Title
Recommendations Related to Genetic Testing for Breast Cancer—Reply

Journal
JAMA, 323(2)

ISSN
0098-7484

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Publication Date
2020-01-14

DOI
10.1001/jama.2019.18222

Peer reviewed

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In Reply Based on the letters from Mr Schneider, Drs Everett and Isea, and Dr Battisti, we find 2 key issues to discuss—transparency and competency. We absolutely agree that increased transparency and access to data, both from medical schools and through ERAS, would facilitate holistic review. Program directors have been lamenting the erosion of meaningful performance measures for years as medical schools increasingly moved to pass-fail grading. We wonder what role the narrow focus on academic metrics in residency selection may have played during this transition. Broadening the selection criteria beyond academic metrics in true holistic review may be a more successful approach for encouraging data release than further demands for score details. Realistic solutions include use of additional information already collected by ERAS, such as student experiences (volunteer work, research productivity) and attributes (language skills, regional ties, distance traveled), to filter applicants for review. Once a reasonable number of applications is identified, each can be individually assessed for mission-specific factors including medical knowledge.

The second point centers on whether the 3-digit score is required to ensure overall competency. Our colleagues cite several articles examining the correlation between USMLE scores and performance, as measured by clinical evaluations and future test scores. However, studies evaluating multiple metrics (ie, grades, class rank) found that other factors were as good or better predictors of performance than USMLE scores.[1,2] It is interesting that the medical profession has accepted subspecialty certification examinations, which are reported in pass-fail format, as the gold standard appraisal of fitness to practice in a particular specialty. We wonder why the same standard cannot apply to the USMLE as a measure of medical students' competency. We acknowledge the comment that the demographic differences in USMLE scores documented by Rubright et al[3] were attenuated by previous academic performance. However, unexplained demographic differences persisted, and we interpret the finding as evidence of potential bias in the evaluation tools, rather than support for the validity of USMLE scores as the best way to identify students with substandard medical knowledge. As Everett and Isea state, medical knowledge is a "foundational element correlating with other beneficial characteristics." We agree but are concerned that using only 1 assessment tool is risky given the potential bias. Score filters select applications for review based solely on a single point difference, far less than the 6- to 8-point standard error of the test.[4] Alternatives such as tiered-score reporting may be a reasonable middle path. We are not arguing that academic metrics have no value, only that they should not carry so much weight.

Medical knowledge will always be central to being a physician, but when a single test score becomes the most important criterion for residency placement, it leads to the imperfect system we described.[5] We agree with the commentators that regardless of the outcome of the USMLE score reporting debate, program directors should be working toward a more comprehensive holistic review.

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Conflict of Interest Disclosures: None reported.

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Recommendations Related to Genetic Testing for Breast Cancer

To the Editor The recent Recommendation Statement by the US Preventive Services Task Force (USPSTF)[1] on risk assessment, genetic counseling, and genetic testing for breast cancer susceptibility (*BRCA*) gene mutations seems to contain some internal inconsistencies. The Summary of Recommendations and Evidence section stated that women with either a personal or family history of *BRCA*-related cancers *or* an ancestry associated with *BRCA* mutations are recommended for risk assessment. However, in the USPSTF Assessment section, net benefit of the intervention was only ascribed to women with the relevant family or personal history, and it was stated that the harms of risk assessment outweigh the benefits "in women whose family or personal history is not associated with an increased risk" for harmful *BRCA* mutations. Therefore, the task force appears to be recommending intervention for women with a *BRCA*-associated ancestry but no personal or family history (since such women satisfy the "or" logic in the recommendation) but also stating that the harms outweigh the benefits for these women. Another sentence in the text, under Estimate of Magnitude of Net Benefit, excluded even personal history, stating that the harms of risk assessment outweigh the benefits for women without a *BRCA*-associated family history. Although readers could presume that the task force would consider these interventions to have net benefit in women with the requisite ancestry but no relevant family or personal history, it is curious that these direct statements would exclude mention

of ancestry. It would be helpful if the task force could provide added clarity with regard to these net benefit statements and their relation to the overall recommendation.

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Conflict of Interest Disclosures: None reported.

