delC allelic variant is not present in

familial and sporadic breast cancer cases from Moroccan population. Springerplus.

2015;4:38.

7. Mohamad S, Isa NM, Muhammad R, et al. Low prevalence of CHEK2 gene mutations in multiethnic cohorts of breast cancer patients in Malaysia. *PLoS One*. 2015;10(1):e0117104.
8. Myszka A, Karpinski P, Slezak R, et al. Irrelevance of CHEK2 variants to diagnosis of breast/ovarian cancer predisposition in Polish cohort. *J Appl Genet*. 2011;52(2):185-191.
9. Palmero El, Alemar B, Schüler-Faccini L, et al. Screening for germline BRCA1, BRCA2, TP53 and CHEK2 mutations in families at-risk for hereditary breast cancer identified in a population-based study from Southern Brazil. *Genet Mol Biol*. 2016;39(2):210-222.
10. Tung N, Battelli C, Allen B, et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer*. 2015;121(1):25-33.
11. Yang Y, Zhang F, Wang Y, Liu SC. CHEK2 1100delC variant and breast cancer risk in Caucasians: A meta-analysis based on 25 studies with 29,154 cases and 37,064 controls. *Asian Pac J Cancer Prev*. 2012;13(7):3501-3505.

#### **Elective Salpingectomy for Ovarian Cancer Prevention in Low Hereditary Risk Women**

1. Chene G, de Rochambeau B, Le Bail-Carval K, et al. Current surgical practice of prophylactic and opportunistic salpingectomy in France. *Gynecol Obstet Fertil*. 2016;44(7-8):377-384.
2. Committee on Gynecologic Practice. Committee opinion no. 620: Salpingectomy for ovarian cancer prevention. *Obstet Gynecol*. 2015;125(1):279-281.
3. Isaacs C, Peshkin BN. Management of patients with hereditary and/or familial breast and ovarian cancer. *UpToDate [online serial]*. Waltham, MA: UpToDate; reviewed January 2016.
4. Kapurubandara S, Qin V, Gurram D, et al. Opportunistic bilateral salpingectomy during gynaecological surgery for benign disease: A survey of current Australian practice. *Aust N Z J Obstet Gynaecol*. 2015;55(6):606-611.
5. National Comprehensive Cancer Network (NCCN). Ovarian cancer. NCCN Clinical Practice Guidelines in Oncology, Version 1.2016. Fort Washington, PA: NCCN; 2016.
6. Walker JL, Powell CB, Chen LM, et al. Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. *Cancer*. 2015;121(13):2108-2120.

#### **Large Genomic Re-Arrangements**

1. Judkins T, Rosenthal E, Arnell C, et al. Clinical significance of large rearrangements in BRCA1 and BRCA2. *Cancer*. 2012;118(21):5210-5216.
2. Manguoglu E, Güran S, Yamaç D, et al. Genomic large rearrangement screening of BRCA1 and BRCA2 genes in high-risk Turkish breast/ovarian cancer patients by using multiplex ligation-dependent probe amplification assay. *Cancer Invest*. 2011;29(1):73-77.
3. Sharifah NA, Nurismah MI, Lee HC, et al. Identification of novel large genomic rearrangements at the BRCA1 locus in Malaysian women with breast cancer. *Cancer Epidemiol*. 2010;34(4):442-447.
4. Ticha I, Kleibl Z, Stribrna J, et al. Screening for genomic rearrangements in BRCA1 and BRCA2 genes in Czech high-risk breast/ovarian cancer patients: High proportion of population specific alterations in BRCA1 gene. *Breast Cancer Res Treat*. 2010;124(2):337-347.

#### **Multigene Breast and Ovarian Cancer Panels**

1. Aloraifi F, McCartan D, McDevitt T, et al. Protein-truncating variants in moderate-risk breast cancer susceptibility genes: A meta-analysis of high-risk case-control screening studies. *Cancer Genet*. 2015;208(9):455-463.
2. Antoniou AC, Foulkes WD, Tischkowitz M. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med*. 2014;371(17):1651-1652.

