

Genetic Counseling Program

The Role of Genetic Testing for the Newly Diagnosed Breast Cancer Patient

Danielle Campfield, MS and Rachel Barnett, MS

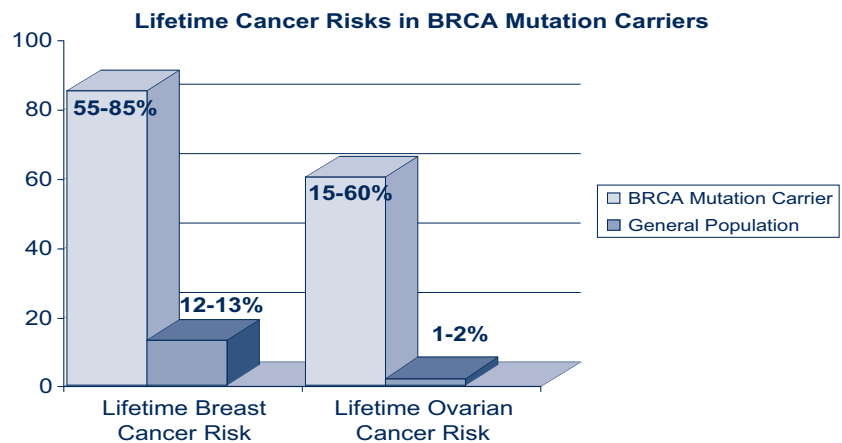
Genetic counseling and testing is a new tool that clinicians can use with their newly diagnosed breast cancer patients to effectively tailor a treatment and surgical decision-making plan.

Germline genetic testing for hereditary breast and ovarian cancer differs from somatic genetic testing in several ways. First, germline testing (e.g., *BRCA1* and *BRCA2*) is performed on a blood sample and provides information about mutations found in almost every cell of the body. Somatic testing (e.g., *her-2* and *Oncotype DX*) is performed on the tumor block and provides information about mutations found only in the tumor and only in that patient. Therefore, germline genetic testing differs from somatic testing by providing patients with information about their risks for future cancers as well as risks for other family members.

Women who carry a *BRCA1* (breast cancer-1) or *BRCA2* (breast cancer-2) mutation are at increased risk of both breast and ovarian cancer. Genetic testing for mutations in these genes has only become clinically available within the past 15 years. For this reason we do not have a great deal of long-term prospective data on individuals who carry mutations in these genes and it is

most accurate to present mutation carriers with a range of cancer risks¹. The available data suggests that mutations within these genes confer a significantly elevated lifetime risk to develop breast cancer (55-85%) and an increased risk to develop a second primary cancer (40-64%)^{2,3,4}. Carriers also have a 15-60% risk to develop ovarian cancer (this includes cancer of the fallopian tubes) by the time they are 70 years of age^{3,4}. These figures are significantly higher than the 12-13% lifetime risk for breast cancer and the 1-2% lifetime risk for ovarian cancer in the general population. Males who carry mutations in either *BRCA* gene have a slightly

continued on page 4 ▶



Chen S, et al. Meta-analysis of *BRCA1* and *BRCA2* Penetrance. *J Clin Oncol* 2007; 25(11):1329-1333.

Aggressive Advertisement Campaign Hits the Northeast

Karina L. Brierley, MS and Ellen T. Matloff, MS

The greatest fear cited by patients considering genetic testing is whether their health insurance company will discriminate against them based on their test results. We now have laws, both state and federal, that help protect patients against genetic discrimination. Luckily, we have not seen the discrimination we feared when this technology began.

Surprisingly, we have found that one of the greatest risks of

genetic testing is more subtle - it is the risk that the patient's test results will be misinterpreted. In fact, we have now seen several patients who have either had prophylactic surgery or considered it, based on result misinterpretation. Why? One of the main issues is that one genetic testing company is aggressively targeting provider offices and encouraging them to order their own genetic testing. In fact, some such companies offer their employees finan-

continued on page 5 >



Editor's Letter

Ellen T. Matloff, MS
(203) 764-8400
ellen.matloff@yale.edu

The Yale Cancer Center Cancer Genetic Counseling Program was created in 1995, and at that time consisted of one genetic counselor and one very small office. We were on the brink of discovering the genes for hereditary breast and ovarian cancer, but clinical testing for the syndrome was not yet available.

