March 17, 2021

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NCCN Guidelines panel:	Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic

Dear NCCN Panel Members,

On behalf of Ambry Genetics, GeneDx, Inc., Illumina, Myriad Genetic Laboratories, Inc., and Quest Diagnostics Laboratories, we respectfully request your review of the following proposed modifications of the "High-Risk Assessment: Breast, Ovarian and Pancreatic guideline, Version 2.2021 – November 20, 2020".

Specific requested changes, in blue, as follows:

- New text has been added in all capital letters; Text for removal has been crossed out.

1. Update panel testing wording to align with current clinical practice.

A. Page EVAL-A 3 of 6, second arrow:
Please change the statement as follows:

> "An individual's personal and/or family history ~~may~~ CAN USUALLY be explained by more than one inherited cancer syndrome; thus, IN MOST CASES phenotype-directed testing based on personal and family history through a multi-gene panel test (TESTING FOR PATHOGENIC VARIANTS IN MORE THAN ONE GENE) WILL ~~may~~ be more efficient and cost-effective…"

B. Page GENE, 1 testing algorithm, under "Genetic Testing" column:
Please remove the words "Recommend" from the upper branch and "Consider" from the lower branch, which would make it consistent with the algorithms on pages LS-2 and POLYP-1 of the NCCN Genetic/Familial High-Risk: Colorectal guidelines.

C. Pages CRIT-4 (LFS criteria) and on page CRIT-5 (PHTS criteria):
Please add the following footnote: "When this gene is included as part of a multigene panel, an individual does not need to meet these testing criteria if testing criteria on pages CRIT-1 or CRIT-2 are met." (We are concerned that the separate criteria on pages CRIT-4 and CRIT-5 may be interpreted to mean that the syndrome-specific criteria must always be met to consider testing for *TP53* and *PTEN*, respectively.)

Rationale:
The reality of current clinical practice is that multigene panel testing has largely replaced more targeted (Kurian et al., 2018) testing, and 90% or more of orders are for multigene panel testing in the experience of most of our labs. In addition, numerous studies have shown that multigene panel testing typically leads to at least a doubling in the number of clinically-actionable pathogenic variants identified (over targeted testing of only the *BRCA* or Lynch syndrome genes), as well as the identification of pathogenic variants in clinically actionable hereditary cancer susceptibility genes not suspected by the clinical presentation in the patient and family (LaDuca et al., 2020; Rosenthal et al., 2017; Susswein et al., 2016).

FDA Clearance: Not applicable

2. **Change to eligibility for multiple primary breast cancer:**

Page CRIT-1, #3 (Personal history of cancer), second arrow:
Please allow first age of breast cancer diagnosis to be at age 70 or under.

Page CRIT-2, "Testing may be considered…" section:
Delete the first point: "Bilateral breast cancer, first diagnosed between the ages of 50 and 65."

Rationale:
The prevalence of breast cancer-associated pathogenic variants is well above 5% among women with two or more breast cancers who developed their first breast cancer age ≤70 (McGreevy et al., 2021). Similar findings were observed in Maxwell et al., even though that cohort excluded evaluation of those with *BRCA1* or *BRCA2* PV (Maxwell et al., 2021). Other multiple primary breast cancer studies have also shown lack of association between the age of first breast cancer diagnosis and whether an individual was carrying a pathogenic variant in a high or moderate penetrance gene (Hauke et al., 2018; Corredor et al., 2020). Collectively, the cited studies suggest no clear decline in PV prevalence if the first breast cancer was after age 50.

Alternatively, the committee could consider expansion to any woman with a second primary breast cancer regardless of initial age diagnosed. This concept is supported by the above referenced publications showing no substantial pathogenic variant prevalence drop off below 5% even if the first breast cancer was diagnosed after age 70.

FDA Clearance: Not applicable

3. **Correction of internal inconsistency regarding breast cancer testing eligibility**.

Page CRIT-1, #3, first bullet, fourth arrow: "Diagnosed at any age with:"
For internal consistency please change the third sub diamond to:

> "≥3 total diagnoses of breast OR PROSTATE (ANY NCCN RISK GROUP) cancer in patient and/or close blood relatives."

Rationale:

> Currently an individual with prostate cancer (at any age, and any NCCN group) meets testing criteria if he has "≥2 close relatives with either breast or prostate cancer (any grade) at any age" (last criterion under #3, bullet 4), as would his unaffected sibling. However, under current guidelines his female relative(s) with breast cancer would not meet testing criteria since for them only relatives affected with breast cancer are counted in the "≥3 total diagnoses" criterion cited above, leaving clinicians confused on the interpretation of guidelines. The proposed wording change would clarify this discrepancy.

4. **Clarification of treatment-related eligibility**.

Page CRIT -1, #3, last bullet:
Please change last bullet point to: "To aid in systemic therapy decision-making, such as for INDIVIDUALS WHO ARE, OR MAY BECOME ELIGIBLE FOR TREATMENT WITH A PARP INHIBITOR, INCLUDING BUT NOT LIMITED TO HER2-negative LOCALLY-ADVANCED OR metastatic breast cancer."

