Proceedings of the International Consensus Conference on Breast Cancer Risk, Genetics, & Risk Management, April, 2007

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A consensus conference including 30 experts was held in April, 2007, to discuss risk factors for breast cancer and their management. Four categories of risk were outlined, from "average" through "very high" risk, the latter including individuals with high penetrance *BRCA1/2* gene mutations. Guidelines for management of patients in each of these categories were discussed, with the major portion of the conference devoted to individuals with *BRCA1/2* mutations. Prevalence of these mutations in the general population was estimated to be 1 in 250-500 individuals, with an increased prevalence in Ashkenazi Jews and other founder groups. Risk-reduction strategies for these individuals included surveillance, with or without chemoprevention drugs, or surgical procedures to remove the organs at risk, ie, bilateral mastectomy and/or bilateral salpingo-oophorectomy. These risk reduction strategies were evaluated fully, and recommendations were made for the care of patients in each risk category. These guidelines for patient care were approved by the entire group of experts. ***Cancer* 2008;113:2627–37.** © *2008 American Cancer Society.*

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TABLE 1
Risk Factors for Breast Cancer (Compared With So-Called "Average" Risk Described in Text)

Major and Minor Risks
Major: >2x average risk (see text)
BRCA1/2 mutation
Family history: 1st degree relative under age 60 y
"Mantle" radiation therapy before age 30
Personal history of DCIS, LCIS, ADH, ALH
Prior personal history of breast or ovarian cancer
Increased breast density (controversial)
Minor: <2x average risk (see text)
Nulliparous or first child after age 35 y
Lactation (none vs any)
Early menarche (before age 12 y)
Late menopause (after age 55 y)
History of HRT use (controversial)
Obesity
Sedentary life style
Breast cancer in 2nd or 3rd degree relatives
Prolonged smoking history
Prolonged alcohol usage (>1-2 oz daily)
High socioeconomic status
Vitamin D deficiency

DCIS indicates ductal carcinoma in situ; LCIS, lobular carcinoma in situ; ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; HRT, hormone replacement therapy.

TABLE 2
Major Factors: Risk of Developing Breast Cancer per Year

Major Risk Factors	Rate Each Year
BRCA1/2 carrier	2-3% (after age 30 y)
DCIS	1-2% lifetime after diagnosis
LCIS, ALH	1% lifetime risk after diagnosis
ADH	0.5% lifetime risk after diagnosis
ADH plus family history (1st degree relative)	1% lifetime risk after diagnosis
Prior invasive breast cancer	0.75% other breast, lifetime risk
Age>60 y	0.3% lifetime risk

DCIS indicates ductal carcinoma in situ; LCIS, lobular carcinoma in situ; ALH, atypical lobular hyperplasia; ADH, atypical ductal hyperplasia.

TABLE 3
Relative Risk of Breast Cancer for Major Factors

Factor	Relative Risk (RR)
Age 30 y vs 60 y	10
LCIS, ALH, ADH	2-10
Prior breast or ovarian cancer	2-10
First degree relative aged <60 y at diagnosis of breast cancer	2-3
Chest radiation aged ≤ 30 y	5-20
High penetrant mutation (*BRCA1/2*)	10-20

LCIS indicates lobular carcinoma in situ; ALH, atypical lobular hyperplasia; ADH, atypical ductal hyperplasia.

Since the identification of the first breast cancer autosomal dominant gene in 1990, the molecular world of breast cancer investigation has exploded. Of the approximately 184,450 invasive breast cancers expected in the USA in 2008, between 5% and 10% affect patients with highly penetrant cancer susceptibility genes. Few of these individuals were known mutation carriers before diagnosis, when this knowledge might have led to an earlier diagnosis. Moreover, many of these cancers were not subsequently identified as "hereditary" when this knowledge might have changed their management or helped other family members still at risk. To address these issues of risk management and prevention, the Sixth International Consensus Conference of the Breast Health Institute convened in Philadelphia, April 26 through April 29, 2007, with invited experts in breast cancer care, cancer genetics and risk assessment, who represented each discipline that is involved in caring for these patients. The goal of the consensus conference was to summarize the state of the art in high-risk patient identification and to discuss various management strategies appropriate to each level of risk. These proceedings were distilled from transcripts of the entire meeting and summarize the opinions of the entire group. Each participant approved the current article.

What Does the Term "Increased Risk" Mean?

A risk factor is any variable that increases risk of breast cancer for affected individuals. Major risk factors are those that at least double (≥2 times) breast cancer risk, whereas minor risk factors are those that increase relative risk by less than double (≤2 times). (Table 1). Both absolute and relative risks are known for many major risk factors such as a *BRCA1* or *BRCA2* mutations, contralateral breast cancer, prior ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), atypical ductal hyperplasia, and atypical lobular hyperplasia (Tables 2 & 3). We are able to provide only relative risk estimates for many minor risk factors. Major risk factors tend to dwarf minor risk factors in individual risk assessment. For a comprehensive risk assessment, information should be sought on all factors in Table 1; however, once a woman has a known factor that increases her risk significantly, such as atypical hyperplasia or a genetic mutation, knowing age at menarche or first live birth adds little additional information.