1. Owens DK, Davidson KW, Krist AH, et al; US Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2019;322(7):652-665. doi:10.1001/jama.2019.10987

To the Editor The USPSTF found adequate evidence of moderate benefit for women whose family or personal history is associated with increased risk for *BRCA1/BRCA2* mutations, whereas for women without such family history, it stated that the benefits are small to none.[1] However, a *BRCA1/BRCA2* mutation carrier without a positive family history still faces a substantial lifetime risk, with more than half the hazard of a *BRCA1/BRCA2* mutation carrier with a positive family history.[2] The proportion of these unsuspected mutation carriers is not negligibly small. In hospital-based settings at Hannover Medical School, current risk assessment tools miss about half of *BRCA1/BRCA2* mutation carriers in breast cancer cohorts because of incomplete penetrance or small pedigrees. A recent population-based study reported that 49.4% of *BRCA1/BRCA2* mutation carriers did not meet guidelines for clinical testing.[3] Such women would, at their asymptomatic stage, be excluded from the possible benefits of counseling, preventive measures, and intensified surveillance.

The USPSTF "found no studies on the benefits of intensive screening for *BRCA*-related cancer on clinical outcomes in women who are *BRCA1/2* mutation carriers."[1] However, intensified surveillance of carriers with annual magnetic resonance imaging detects more breast cancers at an earlier stage.[4] Although evidence for reduced recurrence and mortality is still scarce, early detection clearly can direct clinical management toward more favorable therapeutic options. Furthermore, the USPSTF recommended that clinicians offer to prescribe risk-reducing medications to women at increased risk for breast cancer. Even if beneficial for mutation carriers, this option would not be available for women who escape detection based on family history. Adding to the complexity, there is no clarity about whether this recommendation includes asymptomatic women with mutations in moderate-risk genes or with high polygenic risk scores that can indicate up to a 35% lifetime risk.[5]

No argument for population-wide screening for breast cancer risk mutations may be sufficiently strong, but there is also little reason to reject the specific wish of an individual woman to be tested independent of her pedigree. With the rapid increase in ease and cost-effectiveness of targeted sequencing, it is likely that recommendations will change and more women will be offered genetic testing on demand, rather than just those with a documented family history of breast or ovarian cancer.

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Conflict of Interest Disclosures: None reported.

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In Reply Dr Pinsky asks for more clarity on the USPSTF's recent recommendation. The USPSTF found that women with a personal or family history of breast or ovarian cancer, or an ancestry associated with *BRCA1/2* mutations, are at increased risk for having a *BRCA1/2* mutation.[1] For these women, the benefits of risk assessment and potentially counseling and testing outweigh the harms. Determining whether a woman may be a candidate for referral for counseling and possible genetic testing is a multistep process for primary care clinicians. The first step is to identify women with a personal or family history of breast or ovarian cancer or an ancestry associated with *BRCA1/2* mutations (eg, Ashkenazi Jewish women). For these women, the next step is to perform a risk assessment using 1 of several brief risk assessment tools. Last, for women found to be at higher risk using these tools, clinicians should refer or provide genetic counseling. This includes more definitive risk assessment, counseling about genetic testing, shared decision-making about whether to be tested, and potentially genetic testing.

Dr Dörk and colleagues express concerns about the use of family history in identifying *BRCA1/2* mutation carriers. They contend that current risk assessment tools miss a substantial number of mutation carriers and that the USPSTF underestimated the cancer risk for *BRCA1/2* mutation carriers without a positive family history or with an unknown family history. The USPSTF reviewed more than 12 studies on the accuracy of primary care–based risk assessment tools designed to guide referral to genetic counseling. These tools were determined to have high discriminatory accuracy in estimating the likelihood of having a harmful *BRCA1/2* mutation.[2] We recognize that these tools have limitations, including missing some women with *BRCA1/2* mutations and not working for women

with limited or unknown family history. In the meantime, women with an unknown family history who are concerned about their risk should talk with their physician to decide what is right for them.

The authors claim that intensive surveillance for *BRCA*-related cancer for all women, not just those at risk, demonstrates a clear benefit, yet they do not address the potential harms related to testing. The USPSTF's review of the evidence identified potential harms from genetic testing and follow-up and treatment for women with *BRCA1/2* mutations, including false-positive and false-negative results, unnecessary procedures, complications from procedures, anxiety, and depression.[2] The USPSTF concluded that the benefits only outweighed the harms for women at risk.

We agree with the authors that the landscape of genetic testing is expanding, with more women, including average-risk women, choosing to have genetic sequencing done. However, there are harms associated with genetic testing that should be considered before testing.

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Conflict of Interest Disclosures: All members of the USPSTF receive travel reimbursement and an honorarium for participating in USPSTF meetings.

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