Thirteen short years later the program has expanded to include four full-time cancer genetic counselors, an office manager, three outreach clinics across the state, and more than 2800 families in our practice. We have developed close ties with primary care physicians, surgeons, gynecologists, oncologists, gastroenterologists, nurses, and other health care professionals across Connecticut and in neighboring states. Together we have forged new pathways in using genetic testing to tailor the management of our patients and their entire families. We have also enlisted your help to enroll patients in research studies that will help to propel the field of Cancer Genetics forward. Importantly, we have developed support networks for patients via an e-mail listserv and in-person discussion groups, and have created a database that is utilized for long-term follow-up of these patients.

This issue of *Advances* will outline the risk factors for hereditary cancer, how genetic testing can aid in the management of the newly diagnosed breast cancer patient, and the latest recommendations for determining which patients in your practice are candidates for genetic counseling and testing. We will also discuss the myths in cancer genetics that we need your help to dispel. Lastly, we will discuss a very timely issue in the field that has to do with direct-to-consumer marketing of genetic testing, and what you can do to protect yourselves and your patients from unregulated campaigns.

We hope this issue will be of use to you in your clinical practice and encourage you to contact us if we can provide a curbside consult or be of assistance in the management of your patients.

Sincerely,

Ellen T. Matloff, MS

Greatest Myths About Genetic Counseling and Testing

Rachel E. Barnett, MS and Ellen T. Matloff, MS

MYTH #1: IF YOUR PATIENT HAS GENETIC TESTING, THEIR HEALTH INSURANCE WILL DISCRIMINATE AGAINST THEM.

There are now federal and state laws in place to protect people against group health insurance discrimination. However, few laws currently exist to protect against life and disability insurance discrimination. The greatest risk for possible life and disability insurance discrimination likely exist for individuals without a personal history of cancer. More information about state and federal laws and the status of insurance discrimination based on genetic information can be found at www.yalecancercenter.org/genetics.

MYTH #2: INSURANCE WILL NOT COVER THE COST OF GENETIC COUNSELING AND TESTING.

The majority of insurance companies now cover genetic testing for high-risk patients.

MYTH #3: THE FATHER'S FAMILY HISTORY DOESN'T COUNT.

Genetic mutations for hereditary breast and ovarian cancer can be passed from fathers to both sons and daughters. Therefore, the paternal family history of cancer is just as important as the maternal family history.

MYTH #4: YOUR PATIENT SHOULD ONLY HAVE GENETIC TESTING IF SHE WOULD CONSIDER BILATERAL PROPHYLACTIC MASTECTOMIES.

This is only one option. Other options include increased surveillance and medications, such as Tamoxifen, that reduce breast cancer risks.

MYTH #5: YOUR PATIENT HAS ALREADY HAD CANCER, SO TESTING WON'T HELP.

Genetic testing can be important to determine a treatment plan for a newly diagnosed patient, to reduce the risk of future cancers, and to help family members.

MYTH #6: ONLY ASHKENAZI JEWS ARE AT RISK FOR HEREDITARY BREAST AND OVARIAN CANCER.

There are two mutations in BRCA1 and one mutation in BRCA2 that are more common among individuals of Ashkenazi Jewish ancestry; however, BRCA mutations have been identified in every ethnic background.

MYTH #7: GENETIC COUNSELING IS NEEDED ONLY IF YOUR PATIENT TESTS POSITIVE FOR A MUTATION.

Negative test results are often the most difficult results to interpret. Also, genetic testing requires informed consent. It is impossible to obtain informed consent for testing after testing has been performed. This is a potential area of liability for the provider if proper consent hasn't been obtained prior to testing.

MYTH #8: BRCA1 AND BRCA2 ARE THE ONLY GENES FOR HEREDITARY BREAST AND OVARIAN CANCER.

Mutations in other genes can be responsible for some forms of hereditary breast (e.g. PTEN, p53) and ovarian cancer.

MYTH #9: GENETIC TEST RESULTS ARE EASY TO INTERPRET: IF POSITIVE, THEY HAVE THE DISEASE; IF NEGATIVE, THEY DON'T.

Test results are rarely straight-forward and variants of uncertain significance are sometimes discovered.