It is often stated that the "average" American woman has a lifetime 1 in 8 chance of developing breast cancer. What is forgotten is that this average woman may have 1 or more of these minor factors in her personal history that contribute to this 1:8 risk

assessment. Another problem that should be addressed by primary care physicians is the inaccurate perception of risk by many women, who either overestimate or underestimate their own risk of developing breast cancer.

Family History as a Starting Point for Risk Assessment

The importance of a detailed family history cannot be overemphasized; however, current time constraints in most healthcare systems make a comprehensive family history difficult to record. The best approach suggested at the conference was to emphasize the importance of family history to all clinicians and to encourage development of the electronic medical record (EMR) to collect and record such data.

Every medical record should have a family history section that includes the patient's own medical history, including cancer, past or present, and the cancer history of progeny, siblings, parents, together with second-degree relatives and both sets of grandparents. A cancer history collected through 3 generations is usually sufficient, but in cancer-prone families (eg, Li-Fraumeni), this should be extended as far as possible because diverse cancers may occur.

Other Factors

Breast density

An increase in mammographically measured breast density has recently been identified as another risk factor. The panel considered breast density in their discussions but were frustrated by the lack of evidence-based data on which this conclusion has been reached. The breast imaging specialists were highly critical of the subjective manner in which breast density has been measured. The panel concluded that currently there is no reproducible, quantifiable manner by which to measure breast density that allows an answer to this important question. That this question must be pursued by appropriate clinical trials was emphasized, but the assertion that breast density was a significant factor was disputed.

Cytological atypia in intraductal fluid (ductal lavage)

Whether a finding of atypia in a sample of intraductal fluid obtained by ductal lavage or by specialized devices leads to the same screening recommendations as those for women found to have atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH) in a surgical breast biopsy was addressed. Although approved by the US Food and Drug Administration (FDA) for patient use, these techniques were unanimously deemed to be quasi-experimental by the panel and to be used only in the context of a clinical trial.

Risk Models

Several risk assessment models have been developed that give both short-term and long-term risk estimates and/or the risk of a deleterious mutation. The modified Gail model is the most popular in the United States but considers only 7 variables— race, current age, age at menarche, age at first live birth, number of affected first degree relatives, number of breast biopsies, and whether the biopsy contained atypia (http://www.cancer.gov/bcrisktool). Women who have other risk factors will have their risk underestimated; however, it is currently the model approved by the FDA in the US for determining who should be offered tamoxifen or raloxifene. Other such models are available and widely used, especially abroad; each has its avid proponents and critics; none is perfect.

Risk Categories

The panelists agreed to 4 basic categories of risk:

1. Average risk affects the female population at large.
2. Moderate risk affects those women whose risk is more than average for their age group but whose relative risk is <5-fold.
3. High risk is >5-fold but <10-fold the relative risk for each age group. This includes women with lobular carcinoma in site (LCIS), atypical ductal hyperplasia (ADH), and atypical lobular hyperplasia (ALH), and women with 2 first-degree relatives with breast cancer but without mutation.
4. Very high risk is a >10-fold increase in relative risk due to either a high-penetrance gene mutation (*BRCA1/2, PTEN, or TP53*) or those likely to harbor such a mutation, or a personal history of irradiation to breast or chest wall *before age 30 years*.

Management Strategies by Risk Category

Because no risk model is perfect, how each is used is arbitrary. It is preferable to discuss approaches to risk in a more generic manner, trying to place women in various groups on the basis of their perceived risk of developing breast cancer. Therefore, approaches for different risk groups were discussed individually, with the major focus on women with likely or proven high-penetrance mutations responsible for hereditary breast cancer. However, reasonable recommendations were proposed for each group.

1. Average risk (absence of any of the accepted risk factors)

These women should follow established programs for cancer screening. This implies annual mammography starting at an age customary to a particular country (age 40 years in the US). The panel did not

achieve consensus on when to stop mammography, but most agreed that, if the patient had a reasonable life expectancy (>5 years), mammography should continue indefinitely. Breast (and gynecologic) examinations were recommended at annual intervals. Breast self-examination, despite criticism of its efficacy, should be carried out monthly. Screening for other cancers, eg, colon, should also follow accepted population-based guidelines.

Tamoxifen or raloxifene is not indicated for average-risk women. Menopausal hormone replacement therapy (HRT) using estrogen alone for women without a uterus was considered safe, for up to at least 10 years. Despite the current controversy about breast cancer risk of combined HRT, the panel agreed that there was minimal risk in using combined HRT for up to 5 years to treat quality-of-life issues.

2. Moderate risk: (1 or more of the ''minor'' factors in Table 1)

Screening should be the same as for the average risk group above. No data support more frequent screening or screening with magnetic resonance imaging (MRI) in this group. The group did not support the use of tamoxifen or raloxifene in this population but did recommend that information on these drugs be discussed with patients. Hormone replacement is not contraindicated for symptomatic women in the moderate-risk category, but women with an intact uterus who need estrogen combined with a progestin should use the lowest possible dose for the shortest period of time.

