ICARE NEWSLETTER

WINTER 2019

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About ICARE

ICARE provides individuals interested in participating in inherited cancer research studies the opportunity to enroll in a research registry. Participation in ICARE continues to expand through referrals, events, and active engagement efforts. As of January 2019, there are ~3000 participants enrolled in ICARE, including over 1100 individuals from families with *BRCA1/2* mutations. ICARE participants represent 48 U.S. states, the District of Columbia, and 16 other countries worldwide.

For those affected by inherited cancer, please visit InheritedCancer.net or call 615-875-2444 to learn more about participating. For providers treating or testing patients with inherited cancer, please call 615-875-2444 to learn more about how referring to ICARE may benefit you and your patients.

Welcome Message

As we enter 2019, we continue to experience an incredible pace of discovery in both risk refinement and treatment advances for those with inherited cancer. These types of efforts are only achieved through participation of those interested in inherited cancer research; therefore, we remain tremendously grateful to our ICARE participants as well as our healthcare provider partners, who continue to participate in our registry and engagement efforts.

In the current newsletter, we highlight new treatment advances among *BRCA* carriers with ovarian, breast, and prostate cancer, as well as treatment advances in several other inherited conditions. We also summarize findings from some recent studies that refine risks and expand indications for testing among various groups of cancer patients, which can help identify at-risk family members.

As we embark on another year, we wish you the very best. Thank you for supporting our efforts, as we continue to strive *to end the cycle of inherited cancer through research, education, and engagement.*

Sincerely,

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

New Research and Approvals of PARP Inhibitor Drugs to Treat Cancer in *BRCA* Carriers

The pace of discoveries and approvals for new cancer treatments has accelerated over the last 6 months with the expansion of indications and approvals for PARP inhibitor drugs among *BRCA* carriers as follows:

1) Treatment among patients with advanced or metastatic breast cancer: A PARP inhibitor (talazoparib) was approved by the FDA on October 16, 2018 for *BRCA* carriers with HER2-negative locally advanced or metastatic breast cancer, based on results of the EMBRACA trial outlined in the last ICARE newsletter.[1]

2) First line maintenance treatment among patients newly diagnosed with advanced ovarian cancer: The results of a trial using a PARP inhibitor (olaparib) as maintenance treatment among ovarian cancer patients with advanced disease, a *BRCA* mutation, and complete or partial response to platinum-based chemotherapy showed that survival at 3 years was 60% among those who got the drug versus 27% among those who did not.[2] Investigators concluded that among those with successful first-line chemotherapy, "The use of maintenance therapy with olaparib provided a substantial benefit among women with newly diagnosed advanced ovarian cancer and a *BRCA* mutation, with a 70% lower risk of disease progression or death with olaparib than with placebo." Soon after publication of these results, on December 19, 2018, the FDA approved olaparib for maintenance treatment of *BRCA*-mutation advanced ovarian cancer.

3) Treatment among patients with metastatic castration-resistant prostate cancer: A PARP inhibitor (rucaparib) was granted a breakthrough therapy designation in October 2018 for monotherapy (i.e., sole treatment) among men with metastatic castration-resistant prostate cancer (with a *BRCA1/2* mutation) who have received at least one prior androgen receptor-directed treatment and taxane-based chemotherapy. This designation was granted based on results of the phase II TRITON2 study, some results of which have been presented at national meeting, but not yet published.

[1]Litton JK, et al. *N Engl J Med*. 2018 Aug 23. PMID: 30110579. [2]Moore K, et al. *N Engl J Med*. 2018 Dec 27. PMID: 30345884.

High Proportion of Inherited Genes Detected Among Patients with Advanced Renal Cancer

In a study of advanced renal cell cancer patients, inherited cancer gene mutations were identified in 16%, of which 5.5% had mutations in genes related to renal cell cancer. Among the subgroup with non-clear cell renal cancer, about a fifth had an inherited cancer gene mutation, half of which had a gene mutation that could guide treatment. These findings suggest that more advanced renal cell cancers may arise in individuals with inherited cancer predisposition and are important to identify given their potential importance to guide treatment, inform future cancer risks, and provide patients with the potential to share test results with their family members. Carlo MI, et al. *JAMA Oncol*. 2018 Sept 1. PMID: 29978187.