Rationale:
This change aligns the NCCN language with current FDA companion diagnostic and therapeutic labeling (US Food and Drug Administration 2014; Lynparza package insert, 2018; Talzenna package insert, 2018). The language "who are, or may become eligible for" is further supported by research identifying that 20-30% of individuals will become metastatic over the course of their breast cancer treatment (O'Shaughnessy 2005). The final overall survival data from the OlympiAD trial shows a significant benefit when *BRCA1/2* mutation-positive women receive olaparib treatment before chemotherapy in the

metastatic setting (Robson et al., 2019). Similarly, superiority of olaparib to placebo in germline *BRCA1/2* carriers with chemotherapy-treated early-stage HER2-negative breast cancer was recently announced from the OlympiA trial (similar in name but unique from OlympiAD) with details forthcoming (Cancernetwork.com 2021; ClinicalTrials.gov)**.** Collectively, this highlights the importance of establishing *BRCA* mutation status in HER2-negative disease at the time of initial diagnosis, or at least before a metastatic diagnosis. The current statement in these NCCN guidelines limits access to treatment-directed testing.

While we recognize this committee is not treatment-focused, the hereditary cancer and oncology fields are becoming unavoidably inter-related. This new wording would encourage a partnership between treating physicians and genetics providers to provide appropriate and high-quality genetic counseling/testing that may affect their treatment planning.

FDA Clearance: Yes, 3 FDA labels support this statement.

5. **Clarification of wording.**

Page CRIT-2, #4, bullet 1, arrow 1:

Please consider rewording this statement for clarification as follows:

> "If the affected relative has ISOLATED pancreatic or prostate cancer (metastatic… or Very-High-Risk Group), WITH NO OTHER RELATIVES WITH BREAST, OVARIAN, PANCREATIC OR PROSTATE CANCER MEETING OTHER NCCN TESTING CRITERIA, THEN only first-degree relatives, and not second degree, should be offered testing."

Rationale:
The meaning of the final clause of the current wording ("…unless indicated for other relatives based on additional family history") is unclear and has led to confusion among ordering providers. We believe the proposed wording helps clarify the intent of this criterion.

FDA Clearance: Not applicable

We thank you for your consideration of these requests.

Sincerely,

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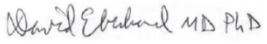

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References

1. Kurian AW, Ward KC, Hamilton AS et al. Uptake, results and outcomes of germline multi-gene sequencing after diagnosis of breast cancer. *JAMA Oncol* 2018;4:1066-1072.

2. LaDuca H, Polley EC, Yussuf A, et al. A clinical guide to hereditary cancer panel testing: Evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. *Genet Med*. 2020;22:407-415.

3. Rosenthal ET, Bernhisel R, Brown K, Kidd J, Manley S. Clinical testing with a panel of 25 genes associated with increased cancer risk results in a significant increase in clinically significant findings across a broad range of cancer histories. *Cancer Genet.* 2017;218-219:58-68.

4. Susswein LR, Marshall ML, Nusbaum R, 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):823-832.

5. McGreevy K, Svirsky K, Kidd J et al. (2021) Multigene assessment of genetic risk with two or more breast cancers. *Breast Cancer Research and Treatment*, manuscript in press.

6. Maxwell KN, Wenz BM, Kulkarni A et al. (2020) Mutation rates in cancer susceptibility genes in patients with breast cancer with multiple primary cancers. *JCO Precision Oncology* 4:916-925.

7. Hauke J, Horvath J, Gross E et al. (2018) Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. *Cancer Med* 7 (4):1349-1358. doi:10.1002/cam4.1376

8. Corredor J, Woodson AH, Gutierrez Barrera A, Arun B (2020) Multigene panel testing results in patients with multiple breast cancer primaries. *Breast J* doi:10.1111/tbj.13762

9. U.S. Food and Drug Administration (FDA). (2014). Premarket Approval; BRACAnalysis CDx. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P140020; relevant supplements S003, S012, and S015

10. Lynparza (olaparib) [package insert]. Gaithersburg, MD: AstraZeneca; 2018

11. Talzenna (talazoparib) [package insert]. New York, NY: Pfizer; 2018

12. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. *Oncologist* 2005;10 (Suppl 3):20–9.

13. Cancernetwork.com, February 17, 2021. Downloaded from: https://www.cancernetwork.com/view/phase-3-olympia-trial-for-her2-negative-breast-cancer-moves-to-early-primary-analysis-per-idmc-recommendation

14. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT02032823.

15. Robson ME, Tung N, Conte P, Im SA, Senkus E, Xu B, Masuda N, Delaloge S, Li W, Armstrong A, Wu W, Goessl C, Runswick S, Domchek SM. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol* 2019;30(4):558-566.