3. High risk

For women at high risk primarily as a result of a diagnosis of ADH, ALH, or LCIS, the risk of invasive carcinoma is increased at least 5-fold, and annual digital mammography was advised from the date of diagnosis, regardless of age. Little data regarding the use of annual screening MRI in addition to mammography are available. The group felt that this was a fertile area for future study.

Semiannual clinical breast examination was recommended. High-risk women generally are candidates for chemoprevention with tamoxifen if premenopausal, or with tamoxifen or raloxifene if postmenopausal, but no evidence yet confirms increased survival when these drugs are prescribed. Aromatase inhibitors in postmenopausal women for prevention are not (yet) indicated, pending results of ongoing phase 3 trials.

For women at high risk primarily because of multiple affected family members but without a *BRCA 1* or *2* mutation, screening recommendations are based on the level of risk. If lifetime risk of breast cancer due to family history exceeds 20%, annual MRI in addition to annual mammography is recommended. Screening should begin at least 10 years before the age of diagnosis of the youngest affected close relative, or by age 40, whichever is earliest. Clinical breast exam is suggested twice yearly. Consideration of chemoprevention should be based on level of risk and anticipated benefit:risk ratio, but at least should be discussed. Risk-reduction surgery, although a subject for discussion, is not a usual recommendation for these patients.

4. Very high risk

The very high-group includes a small group of women who underwent chest or breast radiation before age 30 years (eg, treatment for Hodgkin disease) or who are known to have or be likely to have a deleterious high-penetrance gene mutation.

Women with chest or breast radiation before age 30 years need risk counseling and annual (digital) mammography beginning 5-10 years after the age of their radiation treatment or at age 40 years, whichever is earlier, but not before age 25 years. Annual breast MRI should be considered in these women, alternating at 6-month intervals with mammography, starting at the same age, although there are few clinical trial data to support this recommendation and no data confirming that periodic MRI affects survival. Semiannual clinical examination was recommended. Whether these women should be advised to consider tamoxifen or raloxifene was more controversial, but a majority of the group thought that these would be appropriate choices. Risk-reduction surgery should be discussed but, like Group 3 (high risk) above, is not a usual recommendation.

Women at very high risk because of a *BRCA 1* or *BRCA2* mutation or similar deleterious genes responsible for hereditary breast cancer will be discussed in detail for the remainder of this article.

Identification of Women at Hereditary Risk

The discovery of germ-line mutations that increase breast cancer risk has led to paying greater attention to these factors to determine an individual's lifetime risk and to examine techniques to decrease that risk. In general, genetic factors have been divided into 2 arbitrary categories, namely, those of high and low penetrance.

Low-penetrance genes

The list of low-penetrance genetic markers is lengthy and growing. Each of these mutations probably confers a small to moderate increase in lifetime breast cancer risk. However, because mutations in these

low-penetrance genes are expected in a large number of persons, the population attributable risk (PAR) for breast cancer explained by these genes may be considerably higher than the PAR caused by less frequently encountered mutations of high-penetrance genes such as *BRCA1* and *BRCA2*. Lesser penetrance genes may partly account for the difference in the sensitivity of women to environmental factors, such as the use of alcohol or HRT. When the interaction of environment and low-penetrance mutations becomes elucidated, specific prevention strategies may be possible. Routine clinical testing for low-penetrance gene mutations (such as *CHEK2*) was not recommended by the panel.

High-penetrance genes

Mutations in *BRCA 1, BRCA 2, PTEN*, and *Tp53* are responsible for the hereditary breast cancer syndromes. These are tumor-suppressor genes, creating a protein that repairs DNA and prevents carcinogenesis. Every cell in mutation carriers lacks 1 functional allele; the tumor-suppressor function of that gene is lost, favoring the development of cancer.

Although each of these syndromes expresses a different spectrum of cancers, they share a general set of familial characteristics. Family histories tend to show an unusually large number of relatives with cancers (eg, 3 or more with breast cancers, or 2 or more with ovarian cancers), young age at diagnosis, multiple cancers in a single individual (eg, bilateral breast or breast plus ovary in 1 relative), and/or unusual cancers (eg, male breast cancer) or some common cancers, eg, prostate and pancreas, at earlier ages.

High-penetrance hereditary breast cancer accounts for only 5% to 10% of all breast cancers. However, a disproportionately high number of young women are affected. Recognition of women at risk *before* they develop cancer is important in order to effect strategies to decrease the morbidity and mortality of cancer for these individuals.

Li-Fraumeni syndrome and the Tp53 gene. Li-Fraumeni syndrome is an autosomal dominant disorder caused by mutations in the *Tp53* gene, characterized by an increased risk of soft tissue and osteosarcomas, leukemias, brain tumors, adrenocortical carcinomas, and breast cancers. The risk of developing breast cancer before the age of 45 years is 18 times higher for females who carry this mutation when they are compared with the general population. The relative risk is greatest in women younger than the age of 20 years and declines with increasing age (relative risk [RR] for breast cancer after the age of 45 years is 1.8). Germline mutations in the *Tp53* gene probably account for $<1\%$ of breast cancer cases.

