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Screening for breast cancer by molecular testing for three founder mutations in the *BRCA1* and *BRCA2* genes among women of Ashkenazi Jewish heritage

Two important tumor suppressor genes, *BRCA1* and *BRCA2*, have been identified through family history studies (*BRCA1* in 1994[1] and *BRCA2* in 1995[2]). A deleterious mutation in one of these genes confers substantial additional risk for breast (and ovarian) cancer that varies by gene. Between 45% and 65% of women who carry such a mutation will develop breast cancer by age 70.[3] These women could then choose risk-reducing bilateral reconstructive mastectomy and oophorectomy as soon as they have completed their family. Of immediate interest in considering the question posed in this editorial is the finding that deleterious *BRCA* mutations occur at a much higher rate in Ashkenazi Jewish women (about 1 in 40) than in most other populations (about 1 in 400). In addition, three founder mutations account for nearly all deleterious mutations in this population.[4]

In 2014, the United States Preventive Services Task Force (USPSTF) found strong evidence that Ashkenazi Jewish heritage conferred sufficient risk of breast / ovarian cancer to warrant consideration of *BRCA* testing, even in the absence of a positive family history. The USPSTF recommended against offering *BRCA* mutation testing generally, not only because of the lower mutation prevalence, but also because of the need for full sequencing of the *BRCA1* and *BRCA2* genes that would identify many variants. Some of these would be known deleterious mutations (like the three founder mutations) but others would be of unknown clinical significance. These latter findings would leave some women with uncertainty as to both course of action and future risk.

Testing that is limited to the three founder mutations avoids variants of unknown significance and significantly reduces assay costs. If testing for the three founder mutations were to cost $200, the cost per case detected (BRCA mutation carrier developing cancer by age 70) would be about $19,000.[5] This can be contrasted with a hypothetical effort to offer general population testing for *BRCA* mutations to women in other ethnic groups.[6] In such a circumstance, there would be additional assay costs due to full sequencing and a much lower carrier rate. Together, these factors would increase projected testing costs to $760,000 per case detected.

Reliability of penetrance estimates is an important consideration when determining the extent of added risk conferred by a *BRCA* mutation and in deciding under which conditions to offer testing. Historically, penetrance has been estimated from women within families with strong family histories (index cases) and this may be biased towards overestimating penetrance. This issue can be addressed by using four specified interdependent epidemiological parameters to evaluate internal consistency of publications reporting results of BRCA testing and breast cancer.[4,7] Knowing three of these parameters allows the fourth to be computed. The parameters include: 1) percentage of deleterious *BRCA* mutations in the population (carrier rate), 2) percentage of mutations among women with breast cancer (clinical sensitivity or detection rate), 3) percentage of women with a mutation who develop breast cancer (penetrance), and 4) overall percentage of women developing breast cancer by a given age (population cumulative incidence). In the Ashkenazi Jewish population, the carrier rate is about 1 in 40 (2.5%), the proportion of breast cancer cases caused by these mutations (clinical sensitivity) is about 10% by age 70, and the population cumulative incidence of breast cancer is also about 10% by age 70. The expected penetrance of 40% can be computed by using the other three parameters, [((clinical sensitivity x cumulative incidence) / carrier rate) = penetrance or ((10 x 10) / 2.5) = 40]. This is consistent with the estimate of 49% from a recent study in Israel that used an innovative study design aimed at avoiding bias of ascertainment.[8]

Introducing *BRCA* testing in the present framework would first involve identifying women aged 30 or older (screening question 1) and then determining whether they are of Ashkenazi Jewish heritage (screening question 2). Published research studies often limit the definition of heritage to women identifying all four grandparents as being Ashkenazi Jewish.[9] As the number of grandparents with Ashkenazi heritage decreases, women become classified as being more similar to those with no Jewish ancestry, based on analysis of single nucleotide polymorphisms.[10] Using a simplifying assumption that the deleterious *BRCA* mutations are found in 1 in 40 Ashkenazi Jews but 1 in 400 in all others, the proportion of offspring carrying a mutation can be estimated when four, three, two, one or no grandparents are Ashkenazi Jewish (Table 1). Interestingly, the proportion is only slightly lower when three or two grandparents are Ashkenazi Jewish, and remains elevated with only one grandparent. With four Ashkenazi grandparents, the three mutations can detect an estimated 98% of all

Table 1. Impact of grandparent ethnicity on the probability of carrying one of three BRCA founder mutations and the associated detection rate.

