Entering the Next Era of Genetic Testing

The complexities of ordering and interpreting of genetic testing are increasing exponentially due to the availability of high-throughput genetic sequencing and exome analysis. While these technologies have great potential, their clinical utility is still being explored.

Recently, several genetic laboratories have started to offer testing for panels of genes related to hereditary cancer predispositions. These panels simultaneously analyze groups of genes that contribute to increased risk for breast, colon, ovarian, uterine, and other cancers. Some of the genes included are well-known and well-described (ex: p53, APC, MLH1). This makes testing for multiple genes more efficient and cost effective. For some families, panel testing may reveal a well-classified mutation, provide an explanation for their personal and/or family history of cancer, and enable pre-symptomatic genetic counseling and testing for other family members.

A remarkable limitation of these panels is their exclusion of BRCA1 and BRCA2 analysis, which are likely to be excluded until the resolution of those patent rights. Additional limitations of the panels include several lesser-known genes (ex: BRIP1, NBN, MRE11A, etc.) whose cancer risks are ill-defined and medical management options remain unknown. Because testing for these genes is new to the clinical setting, it is expected to take several years to compile accurate cancer risk estimates and appropriate recommendations for surveillance and risk reduction. Furthermore, the rate of variants of uncertain significance (by far one of the most complex types of results) will likely be several times that of established genes.

The public continues to perceive genetic testing as a simple, straightforward process. However, as genetic testing options grow at expansive rates, the maintenance of high standards for genetic counseling, informed consent, and accurate result interpretation will be paramount in reducing potential risks and maximizing the benefits of this technology.

We encourage you to continue to elicit detailed histories, choose appropriate candidates for genetic counseling, facilitate genetic counseling referrals, and advise your patients what family history information they should collect prior to their genetic counseling appointment. At this time the best candidates for panel testing include affected patients from very high-risk families in which traditional testing has failed to yield an “answer” (“uninformative” patients). We look forward to continuing to care for your patients as the options for genetic testing multiply.

Featured Syndrome: Hereditary Retinoblastoma

Retinoblastoma (RB) is a rare cancer of the retina that occurs in ~1/15,000-1/20,000 children (1,2). It is usually diagnosed at less than 5 years of age and the most common initial presenting sign is white pupillary reflex (leukocoria), although strabismus is also a common presenting sign (1,2). Parents will often notice leukocoria by remarking that a child’s eye appears white in flash photographs or at certain angles.

The familial clustering of retinoblastoma was noted as early as the 1800s and in 1971 Knudson proposed the classic “2 hit” hypothesis, the model for all tumor suppressor genes, based on the observation that retinoblastoma occurred at a significantly younger age in individuals with bilateral disease and/or a family history compared to those with sporadic, unilateral disease (1). This model explains that both hereditary and non-hereditary cases of retinoblastoma are caused by 2 mutations (“2 hits”), but that hereditary cases occur at a younger age because one of these hits is inherited and present in almost every cell at birth (1,3). In 1986, the RB1 gene was identified on chromosome 13, becoming the first identified human tumor suppressor (1,3).

Up to ~30% of all cases of RB are hereditary (3), but the likelihood that a case of RB is hereditary depends on whether the disease is unilateral or bilateral, unifocal or multifocal, and whether or not there is a family history of the disease.
Welcome to the Fall edition of our newsletter. We hope this newsletter finds you enjoying cooler temperatures, fall foliage, and the start of the new academic year.

As you will read in the coming pages, this fall season marks some significant changes in the genetic testing options available for your patients. We now have large gene panels to offer to patients that cover a wide array of cancer genes — one such panel looks at 22 cancer genes. These tests are new and we’re still learning the pros and cons of this strategy, but such panels hold much promise for the future. The National Comprehensive Cancer Network (NCCN) guidelines now include BART testing for patients eligible for BRCA1 and BRCA2 testing and this means that many of your patients who previously were not covered for BART testing may receive coverage by January 2013. This represents good news, particularly for those affected high-risk patients who tested BRCA1 and BRCA2 negative and were deemed ‘uninformative.’