Cowden syndrome and the PTEN gene. Cowden syndrome is an autosomal dominant disorder, caused by a mutation in the *PTEN* gene, characterized by the development of hamartomas and benign tumors. Mutations in the *PTEN* gene are evident in 80% of Cowden syndrome families; these are associated with an increased risk of cancer. Female mutation carriers are believed to have a 25% to 50% lifetime breast cancer risk, although data to support this level of risk is not robust. In sporadic breast cancers, it is not currently known whether *PTEN* plays a role in breast cancer susceptibility.

BRCA1/BRCA2. Although modestly different in their characteristics, these 2 high-penetrance mutations are commonly considered together because their similarities outweigh their differences. Both are tumor-suppressor genes and are those for which commercially available testing is available. Testing for these mutations has led to an explosion of knowledge about hereditary cancers.

Mutations in *BRCA1* and *BRCA2* markedly increase the risk of both breast (at least 60% lifetime risk) and ovarian cancer (15% to 40% lifetime risk) and are responsible for about 45% of families with multiple cases of breast cancer and up to 90% of families with both breast and ovarian cancer. *BRCA1* carriers are of younger age, their breast cancers are more likely to be of high grade, of medullary histology, and "Triple Negative" (not expressing estrogen or progestin (ER/PR) receptors or HER-2). These women also have a much higher risk of ovarian cancer. Breast cancers in *BRCA2* carriers are more likely ER/PR positive. In addition, male carriers with either mutation seem to be at an increased risk for carcinoma of the prostate as well as the breasts, modestly increased with the *BRCA1* mutation but probably at least double the lifetime risk for carriers of the *BRCA2* mutation.

The role of these mutations in the development of DCIS and the significance of relatives with DCIS are uncertain. Therefore, the panel separated these 2 entities, ie, invasive cancer and DCIS, so that all of the discussion and ensuing recommendations apply to invasive cancer only. However, the differences between invasive cancer and DCIS should probably be ignored as physicians ponder whom to send for genetic counseling; they should be counted equivalently.

Current mutation screening methods vary in their sensitivity. DNA sequence analysis is the most sensitive method of detecting unknown mutations and is commercially available. Many published estimates of the prevalence of mutations have been derived from studies that have used methods of gene analysis other than direct sequencing, but discussion

of the pros and cons and the results of these other techniques were beyond the scope of the conference. The panelists agreed that genetic testing for clinical use should be performed only by approved laboratories, regulated in the US by the Clinical Laboratory Improvement Amendments of 1988 (CLIA), Public Law 100-578.

Genetic testing results may identify a deleterious mutation known to cause hereditary breast and/or ovarian cancer or the absence of such a mutation. Even if there is a known family mutation, a tested but negative individual is *not* at hereditary risk. Management should still depend upon the family history.

Approximately 10% to 15 % of all tested individuals will have a variant of uncertain significance (VUS), which may cause substantial problems in counseling, cancer risk estimation, and risk management. Clinical management of such patients needs to be highly individualized and must consider factors such as the patient's personal and family cancer history, as well as the likelihood that the VUS is significant. Additional research will certainly lead to a reclassification of many variants of uncertain significance, which may then change the care of affected individuals. The presence of a VUS is usually reported by the testing laboratory, often with a disclaimer as to its significance.

If a deleterious mutation is identified, genetic testing should be encouraged for all at-risk family members, after full counseling *and* obtaining informed consent. Mutation carriers should begin specialized screening, and noncarriers may revert to general population screening guidelines. Currently, any contact with relatives must be through the known mutation carrier (the patient undergoing testing). The physician's legal responsibilities to the patient's family members when a mutation is identified have not been clearly delineated, once the index patient has been informed of the findings. Legal action has been initiated against physicians who have given this information to relatives without the patient's express permission. Unambiguous, clear, legislative decisions are needed to define the limits of the "duty to warn" family members and the most acceptable means of fulfilling that duty within the constraints of legislation (eg, Health Insurance Portability and Accountability Act [HIPAA]) guarding patient privacy.

The panel agreed that genetic testing in children was indicated only with the Li-Fraumeni syndrome. Most panelists saw little benefit to *BRCA* testing before the age 25 years.

Prevalence of BRCA1 and *BRCA2* mutations. The panel estimated the frequency of these mutations as about 1 per 250-500 individuals in the non-Jewish population. The younger the index patient and the stronger the family history, the higher is the likelihood of a mutation. Up to 20% to 25% of women diagnosed before age 30 years are carriers, as are women with more than 3 first-degree or second-degree relatives with breast cancer. Ovarian cancer in a first-degree relative is also associated with a 25% chance of a *BRCA1* mutation, and up to 40% when that same relative had both breast and ovarian cancer.

Sometimes the same mutation appears in multiple unrelated families, when a contemporary population derives from a small, isolated group of "founders". Two *BRCA1* mutations (185delAG and 5382insC) and a *BRCA2* mutation (6174delT) have been reported in Ashkenazi Jews (those tracing their roots to Central and Eastern Europe). Carrier frequencies for these mutations in an Ashkenazi Jewish population are approximately 1% for the 185delAG mutation, <0.5% for the 5382insC mutation, and 1% for the *BRCA2* 6174delT mutation. Altogether, the frequency of these 3 mutations approximates 1 in 40 among Ashkenazi Jews, accounting for 25% of early onset breast cancer and up to 90% of the families with multiple cases of both breast and ovarian cancer. In suspected Ashkenazi carriers, limited testing for ethnic-specific alleles may be appropriate as a first step. When a test is positive, full sequencing is not continued. This is faster and more cost effective because as many as 90% of the mutations found in the Ashkenazim are 1 of these ethnic-specific alleles. Additional founder mutations have been described in the Netherlands, the French Canadian population, Iceland, and Sweden.