Refining Treatment for Aggressive Prostate Cancer in Men with *BRCA2*

A recent study reported that a large proportion of men with aggressive prostate cancer have inherited cancer gene mutations. Specifically, among 400 patients with castration-resistant prostate cancer, 16.2% had a germline mutation in a DNA damage repair gene, including 3% with a *BRCA2* mutation. Among *BRCA2* carriers, survival was 17.4 months, which was much lower than the 33.2 months observed among non-carriers. Furthermore, the subset of *BRCA2* carriers who received first-line treatment with abiraterone or enzalutamide had better outcomes than those who received taxanes. Consequently, **these findings suggest that determination of *BRCA2* status may help to guide initial treatment of metastatic prostate cancer among *BRCA2* carriers**, although additional studies are needed to confirm these results. Castro E, et al. *J Clin Oncol*. 2019 Jan 9. PMID: 30625039.

Expansion of Lynch Syndrome Tumor Spectrum Which May Have Treatment Implications

Although the Lynch syndrome tumor spectrum is thought to be limited to cancers of the colorectum, endometrium, ovaries, stomach, and a few other cancer types, a recent article suggested there might be a broader tumor spectrum than previously considered. Furthermore, colorectal and endometrial cancers which develop among Lynch syndrome patients frequently are determined on tumor testing to have high microsatellite instability (MSI-H) or mismatch repair deficiency (MMR-D). The recently published study tested tumors in over 15,000 cancer patients with over 50 cancer types and found that among patients identified to have Lynch syndrome (based on germline DNA testing), 50% had tumors at sites other than the colorectum or endometrium, including urothelial, prostate, pancreas, adrenocortical, small bowel, sarcoma, mesothelioma, melanoma, gastric, and germ cell tumors. The investigators concluded that MSI-H/MMR-D predicts the presence of Lynch syndrome across a much broader tumor spectrum than currently appreciated and suggested that **any patient with this tumor characteristic should receive a germline genetic assessment for Lynch syndrome regardless of cancer type or family history**. This is particularly important given that Lynch syndrome tumors often respond to a new class of drugs (immunotherapy); thus, this information may help to guide cancer treatments. Latham A, et al. *J Clin Oncol*. 2018 Oct 30. PMID: 30376427.

Other Advances in Cancer Treatment Among Cancer Patients with Inherited Disease

Pertaining to metastatic prostate cancer, recently published data reported 8.1% of men with advanced prostate cancer had evidence of mismatch repair (MMR) mutations in their tumors.[1] These types of mutations are frequently seen in tumors among **Lynch syndrome** patients. In addition, men with this type of tumor had much poorer survival. Tumors with MMR defects are thought to generate more antigens and be more responsive to a new class of drugs called immunotherapy. The researchers are now planning to conduct a new clinical trial to test the effectiveness of immunotherapy (through checkpoint inhibitors) in this group of patients with particularly aggressive prostate cancer.

Additional exciting advances include the results of a new drug (pazopanib) to treat an inherited cancer condition called **von Hippel-Lindau Disease** (VHL),[2] in which patients are predisposed to kidney cancers, pancreatic tumors, and hemangioblastomas (i.e., tumors involving the blood vessels). Study results showed that among 31 patients with VHL, overall response rate with the drug was 42%, with responses of 52% for renal cell carcinomas, 53% for pancreatic lesions, and 4% for CNS hemangioblastomas. Results are encouraging, and this may be a treatment option for individuals with VHL and growing or unresectable lesions, although safety and activity for these indications warrants further study.

Finally, a new drug (sorafenib) showed promising results among patients with desmoid tumors,[3] which are a type of tumor for which patients with **Familial Adenomatous Polyposis** (FAP) due to *APC* gene mutations are at risk. These tumors frequently grow and encompass internal organs and can be hard to remove surgically. The newly published research showed that treatment with sorafenib doubled the rate of progression-free survival at 2 years among patients with advanced or refractory desmoid tumors. The drug also reduced the risk of death by 87% compared to the placebo, with no major safety concerns.

These advances serve to highlight some of the recent breakthroughs in the treatment of tumors among those with inherited cancer predisposition. [1]Nava Rodrigues D, et al. *J Clin Invest*. 2019 Oct 1. PMID: 30179225. [2]Jonasch E, et al. *Lancet Oncol*. 2018 Sept 17. doi 10.1016/S1470-2045(18)30487-X. [3]Gounder MM, et al. *N Engl J Med*. 2018 Dec 20. doi: 10.1056/NEJMoa1805052.

