ICARE NEWSLETTER

• WINTER 2017 •

What's Inside?

ICARE Recruitment and Participation Update

Participation in the ICARE initiative continues to expand through referrals, events, and active outreach efforts. As of January 2017, there are 2193 participants, including 1049 individuals from families with *BRCA* mutations, enrolled in the registry. Participants in ICARE represent 46 U.S. states, the District of Columbia, Puerto Rico, and 13 countries worldwide.

We appreciate the time our participants have taken to complete their initial and follow-up questionnaires, and assist us in collecting their three-generation family trees, and documentation of genetic test results (as applicable). Your participation directly contributes to learning more about how to identify, evaluate and manage those with inherited cancer. If you have not completed your initial or follow-up questionnaire and would like to be sent an additional paper copy or electronic link, contact the study team via phone at 813-745-6446 or email at ICARE@InheritedCancer.net.

Please visit our newest webpage (inheritedcancer.net/icare-research) dedicated to the research made possible by ICARE efforts!

Welcome Message

We have some very exciting news to share with you! In the New Year, ICARE will begin a transition to our new home at the Vanderbilt-Ingram Cancer Center, an NCI-designated Comprehensive Cancer Center that is part of Vanderbilt University Medical Center in Nashville, Tennessee. A few ICARE team members and I will be moving in March to join renowned clinical cancer geneticist, Dr. Georgia Wiesner, and her team. We do not anticipate any long term disruptions in communications with our participants and healthcare partners as we relocate our efforts. Our email address will remain the same (ICARE@InheritedCancer.net), and once confirmed, you will be notified of our updated phone number and fax line. We remain grateful to the Moffitt Cancer Center for providing us with an incredible place to base our activities since we started about 6 years ago, and we look forward to continuing work with many of our esteemed colleagues and friends at the place we have called 'home' for so many years.

Since initiating the ICARE effort in 2010, our registry has exponentially grown making it possible to contribute to both national and international efforts, while developing ongoing partnerships with healthcare providers. In an attempt to keep you informed of our activities, we have compiled a comprehensive list of presentations and publications, made possible through ICARE efforts, now available on our website at https://inheritedcancer.net/icare-research. Of note, included in these publications is a recent article which outlines the effect of oophorectomy on reducing breast cancer risk among *BRCA* carriers in which data from ICARE participants was included (summarized by Dr. Steven Narod on Page 3 of this newsletter within the 'Ask the Expert' section). We sincerely thank all of you for partnering with us as we strive to meet our mission to "end the cycle of inherited cancer through research, education, and outreach."

Sincerely,

Tuya Pal, MD, FACMG on behalf of the ICARE Team

NCCN Guidelines Version 1.2017: Genetic/Familial High-Risk Assessment: Breast and Ovarian

Additional guidance pertaining to cancer risk management was provided in the most recent version of the NCCN Guidelines for inherited breast and ovarian cancer. These guidelines now include an expanded table outlining cancer risks and management for each gene, taking into account the age at initiation of each risk management modality as well as footnotes to highlight some of the nuances concerning particular mutations in specific genes. For example, among *ATM* and *CHEK2* carriers, recommended age at initiation of high risk breast screening with breast MRI is 40 years. Furthermore, the higher breast cancer risks associated with the *ATM* 7271T>G missense mutation is included as a footnote, as is the fact that the data on increased breast cancer risks associated with *NBN* is almost solely derived from the 657del5 truncating mutation. The full guidelines may be accessed through the NCCN website (www.nccn.org).

Clinical and Research Updates

The potential promise of immunotherapy targeted to those with bi-allelic mutations in Lynch Syndrome genes

People with Lynch Syndrome have a non-working Lynch gene ("mutation"), while the other copy of that gene is normal (recognizing that all of these genes come in pairs, with one member of the pair coming from each parent). Over the last few years, there has been an increased realization that some individuals have a mutation in both copies of their Lynch gene, which leads to a condition called Constitutional Mismatch Repair Deficiency (CMMRD). Those affected with CMMRD often develop cancer in childhood, with the most frequent types of cancer being brain tumors, gastrointestinal (colon or small bowel) cancers, and leukemias.[1] Screening guidelines for children with CMMRD, developed through consortium-based efforts, include upper and lower GI scopes and brain imaging in childhood, followed by additional screening in adulthood.[2] These efforts form the basis of collecting data to someday develop evidence-based screening guidelines.