We have begun a ‘soft launch’ of the Take Charge Clinic, a new concept specialty clinic that combines the expertise of cancer genetics, breast oncology, and gynecologic oncology together under one roof. This means that for patients whose risk is ambiguous and are trying to make difficult decisions about which surveillance and risk reduction options are most appropriate for them, they now have a place to go for a tailored, comprehensive management plan. You can reach the coordinator of this clinic, Stephanie Zito, at (203) 764-RISK (7475).

In the past six months we have given lectures at hospitals all over the state of Connecticut and have enjoyed meeting so many of you in person. We currently have monthly outreach clinics at Greenwich Hospital, The Center for Cancer Care at Griffin Hospital, and the Norma F. Pfriem Cancer Institute in Trumbull. We look forward to serving you and your patients at these facilities, and would be happy to come speak at other hospitals in the region at your request.

Thank you for your continuing commitment to learning more about cancer genetics and referring your at risk patients for genetic counseling and testing. 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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**Oophorectomy after Menopause and the Risk of Breast Cancer in BRCA1 and BRCA2 Mutation Carriers**

*Cancer Epidemiol Biomarkers Prev. 2012 May 21.*

It is known that a prophylactic oophorectomy in a pre-menopausal BRCA mutation carrier reduces her lifetime risk to develop breast cancer. This study demonstrated that prophylactic oophorectomy in a post-menopausal BRCA mutation carrier can also reduce lifetime breast cancer risk; however, the number of post-menopausal women in this study was small and the confidence limits were wide. The reduction in risk was stronger in women who had undergone surgical vs. natural menopause. Also, later age at onset of menstruation and breastfeeding for more than 1 year were both shown to decrease breast cancer risk in BRCA1, not BRCA2, mutation carriers.

**Detection of Breast Cancer with Addition of Annual Screening Ultrasound or a Single Screening MRI to Mammography in Women with Elevated Breast Cancer Risk**


Women included in this study were asymptomatic, had dense breast tissue, and were at increased risk for breast cancer. Less than 1% of participants were BRCA mutation carriers. Approximately 2700 participants were followed with mammogram and ultrasound at the time of study enrollment, then at 12 months and 24 months after enrollment. A subset of women had a breast MRI following their 24 month screening mammogram. Interpretation of the 3 screening modalities was blinded to the results from the other tests. Annual supplemental ultrasound and breast MRI detected additional cancers (additional 5.3 cancers per 1000 in the first year and 14.7 per 1000 women, respectively); however, the rate of false-positives increased in women without a history of a prior breast cancer.

**Pathology of Breast and Ovarian Cancers Among BRCA1 and BRCA2 Mutation Carriers: Results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)**


BRCA2 Mutations and Triple-Negative Breast Cancer


Prevalence of BRCA Mutations in an Unselected Population of Triple-Negative Breast Cancer


Data continue to grow about the pathology and histology of BRCA1 and BRCA2 associated breast and ovarian cancers and this information is becoming increasingly important in risk assessment. These recent publications confirm that:

- Triple negative breast cancers (ER-, PR-, HER2-) are more common among BRCA1 associated breast cancers (69%) compared with BRCA2 associated breast cancers. However, approximately 16% of BRCA2 associated breast cancers were...
triple negative in two of these studies, which is higher than most studies published to date.

- A triple negative breast cancer increased the likelihood of a woman carrying a mutation irrespective of family history in women diagnosed <50 and in women diagnosed >50 with a family history.
- The frequency of ER negative tumors decreased with age at breast cancer diagnosis in BRCA1 mutation carriers. The opposite was true for BRCA2 mutation carriers.
- There was no significant association of HER2 status and BRCA carrier status; however, the numbers may still be too small to assess.
- The most common morphology of ovarian cancers associated with a BRCA mutation were serous and there was no difference in the pathology of ovarian cancers between BRCA1 or BRCA2 mutation carriers.

