Stage I: Rule-Out Dashboard

Incidental Findings in Adults

GENE/GENE PANEL: *BRCA1*, *BRCA2*
HGNC ID: 1100, 1101

DISORDER: Hereditary Breast and Ovarian Cancer
OMIM ID: 604370, 612555

ACTIONABILITY

1. **Is there a qualifying resource, such as a practice guideline or systematic review, for the genetic condition?**

☒ **YES** ☐ **NO**

2. **Does the practice guideline or systematic review indicate that the result is actionable in one or more of the following ways?**

Yes	No	
☒	☐	Patient Management
☒	☐	Surveillance or Screening
☒	☐	Family Management
☒	☐	Circumstances to Avoid

☒ **YES (≥ 1 of above)** ☐ **NO**

3. **Is the result actionable in an undiagnosed adult with the genetic condition?**

☒ **YES** ☐ **NO**

PENETRANCE

4. **Is there at least one known pathogenic variant with at least moderate penetrance (≥40%) or moderate relative risk (≥2) in any population?**

☒ **YES** ☐ **NO**

SIGNIFICANCE/BURDEN OF DISEASE

5. **Is this condition an important health problem?**

☒ **YES** ☐ **NO**

NEXT STEPS

6. **Are Actionability (Q2-3), Penetrance (Q4), and Significance (Q5) all "YES"?**

☒ **YES (Proceed to Stage II)**

☐ **NO (Consult Actionability Working Group)**

- ☐ **Exception granted, proceed to Stage II**
- ☐ **Exception not granted, STOP**

Stage II: Summary Report

Incidental Findings in Adults

Non-diagnostic, excludes newborn screening & prenatal testing/screening

GENE/GENE PANEL: *BRCA1*, *BRCA2*		**DISORDER:** Hereditary Breast and Ovarian Cancer	
Topic		**Narrative Description of Evidence**	**Ref**
1. What is the nature of the threat to health for an individual carrying a deleterious allele?			
Prevalence of the genetic disorder		For women, lifetime risk estimates indicate that 12.3% will develop breast cancer and 2.8% will die from it, while 1.4% will develop ovarian cancer and 1% will die from it. Among these breast and ovarian cancer cases, *BRCA* mutations have a prevalence of 3% and 10%, respectively.	(1;2)
Signif/Burden of Condition	**Clinical Features** (Signs/symptoms)	*BRCA1* and *BRCA2* mutations are associated with increased risks of breast, ovarian, fallopian tube, and primary peritoneal cancers in women. These mutations are also associated with breast cancer and, to a lesser extent, prostate cancer, in males. Both sexes may also be at an increased risk of pancreatic cancer. *BRCA* mutations are associated with a strong family history of breast and ovarian cancers and are found more frequently in the Ashkenazi Jewish population.	(1;3)
	Natural History (Important subgroups & survival/recovery)	*BRCA*-related breast and ovarian cancers occur at a younger age, typically prior to age 50, and breast cancers are more likely to be "triple-negative" (i.e. estrogen and progesterone receptor and HER2 negative). Compared to non-carriers with breast cancer, *BRCA1* mutation carriers have significantly decreased overall survival rates both in the short- and long-term, though similar association was not detected for *BRCA2* mutation carriers.	(1;3)
2. How effective are interventions for preventing the harm?			
Patient Management		Chemoprevention medications (e.g. tamoxifen, raloxifene) have been shown to reduce the incidence of breast cancer in high-risk women in the general population, but their effectiveness has not been assessed in the context of *BRCA* mutations. **(Tier 1)** Prophylactic surgery (e.g. bilateral mastectomy or salpingo-oophorectomy) has been shown to substantially reduce the risk for breast or ovarian cancer in both high-risk women and those who are *BRCA* mutation carriers. Breast cancer risk was reduced by 85-100% with mastectomy and by 37% to 100% with oophorectomy. Ovarian cancer risk was reduced by 69-100% with oophorectomy. Breast cancer-specific mortality was reduced by 81-100% after mastectomy and all-cause mortality was reduced by 55-100% after oophorectomy. **(Tier 1)**	(1;4;5) (1;4-6)
Surveillance		More frequent and intensive breast cancer screening, including clinical breast exams, mammography, and MRI starting at age 25. However, no screening methods have been shown to be effective at reducing breast cancer incidence among *BRCA* mutation carriers. **(Tier 1)** Screening methods for ovarian cancer have not been shown to be effective among women with *BRCA* mutations; however, annual gynecological exam, vaginal ultrasonography, and serum 125 (CA-125) can be used for screening. **(Tier 1)** Male carriers are recommended to have an annual breast exam. Information on effectiveness was not provided. **(Tier 2)**	(1;4;5) (7) (8)
Family Management		Family members at risk of carrying a *BRCA* mutation should undergo genetic testing to determine their genetic risk. **(Tier 1)** First degree relatives of a carrier of a *BRCA* mutation who have not undergone genetic testing themselves are recommended to undergo the same surveillance as carriers. **(Tier 2)**	(4) (8)
Circumstances to Avoid		Oral contraceptive use has been shown to be protective against ovarian cancer. However, some studies have suggested that oral contraceptive use increases the risk of breast cancer in women with *BRCA* mutations, though this effect has not been consistently demonstrated. **(Tier 2)**	(8;9)

