the

INHERITED CANCER REGISTRY®

• JULY 2013 •

What's Inside?

ICARE Recruitment and Participation Update

Participation in the ICARE initiative continues to expand through referrals, events and active outreach efforts. There are almost 1300 participants, including over 800 individuals from families with *BRCA* mutations. Participants in ICARE represent 46 U.S. states and 11 countries worldwide. We continue to foster relationships with healthcare providers across the country and beyond, and hope to maintain our rapid pace of registry growth. We are continually completing research files on our participants through the collection of initial and follow-up questionnaires, three-generation family trees, and documentation of genetic test results (as applicable). We appreciate the time our participants have taken to facilitate collection of these materials. The information you provide to the registry is critical to answer important questions about issues faced by those at risk for inherited cancer predisposition, which helps us learn how to identify, evaluate and manage those with inherited cancer. We are updating our software to make the online ICARE questionnaires more user friendly and visually pleasing. If you have not completed your initial or follow-up questionnaire and would like to be sent an additional paper or electronic copy, please contact the study team via phone (813-745-6446) or email (ICARE@moffitt.org).

Welcome

We are excited to provide you with the fifth update of the ICARE newsletter, since ICARE was initiated in Summer 2010. We have continued to experience tremendous growth, and now have almost 1300 registry participants. We are actively using the information you have contributed to further knowledge about those with inherited cancer predisposition.[1, 2] As well, The ICARE study team recently presented at the 2013 Moffitt Scientific Symposium, and one of our study coordinators (Lucia Camperlengo, MPH) was the winner of an outstanding poster award (based on a poster focused on the impact of genetic counseling on patient knowledge of hereditary breast and ovarian cancer).

As we continue to expand our efforts, we sincerely thank you for your continued support for the ICARE initiative – together, we strive to achieve our mission to "*end the cycle of inherited cancer through research, education and outreach*."

Sincerely,

Tuya Pal, MD, FACMG

1. Pal T, et al. Clin Genet. 2013 Feb 25. [Epub ahead of print]
2. Iqbal J, et al. Br J Cancer. 2012 Dec 4;107(12):2005-9.
3. Finch A,et al. Fertil Steril. 2013 May;99(6):1724-8.

BRCA Testing: Supreme Court Update

In a landmark decision regarding the patenting of human genes on Thursday June 13, 2013, the Supreme Court of the United States unanimously ruled that human genes may not be patented. The case specifically concerned the *BRCA1* and *BRCA2* gene patents, held by the Utah-based company, Myriad Genetics. In the ruling, Justice Clarence Thomas wrote for the court: "Myriad did not create anything. To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention." As a result of this ruling, it is widely believed the cost of testing (currently over $4000 for full gene sequencing and large rearrangement testing when performed through Myriad) will decrease, there will be opportunities for second opinions, and innovation pertaining to *BRCA* testing may be enhanced. Immediately after the decision, several companies (e.g., GeneDx, Pathway Genomics, Quest Diagnostics, Ambry Genetics, DNATraits, and University of Washington) announced plans to launch tests that include the *BRCA* genes, at a cost as low as $995.

Genetic Testing and Clinical Updates •

Sharing BRCA Test Results with Adolescent and Young Adult Children—What Does the Latest Research Show?

While there are specific recommendations against *BRCA* testing for minors,[1] guidelines are less clear about whether parents should share their own test results with their children. Because there are no recommended surveillance or risk reduction options prior to age 25 for known *BRCA* mutation carriers, there has been debate about balancing the benefits of sharing parents' test results with the possible negative psychosocial outcomes. The largest published study on this topic included 253 parents who had undergone *BRCA* testing and their reports of sharing test results with children, ranging in age from ages 10 to 25. Of the 505 children, parents shared test results with 66%. For those who shared true negative results, children often expressed relief. However, the authors encourage parents to take this opportunity to discuss the continued benefits of positive health behaviors (e.g., diet, physical activity); despite decreased cancer risk based on *BRCA* test results. Importantly, parents sharing *BRCA* positive or variant of uncertain significance results perceived distress more frequently than those sharing negative results.[2] Parents considering sharing test results with children may benefit from consultation with a genetic and/or other health care professional with expertise in family communication to help ensure that information is presented in a way that is age-appropriate, helps to reduce distress, and achieves positive psychosocial and behavioral outcomes.