3. Bogdanova N, Sokolenko AP, Iyevleva AG, et al. PALB2 mutations in German and Russian patients with bilateral breast cancer. *Breast Cancer Res Treat.* 2011;126(2):545-550.
4. Buys SS, Sandbach JF, Gammon A, et al. A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes. *Cancer.* 2017;123(10):1721-1730.
5. Casadei S, Norquist BM, Walsh T, et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. *Cancer Res.* 2011;71(6):2222-2229.
6. Churpek JE, Walsh T, Zheng Y, et al. Inherited predisposition to breast cancer among African American women. *Breast Cancer Res Treat.* 2015;149(1):31-39.
7. Cybulski C, Klužniak W, Huzarski T, et al.; Polish Hereditary Breast Cancer Consortium. Clinical outcomes in women with breast cancer and a PALB2 mutation: A prospective cohort analysis. *Lancet Oncol.* 2015;16(6):638-644.
8. Desmond A, Kurian AW, Gabree M, et al. Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. *JAMA Oncol.* 2015;1(7):943-951.
9. Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med.* 2015;372(23):2243-2257.
10. Eliade M, Skrzypski J, Baurand A, et al. The transfer of multigene panel testing for hereditary breast and ovarian cancer to healthcare: What are the implications for the management of patients and families? *Oncotarget.* 2017;8(2):1957-1971.
11. Erkko H, Xia B, Nikkilä J, et al. A recurrent mutation in PALB2 in Finnish cancer families. *Nature.* 2007;446(7133):316-319.
12. Hartley T, Cavallone L, Sabbaghian N, et al. Mutation analysis of PALB2 in BRCA1 and BRCA2-negative breast and/or ovarian cancer families from Eastern Ontario, Canada. *Hered Cancer Clin Pract.* 2014;12(1):19.
13. Institut National d'Excellence en Santé et en Services Sociaux (INESSS). Breast and Pancreatic Cancer – Detecting the Q775X Allele of the Palb2 Gene Using RFLP and Detecting PALB2 Gene Mutations Using HRM and Direct Sequencing (Reference – 2013.02.006.1 and 2013.02.006.2). Notice of Assessment. Montreal, QC: INESSS; December 2013.
14. Institute National d'Excellence en Santé et en Services Sociaux (INESSS). Myriad myRisk – panel de 25 gènes associés aux cancers héréditaires analysés par séquençage de nouvelle génération. Reference 2015.01.001. Avis d'évaluation. Montreal, QC: INESSS; June 30, 2016.
15. Janatova M, Kleibl Z, Stibrna J, et al. The PALB2 gene is a strong candidate for clinical testing in BRCA1- and BRCA2-negative hereditary breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2013;22(12):2323-2332.
16. Judkins T, Leclair B, Bowles K, et al. Development and analytical validation of a 25-gene next generation sequencing panel that includes the BRCA1 and BRCA2 genes to assess hereditary cancer risk. *BMC Cancer.* 2015;15:215.
17. Kapoor NS, Curcio LD, Blakemore CA, et al. Multigene panel testing detects equal rates of pathogenic BRCA1/2 mutations and has a higher diagnostic yield compared to limited BRCA1/2 analysis alone in patients at risk for hereditary breast cancer. *Ann Surg Oncol.* 2015;22(10):3282-3288.
18. Lynce F, Isaacs C. How far do we go with genetic evaluation? Gene, panel, and tumor testing. *Am Soc Clin Oncol Educ Book.* 2016;35:e72-e78.
19. Nguyen-Dumont T, Hammet F, Mahmoodi M, et al. Mutation screening of PALB2 in clinically ascertained families from the Breast Cancer Family Registry. *Breast Cancer Res Treat.* 2015;149(2):547-554.
20. Rahman N, Seal S, Thompson D, et al.; Breast Cancer Susceptibility Collaboration (UK). PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat Genet.* 2007;39(2):165-167.
21. Robays J, Stordeur S, Hulstaert F, et al. Oncogenetic testing and follow-up for women with familial breast/ovarian cancer, Li-Fraumeni syndrome and Cowden syndrome. Good Clinical Practice (GCP). KCE Report 236. Brussels, Belgium: Belgian Healthcare Knowledge Centre (KCE); 2015.
22. Rosenthal ET, Evans B, Kidd J et al. Increased identification of candidates for high-risk

