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 NCCN Guidelines Panel: Genetic/Familial High-Risk Assessment: Breast and Ovarian

On behalf of Illumina, I respectfully request the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian guideline panel to review the enclosed to support the use of next-generation sequencing (NGS)-based multi-gene testing in preference to single-gene testing.

#### **Specific Requested Changes:**

We propose that multi-gene testing be supported as the preferable way to begin testing when interrogating high- and medium-risk mutations in the Genetic/Familial High-Risk Assessment: Breast and Ovarian NCCN Guidelines v 1.2018. Similarly, we propose that the discussion statement favoring the performance of single-gene testing over multi-gene testing be removed from 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 for known high-penetrance mutations in several high-risk genes (*BRCA1/2*, *TP53*, and *PTEN*), as well as multiple moderate-risk genes (*ATM*, *BRIP1*, *CDH1*, *CHEK2*, *NBN*, *PALB2*, *RAD51C*, *RAD51D*, and *STK11*). The presence of pathogenic variants in these genes can alter the clinical management of breast and/or ovarian cancer. Abundant clinical data demonstrate that NGS-based multi-gene testing identifies more women at risk of developing breast cancer, including triple-negative breast cancer,<sup>1</sup> compared to *BRCA1/2* single-gene testing alone.<sup>2-7</sup> In a recent study, a 25-gene panel was used to retrospectively analyze the frequency of pathogenic variants in 35,409 women with a single diagnosis of breast cancer.<sup>4</sup> Multi-gene testing identified pathogenic variants in 9.3% of these women, with more than half of these pathogenic variants in genes other than *BRCA1* or *BRCA2*. Thus, compared to *BRCA* testing, multi-gene testing more than doubled the number of women that could potentially benefit from a change in treatment strategy according to current NCCN guidelines.<sup>4</sup> Comparable results were obtained with a 21-gene panel in a recent study that analyzed breast cancer risk in 65,057 women with breast cancer referred for multigene testing.<sup>7</sup> After excluding *BRCA1* and *BRCA2* variants, pathogenic variants were detected in 6.2 % of these women with breast cancer. Moreover, the efficacy and cost-effectiveness of single-gene *BRCA1/2* testing versus multi-gene NGS testing has been modeled in hypothetical cohorts of 40-year and 50-year old cohorts of women meeting current NCCN criteria for genetic testing for breast cancer or other hereditary syndromes associated with breast cancer. The study estimated that multi-gene testing, followed by risk-reduction management, could cost-effectively improve the life expectancy by 0.007-0.012 life years for women at risk of breast cancer.<sup>8</sup>

Multiple studies have documented higher diagnostic yields for NGS-based multi-gene tests compared with single-tests for *BRCA* mutations.<sup>2,4,9,10</sup> Prospective and retrospective clinical studies have demonstrated that NGS testing is perfectly concordant with traditional single-gene testing, across more than 750 variants,<sup>11</sup> and can identify clinically significant mutations that are not detectable by single-gene testing.<sup>12</sup> In a recent study, NGS testing detected 28 specific mutations in the *SCN1A* gene that were missed by Sanger sequencing, due in part to technical limitations of Sanger sequencing.<sup>13</sup> Similarly, evaluation of *PIK3CA* gene mutations in 186 breast carcinomas by NGS demonstrated that 4.8% of breast tumors had *PIK3CA* mutations that were not detected by Sanger sequencing.<sup>14</sup>

#### **Proposed Changes**

##### **Current Excerpt 1: Footer “k” of Figure BR/OV-2: Breast and/or Ovarian Cancer Genetic Assessment**

*“k In some cases, multi-gene testing may be a preferable way to begin testing over the single-gene testing process.”*

**Proposed Change:**

Delete "In some cases,"

**New statement:**

"Multi-gene testing is a preferable way to begin testing over the single gene testing process."

**Current Excerpt 2: Discussion (MS-10): Genetic/Familial High-Risk Assessment: Breast and Ovarian**

"Second, in some cases, next-generation sequencing may miss some mutations that would have been detected with traditional single-gene analysis."

**Proposed Change**

Delete "Second, in some cases, next-generation sequencing may miss some mutations that would have been detected with traditional single-gene analysis."

The following articles are submitted in support of using NGS as a multi-gene testing technique. 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. 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.
2. Tung N, Battelli C, Allen B, Kaldete 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. Li Y, Arellano AR, Bare LA, Bender RA, Strom CM, Devlin JJ. A Multigene Test Could Cost-Effectively Help Extend Life Expectancy for Women at Risk of Hereditary Breast Cancer. *Value Health*. 2017;20(4):547-55.
9. Kurian AW, Hare EE, Mills MA, Kingham KE, McPherson L, Whittemore AS, et al. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol*. 2014;32(19):2001-9.
10. Castera L, Krieger S, Rousselin A, Legros A, Baumann JJ, Bruet O, et al. Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes. *Eur J Hum Genet*. 2014;22(11):1305-13.
11. Lincoln SE, Kobayashi Y, Anderson MJ, Yang S, Desmond AJ, Mills MA, et al. A Systematic Comparison of Traditional and Multigene Panel Testing for Hereditary Breast and Ovarian Cancer Genes in More Than 1000 Patients. *J Mol Diagn*. 2015;17(5):533-44.
12. Hiemenz MC, Kadauke S, Lieberman DB, Roth DB, Zhao J, Watt CD, et al. Building a Robust Tumor Profiling Program: Synergy between Next-Generation Sequencing and Targeted Single-Gene Testing. *PLoS One*. 2016;11(4):e0152851.
13. Djemie T, Weckhuysen S, von Spiczak S, Carvill GL, Jaehn J, Anttonen AK, et al. Pitfalls in genetic testing: the story of missed SCN1A mutations. *Mol Genet Genomic Med*. 2016;4(4):457-64.
14. Arsenic R, Treue D, Lehmann A, Hummel M, Dietel M, Denkert C, et al. Comparison of targeted next-generation sequencing and Sanger sequencing for the detection of PIK3CA mutations in breast cancer. *BMC Clin Pathol*. 2015;15:20.

Sincerely,

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