

Taking Family History Seriously

With the completion of the Human Genome Project, experts forecast an era of “personalized medicine,” in which measures of individual susceptibility would be used to tailor disease prevention (1, 2). The promise is still largely in the future, but tests for *BRCA* mutations represent an early example of this paradigm. Mutations in the *BRCA1* and *BRCA2* genes confer an elevated risk for breast and ovarian cancer (3). Several preventive measures have been recommended for women with these mutations, including prophylactic surgery and aggressive early cancer screening. These recommendations were made initially on the basis of expert opinion (4). Therefore, the background review from the U.S. Preventive Services Task Force (USPSTF) in this issue (5) provides welcome documentation of a growing body of evidence showing that some of these preventive measures provide benefit. However, if women with *BRCA* mutations are to have the opportunity for individualized cancer prevention, we must be able to find them. The USPSTF concluded that family history can be used as a screening mechanism and offers family history criteria to identify the approximately 2% of women who could be considered for *BRCA* testing (6).

The criteria suggested by the USPSTF require evaluation of breast and ovarian cancer status in first- and second-degree relatives, as well as determination of age at disease onset and presence or absence of bilateral breast cancer in affected relatives. The criteria are consistent with standards of practice that have evolved over the past decade in medical genetics and reflect the epidemiologic finding that only a subset of women with a family history of breast cancer have *BRCA* mutations (5). While the USPSTF recommendations indicate an emerging consensus, they pose serious challenges for clinicians.

Taking a family history has long been considered an integral part of a medical evaluation, but few clinicians gather the detailed information required by the USPSTF guideline (7). Furthermore, primary care providers have strong disincentives to do more, such as lack of reimbursement and the competing demands of patient care (7–9). For these reasons, implementation of the USPSTF recommendations would require a concerted effort to change current practice (8, 10, 11).

After reading the USPSTF evidence review (5), a skeptical clinician might ask whether the current level of evidence justifies the effort. Nelson and coauthors (5), emphasizing the need for further research, noted that no studies have demonstrated reduction in cancer incidence or mortality from *BRCA* testing or have assessed family history screening in primary care practice. However, they noted several potential benefits for women found to have *BRCA* mutations: There is fair evidence that prophylactic mastectomy and oophorectomy reduce cancer incidence; chemoprevention with tamoxifen is probably beneficial for

women with *BRCA2* mutations; and a combined magnetic resonance imaging–mammography screening protocol provides more sensitive (although less specific) detection of early breast cancer than mammography screening alone.

As clinicians assess these findings, they will need to consider not only the effort involved in evaluating family history but also the education and counseling needed to ensure that women with a family history of breast or ovarian cancer are given the opportunity for well-informed decision making. Prophylactic mastectomy, although effective in reducing breast cancer incidence, is an unacceptable option for many high-risk women. In 3 U.S. studies, the proportion of women choosing prophylactic mastectomy after a positive genetic test result ranged from 0% to 15% (12). Prophylactic oophorectomy appears to be more readily accepted (12), perhaps because there is little evidence to suggest efficacy for the screening alternative (5). However, this surgery involves substantive risks, and hormone-related side effects are highest in the premenopausal women most likely to benefit (5). Chemoprevention with tamoxifen may be beneficial only in women with *BRCA2* mutations and also involves substantive risk (5). Although magnetic resonance imaging–mammography screening may detect early cancer effectively, patients should be aware of the uncertain mortality benefit, high cost, and high rate of false-positive results.

Potential candidates for *BRCA* testing also need to know that the preferred testing strategy involves starting with a relative who has cancer. Current testing is estimated to miss 12% to 15% of *BRCA* mutations (5), and other genetic causes of familial breast cancer are likely (13). Thus, in the absence of a known mutation in the family, a negative test result in an unaffected person is difficult to interpret. It could represent a true negative (the absence of a cancer-predisposing mutation) or a false negative (the presence of a mutation not identifiable by current techniques). Another unfortunate risk of testing is the finding of a gene variant of unknown clinical significance; this occurs about 13% of the time (14).