- breast cancer screening through expanded genetic testing. *J Am Coll Radiol.* 2017;14(4):561-568.
23. Snyder C, Metcalfe K, Sopik V, et al. Prevalence of PALB2 mutations in the Creighton University Breast Cancer Family Registry. *Breast Cancer Res Treat.* 2015;150(3):637-641.
  24. Thompson ER, Rowley SM, Li N, et al. Panel testing for familial breast cancer: Calibrating the tension between research and clinical care. *J Clin Oncol.* 2016;34(13):1455-1459.
  25. Tischkowitz M, Capanu M, Sabbaghian N, et al.; WECARE Study Collaborative Group. Rare germline mutations in PALB2 and breast cancer risk: A population-based study. *Hum Mutat.* 2012;33(4):674-680.
  26. Tung N, Battelli C, Allen B, et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer.* 2015;121(1):25-33.
  27. Winship I, Southey MC. Gene panel testing for hereditary breast cancer. *Med J Aust.* 2016;204(5):188-190.
  28. Young EL, Feng BJ, Stark AW, et al. Multigene testing of moderate-risk genes: Be mindful of the missense. *J Med Genet.* 2016;53(6):366-376.

#### Prophylactic Bilateral Oophorectomy

1. Agencia de Evaluacion de Tecnologias Sanitarias de Andalucia (AETSA). Preventive mastectomy and oophorectomy in women who carry mutations in BRCA genes - systematic review. Sevilla, Spain: Agencia de Evaluacion de Tecnologias Sanitarias de Andalucia (AETSA); 2005.
2. Agostini A, Vejux N, Bretelle F, et al. Value of laparoscopic assistance for vaginal hysterectomy with prophylactic bilateral oophorectomy. *Am J Obstet Gynecol.* 2006;194(2):351-354.
3. American College of Obstetricians and Gynecologists (ACOG). Hereditary breast and ovarian cancer syndrome. ACOG Practice Bulletin No. 103. Washington, DC: American College of Obstetricians and Gynecologists (ACOG); April 2009.
4. American College of Obstetricians and Gynecologists (ACOG). Prophylactic oophorectomy. ACOG Technical Bulletin No. 111. Washington, DC: ACOG; 1987.
5. American College of Obstetricians and Gynecologists. ACOG practice bulletin. Prophylactic oophorectomy. Number 7, September 1999 (replaces Technical Bulletin Number 111, December 1987). Clinical management guidelines for obstetrician-gynecologists. *Int J Gynaecol Obstet.* 1999;67(3):193-199.
6. American College of Obstetrics and Gynecology (ACOG). Prophylactic oophorectomy. ACOG Practice Bulletin No 7. Washington, DC: ACOG; September 1999.
7. Averette HE, Nguyen HN. The role of prophylactic oophorectomy in cancer prevention. *Gynecol Oncol.* 1994;55(3):S38-S41.
8. Berchuck A, Schildkraut JM, Marks JR, Futerl PA. Managing hereditary ovarian cancer risk. *Cancer.* 1999;86(11 Suppl):2517-2524.
9. Berek JS, Chalas E, Edelson M, et al; Society of Gynecologic Oncologists Clinical Practice Committee. Prophylactic and risk-reducing bilateral salpingo-oophorectomy: Recommendations based on risk of ovarian cancer. *Obstet Gynecol.* 2010;116(3):733-743.
10. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA.* 2010;304(9):967-975.
11. Eisen A, Rebbeck TR, Wood WC, Weber BL. Prophylactic surgery in women with a hereditary predisposition to breast and ovarian cancer. *J Clin Oncol.* 2000;18(9):1980-1995.
12. Eisinger F, Alby N, Bremond A, et al. Inserm ad hoc committee: Recommendations for the management of women with a genetic risk for developing cancer of the breast and/or the ovary. *Bull Cancer.* 1999;86(3):307-313.
13. Evans DGR, Ribiero G, Warrell D, et al. Ovarian cancer family and prophylactic choices. *J Med Genetics.* 1992;29(6):416-418.
14. Farghaly SA. Current status of management of hereditary ovarian-breast cancer