1. Borry P, et al. Clin Genet 70:374-81, 2006.
2. Bradbury AR, et al. Cancer, 2012.

Male BRCA Carriers have Poorer Outcomes from Prostate Cancer

Over the last few years, a number of studies have suggested that men with germline *BRCA* mutations (especially *BRCA2*) have poorer outcomes when they develop prostate cancer. In fact, a recent study of 2019 patients with prostate cancer, including 18 *BRCA1* carriers, 61 *BRCA2* carriers, and 1940 noncarriers indicated that germline mutations were more frequently associated with: higher Gleason score, later stage (T3/T4), nodal involvement, and metastatic disease present at diagnosis.[1] Thus, these findings suggest that when men with *BRCA* mutations develop prostate cancer, it is more likely to be an aggressive subtype of the disease which may be related to the poorer outcomes observed. Consequently, study authors suggested that consideration should be given for tailoring clinical management for these patients, especially because most *BRCA* carriers with prostate cancer are currently treated through following the same protocols used for noncarriers (due to lack of studies focused on evaluating tailored management strategies in this group of men).

"These findings suggest that when men with BRCA mutations develop prostate cancer, it is more likely to be an aggressive subtype of the disease which may be related to the poorer outcomes observed."

Furthermore, although clinical trials in this group are needed, authors suggested the following as a consideration: "radical treatment with either surgery or radiotherapy seems to be preferable to active surveillance for these patients, even for cases classified as low risk."

1. Castro et al. J Clin Oncol. 2013 May 10;31(14):1748-57.

US Preventive Services Task Force (USPSTF) Guidelines for Inherited Breast and Ovarian Cancer and Implications to the Affordable Care Act (ACA)

Recently, the USPSTF released updated draft guidelines in April 2013 (from those previously published in 2005) for inherited breast and ovarian cancer due to germline *BRCA1* and *BRCA2* gene mutations.[1] USPSTF is comprised of primary care providers who review the available literature and issue guidelines about risk assessment, testing and management based on available evidence. Subsequently, the Department of Health and Human Services, the Department of Labor, and the Department of Treasury issued a clarification addressing coverage for *BRCA* testing under the Affordable Care Act (ACA). Specifically, they indicated that asymptomatic, high-risk women (as defined per the USPSTF guidelines) with a family history of breast or ovarian cancer will be able to get tested for the breast cancer risk genes *BRCA1* and *BRCA2* with no co-pay.[2] This rule applies to non-grandfathered health insurance plans and will likely broaden access to *BRCA* testing, as implementation of the ACA moves forward.

This rule…will likely broaden access to BRCA testing, as implementation of the ACA moves forward.

1. http://www.uspreventiveservicestaskforce.org/uspstf/uspsbrgen.htm
2. http://news.yahoo.com/breast-cancer-genetic-testing-gets-covered-health-care-234648209.html

Genetic Testing and Clinical Updates•

Oophorectomy Following Menopause

Prior studies have indicated that removal of the ovaries and fallopian tubes reduces the ovarian cancer risk by ~80% and breast cancer risk by ~50%, particularly when performed pre-menopausally. However a recent case control study of 2854 pairs of women with a *BRCA1* or *BRCA2* mutation with or without breast cancer showed that the risk of breast cancer was lowered more in those with surgical menopause (OR, 0.52; 95% CI, 0.40–0.66) compared to those with natural menopause (OR, 0.81; 95% CI, 0.62–1.07). Interestingly, this study also found that there was a significant reduction in breast cancer risk even in women who had their ovaries removed after they went through natural menopause (OR, 0.13; 95% CI, 0.02–0.54; P = 0.006). This is an important finding because women with *BRCA* mutations who remove their ovaries after menopause typically do so to lower their ovarian cancer risk – however, this study suggests that they also may be reducing their breast cancer risk at the same time. Finding from this study also highlight the importance for better understanding the protective effect of oophorectomy, as this has very important implications for chemoprevention.

"This study suggests that [women who remove their ovaries after menopause] may be reducing their breast cancer risk at the same time."