Recently, a study of tumors from children with CMMRD showed some unique findings. Specifically, these tumors accumulate mutations at a very high rate (~600 mutations/cell cycle) but do not exceed ~20,000 mutations in <6 months.[3] This finding suggests a new mechanism of cancer progression. The exciting component of this is now that the high mutation load and threshold effect are known, this information can be used to target more effective treatments for these cancers. To this end, high mutation load (which also leads to high neoantigen loads) may respond to immune checkpoint inhibition, which is a new class of immunotherapy drugs. In fact, a recent study demonstrated that neoantigen loads of individuals with CMMRD was substantially higher than those without the condition.[4] Furthermore, based on this preclinical data, study investigators treated two siblings with CMMRD with recurrent glioblastoma multiforme (a rare and aggressive form of brain cancer) with an immune checkpoint inhibitor (PD-1 inhibitor) called nivolumab, which led to a clinically significant response and substantial shrinkage of the tumor on MRI scans. These findings suggest that cancers with exceptionally high mutation loads may more likely respond to immunotherapy because there is a higher chance they have specific neoantigens which activate T cells. Taken together, it is possible that all CMMRD-related cancers may benefit from this type of treatment approach. To investigate this further, a group of international researchers has developed a pilot study of nivolumab in pediatric patients with hypermutated cancers (clinicaltrials.gov identifier NCT02992964) and anticipates beginning enrolling patients in early 2017.

> ***"…high mutation load (which also leads to high neoantigen loads) may respond to immune checkpoint inhibition, which is a new class of immunotherapy drugs…"***

[1]Bakry D, et al. Eur J Cancer. 2014 Mar. PMID: 24440087. [2]Durno CA, et al. Eur J Cancer. 2015 May. PMID: 25883011. [3]Shlien A, et al. Nat Genet. 2015 Mar. PMID:25642631. [4]Bouffet E, et al. J Clin Oncol. 2016 Jul 1. PMID: 27001570.

A Newly Identified Inherited Colon Cancer Gene: FAN1

There continues to be rapid advances in identifying new genes involved in inherited cancer risk. An example of yet another recently identified gene is *FAN1*, in which a nonsense variant (i.e. the premature change or loss of a protein) was identified following exome sequencing in 3 individuals from a family who met clinical criteria for Lynch syndrome yet did not have any mutations identified in Lynch genes and had mismatch-proficient tumors.[1] The *FAN1* gene is involved in the Fanconi anemia DNA repair pathway, but is not known to be a gene involved in Fanconi anemia (a condition which can cause bone marrow failure). Study investigators subsequently tested an additional 176 families with family histories of colorectal cancer and identified *FAN1* mutations in ~3%, of which all met clinical criteria for Lynch syndrome and also had mismatch proficient tumors. These findings suggest that mutations in the *FAN1* gene may lead to inherited susceptibility to colorectal cancer. Additional studies are needed to determine the proportion of inherited colorectal cancer that may be due to mutations in this gene, as well as the level of risk incurred by mutations in this gene.

[1]Seguí N,et al. Germline Mutations in FAN1 Cause Hereditary Colorectal Cancer by Impairing DNA Repair. Gastroenterology. 2015 Jun 4. PMID: 26052075.

New Study Suggesting BRCA1/2 and ATM are associated with Aggressive Prostate Cancer

Among 799 patients with prostate cancer, the rate of *BRCA1/2* mutations was much higher among those who passed away of prostate cancer (6.07%) compared to those with low risk disease (1.44%).[1] Among the group that died of prostate cancer, those with *BRCA1/2* or *ATM* mutations passed away at an earlier age and had a shorter survival time compared to date of diagnosis. These findings suggest that prostate cancer patients with inherited mutations in *BRCA1/2* and *ATM* have a poorer prognosis, with a higher risk of dying at an earlier age. These results are consistent with results of prior efforts, and highlight the importance of genetic testing among these patients to inform decisions regarding prostate cancer screening and treatment.

[1]Na R, et al. Germline Mutations in ATM and BRCA1/2 Distinguish Risk for Lethal and Indolent Prostate Cancer and are Associated with Early Age at Death. Eur Urol. 2016 Dec 9. [Epub ahead of print]; PMID: 27989354.

Clinical and Research Updates

How does having a mother with breast cancer and a BRCA mutation affect adolescent girls?

