Winter 2020

ICARE NEWSLETTER

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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 2020, there are over 3,400 participants enrolled in ICARE, including more than 1,200 individuals with *BRCA1/2* mutations and more than 800 individuals with other inherited cancer gene mutations. ICARE participants represent 50 U.S. states, the District of Columbia, and 17 other countries worldwide.

If you have been affected by inherited cancer or are a provider managing patients with inherited cancer, please visit our website (InheritedCancer.net) to learn more about ICARE and how participating in our efforts may benefit you.

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Welcome Message

In the year 2020, ICARE celebrates its 10th anniversary during which time we have grown to become amongst the largest registries focused on inherited cancers. Many practice and paradigm shifting events have occurred over the last 10 years. Back when we started in 2010, *BRCA1* and *BRCA2* testing cost over $4,000 and was only performed in the United States by a single laboratory that owned the patent for these genes. However, in a landmark Supreme Court decision in June of 2013, the ability to patent genes was invalidated. This event, coupled with tremendous technological advances, led to the expanding use of multi-gene panel tests and testing of more and more genes in a single test.

ICARE's broad focus on inherited cancer has enabled us to continue to grow our efforts, as genetic testing for inherited cancers expands. We have contributed to several national and international efforts to expand our knowledge, including some of the efforts highlighted in the current newsletter. These advances have only been possible because individuals with inherited cancers, such as ICARE participants, have chosen to enroll in registries to further knowledge. It is only through these efforts that we will be able to achieve our mission *to end the cycle of inherited cancer through research, education, and engagement*.

With our sincere gratitude,

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

Updates to National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (*Version 1.2020, posted December 4, 2019*)

There were significant updates and restructuring of the guidelines, with some highlights included below:

- Substantial reorganization of the guidelines as follows:
  - Now organized by organ site, rather than primarily by certain high penetrance genes
  - Focused efforts to simplify genetic testing criteria
  - Only one flow diagram included, to outline the 'genetic testing process'
- Following scenarios now outlined:
  - Situations in which genetic testing may have low yield
  - Situations where referral to a genetics expert is recommended
- *PALB2*: Recognized as a high penetrance gene, for which discussion of risk-reducing mastectomy is appropriate
- *BRCA1/2*: Prostate cancer screening to be initiated at age 40
- Pancreatic screening guidance included:
  - *STK11* starting at age 30-35
  - *CDKN2A* starting at age 40
  - *BRCA1/2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *EPCAM*, *PALB2*, or *TP53*: Only if there is a close family member with pancreatic cancer

For the complete updated versions of the NCCN guidelines, please visit *NCCN.org*
Follow this link to view our social media post*: https://tinyurl.com/ICARE2019124*
Full press release available at*: https://www.nccn.org/about/news/newsinfo.aspx?NewsID=1790*

Treatment Advances Among Those with Inherited Cancer Predisposition

Over the past few months, treatments have continued to rapidly evolve to provide more targeted treatments to those with inherited cancers, including those highlighted below:

Treatments among individuals with pancreatic cancer: Results from a recent study showed olaparib (a PARP inhibitor) nearly doubled the progression-free survival in *BRCA1/2* carriers with metastatic pancreatic cancer.[1] Based on this data, the FDA approved the use of olaparib as a first-line maintenance treatment in *BRCA1/2* carriers with metastatic, platinum-sensitive pancreatic cancer. This represents another treatment advance in pancreatic cancer and highlights the importance of genetic testing for all patients with pancreatic cancer.

Another recent study among pancreatic cancer patients with a *BRCA1/2* or *PALB2* mutation showed that response rates after first line treatment with cisplatin/gemcitabine alone was 65.2%, and with addition of veliparib (a PARP inhibitor), it was 74.1%.[2] The study evaluated each arm separately and did not compare them. Survival at 2 years and 3 years was also encouraging at 31% and 18%, respectively. These data highlight the importance of conducting testing for inherited cancer among all patients with pancreatic cancer, as this information may guide treatment among those identified to have inherited cancer gene mutations such as *BRCA1/2* or *PALB2*.

