ICARE NEWSLETTER

WINTER 2018

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ICARE Recruitment & Participation Update

Participation in ICARE continues to expand through referrals, events, and active engagement efforts. As of February 2018, there are 2544 participants enrolled in the registry, including 1105 individuals with *BRCA* mutations and 455 individuals with other inherited cancer gene mutations. Participants in ICARE represent 47 U.S. states, the District of Columbia, and 15 countries worldwide.

Individuals interested in joining ICARE may enroll in the registry online through the ICARE website (InheritedCancer.net) or request a paper enrollment packet by contacting the study team via phone (615-875-2444) or email (ICARE@InheritedCancer.net).

Welcome Message

We remain tremendously grateful to our ICARE participants, as well as our healthcare provider partners, who enable the continued growth of our registry. Through ICARE, we have been able to both conduct our own research and collaborate with our colleagues at other institutions. The ongoing data collected through efforts such as ICARE have been critical to guide the management of those who are predisposed to inherited cancers.

In the current newsletter, we have highlighted some of the recent clinical and research advances that are relevant to those with inherited cancer predisposition, including progress in refining cancer risks, outcomes from cancer, proportions of certain cancers that may be inherited, and information that has become available on newer genes. We have also reviewed new data about screening in Li-Fraumeni syndrome, which included de-identified data from ICARE participants. We continue to be amazed at the rapid pace of what may come down the pipeline in the future to screen for cancer, including a new study that reported on the development of a blood test that may be able to detect 8 types of cancer early.

We hope you find this information of interest. If there are specific topics that you would like included in future newsletters, please do not hesitate to reach out and let us know.

Wishing you the very best as we embark on another year.

Sincerely,

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

Updates to NCCN Genetic/Familial High Risk Assessment: Breast and Ovarian Guidelines

Version 1.2018, posted Oct. 3, 2017

- Metastatic prostate cancer was added as an indication for evaluation and testing for the *BRCA1* and *BRCA2* genes
- Among *BRCA1*, *BRCA2*, *TP53* and *PTEN* carriers, women between ages 25-29 may consider having an annual mammogram with consideration of **tomosynthesis** if a breast MRI is not available.
- Among female *BRCA2* carriers, language regarding age of risk-reducing salpingo-oophorectomy (surgical removal of one or both ovaries and fallopian tubes) was updated to indicate that it may be delayed to age 40-45
- The table for other inherited breast and ovarian cancer genes was updated per the recent advances.

For the complete updated versions of the NCCN Guidelines, please visit NCCN.org

Getting Closer to Detecting Cancers Early through a Blood Test?

A recent study reported on a single blood test, named "CancerSEEK", which can screen for 8 common types of cancer (ovarian, liver, stomach, pancreas, esophagus, colorectal, lung, and breast) and may help to identify the location at which the cancer started.[1] This test evaluated the blood from over 1000 patients with Stage 1 to 3 cancers that were non-metastatic. The test's ability to detect these cancers was 70% on average, ranging from as high as 98% for ovarian cancer to as low as 33% for breast cancer. This test measures circulating tumor DNA and 8 proteins, and the data is analyzed using machine-based learning. The researchers are conducting additional testing, and the hope is this test will be successful in screening for cancer when in its earliest stage and more treatable.[1] *[1]Cohen et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science. 2018 Jan 18. [Epub ahead of print] PMID: 29348365.*

The Role of "Non-Truncating" Mutations in RAD51D on Ovarian Cancer Risk

As testing has broadened to include newer inherited cancer genes, studies have suggested that mutations which shorten the protein ("truncating mutations") in the *RAD51D* gene are associated with ovarian cancer. However, a recent study examined ovarian cancer risks for a "non-truncating" change (a single base pair within the gene is changed which is called a missense mutation) in the *RAD51D* gene.[1] The study was focused on a French Canadian population in which a specific missense change (c.620C>T) is particularly common. Findings showed that this change substantially raised the risk for high-grade serous ovarian cancer, which was seen in 3.8% of ovarian cancer patients and 0.2% of controls. Furthermore, laboratory studies showed that this gene change may confer sensitivity to PARP inhibitors. This is the first study to confirm a missense mutation in *RAD51D* and suggests that PARP-inhibitor therapies may be of use among this group of ovarian cancer patients. *[1]Rivera et al. Cancer Res. 2017 Aug 15;77(16):4517-4529. PMID: 28646019.*