In addition, there are so-called "cancer families," with significant histories of breast and/or ovarian and other cancers that warrant genetic testing, but they test negative for either *BRCA1* or *BRCA2* or a VUS. Although not treated in the same manner as mutation carriers, these families are at significantly increased risk for cancer, and management recommendations should be individualized on the basis of family history.

Who Should Be Considered for Genetic Testing?

Identification of women and men who should be referred for risk counseling and possible genetic testing has been controversial. Multiple risk-assessment systems have been developed to quantify risk. Many of them are difficult and/or time consuming to use and are best reserved for use in the genetic counseling process once detailed family history information has been obtained. The panelists felt that any patient

with a significant risk of mutation assigned by any of these models would benefit from referral for risk counseling. "Significant' was difficult to define, but most of the panelists felt that a $\geq$10% of mutation was an appropriate definition. The following are guidelines and examples to help clinicians identify candidates for referral:

1. An early age at onset (before age 40 years) of breast (or ovarian) cancer in the index patient is a firm criterion for referral.
2. When there are multiple affected relatives, 2 or more affected relatives in a single bloodline who are younger than age 50 years, including the proband, or 3 or more relatives with 1 of the index cancers in a single bloodline should generate a referral. However, this should be modified by the population frequency of a given cancer and the ages of onset within the family. Two postmenopausal breast cancers in 1 family are not unusual, but 2 ovarian cancers are much less likely to occur by chance. Hence, mutation carriers are more likely to be in a family with 2 ovarian cancers or 2 early onset breast cancers, more so than 1 family with 3 late-onset breast cancers.
3. Multiple primary cancers in an individual, particularly breast and ovarian cancer, should generate a referral.
4. All men with breast cancer should be referred for testing.
5. Patients diagnosed by pathology with medullary or "pseudo-medullary" breast cancer are more likely to be *BRCA1* carriers and should be referred. Those with triple-negative breast cancer (estrogen receptive negative, progestin receptive negative, and HER-2 negative) are also more likely to have a *BRCA1* mutation; they also should be tested, especially when they are under age 50 years or when the patient has a family history of breast cancer.
6. Newly diagnosed breast cancer patients of Ashkenazi Jewish descent, even without any other criteria, should be candidates for referral when the results of testing may change management.
7. When the patient is a member of an ethnic group with a known founder mutation, a family history of ovarian cancer in the absence of family history of another malignancy makes that patient a candidate for referral.
8. A known breast cancer mutation in a first-degree or second-degree relative, on either side, makes a patient a candidate for referral.
9. The occurrence of breast cancer in the index patient and a family history of prostate cancer, thyroid cancer, sarcoma, endometrial cancer, adrenocortical cancer, brain cancer, or pancreatic cancer are much looser criteria than those mentioned in paragraphs 1-8 above.

Barriers to Risk Counseling and/or Genetic Testing

The panelists all expressed their concern about inadequate reimbursement for genetic testing and counseling. In Europe, the testing, when indicated, is usually covered by national health plans, but counseling is not (except in the UK). In the US, reimbursement for testing is an individual issue depending upon the individual's health insurance and/or state programs for the uninsured. For reimbursement by Medicare in the US, the criteria include pretest and post-test counseling by a "qualified and appropriate trained individual," without further definition. Genetic counseling is considered a "screening service" by Medicare and may not be reimbursable. Most academic centers provide genetic counseling at no or very little cost to the patient. This is not a sustainable model. Insurance carriers do not usually reimburse genetics counselors because they are not recognized as ancillary providers, such as nurse practitioners or physicians' assistants. The group unanimously agreed that federal or state-wide licensing programs for genetic counselors was mandatory to permit reimbursement for this grossly undervalued but highly essential service.

Patient and physician fears of genetic discrimination by health insurers have sometimes interfered with women's pursuit of testing. At least in the US, this is no longer a problem. In May 2008, President Bush singed into law the Genetic Information Nondiscrimination Act (GINA) which will protect Americans against discrimination based on their genetic information when it comes to health insurance and employment.

Who Should Screen and Who Should Counsel?

Although many high-quality risk assessment programs exist, they are insufficient to care for all existing high-risk patients. Access to counseling centers may be difficult because of backlogs of several months. To manage the patient load more effectively, the counseling process must be more efficient, with many more trained counselors.

A typical risk counseling session takes at least 1 hour, more often 2-3 hours. Much of a session involves gathering a complete family history and determining risk factors, followed by data entry into pedigree-drawing software to produce a quantitative risk analysis, plus the time to complete the medical record. It is hopeful that innovative software (eg,

HughesRiskApps.com) will fulfill its promises of decreasing workload by adding the ability to electronically reuse previously collected family histories and risk factors and by expediting these tasks.

