Call for Correspondence

JNCCN is committed to providing a forum to enhance collaboration between academic medicine and the community physician. We welcome comments about the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), articles published in the journal, or any other topic relating to cancer prevention, detection, treatment, supportive care, or survivorship. Please submit correspondence at JNCCN.edmgr.com.

Letters should be no more than 400 words, with no more than 5 references if included. Please include the full names, degrees, and affiliations of all letter authors and a phone number or e-mail address for contact.

Letters are considered for publication as space allows. NCCN reserves the right not to publish correspondence for any reason it deems appropriate. All letters are subject to editing and/or abridgment.

To the Editor: I read with interest the recent NCCN Guidelines Insights for Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2015, in the journal.¹ The NCCN Guidelines Insights offer clear evidence-based recommendations regarding how to address identified germline mutations associated with common and uncommon inherited cancer syndromes, the unclear role for multigene testing, and even guidance for patients who have germline variants of uncertain significance.²

However, how does one approach the patient who has a high pretest probability of having a germline mutation whose multigene test results show no mutations? For example, I recently saw a patient who, by age 57, had experienced 2 breast cancers and pancreatic cancer. Her sister had ovarian cancer at a young age. Next-generation sequencing (NGS) for 48 genes revealed no abnormalities associated with increased cancer risk.

The NCCN Clinical Practice Guidelines in Oncology for Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version, 2.2016, suggest “individualized recommendations according to personal and family history” (page BRCA-2).² The footnote mentions testing another family member. Is that based on data showing that patients with a high pretest probability have a significance false-negative testing rate with multigene testing? Are there studies showing that patients with negative multigene test results but who have a high pretest probability are at higher risk for cancers associated with common germline mutations compared with the general population?

With so many potential recommendations involved, citing the evidence for what to do for the patient with negative germline testing results is important as well.

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References

1. Daly MB, Pilarski R, Axilbund JE, et al. NCCN Guidelines Insights for Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2015. J Natl Compr Canc Netw 2016;14:153–162.
2. Daly MB, Pilarski R, Axilbund JE, et al. NCCN Clinical Practice Guidelines in Oncology for Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2016. Accessed April 18, 2016. To view the most recent version of these guidelines, visit NCCN.org.

The Authors' Reply: We thank Dr. Sorscher for his questions regarding the NCCN Guidelines Insights for Genetic/Familial High Risk Assessment: Breast and Ovarian and the NCCN Guidelines they originate from. The NCCN panel attempts to set recommended management guidelines based on the available data, which are at times admittedly limited. The recommendation that individuals who have negative genetic testing should be followed with individualized management “according to personal and family history” is based on the reality that a negative genetic test result does not rule out hereditary risk, because all cancer predisposition genes have not been identified (and testing is not 100% accurate in detecting mutations in the known genes). In these cases, we must manage individuals based on the empiric risks presented by their unique family history.

The recommendation to consider testing another family member is not based on data suggesting a high false-negative rate. Rather it is based on the understanding that sporadic cancers (phenocopies) may arise within families in which a gene mutation is causing most of the other cancers in the family. Because it is possible that the person who had a negative result had a cancer that was a phenocopy, in families with a strong family history of cancer it may be wise to try testing another affected individual.

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Obviously, in both of these situations, good clinical judgement is necessary to guide these decisions. The NCCN Guidelines are intended to aid in such judgement.

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