- syndrome. *Obstet Gynecol*. 2000;95(4 Suppl 1):S51.
15. Gotlieb WH, Baruch GB, Friedman E. Prophylactic oophorectomy: clinical considerations. *Semin Surg Oncol*. 2000;19(1):20-27.
  16. Haber D. Prophylactic oophorectomy to reduce the risk of ovarian and breast cancer in carriers of BRCA mutations. *N Engl J Med*. 2002;346(21):1660-1662.
  17. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2002;346(21):1609-1615.
  18. Kerlikowske K, Brown JS, Grady DG. Should women with familial ovarian cancer undergo prophylactic oophorectomy?. *Obstet Gynecol*. 1992;80(4):700-707.
  19. Kerlikowske K, Brown JS, Grady DG. Should women with familial ovarian cancer undergo prophylactic oophorectomy: An editorial reply. *Obstet Gynecol*. 1993;81(2):315-316.
  20. Lu KH, Garber JE, Cramer DW, et al. Occult ovarian tumors in women with BRCA1 or BRCA2 mutations undergoing prophylactic oophorectomy. *J Clin Oncol*. 2000;18(14):2728-2732.
  21. Meijer WJ, van Lindert CM. Prophylactic oophorectomy. *Eur J Obstet Gynecol Reprod Biol*. 1992;47(1):59-65.
  22. Metcalfe KA. Oophorectomy for breast cancer prevention in women with BRCA1 or BRCA2 mutations. *Womens Health (Lond Engl)*. 2009;5(1):63-68.
  23. Muto MG. Risk-reducing bilateral salpingo-oophorectomy in women at high risk of epithelial ovarian and fallopian tubal cancer. *UpToDate [online serial]*. Waltham, MA: UpToDate; reviewed January 2013.
  24. National Institute for Clinical Excellence (NICE). Familial breast cancer: The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. Clinical Guideline 14. London, UK: NICE; May 2004.
  25. National Institutes of Health. NIH Consensus Development Conference on Ovarian Cancer: Screening, Treatment, and Follow-up. Bethesda, MD: NIH; 1994;12(3):4-9.
  26. Nguyen HN, Averette HE, Janicek M. Ovarian carcinoma. *Cancer*. 1994;74(2):545-555.
  27. Orozco LJ, Salazar A, Clarke J, Tristán M. Hysterectomy versus hysterectomy plus oophorectomy for premenopausal women. *Cochrane Database Syst Rev*. 2008; (3):CD005638.
  28. Parker WH, Broder MS, Liu Z, et al. Ovarian conservation at the time of hysterectomy for benign disease. *Obstet Gynecol*. 2005;106(2):219-226.
  29. Parker WH, Shoupe D, Broder MS, et al. Elective oophorectomy in the gynecological patient: When is it desirable? *Curr Opin Obstet Gynecol*. 2007;19(4):350-354.
  30. Parker WH. Bilateral oophorectomy versus ovarian conservation: Effects on long-term women's health. *J Minim Invasive Gynecol*. 2010;17(2):161-166.
  31. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst*. 2009;101(2):80-87.
  32. Rebbeck TR, Levin AM, Eisen A, et al. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. *J Natl Cancer Inst*. 1999;91(17):1475-1479.
  33. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med*. 2002;346(21):1616-1622.
  34. Rebbeck TR. Prophylactic Oophorectomy in BRCA1 and BRCA2 mutation carriers. *J Clin Oncol*. 2000;18(90001):100S-103S.
  35. Reiter RC, Gambone JC. Editorial reply to Ovarian cancer in women with prior hysterectomy: A 14-year experience at the University of Miami. *Obstet Gynecol*. 1992;79(2):317-319.
  36. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med*. 2006;354(3):261-269.
  37. Schwartz PE. The role of prophylactic oophorectomy in the avoidance of ovarian cancer. *Int J Gynecol Obstet*. 1992;39(3):175-184.
  38. Sightler SE, Bioké GM, Estape RE, Averettte HE. Ovarian cancer in women with prior hysterectomy: A 14-year experience at the University of Miami. *Obstet Gynecol*. 1992;78(4):681-684.
  39. Speroff T, Dawson NV, Speroff L, Haber RJ. A risk-benefit analysis of elective bilateral oophorectomy: Effect of changes in compliance with estrogen therapy on outcome. *Am J Obstet Gynecol*. 1991;164(1 Pt 1):165-174.

