Specific Changes:

1) On GENE-1, replace 2nd bullet with “As many patients have phenotypes that overlap more than one gene/syndrome, clinicians should give strong consideration to multi-gene panel testing when a patient is being assessed for genetic risk. Challenges to testing for only one gene at a time include syndrome overlap, complex or unknown family histories, and inefficiencies in sequential testing.”

2) On ADDIT-2, move RAD51C, RAD51D and BRIP1 to the “Intervention Warranted based on gene and/or risk level” section of the table for RRSO.

FDA Clearance: Not applicable.

Rationale: With the cost reductions that have come with next generation sequencing, the need to identify sequential differential diagnoses for genetic testing is reduced. While we currently rely on personal and family history to identify the most appropriate genetic test, this approach has limited utility among patients with a poor understanding of their cancer family history either due to misattributed paternity, poor communication among family members, ignorance of cancer types or small families. Using a broader pan-cancer panel approach can mitigate the limitations in family history collection and provide efficiency in testing for the multiple genes associated with hereditary cancer risk.

Recent papers have shown RAD51C, RAD51D, and BRIP1 to have ovarian cancer risks similar to the Lynch syndrome genes (6.5%, 7%, 8.3% and 4-24%, respectively). These studies do suggest older ages of onset, making post-menopausal oophorectomy a reasonable consideration for patients with pathogenic variants in these genes.

The following articles are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

Syndrome overlap:


**Challenges in family history collection:**


**Ovarian cancer risk genes:**


Sincerely,

[Signature]

Johnathan Lancaster, MD, PhD
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