Refining Risks and Outcomes of Breast Cancer in BRCA Carriers

In an effort to further study breast cancer risks among *BRCA* carriers, a recently published study compared breast cancer risks among those with and without a close family member (first-degree relative) with breast cancer.[1] Findings showed that risk for breast cancer by age 80 was 60.8% in *BRCA1* carriers and 63.1% among *BRCA2* carriers, with similar risk levels among those with and without breast cancer in a close relative. These findings suggest that breast cancer risks remain high among *BRCA* carriers, regardless of whether a woman has a close relative with breast cancer, thus cancer risk management should be the same for these women.

In considering outcomes of breast cancer, prior studies have not yet provided evidence to draw a definitive conclusion about whether *BRCA* carrier patients with breast cancer do better, worse, or no different, compared to patients with 'sporadic' (or non-hereditary) breast cancer. A new study was recently published to answer this question.[2] In this study, breast cancer patients diagnosed at or below age 40 (within 12 months of their diagnosis) were followed over time to compare the outcome between those with and without a *BRCA* mutation. Findings from this study showed that *BRCA* carriers had similar overall survival to non-carriers. Furthermore, the study showed that those with a *BRCA* mutation and triple-negative breast cancer may have a better outcome (as defined by survival) in the first few years after diagnosis. *[1]Metcalfe et al. Clin Genet. 2017 Dec 5. PMID:29206279. [2]Copson et al. Lancet Oncol. 2018 Jan 11. PMID 29337092.*

Advances in Cancer Screening Among Li-Fraumeni Syndrome Patients

Several research groups from around the world that have conducted cancer screening among patients with Li-Fraumeni syndrome and a germline *TP53* mutation have recently reported on their observations. Specifically, the National Cancer Institute group demonstrated that screening inclusive of rapid total body MRI detected cancers at an early stage,[1] similar to findings published through other recent smaller studies.[2,3] Collectively, these findings demonstrated the extensive screening advised for many Li-Fraumeni patients is feasible; however, some of this screening may lead to false positives (i.e., a positive finding on a cancer screening test that ends up not being cancer) as well as cancer overdiagnosis.[4] Through a recent effort to look at whole body MRI in Li-Fraumeni syndrome patients across several previously published studies, data suggested that this screening test may be clinically useful and an important part of cancer risk management. Additionally, we recently published an article focused on **ICARE participants** with a germline *TP53* mutation, who were identified based on a multi-gene panel test.[6] We found that many of these individuals did not have a family history that would identify them as having Li-Fraumeni syndrome, which suggests that cancer risk in some of these 'non-characteristic' families may not be as high as those with a classic family history of Li-Fraumeni syndrome. This brings up the question about what screening is most appropriate for them. Overall, these articles all highlight the need to generate more evidence to refine screening practices among individuals with Li-Fraumeni Syndrome. *[1]Mai et al. JAMA Oncol. 2017 Dec 1;3(12):1640-1645. PMID:28772286. [2]Ballinger et al. JAMA Oncol. 2017 Dec 1;3(12):1735-1736. PMID:28772290. [3]Ruijs et al. JAMA Oncol. 2017 Dec 1;3(12):1733-1734. PMID:28772294. [4]Asdahl PH, Ojha RP, Hasle H. JAMA Oncol. 2017 Dec 1;3(12):1645-1646. PMID:28772307.[5]Ballinger et al. JAMA Oncol. 2017 Dec 1;3(12):1634-1639.PMID:28772291. [6]Pal et al. South Med J. 2017 Oct;110(10):643-648. PMID:28973705.*

FDA Approval of PARP Inhibitor (Lynparza) for treatment of advanced breast cancer

On January 12, 2018, the FDA approved the first PARP Inhibitor (Lynparza) for treatment in patients with advanced breast cancer due to inherited *BRCA* mutations.[1] This drug is already approved for certain *BRCA* carriers for advanced ovarian cancer. PARP inhibitors were originally developed to target the specific pathway through which cancer develops among those with a *BRCA* mutation. This latest approval demonstrates that developing drugs to target the underlying genetic cause of cancer can be used across cancer types. The approval of this drug was based on a recently published trial which showed that the drug delayed disease progression, which may help preserve quality of life by delaying the use of chemotherapy.[2] It remains to be determined whether further improvements in treatment with this drug can be achieved through using it in combination with other drugs.

