**Cancer-Related Genetic Testing and Counseling: Workshop Proceedings**

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# CANCER-RELATED GENETIC TESTING AND COUNSELING

## Workshop Proceedings

National Cancer Policy Forum

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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*"Knowing is not enough; we must apply.*
*Willing is not enough; we must do."*
—Goethe



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# Contents

# Abbreviations and Acronyms

| | |
|---|---|
| AAFP | American Academy of Family Practitioners |
| ACMG | American College of Medical Genetics |
| ACS | American Cancer Society |
| AHRQ | Agency for Healthcare Research and Quality |
| AMA | American Medical Association |
| ASCO | American Society of Clinical Oncology |
| ASHG | American Society of Human Genetics |
| ASR | analyte-specific reagent |
| CDC | Centers for Disease Control and Prevention |
| CLIA | Clinical Laboratory Improvement Amendments of 1988, or CLIA |
| CME | continuing medical education |
| CMS | Centers for Medicare and Medicaid Services |
| CPT | current procedural terminology |
| DHHS | Department of Health and Human Services |
| DOE | Department of Energy |
| DTC | direct-to-consumer |
| ELSI | ethical, legal, and social implications |
| FAP | familial adenomatous polyposis |

| | |
|---|---|
| FDA | Food and Drug Administration |
| FTC | Federal Trade Commission |
| FTE | full-time equivalent |
| GAO | Government Accountability Office |
| GI | gastrointestinal |
| GINA | Genetic Information Nondiscrimination Act |
| GNRH | gonadotrophin-releasing hormone |
| GRE | Graduate Record Examination |
| HIPAA | Health Insurance Portability and Accountability Act |
| HMO | health maintenance organization |
| HNPCC | hereditary nonpolyposis colorectal cancer |
| HRSA | Health Resources and Services Administration |
| IOM | Institute of Medicine |
| IRB | institutional review board |
| IVDMIA | in vitro diagnostic multivariate index assay |
| MRI | magnetic resonance imaging |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NIH | National Institutes of Health |
| NPI | national provider identification |
| NSABP B-04 | National Surgical Adjuvant Breast and Bowel Project |
| NSGC | National Society of Genetic Counselors |
| OCN | oncology-certified nurse |
| PSA | prostate specific antigen |
| RBRVS | resource-based relative value system |
| RVU | relative value unit |
| UPIN | universal provider identification number |
| USC | University of Southern California |
| USPSTF | U.S. Preventive Services Task Force |

# 1

# Introduction

These proceedings of a workshop presented to the Institute of Medicine's (IOM) National Cancer Policy Forum (the forum) on March 30, 2007, are the result of forum discussions about genetic testing and counseling at its meetings on June 16 and October 30, 2006. Those discussions, led by forum members Betty Ferrell and Patricia Ganz, noted that genetic testing and counseling are becoming more complex and important for informing patients and families of risks and benefits of certain courses of action, and yet organized expert programs are in short supply. The subject matter involves not only the scientific and clinical aspects but also workforce and reimbursement issues, among others. Drs. Ferrell and Ganz proposed that the forum could provide a useful review of the various important implications of these issues by holding and reporting a workshop on the subject. They volunteered to work with staff to organize and lead such a workshop. The agenda for the workshop is reproduced in the appendix to these proceedings. Chapter 2 includes the presentations of the invited speakers and the comments of speakers, forum members, and others in attendance as transcribed and edited to eliminate redundancies, grammatical errors, and otherwise make them more readable. Material from PowerPoint presentations has been added to the text to clarify the speakers' messages as needed.

This workshop consumed the major part of a regularly scheduled meeting of the forum. The forum was established as a unit of the IOM on May 1, 2005, with support from the following agencies of the U.S. Depart-

ment of Health and Human Services (DHHS): the National Cancer Institute (NCI), the Centers for Disease Control and Prevention (CDC), the Agency for Healthcare Research and Quality (AHRQ), the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services (CMS), and the Health Resources and Services Administration (HRSA); as well as from the following private-sector organizations: the American Cancer Society (ACS), the American Society of Clinical Oncology (ASCO), C-Change, and (for the first year only) UnitedHealth Group. The forum is a successor to the IOM and National Research Council's (NRC's) National Cancer Policy Board (1997–2005) and was designed to provide its 21 governmental, industry, and academic members a venue for exchanging information and presenting individual views on emerging policy issues in the nation's effort to combat cancer. Publication of these proceedings informs the forum and, in addition, provides an opportunity to make the information and views presented and discussed at the workshop available to a wider public audience. Only what was actually communicated at the workshop is reported here without additional comment, interpretation, or analysis, although these proceedings might serve as an opening to additional IOM study at some future time.