1. Kotsopoulos J, et al. Cancer Epidemiol Biomarkers Prev. 2012 Jul; 21(7):1089-96.

Ask the Expert

Through each newsletter, we give our participants an opportunity to have their genetics and research questions answered by experts. Please send your questions to ICARE@Moffitt.org so that we may include responses in future newsletter editions. The following question was addressed by Dr. Pal, who is a Clinical Geneticist based at the Moffitt Cancer Center:

Q. Does exposure to radiation increase breast cancer risk in BRCA mutation carriers?

A. A number of studies have been conducted to evaluate whether *BRCA* mutation carriers may be more prone to radiation-induced breast cancer than women without mutations. Two studies failed to provide convincing evidence about the link between ionizing radiation exposure and breast cancer risk in *BRCA* mutation carriers.[1,2] On the other hand, a large international study including 1601 mutation carriers reported a higher breast cancer risk among women exposed to chest X-rays (hazard ratio (HR): 1.54). Breast cancer risk was highest among women age ≤ 40 with any x-ray exposure , and women born after 1949 with x-ray exposure before age 20.[3] Some of these participants were included in a larger international study of 1993 mutation carriers where age-specific total diagnostic radiation exposure (i.e., chest x-rays, mammography, fluoroscopy, and computed tomography) was estimated from self-reported questionnaire data.[4] Results indicated that those exposed before age 30 had an increased risk (HR: 1.90; 95% CI: 1.20-3.00), compared to those never exposed. However, this risk was primarily driven by non-mammographic radiation exposure in women younger than age 20 (HR: 1.62; 95% CI: 1.02-2.58).

Ultimately, it is important to weigh potential risks versus benefits regarding routine use of mammographic screening in conjunction with magnetic resonance imaging (MRI) in *BRCA* mutation carriers, particularly in women below age 30. As there is no clear evidence to suggest that mammograms significantly increase the breast cancer risk in *BRCA* mutation carriers at the current time, the main question that remains is whether mammograms are useful prior to age 30. Currently, NCCN guidelines[5] recommend annual mammography and MRI screening beginning at age 25 years, although some clinics may hold off on the mammography until age 30 after a balanced discussion of risks versus benefits with patients has occurred.

1. Narod SA, et al. Lancet Oncol 7 (5): 402-6, 2006.
2. Goldfrank D, et al. Cancer Epidemiol Biomarkers Prev 15 (11): 2311-3, 2006.
3. Andrieu N, et al. J Clin Oncol 24 (21): 3361-6, 2006.
4. Pijpe A, et al. BMJ 345: e5660, 2012.
5. NCCN Practice Guidelines 2013; V.2.2013: http://www.nccn.org/professionals/physician_gls/recently_updated.asp.

Other Research Opportunities

1. Phase II clinical trial at Moffitt Cancer Center open to men and women with *BRCA1/2* mutations and metastatic breast cancer to evaluate a PARP inhibitor (Veliparib) in combination with other agents, as well as a Platinum-based agent.

2. Phase I/II two-part clinical trial in 5 states and the UK to evaluate safety of dosing regimens in men and women with solid tumors, and men and women with a BRCA mutation and advanced or metastatic breast or ovarian cancer.

3. Phase I clinical trial in 3 states studying the side effects and best dose of Veliparib in treating patients with *BRCA* mutations and malignant solid tumors that did not respond to previous therapy.

4. Phase II clinical trial in 11 states and Canada studying veliparib with carboplatin compared to veliparib alone in treating female patients with stage II or IV breast cancer and a *BRCA* mutation.

Please contact the ICARE study team by phone (813-745-6446), email (ICARE@Moffitt.org) or visit our website www.Moffitt.org/ICARE to learn more.

Plug-in to ICARE

The purpose of our registry is outlined on our website: www.Moffitt.org/ICARE. Please feel free to visit our site to learn about the purpose, find out about other research and/or clinical opportunities that may be of interest to you and meet the ICARE study team (to put a face to the voice you hear over the phone). Through the website, you can submit questions or request information about the registry by submitting an online contact form. Please visit the *"What is ICARE?"* tab on our website to view the short informational video about ICARE.

Featured Organization

Offering Insight and Education on Male Breast Cancer

This informative website was created to assist men, women, health care professionals, and anyone who is interested in learning about the risk, treatment(s), emotional aspect and stigmatization of men dealing with this disease. To learn more about HIS breast cancer awareness, visit http://www.hisbreastcancer.org.

Contributors

Tuya Pal, MD, FACMG
Susan Vadaparampil, PhD, MPH
Emily Robinson, MPH
Lucia Camperlengo, MPH
Meghan Sherman, MS, CGC

Contact Us

Phone: 813-745-6446 *Fax:* 813-449-8403
Toll Free: 1-800-456-3434 ext. 6446
Email: ICARE@Moffitt.org
Website: www.Moffitt.org/ICARE
Facebook: www.facebook.com/ICAREatMoffitt