Basal Cell Cancers May Be a Risk Factor to Predict Inherited Cancer Predisposition

An interesting area of progress to identify individuals with inherited risks included a study of over 13,000 individuals with six or more basal cell cancers (BCC) evaluated through a claims database. Results indicated ~20% of these individuals had a germline mutation in a DNA repair gene, including *BRCA1/2*, *PALB2*, and the Lynch syndrome genes, among others. Furthermore, these individuals had over a 3-fold risk of other malignancies. These findings suggest that frequent BCC may represent a marker to identify potential inherited cancer risk. Cho HG, et al. *JCI Insight*. 2018 Aug 9. PMID: 30089731.

"…these individuals had over a 3-fold risk of other malignancies."

New Online Risk Calculator to More Accurately Predict Breast Cancer Risk

Prediction of breast cancer risk is important to identify those at highest and lowest risks, to help guide screening. A previously developed risk algorithm called Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) was recently extended to include truncating mutations in the *BRCA* genes, *PALB2*, *CHEK2*, and *ATM*. This online risk calculator could help healthcare providers more accurately predict breast cancer risks in patients. To access the risk calculator, please visit: https://ccge.medschl.cam.ac.uk/boadicea/. Lee A, et al. *Genet Med*. 2019 Jan 15. PMID: 30643217.

Advances in Biomarkers to Detect Pancreatic Cancer Early

Early detection of pancreatic cancer is tremendously important, given that most patients who develop the disease are diagnosed at a later stage of the disease when it is usually incurable. Although screening through imaging studies has been proposed (i.e., magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound),[1] data to support this type of screening as an evidence-based recommendation continues to be collected. Consequently, there has been longstanding interest in developing blood tests for early detection of pancreatic cancer. One such effort is represented in a recent study in which a metabolite panel in combination with CA19-9, TIMP1, and LRG1 were shown to be of potential use in the early detection of pancreatic cancer compared to a protein panel alone.[2] These types of efforts are hoped to culminate in the development of a blood test that is reliable in detecting pancreatic cancer early, at a stage when it may be curable. [1]Canto MI, et al. *Gut*. 2012 Nov. PMID: 23135763. [2]Fahrmann JF, et al. *J Natl Cancer Inst*. 2018 Aug 18. PMID: 30137376.

New Genes: *GALNT12*

A gene called *GALNT12* may be yet another inherited colorectal cancer gene,[1] as originally suggested by prior studies.[2] The current study screened almost 500 colorectal cancer patients and identified 8 rare variants that may be disease causing. The frequency of variants among colorectal cancer patients was much higher than that observed among population-matched healthy controls, providing additional evidence to suggest this gene predisposes to inherited colorectal cancer. There remains a need to collect more data to confirm these findings. [1]Evans DR, et al. *Hum Mutat*. 2018 Aug. PMID: 29749045. [2]Clarke E, et al. *Hum Mutat.* 2012 Jul. PMID: 22461326.

Ask the Expert

Through each newsletter, we give our participants an opportunity to have their questions answered by experts. If you have a question you would like addressed, please email the study team at ICARE@InheritedCancer.net for consideration in future newsletters. The following question was addressed by Georgia Wiesner, MD, MS, a nationally renowned clinical cancer geneticist, who is an Ingram Professor of Cancer Research, Professor of Medicine in the Division of Genetic Medicine, and the Director of the Clinical and Translational Hereditary Cancer Program for the Vanderbilt-Ingram Cancer Center in Nashville, Tennessee.

Q. What are the reproductive options for people with a BRCA mutation who do not want to pass their mutation on to their future children?

A. It is important to realize that pregnancy can be achieved without worry about passing on a gene mutation to future generations. There are several options for couples, including adoption, gamete (egg or sperm) donation, and preimplantation genetic diagnosis (PGD) with in vitro fertilization (IVF). PGD begins with the normal process of IVF including egg retrieval and fertilization of the egg in a laboratory. When the fertilized egg (or "embryo") reaches the 8-cell stage, one cell is removed to test it for the familial mutation. Then, embryos without the mutation can be selectively implanted using standard IVF procedures. However, the process of PGD with IVF requires confirmation prior to any procedure so that the lab can unambiguously detect the familial mutation. It can also be costly and may not be covered by insurance and involves invasive procedures. Therefore, couples considering PGD should be counseled by an experienced provider prior to any attempts to achieve a pregnancy. This process may also be relevant to individuals with other inherited gene mutations.

