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

Dear Ms. Gregory:

On behalf of Oneinforty, I respectfully request that the National Comprehensive Cancer Network consider expanding access to lifesaving genetic testing information by recommending that all individuals with at least one Ashkenazi Jewish (AJ) grandparent be offered genetic testing to include, at a minimum, testing for the three founder mutations in BRCA1 and BRCA2.

Specific Change: We recommend that criteria for genetic risk evaluation include women and men with Ashkenazi Jewish heritage, regardless of personal or known family history.

Rationale: The literature is now replete with examples of population screening programs for founder BRCA1/2 mutations and has shown: 1) Risk for cancer remains high in an unselected population, 2) is cost effective, 3) acceptability of streamlined testing approaches, 4) universal screening circumvents



dependence on familial disclosure, 5) risk reduction and 6) screening can be lifesaving – these findings and the number of at risk individuals who remain undetected demand a change in practice.

Inherited mutations in BRCA1 and BRCA2 lead to dramatically increased risks for breast, ovarian and other cancers. While the details of whether to offer only multi-site testing, sequencing of BRCA1/2 with or without del/dup versus panel testing are debated, countless men and women with mutations discovered only *after* their diagnosis of a possibly fatal cancer and/or the diagnoses/deaths of family members could have been spared, had they had access to this critical information. We respectfully suggest that the time is right to consider changing NCCN guidelines to include offering, at a minimum, screening for the three founder mutations in BRCA1/2 in all individuals with Ashkenazi Jewish heritage. While testing is certainly available, without the endorsement of NCCN, many at risk individuals are not being offered testing, informed of the choices for genetic testing strategies, or being given access to critical surveillance and risk reducing options. NCCN endorsement for population screening of Ashkenazi Jewish individuals would likely lead insurers to cover the cost of testing, encourage providers across the spectrum of practice to inquire about ancestry and promote access to this critical testing option for appropriate individuals.

Highlights of the literature are summarized below, in support of the above request.

1. Population screening of Ashkenazi Jewish individuals leads to more efficient identification of carriers than relying on referral to a formal genetic counseling program.
 - Metcalfe K...Narod S et al 2013 studied Jewish population based screening using a streamlined pre-test information approach versus a clinic referral sample. This study found that population screening without regard to known family history identified a greater number of carriers, and that pre-test written information was acceptable. This study concluded that *all Jewish women above age 25 should be offered genetic testing for founder mutations, and that it would be acceptable to offer through a screening program with written pre-test information.*
2. Cancer risk remains high in BRCA1/2 carriers identified through population screening.
 - Gabai-Kapar, E ...Levy-Lahad E et al 2014 conducted a study offering multisite testing to cancer free Ashkenazi Jewish males and found that cumulative lifetime risks for breast and ovarian cancer in mutation positive families remained high. Cancer risks were similar to those ascertained through personal and known family history. This study concluded that *general screening would identify many carriers who are not evaluated by genetic testing based on family history criteria.*
3. Population screening for BRCA mutations in AJ women is cost effective compared with family history based testing.
 - Manchanda R...Jacobs I et al 2015 conducted a study to compare the cost effectiveness of population based BRCA testing with a standard family history based approach in AJ women, using a decision analytic model to compare lifetime costs and effects amongst AJ women in the UK of BRCA founder mutations among all AJ women age 30 or older or just women with over a 10% chance of having a mutation based on family history. This study found that:
 - Population screening was found to save more lives

- Population screening was found to be cost saving
- Population screening lowered the incidence of breast and ovarian cancer above family history based testing
- Concluded that *population based screening for BRCA mutations is highly cost effective compared with a family history based approach in AJ woman age 30 and older.*
- Manchanda R...Legood R et al 2017 conducted a follow-up study showing that *population screening for BRCA mutations is cost saving for those with 1, 2, 3 or 4 Ashkenazi grandparents in the US.*

The following additional literature is submitted in support of this proposed change:

1. Metcalfe KA et al. Is it time to offer BRCA1 and BRCA2 testing to all Jewish women? *Current Oncology* 2015; 22(4): e233
2. Metcalfe KA et al. A comparison of the detection of BRCA mutation carriers through the provision of Jewish population based genetic testing compared with clinic-based genetic testing. *BJC* (2013); 109:777
3. Manchanda R et al. Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry. *Am J Obstet Gynecol* 2017; 217:578
4. Manchanda R et al. Cost-effectiveness of Population Screening for BRCA Mutations in Ashkenazi Jewish Women compared with family history based testing. *J Natl Cancer Inst* 2015;107:1
5. Lieberman S et al. Familial communication and cascade testing among relatives of BRCA population screening participants. *Genet Med* 2017; 19(7):754
6. Lieberman S et al. Population screening for BRCA1/2 mutations: lessons from qualitative analysis of the screening experience. *Genet Med* 2017; 19(6):628
7. Gabai-Kapara E. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. *PNAS* 2014; 111(39):14205
8. Cousens N et al. Community attitudes towards a Jewish community BRCA1/2 testing program. *Familial CA* 2016; 16:17

We truly appreciate your time and the panel's consideration of our request. Please feel free to contact me at 617-823-3630 or laurenc@oneinforty.org with any questions you may have.

Best Regards,



Lauren M. Corduck
 Founder & Executive Director