**Update: BART Testing for BRCA1 and BRCA2**

We have known for many years that Myriad Genetic's Comprehensive BRACAnalysis does not pick up all detectable mutations within BRCA1 and BRCA2. On July 31, 2006 Myriad began offering a separate test called the BRACAnalysis Large Rearrangement Test (BART) to pick up some of the mutations within BRCA1 and BRCA2 that are missed by BRACAnalysis. This test, unfortunately, was offered as a separate test and cost $650, and later $700, per sample. Most insurance companies would not cover the cost of this testing, and most patients who had BRACAnalysis never had BART testing.

Myriad released data in the summer of 2011 showing that of all patients with detectable BRCA1 or BRCA2 mutations, about 10% had mutations that would only be detected by BART analysis. A higher prevalence of these BART mutations was found in people of Latin American/Caribbean and Near/Middle Eastern ancestry.

On May 2, 2012 the National Comprehensive Cancer Network (NCCN) released guidelines recommending that all patients who meet criteria for standard BRCA1 and BRCA2 testing should also have BART analysis. Based on this information, we believe that more insurance companies will now cover the cost of BART analysis.

1. **WHO SHOULD CONSIDER HAVING BART ANALYSIS?**

If you had BRCA1 and BRCA2 testing and no mutation was identified in you or your family members, you may wish to consider having BART analysis. This is especially important for patients who were at high-risk to carry a mutation and were deemed ‘uninformative’ – meaning we believed the cancers in the family were hereditary, and we just couldn’t find the disease-causing mutation.

2. **HOW CAN I FIND OUT IF MY INSURANCE WILL COVER THIS TEST?**

If you had insurance coverage for BRACAnalysis, you may contact your insurance company or Myriad Genetics at 1-800-469-7423 and ask them if your insurance company is now covering BART testing.

3. **HOW CAN I HAVE BART TESTING?**

Please call our office at (203) 764-8400 to schedule an appointment and we will be happy to facilitate this testing for you.
However, all individuals with a diagnosis of RB should be offered genetic counseling and testing. Only ~10-20% of RB1 germline mutations are inherited from an affected parent; the majority of cases occur as a de novo (new) mutation in a sperm or egg cell or in early embryonic development (1-3). In ~5-8% of cases, hereditary retinoblastoma is due to a large deletion or rearrangement of chromosome 13 (2). In these cases, affected individuals often also have developmental delays, birth defects, and distinctive facial features (2).

FEATURES OF UNILATERAL VS. BILATERAL RETINOBLASTOMA

Unilateral Retinoblastoma
- Represent the majority (~60-70%) of cases of retinoblastoma (2,3).
- Are diagnosed at an average age of 22-24 months (1,2).
- Are often unifocal but can be multifocal (1).
- Usually occur in individuals with no family history of RB (1).
- ~14% of individuals with unilateral, unifocal RB with no family history have a germline RB1 mutation (2).
- In cases of unilateral retinoblastoma with no family history, the optimal genetic testing strategy involves starting testing on a fresh frozen tumor sample (if available) (2).

Bilateral Retinoblastoma
- Occur in ~30-40% of cases of retinoblastoma (2,3).
- Are diagnosed at an average age of 11-15 months (1,2).
- Are often multifocal (1).
- In most cases of bilateral RB, both eyes are affected at the time of initial diagnosis (2).
- It is assumed that all cases of bilateral RB are due to a hereditary cause. However, genetic testing on a blood sample identifies a detectable germline RB1 mutation in ~90-95% of these cases (2).

