On behalf of Illumina, I respectfully request the NCCN Breast Cancer guideline panel to review the enclosed to support the consideration of comprehensive genetic testing in the context of genetic counseling.

Specific Requested Changes:
We propose that consideration of comprehensive genetic testing should be considered within the context of genetic counseling, as suggested in the Genetic/Familial High-Risk Assessment: Breast and Ovarian NCCN Guidelines v 1.2018. Similarly, we propose that genetic testing of family members or blood relatives of at-risk individuals be considered within the context of genetic counseling, as suggested in the Genetic/Familial High-Risk Assessment: Breast and Ovarian NCCN Guidelines v 1.2018.

FDA Clearance:
The recommendation to use an NGS-based technique is not associated with any specific FDA-cleared product/s.

Rationale:
The NCCN guidelines currently include recommendations for screening BRCA1 and BRCA2 for known high-penetrance mutations in high-risk individuals. Clinical evidence demonstrates the benefit of enhanced screening and surgery in individuals known to carry BRCA1/2 pathogenic mutations.1,2 Recent studies demonstrate that BRCA1/2 testing is well-accepted in newly-diagnosed breast and ovarian cancer patients,3 and that higher breast cancer genetics knowledge is associated with greater adherence to breast cancer risk management.4 Single-gene testing of BRCA1/2 may not detect DNA structural variants.5,7 In addition, current guidelines recommend genetic testing of additional high-risk genes (TP53, and PTEN), as well as multiple moderate-risk genes (ATM, BRIP1, CDH1, CHEK2, NBN, PALB2, RAD51C, RAD51D, and STK11) in high-risk individuals.8,9 Beyond single-gene testing, abundant clinical data demonstrate that next-generation sequencing-based multi-gene testing identifies more women at risk of developing breast cancer, including triple-negative breast cancer, compared to BRCA1/2 single-gene testing alone.10-14 Consequently, the Genetic/Familial High-Risk Assessment: Breast and Ovarian NCCN Guidelines v 1.2018 call for comprehensive testing of the BRCA1/2 genes, including full sequencing, as well as multi-gene testing (Guideline section MS-9).8

The current guidelines strongly recommend that a genetic counselor with expertise in cancer genetics should be involved in the genetic testing process for high-risk breast cancer, including pre-test counseling. For example, when referring to testing criteria for BRCA1/2, the panel states, “Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.”12 Given the genetic component of risk genes and published clinical data, the U.S. Preventive Services Task Force (USPSTF) currently recommends that genetic counseling include risk assessment for potentially harmful BRCA mutations as well as identification of affected family members who may be preferred candidates for genetic testing.13 Further, the USPSTF recommends testing of family members to determine whether affected family members have clinically significant mutations in breast cancer risk genes.14 Similarly, the Genetic/Familial High-Risk Assessment: Breast and Ovarian NCCN Guidelines v 1.2018 recommends BRCA1/2 genetic testing of patient’s family members stating, “Consider comprehensive BRCA1/BRCA2 testing of patient or if unaffected, test family member with highest likelihood of a mutation.”15

Proposed Changes
Current Excerpt 1: Bullet of Figure BINV-1: Invasive Breast Cancer Workup

“Genetic counseling if patient is high risk for hereditary breast cancer.”

New statement:

“Genetic counseling and consideration of comprehensive genetic testing if patient or family member is at risk for hereditary breast cancers.”
Figures where propose change is suggested:
DCIS-1, BINV-10, BINV-14, BINV-17, IBC-1, MS-6, MS-7, MS-45, MS-51, and MS-70

The following articles are submitted in support of consideration of comprehensive genetic testing of patient and family members in the context of genetic counseling. We would like to acknowledge the contributions of NCCN panel members, who are also co-authors or co-contributors in some of these publications.


Sincerely,

Amy Mueller MD