RISK FACTORS OF HEREDITARY CANCER SYNDROMES

Hereditary Breast and Ovarian Cancer – Risk Factors

A personal and/or family history of:

- Breast cancer diagnosed before age 45.
- Multiple cases of breast cancer on the same side of the family.
- Ovarian cancer in a family with breast cancer.
- Male breast cancer.
- The combination of pancreatic, breast, and/or ovarian cancer on the same side of the family or in a single individual.
- Jewish ancestry in combination with any of the above.
- Jewish ancestry and even one case of breast or ovarian cancer (even in the absence of additional family history).
- Medullary breast cancer and triple negative breast cancer are over- represented in women with *BRCA1* mutations.

Hereditary Colon Cancer – Risk Factors

A personal and/or family history of:

- Colon cancer diagnosed before age 50.
- Multiple cases of colon cancer on the same side of the family.
- The combination of colon, uterine, ovarian, urinary tract, and/or other gastrointestinal cancers on the same side of the family.
- A single individual diagnosed with colon and uterine cancer; synchronous/ metachronous colon cancers, or colon and ovarian cancer.
- Even one sebaceous carcinoma.
- Colon cancer that is MSI (microsatellite instability) positive and/or shows the loss of an HNPCC-related protein via immunohistochemistry.
- Multiple adenomatous, hamartomatous, or juvenile polyps.

Genetic Counseling Program

Ellen Matloff, MS, Director, (203) 764-8400

Allen E. Bale, MD, Medical Director, (203) 785-5749

Karina L. Brierley, MS, Cancer Genetic Counselor,
(203) 764-8400

Rachel E. Barnett, MS, Cancer Genetic Counselor
and Managing Editor of *Advances*, (203) 764-8400

Danielle Campfield, MS, Cancer Genetic Counselor,
(203) 764-8400

yalecancercenter.org/genetics

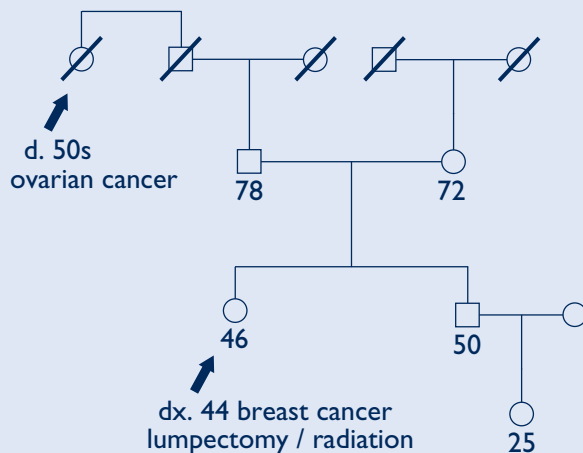
» THE ROLE OF GENETIC TESTING continued from page 1

increased lifetime risk to develop prostate cancer. Individuals who carry *BRCA2* mutations are at increased risk to develop male breast cancer and have a slightly increased risk to develop pancreatic cancer and perhaps melanoma⁵.

SURGICAL IMPLICATIONS

As mentioned above, *BRCA* mutation carriers are at increased risk for a second primary breast cancer, either in the affected or unaffected breast. This lifetime risk ranges from 40-64% and is due to the fact that the *BRCA* mutation is present in every breast cell. Although breast-conserving therapy provides the same degree of disease-free survival as total mastectomy, it does not reduce the risk of a second primary cancer in high-risk women. Some women who learn that they have an increased ipsilateral and contralateral

Susan was diagnosed with breast cancer at age 44 and was treated with a lumpectomy, radiation and Tamoxifen. At a routine follow-up appointment Susan was referred to genetic counseling based on her early age of onset; she then researched her family history and learned that her paternal great-aunt died of ovarian cancer. Genetic testing revealed a *BRCA2* mutation, and she then elected a prophylactic bilateral salpingo-oophorectomy, followed by a bilateral mastectomy. Unfortunately, she developed complications during her reconstruction attributed to the elasticity changes from radiation. Her brother tested positive and will have breast and prostate surveillance, and learned that his 25-year old daughter should have testing.



breast cancer risk may choose immediate bilateral mastectomy instead of breast-conserving therapy or unilateral mastectomy and thus forgo a future surgery^{6,7}. The timing of genetic counseling and testing may be particularly critical in women who choose TRAM (transverse rectus abdominis myocutaneous) flap reconstruction as this method can only be performed one time.