A recent study compared psychosocial adjustment and risk perception among 11 to 19 year old daughters of women with breast cancer, comparing those with a *BRCA* mutation versus those without.[1] The overall findings from the study were reassuring, suggesting that adolescent girls from *BRCA*-positive families had higher self-esteem and similar psychosocial adjustment compared to their peers without a family history of breast cancer. On the other hand, not surprisingly, girls from *BRCA*-positive families experienced more distress related to breast cancer and being susceptible to the disease compared to girls without a family history of breast cancer. Overall, study findings suggest there remains a need to better understand how being from a *BRCA*-positive family may impact adolescent girls, in order to develop strategies which address any psychosocial concerns that may be demonstrated.

"…adolescent girls from BRCA-positive families had higher self-esteem and similar psychosocial adjustment compared to their peers without a family history of breast cancer…"

[1]*Bradbury AR, et ak. Psychosocial Adjustment and Perceived Risk Among Adolescent Girls From Families With BRCA1/2 or Breast Cancer History. J Clin Oncol. 2016 Oct 1;34(28):3409-16. PubMed PMID: 27551110.*

Newly approved PARP-Inhibitor (Rucaparib) to treat BRCA carriers with ovarian cancer

The FDA just approved another PARP inhibitor, rucaparib, for *BRCA* carriers with ovarian cancer who have already been treated with two or more chemotherapies. Among those with *BRCA*-mutant ovarian cancers, 54% had a partial or complete response to the drug with a median duration response of 9.2 months. The agency also approved a companion diagnostic test through Foundation Medicine, FoundationFocus™ which may be used in tandem. FoundationFocus CDx_{BRCA} is a tissue-based test that detects tumor *BRCA1* and *BRCA2* mutations (germline and/or somatic) in ovarian cancer.

"Among those with BRCA-mutant ovarian cancers, 54% had a partial or complete response to the drug…"

What remains interesting is that despite the availability of the companion diagnostic test, FoundationFocus, this test may not be required to determine eligibility for the drug – in fact, those determined to have a germline mutation in *BRCA1/2* through any commercial laboratory may be eligible to receive this drug.

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@InheritedCancer.net so that we may include responses in future newsletter editions. The following question was addressed by Dr. Steven Narod who is a Tier I Canada Research Chair in Breast Cancer and a senior scientist at the Women's College Research Institute in Toronto, Canada. Dr. Narod is a world-leader in the field of breast and ovarian cancer genetics.

Q. Does salpingo-oophorectomy reduce the risk of breast cancer in those with BRCA mutations?

A. Among women in the general population, risk-reducing salpingo-oophorectomy (RRSO) (i.e. removal of the ovaries and fallopian tubes) is recommended to reduce the risk of ovarian and fallopian tube cancer. The removal of the ovaries may reduce the risk of breast cancer as well. In the general population removal of the ovaries before menopause cuts the risk of breast cancer by 30% or more. Similarly, early studies in *BRCA* carriers in the United States (US) suggested that removal of the ovaries also cuts their breast cancer risk by half or more, especially when done at an early age. However, a recent Dutch study did not observe a reduced risk of breast cancer after RRSO in *BRCA1* carriers.[1] The authors of this Dutch study suggest that previous findings may have been due to the design of the studies and how the data was analyzed and casts doubt on the earlier studies. The original US-based study teams subsequently re-analyzed their data but still concluded that RRSO reduced breast cancer risk among *BRCA1* and *BRCA2* carriers.[2]

Subsequently, our group led an international study with data from many centers (including ICARE participants) and included almost 4000 *BRCA* carriers. These women were followed for up to ten years for new cases of breast cancer. The study showed that RRSO reduced the risk of breast cancer risk in *BRCA2* carriers, but did not reduce breast cancer risk among *BRCA1* carriers.[3]

Taken together, data suggest there is a benefit of RRSO to lower breast cancer risk among *BRCA2* carriers, but not *BRCA1* carriers. However, given the strong protective effect of oophorectomy on ovarian cancer risk and on all-cause mortality we recommend an oophorectomy for *BRCA1* carriers at age 35 and for *BRCA2* carriers at age 40.[4]

[1]*Heemskerk-Gerritsen BA, et al. J Natl Cancer Inst. 2015 Mar 18. PMID: 25788320.* [2]*Chai X, et al. J Natl Cancer Inst. 2015 Aug 11. PMID: 26264690.* [3]*Kotsopoulos J, et al. J Natl Cancer Inst. 2016 Sep 6. PMID: 27601060.* [4]*Finch AP, et al. J Clin Oncol. 2014 May 20.PMID: 24567435*