# 2

# Prepared Presentations and Discussion

**Dr. Patricia Ganz, Professor of Medicine, UCLA: The Promise and Pitfalls of Cancer-Related Genetic Counseling and Testing:** I am going to give an overview to explain why we brought up cancer-related genetic testing and counseling as an issue. We have had clinical genetic testing for the BRCA-1 and -2 breast cancer genes for about 10 years. As we end this decade, we feel we have passed an important milestone, and we should think about what has happened over this time. In addition, legislation against genetic discrimination has been on the agenda in Congress for probably 10 or 11 years and has finally been approved in the House of Representatives with hope of passage this year. So I think there are a number of issues that make it timely for us to begin a discussion.

In setting the stage for today's speakers, I will be somewhat anecdotal and provide examples that I hope illustrate why we are here today. As a historical overview and dynamic case study of how we got to our present situation, I will start with what I think has been the successful integration of genetic testing and counseling in the management of breast cancer. I will try to fit clinical cancer genetics into the prevention paradigm, discuss some access and direct-to-consumer marketing issues, and sum up with some of the challenges that I see, hoping that our speakers today will cover them in greater detail.

I started my medical school surgical rotation in 1971 which brought me to part of the breast service and a surgeon at the county hospital who was participating in a National Surgical Adjuvant Breast and Bowel Project

(NSABP B-04) clinical trial that was comparing radical mastectomy to modified radical mastectomy. To my surprise, a woman at that time had to consent to either a radical or modified radical mastectomy before she even knew she had cancer. A frozen section diagnosis of her breast mass was made while she was on the operating table, and if she had cancer she would either have the standard radical procedure or the modified radical mastectomy. She awoke from anesthesia not knowing if she had breast cancer and whether she had the very radical or less radical procedure. This trial was important in showing that radical mastectomy was no better than modified radical mastectomy, and fortunately we have advanced in the local treatment of breast cancer since that time.

Today, most breast cancers are discovered through mammography, and more than 50 percent of them are stage I small tumors. In the early 1980s, advocates suggested that a two-step procedure was needed to provide a diagnosis and an opportunity to consider treatment options before surgery. As a result we now do small incisional biopsies or lumpectomies, sentinel node biopsies, and breast irradiation in many instances. We also have trials going on to examine whole versus partial breast radiation for women with lumpectomies, because long-term survivors may develop a second cancer in the same breast, and if they have already experienced all the radiation they can tolerate in that breast, mastectomy will be their only treatment option at that point.

Clinical genetic testing for breast cancer genes is often done prior to surgical decision making. If a woman is going to need hormonal therapy or chemotherapy before her definitive surgery, genetic testing may weigh very heavily in whether she decides to have a mastectomy on the tumor side or even bilateral mastectomy as part of the initial treatment planning. Because endocrine therapy may be given for up to 10 years for primary or secondary prevention, genetic information may have substantial implications. We recognized that breast cancer is a systemic disease, and through clinical trials and evolving practice, we have achieved important decreases in incidence and improvements in survival. We have eliminated the one-step surgical approach and turned to minimally invasive biopsies, lumpectomies, and radiation, with mounting evidence for as good or better results with less radical options.

The bottom line here is increasing patient involvement in surgical decision making and also now genetic decision making, although what I am describing in terms of the incorporation of genetic testing and decision making as part of treatment management may only be occurring at tertiary

centers—not yet the norm, but the way things are developing. We have important improvements in survival as a result of our progress: 90 percent 5-year survival rate for early stage patients, more than two million breast cancer survivors alive today, and continued improvements expected. These data have important implications: if we expect women to live a long time, having as much information about their potential risks for a second cancer either in the breast or the ovaries or some other organ is critical to decision making and treatment planning.

Important discoveries in the 1990s improved our understanding of risk factors for breast cancer. Two genes, BRCA-1 and -2, thought to be responsible for 5 to 10 percent of breast cancers, were discovered on chromosomes 17 and 13, respectively. They could be responsible for as many as 20,000 of the 200,000 breast cancers diagnosed each year in the United States; these 20,000 women might benefit from genetic information to assist decision making at diagnosis. Certainly after diagnosis in terms of the prevalent cases, there are many women who may be carrying genetic predisposition genes that would affect their future health as well as that of the families, so the potential ramifications of genetic information are important.

What happened at UCLA as an exemplar of progress at the end of the twentieth century? We were involved in the first breast cancer prevention trial, and shortly after that I established a high-risk program within our Revlon/UCLA breast center. It became clear to me that other centers around the country that were doing the leading-edge work in terms of the alpha and beta testing for genetic testing were beginning to see these high-risk populations and that this would be an important clinical service as well as an avenue to do clinical translational research. When clinical testing became available in 1997 for the BRCA-1 and -2 genes, we had a decision to make: were we going to put this into the clinical testing arena with all of the other genetic testing that was done with prenatal and other conditions, or were we going to somehow treat this differently? Because of concerns about the potential for genetic discrimination, the time needed to counsel women or others, we believed it best to proceed through a research protocol, not only to provide these services to people in a situation where they could be protected against potential legal or discriminatory practices, but also to collect research data on outcomes.

