

For the Office-based Teacher of Family Medicine

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Feature Editor

Editor's Note: In a recent column, John Langlois, MD, noted the increasing role that preceptors will have in teaching learners about genetics (Fam Med 2003;35(5):314-5). In this month's column, Robert Gramling, MD, and Sean David, MD, SM, of the Brown University Department of Family Medicine give practical information that office-based teachers can share with learners on the role of genetics in assessing a patient's risk for breast cancer.

I welcome your comments about this feature, which is also published on the STFM Web site at www.stfm.org. I also encourage all predoctoral directors to make copies of this feature and distribute it to their preceptors (with the appropriate *Family Medicine* citation). Send your submissions to williamh@bcm.tmc.edu. William Huang, MD, Baylor College of Medicine, Department of Family and Community Medicine, 5510 Greenbriar, Houston, TX 77005-2638. 713-798-6271. Fax: 713-798-8472. Submissions should be no longer than 3-4 double-spaced pages. References can be used but are not required. Count each table or figure as one page of text.

Genetic Susceptibility to Breast Cancer: Teaching Points

Robert Gramling, MD; Sean David, MD, SM

Recent advances in human genetics are fueling speculation for the use of molecular genetics in the routine practice of primary care.^{1,2} However, recent research reports an existing need for family physician and generalist physician education in this area.² As such, the Society of Teachers of Family Medicine is administering a nationwide program titled "Genetics in Primary Care: a Faculty Development Initiative."³

One aspect of molecular genetics that has the potential to soon impact primary care practice is predictive genetic testing for common adult onset disorders such as breast cancer.¹ This article's goal is to help

the office-based teacher engage learners who are exploring the role of genetic testing for breast cancer risk. We provide risk benchmarks, preventive recommendations, and a brief description of the testing process to advise women considering referral to a genetic specialist.

BRCA1 and BRCA2

Genetic testing for breast cancer is clinically available for predictive use. The breast cancer 1 and breast cancer 2 (BRCA1 and BRCA2) genes code for normally occurring nuclear proteins. Mutations in these genes have been associated with an increased risk of breast, ovarian, prostate, colon, and other cancers.⁴ It is estimated that one to two individuals per 1,000 in the general population carry a pathologic BRCA1 mutation and that these and other cancer susceptibility genes account for approximately 5%–

10% of all cases of breast cancer.⁵ For the BRCA1 and BRCA2 genes, more than 400 mutations and polymorphisms have been identified for each, but the clinical significance of more than one third of these is not known.⁵

Risk Benchmarks and Preventive Recommendations

Table 1 shows the lifetime risks of invasive breast cancer given average risk, a first-degree family history alone, or given a BRCA1 or BRCA2 mutation alone. The testing process described below helps identify which individuals are most likely to carry a mutation that confers a high risk of future breast cancer.

Evidence related to the efficacy and effectiveness of genetic susceptibility testing as a preventive option is limited, and recommendations are largely based on expert

(Fam Med 2003;35(7):466-8.)

Table 1

Lifetime Risks of Invasive Breast Cancer

	CUMULATIVE LIFETIME RISK*		
	Baseline**	One Affected First-degree Relative	BRCA1 or BRCA2 Mutation Carrier
Breast cancer ^{4,13}	10%–13%	14%–17%	36%–85%

* Based on life expectancy= 85 years

** No family history of breast cancer and no known mutations in cancer susceptibility genes

consensus.⁶ Some recent findings suggest that prophylactic mastectomy reduces the incidence of breast cancer in both BRCA1 and BRCA2 carriers,⁷ tamoxifen reduces the incidence of breast cancer in BRCA2 carriers,⁸ and prophylactic salpingo-oophorectomy decreases the incidence of both breast and BRCA-related gynecologic cancer in BRCA1 and BRCA2 carriers.⁹ The recent update of the breast cancer preventive recommendations by the US Preventive Services Task Force “did not examine whether women should be screened for genetic mutations (eg, BRCA1 and BRCA2) that increase the risk of developing breast cancer or whether women with genetic mutations might benefit from earlier or more-frequent screening for breast cancer.”¹⁰ An expert panel sponsored by the National Human Genome Research Institute recommends breast self-examinations monthly, clinical breast examinations, transvaginal ultrasonography and CA-125 levels semiannually or annually, and mammograms annually, beginning at age 25–35 years for carriers of BRCA1 and BRCA2 mutations.⁶

The Genetic Testing Process

Individuals interested in genetics consultation or DNA testing should be aware that this involves the analysis of family members’ history and/or DNA to provide the best estimate of their personal risk. There-

fore, prior to initiating DNA testing, it is essential to evaluate both the individual’s and family’s readiness. Such readiness might include a favorable psychosocial context and the understanding of the implications of, and clinical options for, the potential results. This is a critical step and usually involves one or more specialist counseling sessions before proceeding with testing.

The initial testing process involves the collection and interpretation of a three-to-four generation family history. This and other specific information can be modeled to quantify the risk estimate. The Gail model uses factors such as current age, age at menarche, number of breast biopsies, age at first live birth, and number of first-degree relatives with breast cancer.^{12,13} The Claus model uses the number of first-degree and second-degree relatives with breast cancer and their ages of onset and assumes that breast cancer is transmitted as an autosomal dominant trait.¹⁴

If the family history indicates a high risk for breast cancer (diagnosis of breast cancer in young women, bilateral or multifocal breast cancer, autosomal dominant pattern of inheritance of affected individuals, or breast and ovarian cancer in one individual), DNA testing of family members with the disease may further clarify the risk. This occurs by analyzing the BRCA1 and BRCA2 genes of af-

ected family members, who are available and willing to undergo DNA testing, for known disease-associated mutations. If a disease-associated mutation is identified in one or more affected relatives, then all adults at risk should be offered testing for this specific mutation.

In instances where affected family members are not available or interested in testing, the ability to interpret test results will be compromised. In addition, while disease-associated mutations can be interpreted in a straightforward manner, certain polymorphisms or previously unidentified changes in the gene sequence should be interpreted with much caution.

If an asymptomatic individual at risk for inheriting a BRCA1 or BRCA2 mutation is found not to harbor the mutation that runs in the family, the baseline risk of breast cancer still applies.

Other Resources

Learners who wish to find more information on the genetics of breast cancer and other specific conditions can do so at GeneReviews (www.geneclinics.org), supported by the National Institutes of Health. Those interested in exploring the ethical, legal, and social implications of human genetics can do so at the National Institutes of Health Human Genome Program-sponsored Web site at www.ornl.gov/hgmis/elsi/elsi.html.

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