Summer 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 August 2020, there are over 3,700 participants enrolled in ICARE, including more than 1,200 individuals with *BRCA1/2* mutations and more than 900 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

During these unprecedented times, we are incredibly humbled to report that ICARE activities have continued without lag, as we continue to grow our registry. During our 10th anniversary year, we have exponentially grown our partnerships with providers across North America and beyond, with over 150 providers who have referred their patients to our registry to date. Our growing efforts to share new information through social media (including Instagram, Facebook, Twitter, and LinkedIn) continue to expand, and we encourage you to follow us on your preferred platform. As we have grown, it has also provided us with many opportunities to expand information about those with inherited cancer, both through our own research[1] (for which an overview is included in the 'Guideline-Concordant Care Among Women with Inherited Cancer Gene Mutations' article of this newsletter) and contributing data to efforts led by others.[2-4] Because of ICARE, we will also be opening a new trial to study ways to improve cancer risk management and family sharing of test results, which was recently approved for funding through the National Cancer Institute. We have also been invited to take part in prevention and treatment trials for those with inherited cancer. Once these trials open, we will reach out to ICARE participants who may be eligible to determine their interest in participating.

We hope you and your family are staying safe in these challenging times and thank you for your continued support of our registry. These types of efforts remain critical as we strive 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

[1]Cragun, et al. Breast Cancer Res Treat. 2020 Jul. PMID: 32445176; [2]Kotsopoulos, et al. Breast Cancer Res Treat. 2018 Sep. PMID: 29774471; [3]Yang, et al. J Clin Oncol. 2020 Mar. PMID: 31841383; [4]Metcalfe, et al. Br J Cancer. 2019 Jul. PMID: 30971774.

Updates to National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment: Colorectal Guidelines (*Version 1.2020, posted July 21, 2020*)

For individuals with **Lynch Syndrome**:

- Cancer risks were updated based on information from recent studies:
  - Main updates included cancer risks in *PMS2* (endometrial, ovarian, and prostate cancer), *MSH2* and *EPCAM* (prostate and brain cancer), and *MSH6* (prostate cancer)
- Cancer risk management was updated to include:
  - Recommendations that differ across the various Lynch Syndrome genes, based on their level and type of cancer risk
  - Specific dosing of aspirin use for *MLH1*, *MSH2*, *EPCAM*, and *MSH6* (i.e.,600 mg/daily)
  - Age of colonoscopy for *MSH6* and *PMS2* was changed to start a bit later, at age 30

For individuals with **Familial Adenomatous Polyposis (FAP)**:

- Thyroid cancer screening through ultrasound was spaced out to every 2-5 years (from every year)

NCCN bulletin available at: https://www.nccn.org/about/news/ebulletin/ebulletindetail.aspx?ebulletinid=294
Updated NCCN guidelines are available free-of-charge at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

Treatment Advances Among Those with Inherited Cancer Predisposition

There continue to be ongoing advances in treatment studies among those with inherited cancer gene mutations, which are rapidly being followed by FDA approval for specific cancer treatments. Select studies and advances are summarized below:

BRCA1/2 Carriers

Breast Cancer*:* For those with *later stage or metastatic* breast cancer, the FDA currently has approvals for the use of PARP inhibitors, yet the impact of combination therapy is still under investigation. A recent study suggested veliparib (a PARP inhibitor) in combination with chemotherapy showed benefit.[1] For those with *early stage* breast cancer, a recent study suggested benefit from talazoparib (another PARP inhibitor).[2] New research suggests that platinum-based agents, which have been suggested to be of particular benefit to treat *BRCA1/2*-related breast cancer, are less effective than previously thought in the neoadjuvant setting (treatment given before surgery),[3] and among those with *early stage* triple negative breast cancer in the neoadjuvant setting.[4]

Ovarian Cancer: For those with *advanced* ovarian cancer, the FDA recently approved niraparib (a PARP inhibitor) as first-line maintenance treatment. Among those with platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum-based chemotherapy, olaparib (another PARP inhibitor) showed potential benefit.[5] Subsequently, the FDA approved olaparib as first-line maintenance treatment in those with complete or partial response to first-line platinum-based chemotherapy.

Prostate Cancer: Among those with *metastatic* castration-resistant prostate cancer, a recent study suggested that rucaparib (a PARP inhibitor) may have antitumor activity,[6] which then provided data to support FDA approval of rucaparib among those treated with anti-androgens and/or other treatments. Olaparib (another PARP inhibitor) also received FDA approval recently for a similar indication.