[1]Golan, et al. N Engl J Med. 2019 Jul. PMID: 31157963; [2]Helwick, C. The ASCO Post. 2020 Jan. Available at: https://www.ascopost.com/

Social media post: *https://tinyurl.com/ICARE202013*

Treatments among men with *BRCA*-associated metastatic prostate cancer: A recent study reported a high complete response rate among men with a *BRCA1/2* mutation with metastatic, castration-resistant prostate cancer who were treated with niraparib (a PARP inhibitor) of 63% compared to 17% in the non-*BRCA1/2* group.[1] Based on this data, the Federal Drug Administration (FDA) granted breakthrough therapy designation to niraparib on October 3, 2019 to expand the treatment options for men with *BRCA1/2* positive, metastatic, castration-resistant prostate cancer.[2]

[1]Smith, et al. Presented at 2019 ESMO Congress. 2019 Sept-Oct. Barcelona, Spain. Abstract LBA50. [2]Augenstein S. FDA Grants Breakthrough Therapy Designation to Niraparib for mCRPC. 2019 Oct. Available at: https://tinyurl.com/BRCAassociatedprostatecancer.

Social media post: *https://tinyurl.com/ICARE20191220*

Updated Pancreatic Cancer Screening Guidelines through CAPS Consortium

The International Cancer of the Pancreas Screening (CAPS) Consortium recently published updated recommendations about pancreatic cancer screening through MRI/magnetic retrograde cholangiopancreatography (MRCP) and/or an endoscopic ultrasound (EUS).[1] Specifically, these guidelines now recommend that individuals with a *CDKN2A* or *STK11* mutation begin screening at age 40. Screening for individuals with a *BRCA1/2*, *ATM*, *PALB2*, *MLH1*, or *MSH2* mutation is only recommended if they have at least one first-degree relative with pancreatic cancer, beginning at age 45-50 or 10 years younger than the youngest relative diagnosed with pancreatic cancer. These guidelines were developed through expert consensus based on existing research; however, there remains a need for more information to understand the benefits and risks of pancreatic cancer screening. Both patients and their treating providers should be aware that these guidelines have some differences from the recently published NCCN genetic/familial breast, ovarian, and pancreatic guidelines, as outlined in the table below.[2]

Age to Begin Pancreatic Cancer Screening per NCCN & CAPS

Gene	**NCCN** (V.1.2020)	**CAPS** (2019)
STK11	Begin at 30-35	Begin at 40
CDKN2A	Begin at 40	Begin at 40
BRCA1/2, PALB2, ATM, MLH1, MSH2, MSH6	Begin at 50	Begin at 45-50
EPCAM, TP53	Begin at 50	*Not included*

[1]Goggins, et al. Gut. 2020 Jan. PMID: 31672839; [2]NCCN Practice Guidelines. V.1.2020. 2019 Dec. Available at: NCCN.org

Social media post: *https://tinyurl.com/ICARE202026*

Lynch Syndrome Cancer Risks Across Genes

A worldwide study reporting on cancer risks among individuals with mutations in Lynch syndrome genes showed that there are substantial differences in cancer risks across the various genes.[1] Specifically, the risk for colorectal cancer in those with *MLH1*, *MSH2*, and *MSH6* mutations was substantially higher than what was seen for those with *PMS2* mutations. Additionally, the risk for prostate cancer among men with an *MSH2* mutation was elevated at ~30% lifetime risk, with higher risks among men over 50 years of age. Additionally, the risks of cancers of the urinary tract and small bowel were higher among those with *MLH1* or *MSH2* mutations. *MLH1* or *MSH2* carriers over the age of 50 had the highest risks for urinary tract and small bowel cancers. Another study focused on *PMS2* and *MSH6* carriers found that overall risks for colorectal cancer to age 70 was 8.7% and 11.8%, respectively.[2] For *PMS2*, colorectal cancer risk for men was 9.9%, whereas for women it was lower at 5.9%. For *MSH6*, risks were similar between men and women at 10% and 11.7%, respectively. It remains important to refine cancer risks across the various Lynch syndrome genes as this information is needed to develop gene-specific cancer risk management guidelines.