The panel was enthusiastic about developing new and innovative ways to improve counseling efficiency and access, such as telephone counseling and internet-based data collection. However, the panel believed that these approaches should be used cautiously and be vetted as safe and appropriate before their use becomes widespread.

The panelists agreed that counseling should be undertaken by trained, experienced individuals, but there was little agreement on defining adequate preparation. In general, all concurred that a committed clinician, genetic counselor, nurse practitioner or other medical professional, also able to provide the elements of informed consent required before genetic testing as delineated by ASCO, could provide a high-quality service. Hospitals or practices lacking a committed individual should refer elsewhere.

The panel strongly disapproved of current internet-based advertising for home-based testing with telephone counseling. The safety and efficacy of these approaches have not been established. Similarly, the group frowned upon direct advertising by commercial laboratories to primary care physicians. There was no suggestion that a primary physician, who has the interest and expertise and who knows the patient, be restricted from ordering genetic tests when appropriate counseling and informed consent have been obtained.

Timing

Another major concern of the panelists was the delay from blood draw to delivery of results. This delay may be weeks long, which is untenable for the patient who begins the process after a diagnosis of breast cancer, as many do. The panelists strongly endorsed urgent genetic counseling and testing for selected, newly diagnosed, breast cancer patients. As more counseling centers become available, this should become less of an issue. Part of the informed consent for all of these patients who begin their risk assessment after a diagnosis of breast cancer is their understanding that a reasonable delay in reporting results is not harmful to their outcome.

Currently, preoperative chemotherapy in selected patients allows systemic treatment to be initiated and completed while laboratory results are pending. Surgical treatment can then be planned after receipt of genetic test results.

TABLE 4
Cumulative Risks of Breast and Ovarian Cancer for Women With *BRCA1/2* Mutations*

	Breast Cancer		Ovarian Cancer	
	BRCA1	*BRCA2*	*BRCA1*	*BRCA2*
% Risk by age, y				
30	3	0	<2	1
40	21	17	5	2
50	39	34	20	10
60	58	48	40-50	18
70	69	74	50-60	18
80	81	85	>60	23
% Lifetime risk	85	85	62	25
% Male carriers lifetime risk	6	7	—	—
% General population risk	Not Calculated by *BRCA1/2*			
Women	12.5		—	
Men	<1		—	
Ovarian cancer	—		1-2	

*Modified from King MC, Marks JH, Mandell JB, et al. Breast and ovarian cancer risks due to inherited mutations in *BRCA1* and *BRCA2*. *Science*. 2003;302:643-646.

Management of the Patient With a Mutation

Current genetic testing includes full-sequence testing in the non-Ashkenazi patient. In Ashkenazim, testing for the 3 common founder mutations is performed first, and only when these 3 tests are negative should full-sequence testing be completed. When full-sequence teseting or if 1 of the known mutations is detected, management is reasonably established. However, the management of individuals with variants of uncertain significance (VUS) is not clear. Currently, the only recommendations made in this situation should be careful surveillance on the basis of the factors that led to the genetic testing.

Carriers should be advised of the findings, and recommendations for management should be directed by a physician knowledgeable about the implications and lifetime risks of both breast and ovarian cancer (Table 4). The genetics professional who provides pretest and post-test counseling should share the test results with the patient, but a geneticist without specialized training in oncology should not make specific recommendations. Management will differ on the basis of several variables, for example, a patient with newly diagnosed breast cancer who needs to decide upon a treatment. In addition, the patient should be made aware of the likelihood that the same mutation could be present in children or siblings, so they can be appropriately informed. Previously noted is the ethical and legal dilemma surrounding the "need to know" for the proband's family.

For *BRCA1* or *BRCA2* mutation carriers, there are really only 2 major choices with respect to manage-

ment of each organ at risk, namely careful, lifetime follow-up, with or without chemopreventive agents or risk reduction surgery. Regardless of the initial management, continued lifetime follow-up is essential.

Management of Breast Cancer Risk

The most careful or frequent nonsurgical follow-up cannot guarantee that a lethal breast cancer will not occur, so the panel endorsed preemptive bilateral total mastectomy (±reconstruction), an almost certain technique of breast cancer prevention. The major question was timing, ie, at the time the mutation was confirmed, at some time in the future, or a date chosen by the patient. Most panelists felt that surgery was best performed in patients aged late 30s in years, and this surgery should not be delayed past the mid-50-year mark in age. Reconstruction was stressed as available to virtually all patients.

Nipple-sparing mastectomy was addressed; all agreed that this innovation should be studied selectively. It was not to be used currently by the "occasional" breast surgeon. Although potentially as effective as total mastectomy in reducing risk, critical comparative studies comparing total mastectomy and nipple-sparing mastectomy are required before this option can be recommended.

The controversial role of axillary sentinel lymph node biopsy (SLNB) in mutation carriers who are undergoing prophylactic mastectomy was addressed because of the unexpected detection of invasive cancer in these specimens and the technical difficulty of SLNB after latissimus-flap reconstruction. The almost unanimous view of the panel was that a negative MRI before surgery made the likelihood of an unexpected invasive cancer so low that routine SLNB was not justified.