40. Tice JA. Prophylactic oophorectomy - what is the effect on breast and ovarian cancer for BRCA+ women? Technology Assessment. San Francisco, CA: California Technology Assessment Forum; October 8, 2003.
41. van Eijkelen MA, de Graaff J, van Etten FHPM. Familial ovarian cancer. Eur J Obstet Gynecol Reprod Biol. 1992;47(3):263-266.
42. Wolff BG. Current status of incidental surgery. Dis Colon Rectum. 1995;38(4):435-441.

#### Prophylactic Mastectomy

1. Agochukwu NB, Wong L. Diabetic mastopathy: A systematic review of surgical management of a rare breast disease. Ann Plast Surg. 2017;78(4):471-475.
2. Alberta Health Services. Breast reconstruction following prophylactic or therapeutic mastectomy for breast cancer. Clinical Practice Guideline BR-016, version 1. Edmonton, AB: Alberta Health Services; September 2013.
3. American College of Medical Genetics Foundation (ACMG). Genetic susceptibility to breast and ovarian cancer: Assessment, counseling, and testing guidelines. Albany, NY: State of New York; 1999.
4. Association of Breast Surgery at BASO; Association of Breast Surgery at BAPRAS; Training Interface Group in Breast Surgery; Baildam A, Bishop H, Boland G, et al. Oncoplastic breast surgery -- a guide to good practice. Eur J Surg Oncol. 2007;33 Suppl 1:S1-S23.
5. Balmaña J, Díez O, Rubio IT, Cardoso F; ESMO Guidelines Working Group. BRCA in breast cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2011;22 Suppl 6:vi31-4.
6. Baron RH, Borgen PI. Genetic susceptibility for breast cancer: Testing and primary prevention options. Oncol Nurs Forum. 1997; 24(3):461-468.
7. Bilimoria MM, Morrow M. The woman at increased risk for breast cancer: Evaluation and management strategies. CA Cancer J Clin. 1995;45(5):263-278.
8. Boice JD Jr, Olsen JH. Prophylactic mastectomy in women with a high risk of breast cancer. N Engl J Med. 1999;340(23):1838-1839.
9. Bostwick J 3rd, Wood WC. Contralateral prophylactic mastectomies. Ann Surg Oncol. 1999;6(6):519.
10. Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer Genetics Studies Consortium. JAMA. 1997;277(12):997-1003.
11. Cordeiro PG. Breast reconstruction after surgery for breast cancer. N Engl J Med. 2008;359(15):1590-1601.
12. Curry P, Fentiman IS. Management of women with a family history of breast cancer. Int J Clin Pract. 1999;53(3):192-196.
13. Eisen A, Rebbeck TR, Wood WC, et al. Prophylactic surgery in women with a hereditary predisposition to breast and ovarian cancer. J Clin Oncol. 2000;18(9):1980-1995.
14. Giordano SH, Buzdar AU, Hortobagyi G. Breast cancer in men. Ann Intern Med. 2002;137(8):678-687.
15. Grann VR, Panageas KS, Whang W, et al. Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients. J Clin Oncol. 1998;16(3):979-985.
16. Hanson H, Astiazaran-Symonds E, Amendola LM, et al; ACMG Professional Practices and Guidelines Committee. Management of individuals with germline pathogenic/likely pathogenic variants in CHEK2: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023;25(10):100870.
17. Hartmann LC, Degnim AC, Santen RJ, et al. Atypical hyperplasia of the breast -- risk assessment and management options. N Engl J Med. 2015;372(1):78-89.
18. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med. 1999;340(2):77-84.
19. He BK, Chu CD, Smith CE, et al. Trends in contralateral prophylactic mastectomies before and after the American Society of Breast Surgeons consensus statement. J Surg Res. 2024;303:545-553.
20. Jaiyesimi IA, Buzdar AU, Ross MA. Carcinoma of the male breast [reply]. Ann Intern Med. 1993;118(9):749.