In one study, 167 newly diagnosed breast cancer patients pursued genetic counseling and testing, 31 (16%) were found to carry a *BRCA* mutation and of those 15 (48%) opted for bilateral mastectomy as part of their treatment plan⁶. In a similar study, 32 newly diagnosed breast cancer patients pursued genetic counseling and testing, 7 (22%) were found to carry a *BRCA* mutation and all 7 (100%) pursued bilateral mastectomy⁷. Several studies have demonstrated that prophylactic bilateral mastectomy drastically reduces the subsequent risk of breast cancer in *BRCA* carriers^{8,9} and should therefore be discussed, along with its risk and limitations, with mutation carriers. The emotional and psychological effects of bilateral mastectomy are notable, but the surgery itself is associated with a relatively low rate of morbidity and mortality¹⁰.

RADIATION IMPLICATIONS

Genetic status may also impact the decision to undergo radiation therapy. One advantage of immediate bilateral mastectomy is the avoidance of radiation treatment in patients with early-stage disease. Women who choose to delay genetic testing and proceed with breast conserving therapy may compromise their reconstruction options and cosmetic outcomes if they later learn they carry a *BRCA* mutation and wish to pursue mastectomy. Chest irradiation makes tissue expansion difficult, sometimes impossible, and is associated with increased pain, infection, necrosis, delayed healing, ribcage contour deformities, and expander extrusion. Radiation changes also make the tissue less pliable, unpredictable, and predisposed to breakdown¹¹. The affects of previous chest irradiation can result in reconstructed breasts that are harder, more asymmetrical, and often require additional surgery¹². Although flap reconstruction was once thought to be a better alternative for these patients, even this technique can be complicated by the tissue's overall ability to heal and its predisposition to complications. One study reported a 43% complication rate in women opting for mastectomy with reconstruction following radiation and of those 29% had failed reconstruction¹³. Another study reported a rate of complications and unfavorable aesthetic results up to 60% in previously irradiated patients¹⁴.

Of course, women who indicate that they would not consider bilateral mastectomy are certainly still good candidates for genetic counseling as there are other options for risk reduction and increased surveillance for breast cancer, other cancer risks that are

associated with BRCA mutations (such as ovarian cancer) and possible risks for other family members. However, genetic counseling and testing should be discussed with high-risk women close to the time of their diagnosis to aid them in making fully informed treatment and surgical decisions.

Due to the increasing complexity of genetic testing and results interpretation (including that of an uninformative test result) genetic counseling with informed consent is essential for these patients. As genetic testing options grow at expansive rates, physicians will continue to play a central role by eliciting a detailed history from their patients and choosing which patients are appropriate candidates for genetic counseling. It is quite possible that the results from genetic counseling and testing will be one of patients' most valuable pieces of information in the treatment of their breast cancer.

References

1. Matloff ET, et al. Complexities in cancer genetic counseling: breast and ovarian cancer. PPO Updates 1998;12(1):1-11.
2. Ford, D. et al. Risks of cancer in BRCA1-mutation carriers. Lancet 1994;343(8899) :692-5.
3. Chen S, et al. Meta-analysis of BRCA1 and BRCA2 Penetrance. J Clin Oncol 2007; 25(11):1329-1333.
4. King M, et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302(5645):643-646.
5. van Asperen C, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genetics 2005; 42:711-719.
6. Weitzel JN, et al. Effect of genetic cancer risk assessment on surgical decisions at breast cancer diagnosis. Arch Surg 2003;138(12):1323-8.
7. Schwartz et al. Utilization of BRCA1/BRCA2 mutation testing in newly diagnosed breast cancer patients. Cancer Epidemiol Biomarkers Prev 2005;14(4):1003-7.
8. Meijers-Heijboer E, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. NEJM 2001; 345:159-164.
9. Rebbeck T, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE study group. J Clin Oncol 2006; 22(6):1055-1062.
10. Lodder L, et al. One-year follow-up of women opting for presymptomatic testing for BRCA1 and BRCA2: emotional impact of the test outcome and decisions on risk management (surveillance or prophylactic surgery). Breast Cancer Res Treat 2002; 73:97-112.
11. Kraemer O, Andersen M, Siim E. Breast reconstruction and tissue expansion in irradiated versus nonirradiated women after mastectomy. Scand J Plast Reconstr Surg Hand Surg 1996;30(3):201-6.
12. Jugenburg, M, et al. Impact of Radiotherapy on Breast Reconstruction. Clin Plastic Surg 2007; 34:29-37.
13. Contant CME, et al. Clinical experience of prophylactic mastectomy followed by immediate breast reconstruction in women at hereditary risk of breast cancer (HBOC) or a proven BRCA1 or BRCA2 germ-line mutation. EJSO 2002; 28:627-632.
14. Forman DL, Chiu J, Restifo RJ, et al. Breast reconstruction in previously irradiated patients using tissue expanders and implants: a potentially unfavorable result. Ann Plast Surg 1998;40(4):360-3.