The *BRCA* story illustrates the complexity inherent in the promise of genetically tailored health prevention. As new opportunities to define genetic susceptibility arise, evidence will be needed on measures to reduce risk. Evidence of varying quality will emerge incrementally, requiring an ongoing assessment of thresholds for action and practical strategies for implementation. In the case of *BRCA* testing, the assessment starts with a serious consideration of family history, not least because referral for testing could be harmful to women whose family history of cancer does not meet referral criteria (6). Even among those referred for testing, only a minority will have *BRCA* mutations, and women with *BRCA* mutations may decide not to pursue current

preventive options because of associated risks or uncertainties.

Even when genetic counseling is readily available, primary care physicians will serve as an important source of advice for patients considering these complexities, including whether to pursue *BRCA* testing, the appropriate timing, the best approach to involving family members in the testing process, and the tradeoffs and uncertainties involved in the different preventive strategies available to woman found to have a *BRCA* mutation. The latest USPSTF report (5) and recommendations (6) will provide invaluable assistance to clinicians seeking to help patients traverse this new terrain.

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Ann Intern Med. 2005;143:388-389.

References

- Hood L, Heath JR, Phelps ME, Lin B. Systems biology and new technologies enable predictive and preventative medicine. *Science.* 2004;306:640-3. [PMID: 15499008]
- Collins FS. Shattuck lecture—medical and societal consequences of the Human Genome Project. *N Engl J Med.* 1999;341:28-37. [PMID: 10387940]
- Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al.

- Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet.* 2003;72:1117-30. [PMID: 12677558]
- Burke W, Daly M, Garber J, Botkin J, Kahn MJ, Lynch P, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. *BRCA1* and *BRCA2*. Cancer Genetics Studies Consortium. *JAMA.* 1997;277:997-1003. [PMID: 9091675]
- Nelson HD, Huffman LH, Fu R, Harris EL. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility: systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2005;143:362-79.
- U.S. Preventive Services Task Force. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility: recommendation statement. *Ann Intern Med.* 2005;143:355-61.
- Suther S, Goodson P. Barriers to the provision of genetic services by primary care physicians: a systematic review of the literature. *Genet Med.* 2003;5:70-6. [PMID: 12644775]
- Rich EC, Burke W, Heaton CJ, Haga S, Pinsky L, Short MP, et al. Reconsidering the family history in primary care. *J Gen Intern Med.* 2004;19:273-80. [PMID: 15009784]
- Yarnall KS, Pollak KI, Ostbye T, Krause KM, Michener JL. Primary care: is there enough time for prevention? *Am J Public Health.* 2003;93:635-41. [PMID: 12660210]
- Guttmacher AE, Collins FS, Carmona RH. The family history—more important than ever. *N Engl J Med.* 2004;351:2333-6. [PMID: 15564550]
- Yoon PW, Scheuner MT, Peterson-Oehlke KL, Gwinn M, Faucett A, Khoury MJ. Can family history be used as a tool for public health and preventive medicine? *Genet Med.* 2002;4:304-10. [PMID: 12172397]
- Wainberg S, Husted J. Utilization of screening and preventive surgery among unaffected carriers of a *BRCA1* or *BRCA2* gene mutation. *Cancer Epidemiol Biomarkers Prev.* 2004;13:1989-95. [PMID: 15598752]
- Pharoah PD. Genetic susceptibility, predicting risk and preventing cancer. *Recent Results Cancer Res.* 2003;163:7-18; discussion 264-6. [PMID: 12903839]
- Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, et al. Clinical characteristics of individuals with germline mutations in *BRCA1* and *BRCA2*: analysis of 10,000 individuals. *J Clin Oncol.* 2002;20:1480-90. [PMID: 11896095]

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