For patients who retain their breasts, semiannual clinical examination should be supplemented by annual mammography and annual breast MRI scans, scheduled alternately at 6-month intervals, even though current data on the use of periodic screening MRI scans do not yet confirm an increase in patient survival. The role of tamoxifen to reduce risk in women who retain their breasts was discussed. Lack of data prevented a substantive recommendation beyond a need to discuss the pros and cons of tamoxifen with each patient.

Women must be advised that premenopausal prophylactic oophorectomy reduces the lifetime risk of breast cancer by as much as 50% in women with either *BRCA* mutation, even when HRT is used. This diminution in risk may affect a decision to perform (or not) a prophylactic mastectomy.

Management of the Mutation Carrier *After* the Diagnosis of Breast Cancer

Despite the unanimous preference of the panel that every attempt be made to identify mutation carriers before their diagnosis, many patients learn of their high-risk status only then. When breast cancer is confirmed, and when the patient falls into 1 of the previously mentioned categories of increased risk, genetic testing can proceed before a definitive therapeutic decision is made. The panel unanimously agreed that the newly diagnosed breast cancer patient who proves to be a mutation carrier can be safely treated by breast conservation, expecting about the same in-breast recurrence rate as a noncarrier within 5 years, although likely having a higher rate of in-breast recurrence after approximately 5 to 10 years. Bilateral breast MRI should be performed before any surgery to identify multicentric disease or occult contralateral cancer, which may affect a patient's decision.

Because of the high risk of subsequent contralateral breast cancer, bilateral mastectomy should be discussed, but the decision is not an urgent one. Several options are available, including preoperative chemotherapy without further surgery, while genetic testing proceeds, or local excision of the primary tumor with or without chemotherapy. After these have been completed, and after results of the genetic tests are available, but *before* radiation, a decision can be made about definitive surgery. To radiate the patient and then perform mastectomy would be redundant, unreasonable, and may limit reconstructive options. The detection of an invasive cancer would generally mandate ipsilateral axillary staging (SLNB) as part of the treatment regardless of the final surgical decision. This procedure may be accomplished separately while awaiting results of genetic tests, if desired.

Panelists were concerned about the role of prophylactic mastectomy in the patient with advanced breast cancer. A patient with multiple positive nodes derives little benefit from a contralateral prophylactic mastectomy if her life expectancy is limited. The group stressed the need for accurate staging before undertaking contralateral mastectomy in these patients.

The group also agreed that, after a diagnosis of breast cancer, mutation status should not influence adjuvant therapy recommendations. As yet, response to therapy and long-term prognosis are the same for carriers and noncarriers when matched by age, stage, and tumor characteristics. Mutation carriers should receive the same adjuvant therapy, based on their age and cancer characteristics, as women without mutations.

Management of Ovarian Cancer Risk

If risk reduction surgery is not chosen, pelvic examination and measurement of serum CA-125 at 6-month intervals were recommended. Transvaginal pelvic ultrasound was suggested every 6 months, starting at age 35 years or 5-10 years younger than the earliest ovarian cancer in the family, even though clinical trial data substantiating the efficacy of these recommendations is limited.

Oral contraceptives (OCs) appear to decrease the risk of ovarian cancer but may slightly increase the risk of breast cancer. Optimal duration of use or whether their use should be occasionally interrupted was not clear. Little is known about the effects of pregnancy on the natural history of breast or ovarian carcinoma in mutation carriers, but currently pregnancy is not interdicted in these women.

Oophorectomy was considered critical, because most ovarian cancers are detected when the disease is locally advanced. Breast cancer is often detected at an early stage by screening so that oophorectomy was considered more essential than mastectomy. In carriers with previously treated breast cancer, prophylactic oophorectomy should be offered despite amenorrhea from prior chemotherapy, hormone receptor status of their breast cancer, or prior naturally occurring menopause.

For mutation carriers, bilateral salpingo-oophorectomy was recommended, and the major question was the timing of this procedure. The group suggested that surgery should be considered after childbearing is completed, but the earlier, the better. Both bilateral salpingo-oophorectomy alone and total abdominal hysterectomy with bilateral salpingo-oopherectomy have advantages and disadvantages, so these procedures should be contemplated for each patient individually. Bilateral salpingo-oophorectomy is certainly the faster, less morbid approach, but the residual small portion of fallopian tube may develop cancer, and the uterus is at risk if tamoxifen is used. Conversely, the increased cost and morbidity of total abdominal hysterectomy are not easily justified on a universal basis. The advantage of hysterectomy is avoiding the need for a progesterone derivative when HRT is used postoperatively. Regardless of procedure chosen, the surgical specimen must be examined in toto by a skilled pathologist because the rate of occult ovarian cancer and fallopian tube dysplasia is high.

Bilateral salpingo-oophorectomy does not eliminate the risk of a primary peritoneal carcinoma. The mesothelium of the peritoneum and the germinal epithelium of the ovary share the same embryologic origin; therefore, the peritoneum may retain the multipotentiality that allows development of a primary carcinoma microscopically resembling ovarian carcinoma. For this reason, even after bilateral salpingo-oophorectomy, women must be carefully followed by their gynecologist.