CANCER RISKS AND SCREENING RECOMMENDATIONS FOR INDIVIDUALS WITH HEREDITARY RETINOBLASTOMA
- ~94% of individuals with a germline RB1 mutation develop retinoblastoma. If these cancers are detected at an early stage, survival exceeds 90-95% and the eye can be spared more often (3).
- Individuals with hereditary RB have a significantly increased risk of developing secondary cancers with a lifetime risk as high as ~36%-68% (2,4,5).
- The most significant risks for a secondary cancer are pinealomas (tumors of the "retinal-like" tissue of the pineal gland), osteosarcomas, soft tissue sarcomas, melanoma, brain tumors, and cancers of the nasal cavities (2,4,5). However, lung, breast, colon, uterine, and other epithelial cancers can also occur (2,4,5).
- Risk of additional cancers increases significantly when radiation therapy is used to treat the initial retinoblastoma and/or secondary cancers (2,5,6).
- At-risk children should have an eye exam every 3-4 weeks until age 1 and then less frequently until age 3 (2). There are no specific screening or risk reduction guidelines for secondary cancers for individuals with hereditary retinoblastoma (2). However, due to the significant risk for sarcomas, any lumps or complaints of bone pain should be carefully evaluated (2). Individuals with hereditary RB should also limit their exposure to potential carcinogens including radiation therapy, tobacco, and UV radiation (excess sun exposure and sunburns) (2,4).
- Close relatives of individuals with retinoblastoma should have a specialized ophthalmologic exam to look for signs of retinal scars, retinocytoma, or retinoma, which are lesions thought to result from either spontaneous growth arrest or regression of retinoblastoma (2).

RESOURCE FOR PATIENTS WITH RETINOBLASTOMA AND THEIR FAMILIES
www.specsforlittleheroes.com
Specs for Little Heroes is an organization started by a local family whose 4-year-old son lost his eye to retinoblastoma. Children with retinoblastoma and their families face many physical, emotional, and financial challenges. These children need to take lifelong precautions including wearing expensive protective glasses to prevent further eye injuries and blindness. This organization raises money to provide free protective eyewear to children with retinoblastoma.

References:
Why should clinicians care about the BRCA patent?

The patent on BRCA1 and BRCA2 excludes other companies from offering testing for or conducting research on these genes. This means that the patent holder has complete control over what testing is offered, the price of testing, and what research is performed. Many experts agree that this has limited access to this expensive testing (particularly for uninsured and underinsured individuals), limited how many patients receive all of the BRCA testing available and recommended for each patient (e.g., deletion and rearrangement testing), and has had a negative impact on research and interpretation of test results.

References:

I take back my genes.

Share your story through the ACLU’s public campaign, Take Back My Genes

In 2009, 20 professional medical associations, geneticists, breast cancer and women’s health groups, and patients filed a lawsuit charging that patents on two human genes associated with hereditary breast and ovarian cancer (BRCA1 and BRCA2) are invalid and unconstitutional. The Supreme Court is now hearing an appeal on the case.

For more information please visit: http://www.aclu.org/take-back-your-genes

Announcements

THE TAKE CHARGE CLINIC
Know it. Face it. Change it.
We are excited to announce the launch of a new concept, multi-disciplinary clinic that will bring together the expertise of Genetic Counseling & Risk Assessment, Breast Oncology, and Gynecologic Oncology in one coordinated Team. Each patient will be seen for risk assessment and then a Personalized Passport will be created for that patient that will guide her to our experts in cancer surveillance, chemoprevention, sexuality, and menopause based on her specific risks, age, needs, and personal and family history. Call us at (203) 764-RISK (7475) for more information.

NEW OUTREACH CLINICS
We are pleased to announce the opening of Yale Cancer Genetic Counseling Clinics at The Center for Cancer Care at Griffin Hospital in Derby and the Norma F. Pfriem Cancer Institute in Trumbull. A certified genetic counselor from our program will staff each monthly clinic. To make an appointment at either clinic, please call our main phone number (203) 764-8400.
And, although change and growth are the norm in the field of cancer genetics, this year marks some exceptional changes for our program.