Characterizing breast cancers that develop among women with a CHEK2 mutation

With increasing use of multi-gene panel tests, one of the genes in which mutations are frequently detected among breast cancer patients and others is the *CHEK2* gene. This gene has been shown to have a 2-3 fold excess risk for breast cancer. There are many *CHEK2* mutations that have been identified that generally fall into two broad categories: those that prematurely shorten the protein that is made from the gene (called "truncating" mutations) and those that change a single base pair within the gene that impairs it from working normally (called "missense" mutations). Most completed studies have focused on a specific "truncating" mutation called "1100delC", as it is a relatively common change particularly among European populations.

A few studies have tried to assess if breast cancers associated with *CHEK2* mutations may have specific characteristics, although results have not been consistent. For example, a study from 2014 which included 3 *CHEK2* truncating mutations (including the 1100delC mutation) found no differences in survival between those with and without mutations,[2] while an earlier study from 2012 suggested that these *CHEK2*-associated breast cancers might have a poorer prognosis.[1] More recently, a study focused on a *CHEK2* missense mutation (p.1157T) suggested this change was not associated with poorer prognosis. Overall, there is currently insufficient evidence to conclude an association between a *CHEK2* mutation and poorer breast cancer prognosis; however, additional studies are warranted to better understand this relationship.

[1]Weischer M, et al. J Clin Oncol. 2012 Dec 10. PMID: 23109706. [2]Huzarski T, et al. Breast Cancer Res Treat. 2014 Apr. PMID: 24557336. [3]Muranen TA, et al. Breast Cancer Res. 2016 Oct 3. PMID: 27716369.

Community Spotlight

On my 43rd birthday I was diagnosed with an advanced stage breast cancer. Although my *BRCA1* and *BRCA2* results were surprisingly negative, I was certain there must be a genetic component to my breast cancer since I was diagnosed at a fairly young age. I remained in contact with my geneticist, Dr. Georgia Wiesner, and in 2016 she suggested I have more genetic testing for inherited breast cancer through a multi-gene test, which wasn't available in 2011 when I was initially diagnosed. As a result of my additional testing performed through Dr. Wiesner, I found out I was positive for the *CHEK2* mutation which not only explains my personal history of breast cancer but affords me the knowledge of additional screenings I may choose to have in the future. There was not a lot of information on the *CHEK2* mutation and I found myself very fortunate to find a closed support group on social media for women and men that have also tested positive for a *CHEK2* mutation (Facebook *CHEK2* Mutation Support Group). I subsequently brought a family member to Moffitt for testing, at which time I came to know about and enroll in the Inherited Cancer Registry (ICARE) and am passionately dedicated to helping find answers with regards to how our genes may play a significant role in our cancer diagnosis and potentially our clinical outcome.

If you are interested in joining this *CHEK2* support group on Facebook, simply search for "*CHEK2* Mutation Support Group" and request to join. As this is a private group, moderators will screen individuals who request to be added to the group.

– Christy Mattey, ICARE Participant

PALB2 Effort through ICARE

Together with Dr. Tischkowicz, a leading expert on *PALB2*, Drs. Narod, Metcalfe, and Pal are recruiting women with *PALB2* mutations to help determine breast cancer characteristics and outcomes. Only through these types of research efforts will we be able to learn more about this gene and figure out how to help those with mutations. If you are a *PALB2* carrier, have a relative with a *PALB2* mutation, or are a healthcare provider with a *PALB2* positive patient, please contact us (*see below for contact information*).

PMS2 Effort through ICARE

ICARE is recruiting *PMS2* mutation carriers to help determine the cancers associated with *PMS2* mutations and an individual's risk of developing such a cancer. Through this focused research effort, we can learn more about this gene and help detect cancers early or even prevent them in at-risk family members. If you are a *PMS2* carrier, have a relative with a *PMS2* mutation, or are a healthcare provider with a *PMS2* positive patient, please contact us (*see below for contact information*).

*Please note **for those with a PALB2 or PMS2 mutation who are already enrolled in ICARE**, we have collected much of the information needed from you to contribute to these focused efforts. We will inform you of additional information that may be needed for these focused efforts.*

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