Hormone Replacement Therapy and Oral Contraceptives

Whether premenopausal women who undergo prophylactic oophorectomy should be offered hormone replacement therapy (HRT) was another contentious question. If bilateral mastectomy is performed, then this question becomes moot. The panelists favored HRT for premenopausal women, to be continued until the time at which natural menopause occurs (usually in women aged 50-55 years), with individual decisions subsequently based upon quality-of-life issues.

For premenopausal women who undergoing oophorectomy but who are not undergoing prophylactic mastectomy, most of the group of panelists advocated adding HRT. They felt that it would be unconscionable to perform oophorectomy on a young woman and then commit her to premature menopause. HRT would then be continued as above, until natural menopause occurs. For already postmenopausal women who are not undergoing mastectomy, most of the panelists opposed adding HRT except to address quality-of-life issues.

Published studies show a similar reduction in risk of breast cancer after oophorectomy whether HRT is given or not. All agreed that up to 5 years of HRT was without harm but did recognize the lack of convincing evidence-based data to support either position.

The "Cancer Family" Without a Mutation

The management of the so-called cancer family without a documented genetic mutation requires clarification. This group includes patients with breast cancer whose family history strongly suggests that the index patient would be a mutation carrier, as well as patients without breast cancer whose family histories are rife with malignancies, including breast and/or ovary. When, despite the expectation that a mutation would be detected, the results of genetic testing of a patient or family member(s) are negative for *BRCA1*, *BRCA2*, and VUS, it is more difficult to advise these patients of the appropriate course to follow, because risk-reduction surgery, ie, oophorectomy and/or bilateral mastectomy, would not usually be recommended. It is likely that these patients carry an as yet undiscovered mutation. The panel advised, however, the same type of nonsurgical follow-up for these individuals, ie, annual mammography and annual breast MRI, alternating every 6 months, along

with semiannual clinical breast examinations and at least yearly pelvic examinations, as for known mutation carriers. These patients would also be suitable candidates for tamoxifen. It is essential that these patients be made aware of their need to remain in contact with their physicians so that new genetic tests, etc, may be shared with them as they are discovered. It is likely that some of these women would opt for risk-reduction surgery, despite the absence of a proven deleterious mutation; this decision is an appropriate one for some women, even when not fully supported by current data.

Follow-up

The group unanimously concurred that lifetime follow-up was appropriate for all women with *BRCA1/2* mutations, regardless of whether or not they chose risk reduction surgery. For those women who do not undergo an oophorectomy, their follow-up should be as already mentioned previously for those women awaiting the end of childbearing for surgery. For women not choosing prophylactic mastectomy, breast surveillance should be as already discussed above. If one or the other surgical procedure is chosen, the follow-up of the other organ should be as above. Even if both target organs are removed, continued surveillance was stressed, because mastectomy is only around 95% effective at preventing breast cancer. Annual examination of the chest wall and annual pelvic examination were still recommended. The role of CA-125 determinations and/or pelvic ultrasound was unclear.

Future Directions

The panelists were aware and supportive of the increasingly valuable information from molecular and genomic profiling of breast malignancies and their enormous importance in the classification and management of breast cancer. Advances in the identification of genetic markers that predict the risk of breast cancer or its recurrence are exploding. This information is already having a major impact on reclassifying and managing breast malignancies, particularly for using systemic therapies. What role these may play in the assessment and management of risk remains speculative.

Very new, and as yet immature, data indicate that genomic rearrangements within the same genes may occasionally identify additional carriers of nonfunctional *BRCA1* and *BRCA2* genes missed by conventional sequencing. In addition, breast cancers in families without *BRCA1/2* mutations are presumably due to other, as yet unidentified, high-penetrance genes. Other genetic transformations or low-penetrance tumor susceptibility genes are likely to account for a greater proportion of familial breast cancers in patients who were sent for genetic tests and who were not identified as *BRCA1/2* mutation carriers. In the next decade, screening for combinations of high-pentrance and low-penetrance genes will likely permit identification of additional groups of individuals who have inherited breast cancer.

Newer functional imaging techniques are rapidly being developed. These hold great promise for earlier detection of breast cancer, which may shift the risk-reduction paradigm away from prophylactic surgery toward surveillance alone, depending upon the impact of these techniques on survival after detection.

Final Remarks

The faculty of this conference represented each of the major medical specialties involved in the care of breast cancer patients, and they unanimously agreed with the concept of multidisciplinary centers as the most efficient and the most effective manner in which breast cancer should be studied. As the molecular biology of breast cancer expands, the mutual interdependence of each specialty will demand their continuing collaboration and cooperation.

All of the panelists agreed that the major issues in breast cancer genetics, risk, and risk management had been addressed in enough detail to permit the promulgation of these guidelines for patient care. The group recognized, however, that these published proceedings[1] are editorial opinions of the group and only partly based on evidence. Therefore, these published proceedings and guidelines must not be construed as establishing a standard of care to which all treating physicians should adhere. Individual patient management needs to be determined on the basis of unique patient clinical circumstances. Recommendations for genetic counseling and management of identified risk are the responsibility of individual physician(s) with the full participation of the patient. This consensus report has neither established standards of care for all patients nor established guidelines for diagnostic or treatment management decisions by third-party payers.