

## Cancer Genetic Counseling

### Genetic Information Nondiscrimination Act

By Danielle Campfield, MS

The passage of the Genetic Information Nondiscrimination Act (GINA) in May of 2008, signals a new era in the field of genetic counseling and testing. It is the first and only federal law that provides broad protection of an individual's genetic information against health insurance and employment discrimination. Healthcare providers can now confidently reassure their patients that genetic counseling and testing will not put them at risk of losing group or individual health insurance.

Before GINA, both the federal government and individual states have tried to address genetic discrimination through legislation. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 took large strides to protect genetic information, forbid exclusion, prohibit higher premiums, and ban the use of genetic information as a preexisting condition. However, HIPAA and other state laws did not fully define genetic information, protect predictive information, apply to individual health plans, or address employment.

GINA specifically **prohibits** issuers of health insurance (including group, individual and Medicare supplement policies) from using genetic information to:

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#### Information on the Genetic Information Nondiscrimination Act (GINA)

##### What GINA does:

Prohibits use of an individual's genetic information in setting eligibility or premium or contribution amounts by group and individual health insurers.

Prohibits health insurers from requesting or requiring an individual to take a genetic test

Prohibits use of an individual's genetic information by employers in employment decisions such as hiring, firing, job assignments, and promotions.

Prohibits employers from requesting, requiring, or purchasing genetic information about an individual employee or family member.

##### What GINA does NOT do:

Does not prohibit medical underwriting based on current health status.

Does not mandate coverage for any particular medical tests or treatments.

Does not interfere with the ability of a treating health care professional to request that an individual or family member undergo a genetic test. Nor does it limit the authority of a health care professional who is employed by or affiliated with a health plan or issuer from notifying an individual about genetic tests or providing information about a genetic test as part of a wellness program.

Does not subject employers to remedies and procedures that are any different from those in other civil rights laws such as Title VII and the Americans with Disabilities Act.

Does not prohibit workplace collection of genetic information for toxic monitoring programs, employer-sponsored wellness program, administration of federal and state Family and Medical Leave laws, and in certain cases of inadvertent acquisition of information. However, the employer may not use or disclose the information.

Source: Genetics and Public Policy Center, Johns Hopkins University, [dnapolicy.org](http://dnapolicy.org) (1)

### Hereditary Breast Cancer: Beyond BRCA1 and BRCA2

By Rachel Barnett, MS

It is well known that mutations in the genes BRCA1 and BRCA2 account for the majority of autosomal dominant hereditary breast and ovarian cancer. Although BRCA testing has been heavily advertised by the company that sells the test, these are not the only genes associated with hereditary breast cancer. In fact, BRCA1 and BRCA2 genetic testing is

not the most appropriate test for every patient with a personal and/or family history of breast cancer. A detailed family history, including at least three generations, and a thorough cancer and genetic history, is necessary to determine which genetic testing is the most appropriate.

This article will provide a summary of the unique features of

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## Editor's Letter

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I had the pleasure of attending the American Society of Clinical Oncology (ASCO) meeting this spring in Chicago, IL and while there I had time to reflect over the changes in cancer genetics over the past fifteen years. It is amazing to think that in 1995 clinical BRCA1 and BRCA2 testing was not yet available. We had no prospective data on prophylactic mastectomy or oophorectomy. We had no data on ovarian cancer risk reduction or breast cancer risk associated with oral contraceptives, and tamoxifen was not FDA approved for prophylactic use. We had little data on surveillance methods in high-risk populations. Our understanding of hereditary colon cancer was basically limited to HNPCC and FAP. We imagined full genome sequencing, but never dreamed that it would be available on the internet and discussed at ASCO in 2008.

As I sat in a conference room at ASCO listening to Mary Claire King, PhD, one of the pioneers and shining stars of cancer genetics, I remembered that fifteen short years ago cancer genetic counseling and testing was a fledgling specialty whose short- and long-term usefulness was questioned regularly. Few would have believed that it would become an integral part of patient management, and would guide surveillance, chemoprevention, surgical decision-making, and management of the entire family in such a short time.

Advances in technology, the human genome project, and integration of genetics into clinical care mean that the progress we will see over the next fifteen years will likely outpace the changes we've seen in the last fifteen. We look forward to working with you and your patients in these exciting times.

Sincerely,

Ellen T. Matloff, MS  
Director, Cancer Genetic Counseling

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- establish eligibility, contribution amounts, and premium fees;
- specify the conditions of the policy;
- impose a preexisting condition exclusion.

GINA specifically **prohibits** employers, labor organizations, employment agencies, and joint labor-management committees from using genetic information to:

- fire or refuse to hire an employee;
- discriminate against an employee with respect to compensation, promotions, or terms, conditions, or privileges of employment;
- treat employees differently in admission to apprenticeships, training, or retraining programs.

GINA also specifically **prohibits** employers and health insurers from requesting, requiring, disclosing, or purchasing the results of a genetic test or genetic information. It has also been proposed that GINA will enable the progress of genetic research because participants in these studies can be reassured that their information is protected by this new law. It is the first piece of legislation that details

actions patients can take if they do experience genetic discrimination. Sanctions include government fines and lawsuits in federal courts.

