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

I respectfully request the NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian panel to review the enclosed proposal and literature for consideration of a change in criteria for further genetic risk evaluation regarding Ashkenazi Jews.

Specific Changes: Recommend the criteria for genetic risk evaluation to include patients of Ashkenazi Jewish ancestry, regardless of personal or family history.

In the absence of a personal or family history of cancer, this may be limited to testing for the 3 *BRCA*1/*BRCA*2 founder mutations that are common in this population.

Rationale: *BRCA*1/2 founder mutations are present in 1:40 individuals of Ashkenazi Jewish ancestry, responsible for patients having a high risk for breast and ovarian cancer, as well as significantly increased risks for prostate and pancreatic cancer. Aggressive surveillance and risk reducing surgeries have been shown to be effective in reducing breast and ovarian cancer risks in female mutation carriers.

Literature supporting the potential value of *BRCA*1/2 founder mutation population screening in Ashkenazi Jews includes pilot studies showing that: 1) *BRCA*1/2 mutation carriers have significant cancer risks regardless of family history, 2) close to 50% of mutation carriers are missed if testing is based on adherence to current criteria based on personal and family cancer histories, 3) interest and uptake in the Ashkenazi community is high, with no evidence for significant adverse impacts, and 4) this is likely to be a cost-effective approach for the prevention of illness and death due to breast and ovarian cancer.

As an Ashkenazi Jewish gynecologist who serves Baltimore, Maryland where 100,000 Jews reside, a grassroots movement to educate about the *BRCA* genes and related diseases has taken hold. Educational programs have been active in synagogues, homes, and community centers. I have seen Jews of all denominations: men, women, young, and old who want to prevent cancers for themselves, their families, and future generations due to this high carrier rate.

In my practice, I am caring for a large Jewish Family who stumbled upon their diagnosis of *BRCA* as a result of ancestry genetic testing. There was no personal or family history of breast, ovarian, or pancreatic cancers. At the time of diagnosis, a 37 year old woman, who would not have met current criteria for either mammogram or *BRCA* testing, was diagnosed on MRI and confirmed pathologically with Stage 1A breast cancer. We have since identified 11 additional family members who also carry the BRCA gene.

With rapid, more affordable testing availability, and clear algorithms for management and surveillance, a dialogue should be opened to consider population screening for all Ashkenazi Jews in the United States.

The following articles are submitted in support of this proposed change:

1. Daly MB, et al. NCCN Guidelines Version 2.2017. Genetic/Familial High-Risk Assessment: Breast and Ovarian. Accessed 070117
2. Moyer VA. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014; 160 (4): 271 - 281.
3. Gabai-Kapara E, Lahad A, Kaufman B et al. Population-based screening for breast and ovarian cancer risk due to *BRCA*1 and *BRCA*2. Proc Natl Acad Sci USA. 2014; 111 (39): 14205-14210.
4. Roa BB, Boyd AA, Vocik K, et al: Ashkenazi Jewish population frequencies for common mutations in *BRCA*1 and *BRCA*2 Nat Genet 14: 185- 187, 1996
5. Metcalfe, K. A. et al. Screening for founder mutations in *BRCA*1 and *BRCA*2 in unselected Jewish women. J. Clin. Oncol. 28, 387-391 (2010).
6. Manchanda R, Loggenberg K, Sanderson S, et al. Population testing for cancer predisposing *BRCA*1/*BRCA*2 mutations in the Ashkenazi-Jewish community: a randomized controlled trial. J Natl Cancer Inst. Jan 2015.
7. Weisman et al. Experiences from a pilot program bringing *BRCA*1/2 genetic screening to the US Ashkenazi Jewish population. Genet. Med. Oct 2016.
8. Domchek SM, Friebel TM Singer CF, et al. Association of risk-reducing surgery in *BRCA*1 or *BRCA*2 mutation carriers with cancer risk and mortality. JAMA. 2010; 304: 967 - 975.
9. Rubinstein WS, Jiang H., Dellefave L., et al: Cost-effectiveness of population based *BRCA*1/2 testing and ovarian cancer prevention for Ashkenazi Jews: A call for dialogue. Genet. Med. 11, 629-639 (2009).
10. Manchanda R, Legood R, Burnell M, et al. Cost effectiveness of population screening for *BRCA* mutations in Ashkenazi-Jewish women compared to family-history based testing. J Natl Cancer Inst. 2015.
11. King MC, Marks JH, Mandell JB, et al. Breast and Ovarian Cancer Risks Due to Inherited Mutations in *BRCA*1 and *BRCA*2. Science 2003 Oct 24; 302 (5645):643-6.