[1]Dominguez-Valentin, et al. Genet Med. 2020 Jan. PMID: 31337882; [2]Suerink et al. Genet Med. 2019 Dec. PMID: 31204389

Social media post: *https://tinyurl.com/ICARE202027*

PALB2 Mutations & Cancer Risk

A newly published study of 524 families with pathogenic *PALB2* mutations from around the world, including almost 50 ICARE participants, represents the largest, most comprehensive effort to evaluate cancer risks.[1] Results showed increased risks for female breast cancer (53%), ovarian cancer (5%), pancreatic cancer (2-3%), and male breast cancer (1%). Findings did not suggest higher risks for prostate cancer or colorectal cancer. Additionally, the risks of breast cancer were highest for younger women and declined with age. Results from this study confirm *PALB2* to be an important breast cancer gene, with risks overlapping with *BRCA1/2*, and highlight the importance of breast cancer risk management among individuals with *PALB2* mutations.

[1]*Yang, et al. J Clin Oncol. 2019 Dec. DOI: 10.1200/JCO.19.01907.*

Social media post: *https://tinyurl.com/ICARE20191216*

Video of Dr. Marc Tischkowitz (Senior Author): *https://inheritedcancer.net/featured-videos/*

New Study Based on ICARE Participants with *ATM & CHEK2* Mutations

We are excited to tell you about our recently published results based solely on data from ICARE participants with *ATM* and *CHEK2* mutations. Our findings suggest most female family members of *ATM* and *CHEK2* mutation carriers do not qualify for breast MRI screening based on family cancer history alone. This emphasizes the need to share positive *ATM* and *CHEK2* test results with family members so they can consider undergoing genetic testing themselves, which could impact their eligibility for breast MRI screening. Specifically, women with *ATM* and *CHEK2* mutations have a lifetime breast cancer risk greater than 20%, which is the threshold at which screening through a breast MRI is recommended. Results of our study showed:

- Among 56 *ATM* carriers in ICARE, less than 25% of their close female relatives had a lifetime breast cancer risk >20% based on family cancer history alone.
- Among 69 *CHEK2* carriers in ICARE, less than 15% of their female relatives had a lifetime breast cancer risk >20% based on family history alone.

Consequently, testing in these female family members would identify those who were positive for the same *ATM* or *CHEK2* mutation and therefore have a >20% risk for breast cancer, making them eligible for breast MRI screening.

[1]*Weidner, et al. Cancer. 2020 Jan. PMID: 31967672.*

To help share test results with family members, check out our **FREE** online resource at: www.GeneSHARE.net

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 Ben Ho Park, MD, PhD, who is the Donna S. Hall Chair in Breast Cancer, Co-Leader of the Breast Cancer Research Program, Associate Director for Translational Research, and Director of Precision Oncology at Vanderbilt-Ingram Cancer Center. Dr. Park is also a Professor of Medicine and Associate Director for Basic and Translational Research in the Department of Medicine's Division of Hematology and Oncology.

Q. How is DNA testing done on someone's tumor different from testing done on someone's normal DNA from their blood or saliva sample?

A. When we extract DNA from a biopsy or surgical sample of a tumor, usually it is a mixture of both normal cells and tumor cells. This is because normal cells such as blood vessels and blood cells are found within the tumor itself. However, all tumors arise because of changes in our normal DNA. Sometimes we have inherited DNA changes like *BRCA1/2*, but all tumors, including *BRCA1/2*-associated tumors, will have additional DNA changes that are present only in the tumor cells. Usually it takes 3 to 8 DNA changes to make a normal cell cancerous. Therefore, when we analyze these changes using a biopsy or surgical sample, we cannot tell whether the changes are in the tumor cells only, or present in both tumor and normal cells, since it is a mixture of these cells. DNA that has changes in normal cells, like *BRCA1/2* mutations, are called "germline". These are DNA changes that a person was born with and present in almost every cell of their body. These DNA changes can be passed to their children.