"… the drug delayed disease progression, which may help preserve quality of life…"

[1] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm592347.htm
[2] Robson et al. N Engl J Med. 2017 Aug 10;377(6):523-533. PMID: 28578601.

Advances in New Treatments for Individuals with Lynch Syndrome

A recently published phase II clinical trial investigated the use of a new class of drugs (called PD-1 Inhibitors) in DNA mismatch repair-deficient/ microsatellite instability-high colorectal tumors (which are features seen in the majority of colorectal tumors from individuals with Lynch Syndrome) among patients with metastatic disease.[1] Investigators found patients who received two PD-1 Inhibitors (compared to just one PD-1 inhibitor, which had already shown to be of benefit[2]) had better response rates which lasted longer while maintaining the safety of the drug. Overall, 50% of these patients did not have progression of their colorectal cancer after 2 years. This treatment strategy represents a promising new option. Additional studies are already underway to evaluate this drug combination as a first line of treatment.

"Overall, 50% of these patients did not have progression of their colorectal cancer after 2 years."

[1] Overman et al. J Clin Oncol. 2018 Jan 20:JCO2017769901. PMID:29355075.
[2] Overman et al. Lancet Oncol. 2017 Sep;18(9):1182-1191. PMID:28734759.

Ask the Expert

Through each newsletter, we give our participants an opportunity to have their genetics and research questions answered by experts. If you have a question you would like addressed, please email the study team at ICARE@InheritedCancer.net so we may include responses in future newsletters. The following question was addressed by Dr. Ingrid Meszoely is a breast surgeon and Clinical Director of the Vanderbilt Breast Center at One Hundred Oaks. She leads a high-risk clinic, through which she and her team of nurse practitioners manage patients with inherited breast cancer predisposition. Her research interests include both clinical and translational breast cancer-related research.

Q. Is it reasonable to consider hormonal replacement therapy (HRT) in BRCA carriers without breast cancer, after a prophylactic oophorectomy (surgical removal of one or both ovaries)?

A. There have been prior concerns that HRT may raise the risk of breast cancer among *BRCA* carriers, yet data from multiple studies which have evaluated this question have been reassuring. Specifically, three studies (observational and retrospective studies) have been completed in *BRCA* mutation carriers without a history of breast cancer, in which HRT did not raise the subsequent risk of breast cancer, nor did it appear to reduce the protective effect of oophorectomy on breast cancer risk.[1,2,3] While it would be ideal to confirm these findings through a randomized control trial, data are currently reassuring that HRT is an option that may be considered among *BRCA* carriers, particularly those with severe menopausal symptoms or other issues that compromise their quality of life. In fact, a recent study on a group of 178 premenopausal women at high risk for ovarian cancer reported that about one third (n=57) opted for risk-reducing salpingo-oophorectomy (RRSO; removal of both ovaries and fallopian tubes).[4] Of those with RRSO, 27 used HRT after surgery and 30 did not. HRT users had less menopausal side effects (i.e., endocrine symptoms, sexual symptoms) compared to those with did not use HRT, suggesting the potential benefits of this treatment in the first year following RRSO. [1] Eisen, A. et al. J Natl Cancer Inst. 2008 Oct 1;100(19), 1361-7. PMID:18812548. [2] Rebbeck, T.R., et al. J Clin Oncol. 2005 Nov 1;23(31), 7804-10. PMID:16219936. [3] Kotsopoulos et al. Breast Cancer Res Treat. 2016 Jan;155(2):365-73. PMID:26780555. [4] Vermeulen et al. Eur J Cancer. 2017 Oct;84:159-167. PMID: 28818705.