>> AGGRESSIVE ADVERTISEMENT CAMPAIGN continued from page 1

cial incentives for the *number of test kits sold*, and the *number of kits ordered by new providers*. These employees have been known to discourage ordering physicians from referring their patients to graduate-trained cancer genetic specialists (even in areas like Connecticut, where these services are widely available), and encourage them to order the testing themselves after little or no training in genetics. This likely presents a medical-legal liability for busy providers who are not well-versed in genetics, and do not have time in their busy practices to provide genetic counseling, testing, and long-term follow-up.

Myriad Genetics launched a direct-to-consumer campaign via television and magazine ads that hit Connecticut, Massachusetts, Rhode Island and New York this fall. Unlike ads for prescription medications, these ads receive minimal regulation by the federal government.¹⁻⁵ As a result, they include little, if any, information about the risk factors for hereditary cancer, and have been described as inaccurate, misleading, and utilizing scare tactics in several publications.^{2,3,6} These ads end by encouraging consumers to contact the company directly. The conflict of interest is clear.

We have joined with other professionals across the country to counter this campaign and others like it. Go to www.responsiblegeneticstesting.org to learn more and to sign a petition asking for federal oversight before this campaign can launch. You may also go to www.yalecancercenter.org and click on 'Learn the Facts about BRCA Testing' for a patient fact sheet on this campaign.

References:

1. Gray S and Olopade OI. Direct-to-Consumer Marketing of Genetic Tests for Cancer: Buyer Beware. JCO 2003; 21(17):3191-3193.
2. Williams-Jones B. 'Be ready against cancer, now': direct-to-consumer advertising for genetic testing. New Genetics and Society 2006; 25(1):89-107.
3. Gollust SE, Hull SC, and Wilfond BS. Limitations of direct-to-consumer advertising for clinical genetic testing. JAMA 2002; 288(14):1762-1767.
4. Javitt GH and Hudson K. Federal Neglect: Regulation of Genetic Testing. Issues in Science and Technology 2006; 22(3):59-66.
5. Hudson K. Genetic Testing Oversight. Science 2006; 313:1853.
6. Hull SC and Prashad K. Reading between the lines: Direct-to-consumer advertising of genetic testing. Hastings Center Report 2001; 31(3):33-35.
7. Greendale K and Pyeritz RE. Empowering primary care health professionals in medical genetics: How soon? How fast? How far? Am J Med Genet 2001;106:223-232.

Please visit our new website to learn the facts about genetic testing and to refer a patient for counseling at yalecancercenter.org/genetics.

THE ROLE OF GENETIC TESTING FOR THE NEWLY DIAGNOSED BREAST CANCER PATIENT 1

AGGRESSIVE ADVERTISEMENT CAMPAIGN HITS THE NORTHEAST 1

EDITOR'S LETTER 2

GREATEST MYTHS ABOUT GENETIC COUNSELING AND TESTING 2

RISK FACTORS OF HEREDITARY CANCER SYNDROMES 3

advances

Genetic Counseling Program

As genetic testing options grow at expansive rates, physicians will continue to play a central role by eliciting a detailed history from their patients and choosing which patients are appropriate candidates for genetic counseling.

333 Cedar Street
P.O. Box 208028
New Haven, CT 06520-8028

Yale CANCER CENTER
A Comprehensive Cancer Center Designated
by the National Cancer Institute

NON-PROFIT ORG.
U.S. POSTAGE
PAID
NEW HAVEN, CT
PERMIT #526