Pancreatic Cancer: Among *BRCA1/2* or *PALB2* carriers with *stage 3 or 4* pancreatic cancer, the addition of veliparib (a PARP inhibitor) did not provide additional benefit over cisplatin and gemcitabine alone.[7]

Lynch Syndrome

Colorectal Cancer: Among patients with MSI-H or MMR-deficient colorectal cancers (frequently seen among those with Lynch syndrome), pembrolizumab (an immunotherapy drug) improved survival,[8] which then led to subsequent FDA approval of its use as first-line treatment in *unresectable or metastatic*, MSI-H or MMR-deficient colorectal cancer.

Endometrial Cancer: Among women with MMR-deficient endometrial cancer, a recent study showed potential benefit from avelumab (an immunotherapy drug).[9]

Neurofibromatosis Type 1 (NF1)

The FDA granted selumetinib (a MEK inhibitor) breakthrough therapy designation for treatment of inoperable plexiform neurofibromas.

Von-Hippel Lindau (VHL) Disease

Among patients with VHL-associated clear cell renal cell carcinoma (RCC), a recent study suggested potential benefit from MK-6482,[10] which subsequently led to the FDA breakthrough therapy designation for those with *nonmetastatic* RCC tumors < 3 cm in size.

[1]Dieras, et al. ESMO 2019 Congress. 2019 Sep. Available at: https://tinyurl.com/dieras2019; [2]Litton, et al. J Clin Oncol. 2020 Feb. PMID: 31461380; [3]Tung, et al. J Clin Oncol. 2020 May. PMID: 32097092; [4]Pohl-Rescigno, et al. JAMA Oncol. 2020 Mar. PMID: 32163106; [5] Penson, et al. J Clin Oncol. 2020 Feb. PMID: 32073956; [6]Abida, et al. J Clin Oncol. 2020 Aug. PMID: 32795228; [7]O'Reilly, et al. J Clin Oncol. 2020 May. PMID: 31976786; [8]Andre, et al. ASCO Meeting. 2020 May. Available at: https://meetinglibrary.asco.org/record/186928/abstract; [9] Konstantinopoulos, et al. J Clin Oncol. 2019 Aug. PMID: 31461377; [10]Jonasch, et al. J Clin Oncol. 2020 May. Available at: https://tinyurl.com/jonasch2020

Guideline-Concordant Care Among Women with Inherited Cancer Gene Mutations

Testing for inherited cancer among breast cancer patients has tremendous potential to guide appropriate care following testing. Yet, a number of efforts suggest that women are not consistently receiving care according to current national guidelines based on their genetic test result. In fact, results from studies suggest many women for whom risk-reducing mastectomy would not be recommended based solely on their genetic test result, may be receiving this procedure. Specifically, high rates of bilateral mastectomy have been reported among those with a *BRCA1/2* variant of uncertain significance[1] as well as those with non-*BRCA1/2* moderate penetrance genes,[2,3] suggesting potential overtreatment. Additionally, a recently published cancer registry-based study suggested that those with a *BRCA1/2* mutation may be more likely to receive bilateral mastectomy for a unilateral tumor, less likely to receive post-lumpectomy radiotherapy, and more likely to receive chemotherapy for early-stage, ER/PR-positive disease.[2] Similarly, we have previously reported on risk-reducing oophorectomies conducted among *BRCA1/2* carriers, which showed lower rates among Black women compared to non-Hispanic Whites.[4] More recently, our study **based directly on ICARE participants**, as well as another registry study, suggested there may be potential overtreatment with oophorectomy among women with non-*BRCA1/2* inherited breast cancer genes in which oophorectomy is not generally recommended for risk reduction based on current ovarian cancer risk estimates.[3,5] These findings highlight the importance of promoting guideline-adherent care and avoiding overtreatment.[6]

[1]Kurian, et al. J Clin Oncol. 2017 Apr. PMID: 28402748; [2]Kurian, et al. JAMA Oncol. 2020 Feb. PMID: 32027353; [3]Cragun, et al. Breast Cancer Res Treat. 2020 Jul. PMID: 32445176; [4]Cragun, et al. Cancer. 2017 Jul. PMID: 28182268; [5]Domchek, et al. J Clin Oncol. 2020 May. Available at: https://tinyurl.com/domchek2020; [6]MyGeneCounsel. 2019 Oct. Available at: https://tinyurl.com/MyGeneCounselWhitePaper