21. Jaiyesimi IA, Buzdar AU, Sahin AA, Ross MI. Carcinoma of the male breast. *Ann Intern Med.* 1992;117(9):771-777.
22. King TA, Gurevich I, Sakr R, et al. Occult malignancy in patients undergoing contralateral prophylactic mastectomy. *Ann Surg.* 2011;254(1):2-7.
23. Lanitis S, Tekkis PP, Sgourakis G, et al. Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: A meta-analysis of observational studies. *Ann Surg.* 2010;251(4):632-639.
24. LeBlond RF. Carcinoma of the male breast [letter]. *Ann Intern Med.* 1993;118(9):749.
25. Lerman C, Narod S, Schulman K, et al. BRCA1 testing in families with hereditary breast-ovarian cancer. A prospective study of patient decision making and outcomes. *JAMA.* 1996;275(24):1885-1892.
26. Lopez MJ, Porter KA. The current role of prophylactic mastectomy. *Surg Clin North Am.* 1996;76(2):231-242.
27. Lostumbo L, Carbine N, Wallace J, Ezzo J. Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database Syst Rev.* 2004;(3):CD002748.
28. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database Syst Rev.* 2010;11:CD002748.
29. Lynch HT, Lynch J, Conway T, et al. Hereditary breast cancer and family cancer syndromes. *World J Surg.* 1994;18(1):21-31.
30. Mann GB, Borgen PI. Breast cancer genes and the surgeon. *J Surg Oncol.* 1998;67(4):267-274.
31. Metcalfe KA, Goel V, Lickley L, et al. Prophylactic bilateral mastectomy: Patterns of practice. *Cancer.* 2002;95(2):236-242.
32. National Comprehensive Cancer Network (NCCN). Genetic/familial high-risk assessment: breast, ovarian, and pancreatic. NCCN Clinical Practice Guidelines in Oncology, Version 2.2024. Plymouth Meeting, PA: NCCN; 2024.
33. Newman LA, Kuerer HM, Hung KK, et al. Prophylactic mastectomy. *J Am Coll Surg.* 2000;191(3):322-330.
34. Page DL, Dupont WD. Premalignant conditions and markers of elevated risk in the breast and their management. *Surg Clin N Amer.* 1990;70:831-851.
35. Peshkin BN, Isaacs C. Overview of hereditary breast and ovarian cancer syndromes. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2023.
36. Prpic I, Jakic-Razumovic J, Oberman B, et al. Developmental and involutional breast disorders. *Lijec Vjesn.* 1992;114(5-8):105-109.
37. Sabel MS, Collins LC. Atypia and lobular carcinoma in situ: High risk lesions of the breast. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2016.
38. Sabel MS. Overview of benign breast disease. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2017.
39. Sakorafas GH, Tsiotou AG. Prophylactic mastectomy; evolving perspectives. *Eur J Cancer.* 2000;36(5):567-578.
40. Schrag D, Kuntz KM, Garber JE, et al. Benefit of prophylactic mastectomy for women with BRCA1 or BRCA2 mutations. *JAMA.* 2000;283(23):3070-3072.
41. Schrag D, Kuntz KM, Garber JE, et al. Decision analysis--effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. *N Engl J Med.* 1997;336(20):1465-1471.
42. Solomon JS, Brunicardi CF, Friedman JD. Evaluation and treatment of BRCA-positive patients. *Plast Reconstr Surg.* 2000;105(2):714-719.
43. Srethbhakdi A, Brennan ME, Hamid G, Flitcroft K. Contralateral prophylactic mastectomy for unilateral breast cancer in women at average risk: Systematic review of patient reported outcomes. *Psychooncology.* 2020;29(6):960-973.
44. Unic I, Stalmeier PF, Verhoef LC, et al. Assessment of the time-tradeoff values for prophylactic mastectomy of women with a suspected genetic predisposition to breast cancer. *Med Decis Making.* 1998;18(3):268-277.
45. Vadlakonda A, Curry J, Gao Z, et al. Current status of contralateral prophylactic mastectomy: Investigating structural racial disparity. *J Am Coll Surg.* 2024;239(3):253-262.
46. van Geel AN, Rutgers EJ, Vos-Deckers GC, et al. Women with hereditary risk of breast cancer: Consensus of surgical representatives of study groups for hereditary tumors regarding intensive monitoring, diagnosis and preventive resection. *Ned Tijdschr*