While GINA is the most comprehensive law of its kind, it is important to note that it does not apply to members of the United States military, veterans obtaining healthcare through the Veteran's Administration, or the Indian Health Service. It also does not address life insurance, disability insurance, or long-term-care insurance. However, it is still unclear if discrimination in these areas poses a significant threat.

The legislation was signed into law on May 21, 2008 and will take effect in twelve and eighteen months for health insurance and employment protections, respectively.

For more information about GINA, please see the following resources:

1. Summary chart of what GINA does and does not cover prepared by the Genetic and Public Policy Center  
<http://www.dnapolicy.org/resources/WhatGINAdoesanddoesnotdochart.pdf>

Library of Congress entry for the GINA bill (H.R. 493)  
<http://thomas.loc.gov/cgi-bin/bdquery/z?d110:h.r.00493>:

## California Orders Companies to Cease Direct-To-Consumer Genetic Tests

In response to continued consumer complaints, the California State Health Department has ordered thirteen genetic testing companies (including Navigenetics and 23andMe) to stop selling tests directly to consumers via the Internet. The letters sent to each of the companies instructed them to stop selling these tests until they were in compliance with state laws. California State law requires laboratories to have a clinical laboratory license and that lab tests be ordered by a licensed physician and validated for accuracy and medical utility.

Several of these laboratories perform "personalized whole genome profiles," which scan the genome for markers that have been associated with numerous diseases and traits (including ancestral background, athletic ability, lactose intolerance, diabetes risk). Many of these tests have not been validated for clinical utility and accuracy. These tests differ from tests, which directly test for mutations in specific genes (e.g. BRCA1 or BRCA2) of known clinical significance. Authorities in New York State sent similar letters to a number of companies back in April.

## RISK FACTORS OF HEREDITARY CANCER SYNDROMES

### Risk Factors Hereditary Breast and Ovarian Cancer

#### 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.

### Risk Factors Hereditary Colon Cancer

#### 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.

### Cancer Genetic Counseling Program

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other hereditary cancer syndromes that demonstrate an increased lifetime risk of breast cancer:

### 1.) LI-FRAUMENI SYNDROME (LFS) (P53) (1)

- Increased risk of soft tissue sarcoma, adrenal cortical tumors, cancers of the breast, brain, bone, colon, pancreas, and stomach, leukemia, lymphoma, melanoma, and gonadal germ cell tumors.
- Cancer risks approach 50% by age 30 years and ~90% by age 60 in classic LFS.
- Germline mutations are rare, highly penetrant, and overall account for less than 1% of all breast cancers.
- Clinical criteria for LFS (2):
  - Proband with sarcoma <45 years, AND
  - First-degree relative with any cancer < 45 years, AND
  - First- or second-degree relative with any cancer < 45 years, or sarcoma at any age.
- Clinical criteria for Li-Fraumeni like (LFL) syndrome (2):
  - A proband with any childhood cancer or sarcoma, brain tumor, or adrenal cortical tumor diagnosed before 45 years of age, AND
  - A first- or second-degree relative with a typical LFS cancer (see above) at any age, AND
  - A first- or second-degree relative with any cancer under the age of 60.

### 2.) HEREDITARY DIFFUSE GASTRIC CANCER (CDH1) (3)

- Increased lifetime risk of lobular breast cancer and diffuse gastric cancer. (Reviewed in the Spring 2008 issue of *Advances*, available online at: [yalecancercenter.org/trials/advances.html](http://yalecancercenter.org/trials/advances.html) )
- In families with a CDH1 mutation, a family history of lobular breast cancer may be seen in the absence of gastric cancer; and vice versa.

### 3.) COWDEN SYNDROME (PTEN) (4)

- A multiple hamartoma syndrome characterized by an increased risk of benign and malignant findings of the breast, thyroid, endometrium, and colon and macrocephaly.
- Also associated with specific skin findings, including trichilemmomas and cutaneous or oral papillomas.

### 4.) PEUTZ-JEGHERS (STK11) (1)

- Rare syndrome associated with hamartomatous polyps of the gastrointestinal tract, small bowel obstructions, and cancer of the breast, colon, ovary, uterus, and pancreas.
- Associated with blue or brown pigmented spots (freckling) on lips and buccal mucosa, and hyperpigmented macules on the fingers that may fade in adulthood.

### 5.) CHEK2 (5,6)

- A recently identified gene of low-moderate penetrance.

- The 1100delC mutation is estimated to be found in increased frequency among individuals of Northern and Eastern European ancestry; however, this particular mutation does not appear to play a role in Ashkenazi Jewish families.
- Associated with as high as a 3-5 fold increased risk of breast cancer.
- The phenotype and clinical recommendations are unknown and more research is needed in this area before testing is routinely offered (7).

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A detailed family history, including at least three generations, and a thorough cancer and genetic history, is necessary to determine which genetic testing is the most appropriate.