We started this as the UCLA Family Cancer Registry and Genetic Evaluation Program, a shared resource at the cancer center. We opened this up to anyone who had a cancer history, so it wasn't just breast and ovarian cancer. Patients who enter this program are not necessarily seen just once,

but may be seen repeatedly and benefit as new science provides new information on their condition and leads to new decision making.

A woman came to us in 1996 for high-risk surveillance in the course of clinical assessment and evaluation. Her sister had bilateral breast cancer diagnosed at age 35, and her mother had breast cancer diagnosed at age 45 and died at age 48 with metastases. Annual screening mammography and clinical breast exams three to four times a year were recommended. In 1999 she joined the family registry. In November of 2000, her mammogram was negative, but early in 2001, at age 41, she was diagnosed with breast cancer. As she was going through her surgical decision making, she considered whether she should have bilateral mastectomies. Because of her strong family history, we did genetic testing, and she had no evidence of a deleterious breast cancer gene mutation. We also pursued this further by testing for the tumor suppressor gene, PTEN, because of her very strong family history. When this turned out to be negative, she decided just to have a lumpectomy and radiation therapy because no genetic predisposition could be found in spite of three first-degree relatives with breast cancer, one of them bilateral.

Subsequently, we learned of new mutations (large deletions) in BRCA-1 that were associated with the risk of breast cancer in similar families, and on retesting she was found to have one of these very large deletions that was the cause of what was going on in her family. She then elected to have bilateral prophylactic mastectomies and also bilateral oophorectomies because of the very strong risk of both of these diseases. The 2002 update of her pedigree at this point in time is displayed in Figure 2-1 with a summary of the relevant events. The patient is indicated in this pedigree by the large arrow.

We fortunately have had the ability to perform long-term tracking of the people in our registry. We send them an annual questionnaire. I have had very good genetic counselors who work with me and who remember these cases. We probably have many more of them in our registry with family histories and unknown mutations. This is the luxury of having a research registry, but the average patient who has his or her blood drawn by a medical oncologist or even a clinical genetics counselor may not have such a luxury. The patient may not be well enough informed to follow through in this evolving field, where new information is coming continually. This is going to be a long-term problem.

**Ellen Stovall, CEO, National Coalition for Cancer Survivorship:** Are you still following this woman, and if so, how is she doing?

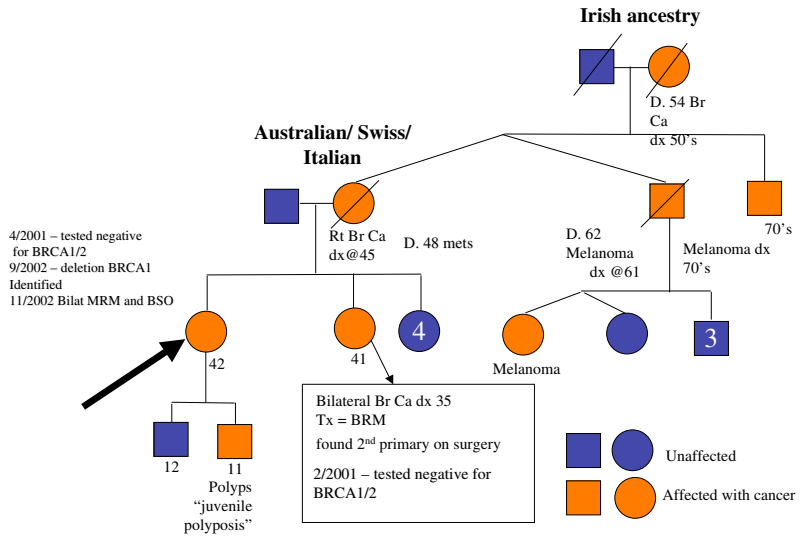


FIGURE 2-1 Pedigree of a high-risk patient.

**Dr. Ganz:** Yes, we are. She is doing very well, and she is a very outspoken advocate for this kind of testing and follow-up.