Number of grandparents of Ashkenazi Jewish heritage	Probability (odds) of carrying one of three founder mutations[1]	Overall detection rate for all deleterious mutations[2]
Four	0.0250 (1 in 40)	98%
Three	0.0194 (1 in 52)	95%
Two	0.0138 (1 in 73)	90%
One	0.0081 (1 in 123)	78%
None	0.0025 (1 in 400)	10%

[1]Assumes a carrier rate of 1 in 40 for an individual with four grandparents of Ashkenazi Jewish heritage and 1 in 400 for all other individuals.
[2]Assumes that 98% of BRCA mutations in individuals with four grandparents of Ashkenazi Jewish heritage and 10% for those with no such inheritance.

Table 2. Proportion of all BRCA mutations identified by testing only those with Ashkenazi Jewish heritage.

Proportion of the population with at least one grandparent of Ashkenazi Jewish heritage[1]	Overall detection rate (%) of all deleterious BRCA mutations in the entire population[2]
2%	12%
4%	22%
6%	30%
8%	37%
10%	43%
12%	48%
14%	52%
16%	56%
18%	59%
20%	63%
22%	65%

[1]Assumes the carrier rate of 1 in 60 for the mixture of screen positive women with one, two, three or four grandparents with Ashkenazi Jewish heritage.
[2]Assumes the carrier rate of 1 in 400 for those with non-Ashkenazi Jewish heritage.

deleterious mutations, and that rate remains high at 78% for even one grandparent. Thus, screening may not need to be restricted to those with four grandparents, but could be offered to those with three, two or even one grandparent of Ashkenazi Jewish heritage. It would, however, be important to inform those identifying only one or two grandparents, that the detection rate for the three mutation panel is reduced.

Also of public health interest is the proportion of all *BRCA* mutations that could be accounted for by those women with at least one Ashkenazi Jewish grandparent. Table 2 shows the proportion of women with a positive response to the question 'Were at least one of your grandparents Ashkenazi Jewish?'. Even if only 2% of women in the population were to answer "Yes" to this question, about 12% of all mutation carriers would be accounted for. If 13% of the women answered "Yes", the mutation detection rate would increase to 50%. A "Yes" answer as high as 22% would increase mutation detection to about two-thirds. In the US, estimating the proportion of the population that would qualify for testing with one Ashkenazi grandparent is complicated by the ethnicity definition. In 2012, the two most current estimates of the US Jewish population were 6.4[11] and 6.7[12] million; or about 2.1 to 2.2%. Two large states have rates over 10%.[12] The methods included random digit dialing and interviews, distinctive Jewish names, US census estimates, mailing list of Jewish organizations and internet sources. By including those with only one or more grandparents, this number might be 5% or even higher. The American Jewish population is concentrated in the Northeast, Florida and the West Coast, and these areas might be logical choices for implementing a pilot screening programme.

In summary, there are now no important gaps in knowledge that would preclude broad-based screening for *BRCA* mutations when preceded by screening questions regarding age and grandparents' ethnicity. Demonstration projects would be helpful in documenting initial positive rates on the questions, proportion of screen positive results that may have already had *BRCA* mutation testing, uptake rate of mutation testing in those who had not been tested, and subsequent decision-making in those with a founder mutation. If such screening were eventually implemented throughout the US, perhaps 4 million (5% of the 81 million females age 30 to 69 in the US in 2013) could be offered screening and approximately 67,000 women with a deleterious mutation could be identified (1 in 60 of the 4 million). This would represent about one-quarter of all adult women that carry a deleterious *BRCA* mutation.

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