Identifying Individuals At-Risk for Inherited Cancer

We have known for a while that many people who have mutations in *BRCA1/2* and other inherited cancer risk genes are unaware of their mutation as they have not yet had genetic testing. A recent study among women aged 20 or older living in California and Georgia, which included almost 80,000 breast cancer patients and 6,000 ovarian cancer patients, found that about a quarter of those with breast cancer and a third of those with ovarian cancer had genetic testing.[1] Of individuals who had testing, 7.8% of those with breast cancer and 14.5% with ovarian cancer were found to have a mutation in an inherited cancer gene.[1] Testing among breast cancer patients was lower as age and poverty level increased, but was similar across racial/ethnic groups (such as Whites, Blacks, American Indians, Asians, and Hispanics).[1] In contrast, for ovarian cancer patients, testing was lower among Black compared to White patients (21.6% versus 33.8%) and among those without insurance compared to those with insurance (20.8% versus 35.3%).[1] These results continue to identify substantial gaps in testing among cancer patients, and highlight existing disparities in cancer care which need to be addressed and improved.

Findings from another study based in a health system where patients were insured and had access to genetic services were recently published.[2] Results showed that annual rates of genetic testing increased between 2005 to 2015 among women with breast and ovarian cancer overall; however, rates of genetic testing among women with newly diagnosed breast and ovarian cancers fell from 71.5/1000 person years in 2005 to 44.4/1000 person years in 2015.[2] This study highlights that many women who are eligible to have *BRCA1/2* testing covered by their health insurance did not have it, suggesting there is **much work to be done for more people to benefit from testing** and the medical care options that testing may provide. *[1]Kurian, et al. J Clin Oncol. 2019 May. PMID 30964716. [2]Knerr, et al. J Natl Cancer Inst. 2019 Feb. PMID 30753636.*

Polygenic Risk Scores & Colon Cancer

A recent study focused on how polygenic risk scores (PRS) may be related to colorectal cancers. Of note, PRS are calculated using genetic differences throughout someone's DNA, in combination with their clinical and family history of cancer. PRS, alongside environmental and lifestyle risk factors, may help to identify people who may benefit from screening at an earlier age.

Important facts about PRS include: (1) It does NOT look for changes in specific cancer predisposition genes, but rather looks at changes across many genes; and (2) It should NOT be used to diagnose hereditary cancer predisposition.

This study was based on over 12,000 individuals less than 50 years old who were compared to almost 96,000 individuals aged 50 or older. Findings showed that PRS were higher among younger individuals, as well as those with a family history of colorectal cancer. Although this type of information is not yet ready to use in clinical practice, it might someday help to identify those who may benefit from earlier screening or surgery. *Archambault, et al. Gastroenterology. 2020 Apr. PMID: 31866242.*

Ask the Expert

In each newsletter, we give participants the opportunity to have their questions addressed by experts in the field. This 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. If you have a question you would like addressed, please email the ICARE team at ICARE@inheritedcancer.net for consideration in future newsletters.

Q. How common is it for a genetic test result to be downgraded from a positive result to an uncertain result?

A. A pathogenic (or 'positive') test result means an individual has been identified with an inherited cancer gene mutation that places them at higher cancer risk. However, the issue of a positive result being downgraded was recently highlighted in *The Wall Street Journal* about a family who was tested in 2015 and found to have a positive *BRCA2* mutation that was later interpreted in 2019 as an uncertain result. Unfortunately, the knowledge of the mutation had prompted multiple family members to have preventive surgeries[1] which may not have been necessary. Downgrading of a positive test result to a variant of uncertain significance (VUS; unknown cancer risk) or a benign result (no increased risk for cancer) is very uncommon. In fact, a recent study by our group of 338 patients who had a positive result on cancer susceptibility testing showed that only 2% were downgraded to a VUS.[2] The majority of variant reclassifications are for uncertain results being downgraded to benign. Ultimately, these findings highlight the need for laboratories to share variant classification data, so it is easily accessible to everyone, including other laboratories. There are several websites with searchable databases of variant classification (ncbi.nlm.nih.gov/clinvar/ and clinicalgenome.org); however, this remains an issue as some laboratories will not share this data with the public. The American College of Medical Genetics (ACMG) continues to call on these laboratories to end the practice of maintaining proprietary classification databases and to begin publicly sharing this data.[3] When a test result is reinterpreted, a new report is issued by the laboratory and the ordering provider is notified. If you have been told that you have a positive (pathogenic) test result, it is very unlikely that this interpretation will change in the future.