Community Spotlight

A cancer diagnosis is a life-changing event for every patient and their extended family. However, how we respond to this diagnosis are as individual as our very existence as evidenced by our looks and personalities. Following my diagnosis of stage 4 prostate cancer in 2014 at age 54 which had spread to my bones, I was initially crushed, especially when I found out that I was in the very small percentage for whom there really was no cure. I then did what I always do, just like I did when my son with Down's syndrome was born - I tried to gather all the knowledge to make the best decisions to move forward. As with my son, who is now a 22 year old with a loving personality and working, my goal is to pursue the best outcome possible.

With a background of many immediate and extended family members with cancer, the decision to do genetic testing was easy, through which I found out that I was positive for the *BRCA2* genetic mutation, which was not very surprising. Since all four of my children are now young adults between 21-33 years old, we had a great discussion about future testing and what this means. To my knowledge, none of them have completed testing yet, but they have all been like their old man…happy to have the knowledge to help them make good decisions on their own future preventive care. I am also personally glad they are armed with good information.

As for my own future, so far I am exceeding expectations. The first treatment was expected to last 18-24 months, but mine lasted 40 months! Now moving into what is called "advanced prostate cancer" I continue to be happy that my quality of life is still good. I also continue to rest in my faith and trust God for whatever future that remains.

- *Ben Williams, Colonel, US Army, Retired*

Study Suggests Inherited Cancer Genes are Important in Pancreatic Cancer

In a recent study which included over 800 patients with pancreatic ductal cancer, inherited cancer gene mutations were found in a much higher proportion than expected.[1] Almost 5% of these patients had mutations identified in inherited cancer genes, the majority of which were in genes thought to be associated with pancreatic cancer (including *BRCA2, ATM, BRCA1, PALB2, MLH1, CDKN2A,* and *TP53*). Those that had mutations identified tended to be younger on average, however most did not have a family history of cancer that would suggest the presence of inherited mutations. These findings demonstrate that a meaningful number of patients with inherited risk for pancreatic cancer will be missed if relying on only family history. With the development of drugs to target cancers which develop among those with inherited disease, this study shows that relying too heavily on family history may lead to missing patients who would otherwise be eligible for these targeted treatments.

[1]Shindo et al. J Clin Oncol. 2017 Oct 20;35(30):3382-3390. PMID: 28767289.

Advances in the Understanding of Inherited Prostate Cancer

Findings through a recent study reported that inherited cancer gene mutations were present in 8.2% of those with advanced or metastatic prostate cancer, which provides additional support to include this group of men in broader testing, particularly as targeted treatments based on inherited gene mutations becomes increasingly available.[1] Another recent study suggested that those with a stronger family history of prostate cancer were more likely to present with more advanced prostate cancer, suggesting that familial or hereditary prostate cancer may be associated with a more aggressive disease.[2] In view of these and other recent advances in the understanding about inherited prostate cancers, a group of experts convened to develop a consensus statement to guide the identification, management, and testing of men at risk for inherited prostate cancer.[3] Overall, there was broad agreement for discussion of prostate cancer screening among *BRCA2* carriers. Furthermore, there was moderate consensus that *BRCA2* should be factored into management decisions from an early stage in the patient's treatment, with stronger consensus that this is very important to consider among those with advanced or metastatic disease. Genetic testing for all men with metastatic castration-resistant prostate cancer regardless of family history was also considered to be important to inform prognosis and targeted therapy, particularly for the *BRCA1* and *BRCA2* genes, and possibly for the *ATM* gene.

[1]Thalgott et al. World J Urol. 2017 Nov 21. PMID:29164326. [2]Giri et al. JCO Precision Oncology 2017 May 4;1, 1-17. [3]Giri et al. J Clin Oncol. 2017 Dec 13. PMID:29236593.

Tuya Pal, MD, FACMG | Anne Weidner, MPH | Ann Tezak, MA, MPH
Cristi Radford, MS, CGC | Ingrid Meszoely, MD

Phone: 615-875-2444 | **Email**: ICARE@InheritedCancer.net | **Website**: InheritedCancer.net