Testing Interpretation and Variant Reclassification

Results of germline genetic testing generally yield three types of test results: Deleterious (positive), Negative (no mutation detected), and Variant of Uncertain Significance (VUS). As more genes are tested, the chance for a positive result goes up, as does the chance of receiving a VUS result.[1] VUS results tell us that it remains uncertain whether the test result is positive or negative. A recently published study demonstrated that most VUS results are downgraded to negative over time.[2] Specifically, of more than 25,000 VUS results reported through a single testing laboratory, about a quarter were reclassified over time, of which over 90% were downgraded to negative (benign or likely benign). Information from this study is important when counseling patients with VUS results, informing them that most VUS results that are reclassified are downgraded, and explaining that VUS results are generally not used to direct medical care.

On the topic of interpretation of genetic test results, another paper reported on a novel method to better classify *BRCA1* mutations as positive or negative, through tracking how cells with specific *BRCA1* changes, growing in lab dishes, respond.[3] These types of efforts are important to better classify gene changes identified through genetic testing, and hopefully will serve to reduce the number of VUS results received by patients in the future.

VUS results: "…over 90% were downgraded to negative (benign or likely benign)."

Finally, as knowledge expands, it becomes more important to make interpretation of genetic test information widely available for it to be maximally used to improve patient care. To that effect, a recent report outlined a global resource that includes data on more than 20,000 unique *BRCA1* and *BRCA2* variants, called the "*BRCA* Exchange".[4] Over 6,100 variants in this database have been classified by an expert panel, and approximately 3,700 are established to be positive (i.e., they raise the risk for cancer). This dataset was set up to pull in information from existing clinical databases, including the Breast Cancer Information Core (BIC), ClinVar, and the Leiden Open Variation Database, as well as other databases and data worldwide. It has a single-point-of-access website (https://brcaexchange.org/) and serves to demonstrate that this type of widespread data sharing across multiple entities is possible for other inherited cancer genes and genes associated with other diseases.

[1]Kurian AW, et al. *JAMA*. 2018 Aug 1. PMID: 29801090. [2]Mersch J, et al. *JAMA*. 2018 Sept 25. PMID: 30264118. [3]Findlay GM, et al. *Nature*. 2018 Oct. PMID: 30209399. [4]Cline MS, et al. *PLoS Genet*. 2018 Dec 26. PMID: 30586411.

Community Spotlight

When I was 50 years old I was in pretty good physical shape and I thought I was finally getting six pack abs. I was wrong – those abs were a large football sized tumor, along with a variety of smaller tumors. I was diagnosed with Stage 4 ovarian cancer. I had a hysterectomy and fibroid removal when I was 40 years old, but we left the ovaries because of my age – if only I knew then what I know now.

My mom died of adenocarcinoma (lung cancer common in non-smokers) at 62 years old. My middle sister had Acute Lymphoblastic Leukemia in her 20's (twice)! My dad (a few years after donating bone marrow to my sister – he is a hero) was diagnosed with Post-Polio Syndrome and Multiple Sclerosis – and that is just my immediate family's medical history! Based on this and my personal history, genetic testing was a no brainer for me. It turns out I carry the *BRIP1* gene. My youngest sister decided to have a hysterectomy with her ovaries removed at age 47 after learning about my genetic test results – if she had to do it over again, she may have had genetic testing of her own and regular screenings instead (because menopause is not fun).

I am grateful to be able to share this information, especially if it can help protect future generations. It took very little effort to get genetic testing and if I can help a family member (or anyone for that matter) by sharing my genetic makeup, it is the least I can do to contribute to the prevention and early detection of cancer. To me, genetic testing is a way for me to help someone else. If there is a possibility of treating, preventing, or curing cancer, I am all IN - take all the blood, genes, and body parts you want!

I am not sure how or why, but I am one of the lucky few. I know a lot of women are in a constant battle trying to get where I am – 4 years with no evidence of disease (NED). I will do anything I can to help, and I am grateful to the scientists and doctors working so hard to find a cure or better ways to detect cancer early.

– ICARE Participant, Kelly Frank, from Montana