I have shown you a nice example of how this can work and work well. But I don't think this is the routine around the country. I think my colleagues today who are going to be discussing this will tell us about what is going on in the real world. If you think about where clinical cancer genetics belongs, it is in the prevention paradigm: either primary or secondary prevention. In somebody who doesn't have cancer yet, we want to prevent cancer in the future. If somebody, genetically predisposed or not, has already had cancer and is, therefore, at highest risk for a second cancer, we want to intervene there too. Survivors account for about 15 percent of all new cancer diagnoses that occur every year. It takes a very long period of time for breast cancer to develop from the very first cell that is malignant to one that we can detect—dissemination occurs in the interval between the first cancer cells and cancer detection. We know that hereditary cancers account for about 5 to 10 percent of all cancers. If we can find people with the first hereditary mutation who then are going to acquire other mutations that will lead to cancer, we have a real opportunity to intervene.

How do we find who is at risk for breast, colon, or prostate cancer, or melanoma and other diseases where we either have those genes identified or will in the future, when there are so few individuals? I think this is the real challenge that we face from the prevention and population perspective. Characteristically, in families with sporadic breast cancer, none of the cancer is diagnosed prior to age 60, there is no ovarian cancer, and no clear pattern on one side of the family or the other. Characteristically, in hereditary breast cancer, onset of cancer is under age 50, ovarian cancer (though not always present) occurs at any age, breast and ovarian cancer occurs in the same individual, there is male breast cancer, and there is Ashkenazi ancestry. We know that one in 40 to one in 50 individuals of Ashkenazi heritage are likely to carry one of the three founder mutations for breast cancer. The American Society of Clinical Oncology's (ASCO's) most recent guidelines for breast cancer care and surveillance recommend that any younger woman of Ashkenazi Jewish heritage with breast cancer, even if there is no family history, should have genetic testing.

So the key is the family history on both sides of the family, maternal and paternal, to accurately assess risk and make decisions about whether it is appropriate to do testing and genetic counseling. From the speakers today, we will hear who in the workforce should be doing that genetic counseling, whether we have enough people in the workforce, and whether we can rely on primary care physicians to take the appropriate family histories. Genetic testing just gives you information; it doesn't tell you what to do. We need the expertise of someone who knows about the genetics and the risks for various cancers and what the preventive strategies might be. We should suspect hereditary cancer when there are two or more relatives on the same side of the family, an early age at diagnosis, multiple primary tumors, bilateral or rare cancers, a constellation of tumors consistent with a specific cancer syndrome (e.g., breast and ovarian cancer, colon and uterine cancer, colorectal cancer associated with polyposis), autosomal dominant transmission, and the Ashkenazi heritage in particular.

Increasingly there are reports of multiple cancers associated with hereditary predisposition genes. Genetic testing of incident cases of ovarian cancer in the population identified high rates of BRCA-1 and -2 expression, and complete pedigrees found that the women who were gene carriers had many other family relatives with a constellation of other common solid tumors—a different way of case finding. This finding needs to be corroborated, but we know already about the breast-ovarian association or the association between BRCA-2 and pancreatic and possibly prostate

cancer and melanoma, or BRCA-1 and possibly testicular and some gastrointestinal (GI) cancers.

**Dr. Harold Moses, Director Emeritus, Vanderbilt-Ingram Cancer Center:** What proportion of pancreatic cancer patients have BRCA-2?

**Dr. Ganz:** It is about 5 to 10 percent, so it accounts for a lot of the familial pancreatic cancers. We have now a funded screening study to go back to our registry and identify BRCA-2 carriers with pancreatic cancer in the family. I think this is the tip of the iceberg in what we understand. I think as clinical genetic testing becomes more widespread for cancer predisposition and people recognize this, we are going to become more aware of other sites. Because most of us do not routinely take a thorough family history of our cancer patients, we don't consider or discover family connections. But I think as research evolves we are going to see predispositions in other organs.

You have heard already about the success in tertiary centers of the integration of breast and ovarian cancer, genetic testing, and screening. This has likely occurred because we have had people who have been interested from the research standpoint, but also there is a high level of consumer awareness and a lot of available breast cancer information, and physicians who are treating these patients are aware that this is an issue particularly in the young patients who present to them.

We have a diametrically different experience with colorectal cancer patients. It has been very difficult to get the attention of gastroenterologists. There are many published papers describing that people who have family histories of colorectal cancer are not coming in for genetic testing. Clearly, a colon full of adenomatous polyps in familial adenomatous polyposis (FAP) is a signal, and those patients will be referred for testing. However, in attenuated FAP, there may not be as many polyps in the colon, so it requires an astute gastroenterologist to take a history and refer. There are new mutations, spontaneous mutations where the family history may not be as strong.

There has not been as much patient demand from the colorectal cancer community. We are talking about a community that perhaps is not as active as the breast cancer community in advocacy. There is also the thought that the family members will be screened with colonoscopy. If your mother has colon cancer at age 40, it is agreed that her children need to be screened, but half of them might be screened intensively unnecessarily because they don't carry a mutation. Similarly, her children would begin screening at a