Geneesk, 1997;141(18):874-877.

47. Vogel VG. Breast cancer prevention: A review of current evidence. CA Cancer J Clin. 2000;50(3):156-170.
48. Wolpert N, Warner E, Seminsky MF, et al. Prevalence of BRCA1 and BRCA2 mutations in male breast cancer patients in Canada. Clin Breast Cancer. 2000;1(1):57-65.
49. Wong SM, Freedman RA, Sagara Y, et al. Growing use of contralateral prophylactic mastectomy despite no improvement in long-term survival for invasive breast cancer. Ann Surg. 2017;265(3):581-589.
50. Yao K, Liederbach E, Tang R, et al. Nipple-sparing mastectomy in BRCA1/2 mutation carriers: An interim analysis and review of the literature. Ann Surg Oncol. 2015;22(2):370-376.
51. Yao M, Peng P, Chen L, Xu Z. Impact of contralateral prophylactic mastectomy on survival outcomes in patients with unilateral breast cancer: A systematic review and meta-analysis. Pak J Med Sci. 2024;40(8):1873-1881.
52. Zakaria S, Degnim AC. Prophylactic mastectomy. Surg Clin North Am. 2007;87(2):317-331, viii.

#### Testing for BARD 1 and RAD51D Mutations for Ovarian Cancer

1. Chen L-M, Berek JS. Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Clinical features and diagnosis. UpToDate [online serial]. Waltham, MA: NCCN; reviewed January 2016.
2. Huang JW, Wang Y, Dhillon KK, et al. Systematic screen identifies miRNAs that target RAD51 and RAD51D to enhance chemosensitivity. Mol Cancer Res. 2013;11(12):1564-1573.
3. Konstantinopoulos PA, Bristow RE. Neoadjuvant chemotherapy for newly diagnosed advanced ovarian cancer. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed January 2016.
4. Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet. 2011;43(9):879-882.
5. National Comprehensive Cancer Network (NCCN). Ovarian cancer. NCCN Clinical Practice Guidelines in Oncology, Version 2.2015. Fort Washington, PA: NCCN; 2015.
6. Ratajska M, Antoszewska E, Piskorz A, et al. Cancer predisposing BARD1 mutations in breast-ovarian cancer families. Breast Cancer Res Treat. 2012;131(1):89-97.
7. Thompson ER, Rowley SM, Sawyer S, et al. Analysis of RAD51D in ovarian cancer patients and families with a history of ovarian or breast cancer. PLoS One. 2013;8(1):e54772.

#### Blood Lead Level as Marker of Increased Risk of Ovarian Cancer in BRCA1 Carriers

1. Kiljanczyk A, Matuszczak M, Marcinia W, et al. Blood lead level as marker of increased risk of ovarian cancer in BRCA1 carriers. 2024;16(9):1370.

#### Testing for Germline FANCG Variants in Predisposition to Breast and Ovarian Cancer

1. Song H, Dicks EM, Tyrer J, et al. Population-based targeted sequencing of 54 candidate genes identifies PALB2 as a susceptibility gene for high-grade serous ovarian cancer. J Med Genet. 2021;58(5):305-313.
2. Soukupova J, Stastna B, Kanwal M, et al; CZECANCA consortium. A comprehensive study evaluating germline FANCG variants in predisposition to breast and ovarian cancer. Cancer Med. 2024;13(16):e70103.



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