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Description of sources of evidence:

Tier 1: Evidence from a systematic review, or a meta-analysis or clinical practice guideline clearly based on a systematic review
Tier 2: Evidence from clinical practice guidelines or broad-based expert consensus with non-systematic evidence review
Tier 3: Evidence from another source with non-systematic review of evidence with primary literature cited
Tier 4: Evidence from another source with non-systematic review of evidence with no citations to primary data sources
Tier 5: Evidence from a non-systematically identified source

GENE/GENE PANEL:	DISORDER:	
Topic	**Narrative Description of Evidence**	**Ref**
3. What is the chance that this threat will materialize?		
Mode of Inheritance	Autosomal dominant	
Prevalence of Genetic Mutations	*BRCA* mutations have an estimated 0.2-0.3% prevalence in the general population and 2.1% among women with Ashkenazi Jewish heritage. **(Tier 1)**	(1)
Penetrance OR Relative Risk (include high risk racial or ethnic subgroups)	Clinically significant mutations in *BRCA1* are associated with a 46-57% risk of breast cancer and 40% risk of ovarian cancer by age 70. *BRCA2* mutations are associated with a 50% risk of breast cancer and almost 20% risk of ovarian cancer by age 70. **(Tier 1)**	(1;10)
	Information on relative risk was unavailable.	
Expressivity	The pathologic and clinical characteristics of tumors can differ by the type of mutation, including progression and variability in estrogen, progesterone, and human epidermal growth factor receptor status. **(Tier 3)**	(1)
4. What is the nature of the intervention?		
Nature of Intervention	The interventions identified in this report include prophylactic surgery to remove target organs, invasive screening tests, and medications with potential side effects.	
5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?		
Chance to Escape Clinical Detection	Current screening procedures for women of average risk are not likely to detect breast and ovarian cancer at an early enough stage to cure the disease. The age at onset of breast cancer is typically prior to age 50, before the start of typical surveillance among average risk populations. Ovarian cancer is typically metastatic when diagnosed, thus risk-reducing BSO bilateral salpingo-oophorectomy is currently the only effective strategy to reduce the risk of dying from ovarian cancer. **(Tier 1)**	(1;4)

Final Consensus Scores						
Gene(s)	**Outcome/intervention pair**	**Severity**	**Likelihood**	**Effectiveness**	**Nature of the Intervention**	**Total Score**
BRCA1	Breast Cancer/Surveilance	2	3A	2A	3	10AA
	Breast Cancer/Mastectomy	2	3A	3A	1	9AA
	Ovarian Cancer/Oophorectomy	2	2A	3A	1	8AA
BRCA2	Breast Cancer/Surveillance	2	3A	2A	3	10AA
	Breast Cancer/Mastectomy	2	3A	3A	1	9AA
	Ovarian Cancer/Oophorectomy	2	2A	3A	1	8AA

To see the scoring key, please go to: https://clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-based-summaries/.

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Date of Search (MM.DD.YYYY): 01.28.2014

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