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Editorial

EDITORIAL

Persistent Underutilization of *BRCA1/2* Testing Suggest the Need for New Approaches to Genetic Testing Delivery

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Testing for mutations in *BRCA1* and *BRCA2* genes, which confers high risks of breast and ovarian cancer, has been available since the mid-1990s. The results published by Knerr et al. (1) in this issue of the Journal suggest that 20 years later, *BRCA1/2* testing remains poorly integrated into patient care.

The authors assessed the use of *BRCA1/2* testing among patients enrolled in an integrated health system (1). Consistent with numerous previous studies (2–12), the authors found substantial underutilization of genetic testing. Among women never diagnosed with breast or ovarian cancer, genetic testing rates were low, even among women who met *BRCA1/2* testing criteria, and there was little change in testing rates over the 10-year study period. Genetic testing prior to cancer diagnosis should be the goal, because effective interventions can prevent cancer altogether or detect cancer early. For women recently diagnosed with breast or ovarian cancer, over time a greater proportion of patients received *BRCA1/2* testing shortly after diagnosis and before initial surgery, suggesting that mutation status is being used to guide treatment decisions for some patients. However, the overall rate of *BRCA1/2* testing decreased among cancer patients over the study period, suggesting that patients who do not receive genetic testing soon after diagnosis are not getting tested later.

There are several limitations to the analysis by Knerr et al. (1). Women may have received *BRCA1/2* testing outside of the study timeframe or health system, which was not documented in electronic medical records (EMR). In addition, the authors did not assess referral to or participation in genetic counseling. Some women may have declined genetic counseling, or decided against testing following genetic counseling. However, given that more than 10 000 women in the cohort had a family history indicative of hereditary breast and ovarian cancer (HBOC) risk, but only about 700 of these women received testing, it seems unlikely that underestimates of testing rates or patient refusal fully explain the results, given published estimates of uptake of genetic testing (13).

The findings of Knerr et al. (1) are particularly concerning because, in theory, all patients enrolled in the Kaiser Permanente Washington health system had access to genetics specialists, genetic testing was covered by their insurance if they met testing criteria, and there was a concerted effort by the health system to encourage genetic testing. This is an ideal scenario for genetic testing. These results in combination with the large literature on underutilization of *BRCA1/2* testing generally (2–8) and large racial and ethnic and socioeconomic disparities in testing (9–12) suggest that current delivery of *BRCA1/2* testing is ineffectual and in need of redesign.

Perhaps the most striking insight by the analysis of Knerr et al. (1) is that family history of cancer was unknown for 70% of the cohort. This highlights a main barrier to HBOC risk assessment: performing a detailed family history assessment is time-consuming and family history is not well documented in EMR. Although family history of breast cancer is often collected at mammography clinics, as was the case in this study, this information is generally not documented in EMR and is not shared with primary care providers, and risk is not always communicated to patients. Family history may be collected in primary care, but again documentation in EMR is limited. Even if family history of cancer is discussed with a provider, the complicated guidelines for *BRCA1/2* testing [see box 1 in (1)] make discerning eligibility for test coverage burdensome, particularly for primary care physicians already constrained for time in clinic visits. For family history-based testing to be used more broadly, automated family history assessment tools that interface with EMR are needed. Several tools have been developed (14), but integrating such technology into clinical care is an expensive, slow, and laborious process.

Beyond difficulties in performing risk assessment, testing guidelines (15) may need revision. A considerable proportion of women with *BRCA1/2* mutations—as many as 50%—do not

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meet family history criteria for testing (16–21). As family sizes shrink, family history becomes less informative, and test criteria requiring multiple affected relatives become increasingly irrelevant. Additionally, genetic testing has moved from testing for *BRCA1* and *BRCA2* to multigene panel testing for multiple high and moderate penetrance cancer mutations, including *PALB2*, *ATM*, *CHEK2*, *MSH6*, *MUTYH*, *RAD50*, *RAD51C*, and *RAD51D*, and non-BRCA mutations are frequently missed by current HBOC testing guidelines (22).

The serious issues with current genetic testing delivery raise the question of whether it is time to consider population screening for breast and ovarian cancer risk. Whole-genome sequencing technology is rapidly advancing and costs are falling, making large-scale screening increasingly plausible. A recent cost-effectiveness analysis found population screening of women aged 30 years and older for mutations in *BRCA1/2*, *RAD51C*, *RAD51D*, *BRIP1*, and *PALB2* was more cost-effective than current clinical and family history-based testing strategies (23). These results need to be thoroughly vetted and confirmed, but they suggest that the trade-offs of risks and benefits of population screening are shifting in the direction of wider genetic testing. Given this reality, our research priorities should similarly shift to developing an evidence base to inform implementation of population screening.

Moving testing into the general population will result in identifying more variants of unknown significance (VUS) (24,25). Additionally, mutation penetrance for carriers without a family history of cancer are likely lower than estimates derived from family-based studies. Both situations dampen the benefits of genetic testing and may lead to harms of aggressive prevention strategies outweighing cancer risk. Prophylactic oophorectomy prior to menopause, for example, is associated with increased risks of cardiovascular disease and all-cause mortality (26). However, the only solution to clarify risks of VUS and mutation penetrance is more data. Withholding wider testing entirely while awaiting more data seems counterproductive. As population screening advances in various settings, gene prevalence, VUS risks, and penetrance should be carefully tracked and meta-analyses performed to update risk estimates. The Global Alliance for Genomics and Health recently launched the BRCA Exchange (27), a global data platform to collect and share data on the pathogenicity and penetrance of more than 20 000 *BRCA1/2* variants. Similar initiatives could include other cancer susceptibility genes, leveraging the growing number of large, population-based genetic consortia and biobanks (28–30).

Perhaps the most challenging barriers to population screening are how to build greater capacity for genetic counseling, testing, and clinical management. Strategies to provide genetic counseling outside of the clinic visit, such as employing remote appointments, phone, and video counseling, are showing promise (31–39) and may enable delivery of care to broader populations more efficiently.

There are many issues that need to be addressed before population screening for breast and ovarian cancer mutations can be successfully implemented. But weighed against the alternative of allowing patients with identifiable genetic risk to present with breast or ovarian cancer, often at a young age, surmounting the challenges are well worth the effort and investment.

Note

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