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In a recent study of 300 families with 4 or more cases of breast and/or ovarian cancer who tested BRCA 1/2 negative, only 1% carried a p53 mutation. *All of these carriers met criteria for LFS/LFL syndrome.* In this same study, 0% carried a PTEN mutation and 5% carried a CHEK2 mutation (8). Thus, it is premature to offer genetic testing for other hereditary breast cancer genes to all women who test BRCA negative.

When should clinical genetic testing for other known hereditary breast cancer genes be considered?

- 1.) If the family history meets clinical criteria for another hereditary cancer syndrome.
- 2.) If the patient has a personal or family history of rare malignant or non-malignant findings described above.

#### References:

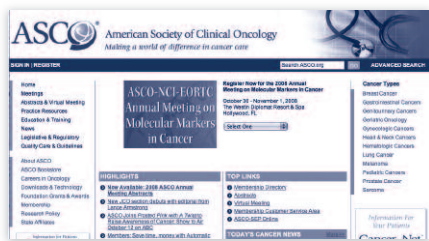
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## Conference Highlights

### AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) / CHICAGO, IL, MAY 2008

Many exciting advancements in the field of oncology were discussed during this five-day conference. The highlights in cancer genetics included:

- Screening breast MRI is emerging as the surveillance method of choice in women at high-risk to develop breast cancer. This is particularly true in women younger than 45 years of age, who have dense breast tissue. In fact, breast MRI may replace mammography in young women because it is more effective and does not expose them to the radiation associated with mammography. Screening ultrasound was found to be redundant with either mammography or MRI.
- Prophylactic removal of the ovaries and fallopian tubes (as opposed to a total hysterectomy) in BRCA carriers is highly effective. Almost all cancers of the fallopian tube were detected in the distal portion of the tube, so retraction of a stump into the uterine wall does not seem to be a major issue. A very high percentage (25-50%) of apparently prophylactic BSO samples in BRCA carriers are actually malignant on pathological examination. For this reason, very careful examination of all specimens is critical. Ovarian cancer surveillance still has a long way to go.
- Whole genome testing (testing many different genes for different genetic changes) will be clinically available in the next few years, particularly for hereditary prostate cancer.



For more information, please visit: [asco.org](http://asco.org)

## New Blog on Cancer Genetics

We are very excited to announce the launch of our new Blog! This innovative resource will help keep patients and providers updated on the newest research, announcements, and events at the Yale Cancer Center Genetic Counseling Program.

For more information please visit: [yalecancergeneticcounseling.blogspot.com](http://yalecancergeneticcounseling.blogspot.com)



## Journal Clips

### ORAL CONTRACEPTIVES AND LONG-TERM OVARIAN CANCER RISK REDUCTION LANCET 2008; 371: 303-314.

This meta-analysis of data from 23,257 women with ovarian cancer and 87,303 controls from 45 epidemiological studies in 21 countries confirms that oral contraceptive (OC) use is associated with a significant, long-term reduction in ovarian cancer risk. Overall, ever-users had a ~27% reduction in ovarian cancer risk compared to never-users. Longer duration of use was associated with lower risk with a ~20% risk reduction for every 5 years of use and >50% risk reduction after 15 years of use. Although the greatest risk reduction was seen in women who had recently used OCs, significant risk reduction lasted for over 30 years after cessation of use. Risk reduction did not vary significantly by OC preparation, parity, family history of breast cancer, age at menarche, use of hormone replacement therapy, or BMI. OC use provided protection against almost all epithelial and nonepithelial ovarian cancers with the possible exception of mucinous ovarian cancer.

### RISK REDUCING SALPINGO-OOPHORECTOMY FOR THE PREVENTION OF BRCA1- AND BRCA2-ASSOCIATED BREAST AND GYNECOLOGIC CANCER J CLIN ONCOL 2008; 26(8):

This is the first known prospective study to separately assess the efficacy of bilateral salpingo-oophorectomy (BSO) for BRCA1 mutation carriers and BRCA2 mutation carriers. It combines data collected from 11 centers (including Yale) on >1,000 women who carry either a BRCA1 or BRCA2 mutation, were age 30 or older, and had at least one intact ovary at the time of genetic testing. Sixty-five percent of the BRCA1 mutation carriers and 63% of the BRCA2 mutation carriers chose to have prophylactic BSO. BSO was associated with an 85% reduction in BRCA1-associated gynecologic cancers (ovarian, fallopian tube, and primary peritoneal) and a 72% reduction in BRCA2-associated breast cancer risk. The data also suggest a reduction in BRCA2-associated gynecologic and BRCA1-associated breast cancer risk following BSO but these outcomes did not reach statistical significance. Although the cancer risk reduction associated with BSO may vary between BRCA1 and BRCA2 carriers, BSO is still recommended for all BRCA1 and BRCA2 carriers who have completed childbearing and/or are over age ~35 due to the limitations of current ovarian cancer surveillance options.

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*Cancer Genetic Counseling*

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

Advances in technology, the human genome project, and integration of genetics into clinical care mean that the progress we will see over the next fifteen years will likely outpace the changes we've seen in the last fifteen.