The reason it is important to test tumor DNA is because it can help guide treatment based on mutations that are found in the tumor cells. However, we can now identify whether a DNA change is in the germline vs. the tumor only by also testing normal DNA separately, usually through a blood or saliva sample and comparing germline vs. tumor DNA changes. Testing someone's normal DNA can now help guide treatment since we have newer therapies against germline DNA changes. It can also tell us about future cancer risks and how to best manage those risks, as well as tell us about potential cancer risks for someone's blood relatives. It is also important to remember that when testing is done on tumor and/or germline DNA, it may also uncover potential germline mutations found in the normal cells that are unexpected and not related to someone's cancer. However, this information is still potentially important to help guide future cancer risks and management and to inform potential inherited cancer risks for family members.

Community Spotlight

I was diagnosed with breast cancer in December 2018 and was found to be *PALB2+*. The *PALB2* gene had not been tested for when my older sister was diagnosed with breast cancer and had genetic testing done four years earlier. This was new! My cancer was very similar to my sister's, but being *PALB2+* changed my treatment plan and informed me of my possible higher cancer risks for recurrence and other cancers. Like my sister, I had one small tumor in one breast. I could have just had a lumpectomy with radiation and chemo (depending on ONCA result) followed by oral medication, and then just live with a risk of recurrence. The other treatment option was a skin saving, nipple sparing bilateral mastectomy with FLAP reconstruction followed by 5-10 years of oral medication. This would have reduced my risk of recurrence to below 10%. It was a no brainer for me -- I chose the latter. After my breast surgery, I was then told *PALB2* was linked to ovarian cancer, so I started seeing a high-risk gynecologist. After months of discussions with my gynecologist and oncologist, I decided to have an oophorectomy. This was prompted by my *PALB2* risk and my adverse reaction to Tamoxifen. The only way to get off the Tamoxifen was to put me into menopause by removing my ovaries, which at the same time, would lower my ovarian cancer risks. Again, this was a no brainer. It's two years after my diagnosis, and I'm in a really good place. My cancer is nearly behind me, as I don't think about it on a daily basis. I'm feeling great and look even better ;) My energy levels are back to normal, I'm playing competitive tennis, and I'm spending time with my family traveling and enjoying life. We look to the future with positivity. We know there is a chance that I have passed the mutation onto my three kids but we feel empowered by the knowledge of knowing about it, and we will test them for it when they get older. My family is empowered too. We recently found out that my mother is *PALB2+*. Great news, she's 75 years old and has never had breast cancer! So *PALB2* doesn't necessarily mean a cancer sentence! I have personally known many family and friends diagnosed with breast cancer; my best friend being one who was diagnosed 8 years ago with stage 4, triple positive, metastatic inflammatory breast cancer. She has had radiation, chemo, had her spine rebuilt, and been on numerous clinical trials. She is here today, and her tumor has shrunk by 67%. What I learned from her: "*Always have a note taker with you at EVERY appointment because there is always too much info to absorb. Don't ever give up and never let it define you. Fight your battle your way. And when you need it, ask for help*."

\- *ICARE Participant, Jennifer Clarke from New Orleans, LA*

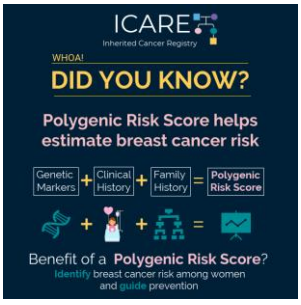
Featured Highlights

Since our last newsletter, we have featured over 40 informational posts on social media. We are grateful to our followers for their support. If you haven't done so already, please consider liking or following ICARE on your favorite social media platform to obtain updates on new inherited cancer genes, treatment advances, cancer risks, and updates to inherited cancer screening guidelines.

Below we have highlighted a few social media posts containing information beyond what is included in our newsletters:

@INHERITEDCANCER

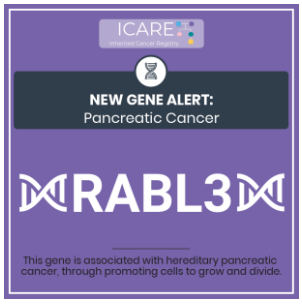
DID YOU KNOW?



TREATMENT ADVANCES

CANCER RISKS

NEW GENES



GUIDELINE UPDATES

All social media posts and newsletter articles can be searched on our ICARE website:
https://inheritedcancer.net/category/newsletter-articles/

VANDERBILT-INGRAM CANCER CENTER

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