[1]Marcus. WSJ. 2019 Dec. Available at: https://tinyurl.com/wksxknr; [2]Turner, et al. Genet Med. 2018 Jun. PMID: 29875428; [3]Marcus. WSJ. 2020 Jan. Available at: https://tinyurl.com/rpvq692

Community Spotlight

PTEN is one of the body's tumor suppressor genes, which controls cell growth. When a *PTEN* mutation is present, cells may grow uncontrollably, causing tumors to develop that may become cancerous. A patient born with a *PTEN* mutation is at high risk for developing breast, thyroid, kidney, colon, and endometrial cancer. My *PTEN* journey began after being diagnosed with thyroid cancer in 2009. This diagnosis, along with breast health issues and a family history of breast cancer, raised health concerns prompting me to consult a skilled genetic counselor where I learned I have a rare and underdiagnosed disease known as Cowden Syndrome or *PTEN* Hamartoma Tumor Syndrome (PHTS).

I was relieved to have a diagnosis yet overwhelmed about what would come next. Since the diagnosis, I have had two melanoma removal surgeries, a preventative hysterectomy, and preventative mastectomies. I also have annual colonoscopies due to polyposis (a *PTEN* outcome) and preventive kidney screenings. With hereditary cancer syndromes, it's essential to stay a step ahead; knowledge is power. I found that many physicians in my community had very little understanding of Cowden Syndrome and that getting a diagnosis is difficult. That, coupled with lack of educational information about PHTS, motivated me to start the PHTS Foundation in December 2013. I want people to know that if they have a large head and family history of cancer or autism, that is enough to consult their physician for *PTEN* testing. Patients are their own best advocates.

As a three-time cancer survivor and President of the PHTS Foundation, I work to raise funds for PHTS research and educate the public about PHTS. In my role, I am a twice-nominated Global Genes Champion of Hope, a top 10 Wego patient leader hero, and an inaugural member of Alabama's Rare Disease Advisory Council appointed by Governor Ivy. I was invited by Europe's Orphanet group to provide PHTS expertise for their disability project, and consistently work to advocate for *PTEN* families and all in the rare disease and hereditary cancer community by speaking about the importance of the patient experience and lobbying for policies that will benefit patients and families affected by genetic cancer syndromes. I am fortunate to have received top-notch care thus far, including current care by Dr. Galen Perdikis and the VUMC Breast Center care team for recent breast implant removal to DIEP breast reconstruction.

– Kristin Anthony, President and Founder of the *PTEN* Hamartoma Tumor Syndrome Foundation, from Huntsville, AL

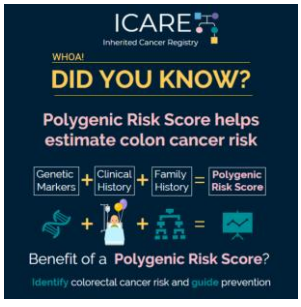
Featured Highlights

Since our last newsletter, we have featured over 50 informational posts on social media. We are grateful to our followers for their support and encourage you to consider liking or following ICARE on your favorite social media platform to obtain regular updates on treatment advances, cancer risks, and inherited cancer screening guidelines.

Below we have highlighted a few of our recent social media posts:

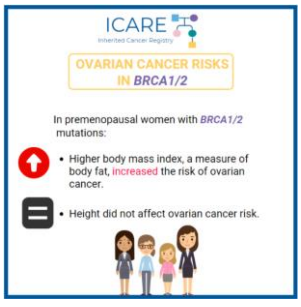
@INHERITEDCANCER

DID YOU KNOW?

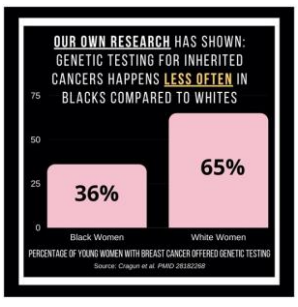


TREATMENT ADVANCES

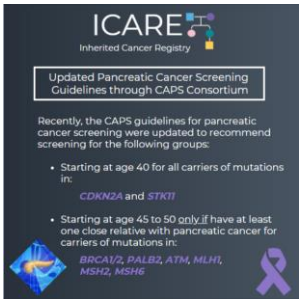
CANCER RISKS



RACIAL INEQUALITIES



GUIDELINE UPDATES



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