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NCCN Guidelines Panel: Breast Cancer

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,[10] compared to *BRCA1/2* single-gene testing alone.[11-16] 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."[8] 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.[17] Further, the USPSTF recommends testing of family members to determine whether affected family members have clinically significant mutations in breast cancer risk genes.[17] 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."[8]

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.

1. Domchek SM, Friebel TM, Singer CF, et al. (2010) Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304:967-975.

2. Hartmann LC and Lindor NM (2016) The Role of Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer. N Engl J Med. 2016;374:454-468.

3. Hoberg-Vetti H, Bjorvatn C, Fiane BE, et al. (2016) BRCA1/2 testing in newly diagnosed breast and ovarian cancer patients without prior genetic counselling: the DNA-BONus study. Eur J Hum Genet. 2016;24:881-888.

4. Buchanan AH, Voils CI, Schildkraut JM, et al. (2017) Adherence to Recommended Risk Management among Unaffected Women with a BRCA Mutation. J Genet Couns. 2017;26:79-92.

5. Weitzel JN, Lagos VI, Herzog JS, et al. (2007) Evidence for common ancestral origin of a recurring BRCA1 genomic rearrangement identified in high-risk Hispanic families. Cancer Epidemiol Biomarkers Prev. 2007;16:1615-1620.

6. Walsh T, Casadei S, Coats KH, et al. (2006) Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA. 2006;295:1379-1388.

7. Palma MD, Domchek SM, Stopfer J, et al. (2008) The relative contribution of point mutations and genomic rearrangements in BRCA1 and BRCA2 in high-risk breast cancer families. Cancer Res. 2008;68:7006-7014.

8. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian (Version 1.2018). https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed January 18, 2018.

9. Daly MB, Pilarski R, Axilbund JE, et al. (2016) Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2015. J Natl Compr Canc Netw. 2016;14:153-162.

10. Couch FJ, Hart SN, Sharma P, Toland AE, Wang X, Miron P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015;33(4):304-11.

11. Tung N, Battelli C, Allen B, Kaldate R, Bhatnagar S, Bowles K, 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.

12. Tung N, Lin NU, Kidd J, Allen BA, Singh N, Wenstrup RJ, et al. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer. J Clin Oncol. 2016;34(13):1460-8.

13. Buys SS, Sandbach JF, Gammon A, Patel G, Kidd J, Brown KL, 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):1721-30.

14. Susswein LR, Marshall ML, Nusbaum R, Vogel Postula KJ, Weissman SM, Yackowski L, et al. Pathogenic and likely pathogenic variant prevalence among the first 10,000 patients referred for next-generation cancer panel testing. Genet Med. 2016;18(8):823-32.

15. Desmond A, Kurian AW, Gabree M, Mills MA, Anderson MJ, Kobayashi Y, et al. Clinical Actionability of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer Risk Assessment. JAMA Oncol. 2015;1(7):943-51.

16. Couch FJ, Shimelis H, Hu C, Hart SN, Polley EC, Na J, et al. Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. Ibid.2017;3(9):1190-6

17. Force USPST (2015) Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: Recommendation Statement. Am Fam Physician. 2015;91:Online.

Sincerely,

Amy Mueller MD