Fall 2021

ICARE NEWSLETTER

"To end the cycle of inherited cancer through research, education, and engagement"

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

Table of Contents

About ICARE

ICARE growth continued without pause over the past year, reaching over 4200 participants, including more than 1300 individuals with *BRCA1/2* mutations and more than 1000 individuals with other inherited cancer gene mutations. ICARE participants represent 50 U.S. states, the District of Columbia, and 22 other countries worldwide. If you have been affected by inherited cancer or are a provider caring for patients affected by inherited cancer, please visit our website (InheritedCancer.net) to learn more about ICARE and how participating in our efforts may benefit you.

FOLLOW US @INHERITEDCANCER

Welcome Message

The rapid pace of discoveries has enabled tremendous advances in inherited cancer care, including refining cancer risks, prevention approaches, and cancer treatments. These updates are incorporated into practice guidelines, including those recently released through the National Comprehensive Cancer Network (NCCN) and reviewed below. Alongside these advances is our responsibility to share this information with those it could benefit most, so we continue to focus on efforts to share information through ICARE, including posting regular updates through social media, providing resources to help share genetic information with family members (available at www.geneshare.net), and conducting research to evaluate web-based strategies to improve both cancer risk management and family sharing among those with inherited cancer gene mutations (additional details available at: https://inheritedcancer.net/impact-study/). These are both challenging and exciting times – we thank you for your partnership as we strive *"to end the cycle of inherited cancer through research, education, and engagement."*

Sincerely,

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

Updates to NCCN Genetic/Familial High-Risk Assessment

Breast, Ovarian, and Pancreatic Guidelines V.1.2022: *Released August 11th, 2021*

- The overall document was reorganized to help make it easier to find what you are looking for. Some highlights include:
  - 'Principles of Cancer Risk Assessment and Counseling' section was moved to the beginning (pages EVAL-A 1 to 7)
  - Testing criteria were substantially reorganized and put into a table format, divided into general criteria relevant to all cancers and cancer-specific criteria (starts on page Crit-1)
- Testing based on PARP inhibitor eligibility for earlier stage/high-risk *BRCA*-associated breast cancers (based on OlympiA trial results) was incorporated (page Crit-2)
- In recognition that many other NCCN guidelines include inherited cancer content, a list of guidelines was compiled that include a 'Principles' section, testing indications, and/or cancer risk management (bottom of page Crit-1)
- Gene-A table was updated as follows:
  - The information and order were revised to include absolute risk, management, and strength of evidence
  - Where available, type of breast cancer (or over-representation of specific type) was included
  - *CDH1* – added 'discussion of option for risk-reducing mastectomy'
  - Lynch Syndrome genes – ovarian cancer risks updated by gene
  - *STK11* – clarified that ovarian cancer risk is for non-epithelial (sex cord) tumors
- Added Gene-B table to list information on autosomal recessive conditions related to the inherited cancer genes listed in Gene-A table

Colorectal Cancer Guidelines V.1.2021: *Released May 11th, 2021*

- Lynch Syndrome: Extensive updates to cancer risks among individuals with Lynch Syndrome (specified by gene – *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*)
- Familial Adenomatous Polyposis: extensive revisions to duodenal findings and management
- Peutz-Jeghers Syndrome: section extensively revised
- Juvenile Polyposis Syndrome: section extensively revised
- Gene table (Table 3 – starting on page GENE-3) updated and revised

Check out the full NCCN guidelines by creating a FREE account at www.nccn.org

PALB2: Increasingly Recognized as the Third Most Important Inherited Breast Cancer Gene

In May 2021, a clinical practice resource was released by the American College of Medical Genetics and Genomics (ACMG) from a global team of cancer genetics specialists (*see figure*) to help guide the care of *PALB2* carriers.[1] *PALB2* is considered the third most important breast cancer risk gene, after *BRCA1* and *BRCA2*, with *PALB2* carriers at a substantially higher risk for developing female breast cancer and slightly higher risk for developing both pancreatic and ovarian cancer. Yet despite the emerging importance of the *PALB2* gene, there has been a lack of resources to guide care, which this guideline sought to address. This information was more recently highlighted in multiple news outlets, after *The New York Times* published an article entitled "This Breast Cancer Gene Is Less Well Known, but Nearly as Dangerous"[2] describing the importance of *PALB2* and referencing the ACMG practice resource.

Key recommendations included:

- Personalized risk estimates (e.g., CanRisk) should be used in guiding clinical management
- Prospective collection of *PALB2* patient clinical data should be used to establish clear metrics on treatment outcome and survival
- *PALB2* patients should be offered similar surveillance to *BRCA1/2*, modified according to individual risk
- Risk-reducing mastectomy can be considered as an option guided by personalized risk assessments
- Pancreatic cancer surveillance may be considered in the context of family history, ideally as part of a clinical trial
- Ovarian cancer surveillance should not be offered; risk-reducing salpingo-oophorectomy should include shared decision-making and should rarely be considered before age 50
- Given mechanistic similarities, *PALB2* patients may be considered for the same therapeutic regimens & trials as *BRCA1/2* patients

[1]Tischkowitz, et al. Genet Med. 2021 Aug. PMID: 33976419. [2]Berger. The New York Times. 2021 Aug. https://www.nytimes.com/2021/08/17/health/breast-cancer-palb2-brca.html

Prostate Cancer and *PALB2*

A new Polish study based on two specific founder mutations in *PALB2* reported that mutations in this gene may predispose to an aggressive, lethal form of prostate cancer.[1] The investigators studied *PALB2* prostate cancer risks, characteristics, and outcomes in almost 5,500 men with prostate cancer and compared them to over 8,000 cancer-free adults from Poland.

Their findings showed:

- no increase in prostate cancer risk in male *PALB2* carriers (Odds Ratio (OR): 1.38; p=0.45)
- high grade prostate cancers were more common in *PALB2* carriers versus non-carriers (64% vs. 18% with Gleason score ≥ 7; OR: 8.05 (95% CI: 3.57-18.15, p< 0.001))
- *PALB2* was associated with poor prostate cancer-specific survival

While these results are important, it remains to be seen whether *PALB2* mutations predispose to prostate cancer across all populations, or if this is a finding specific to the Polish population. In fact, a prior Polish study suggested that *PALB2* may be associated with aggressive forms of breast cancer with poorer outcomes.[2] These findings continue to require confirmation and are part of our efforts to study breast cancer characteristics and outcomes among *PALB2* carriers (https://inheritedcancer.net/palb2-study).

[1]Wokolorczyk, et al. Br J Cancer. 2021 Aug. PMID: 34006922. [2]Cybulski, et al. Lancet Oncol. 2015 Jun. PMID: 25959805.

Breast Cancer Risks Remain High in *PALB2* & *BRCA*

A new study found that lifetime breast cancer risk is 15% or more in female *BRCA1*, *BRCA2*, and *PALB2* carriers over age 65. This level of risk warrants consideration for continuing breast MRI.[1] These results are similar to those of a study **that included ICARE participants**,[2] which reported the risk of developing breast cancer remains high after age 60 in both *BRCA1* and *BRCA2* carriers, supporting continued cancer screening in older mutation carriers.

[1]Boddicker, et al. J Clin Oncol. 2021 Jul. PMID: 34292776. [2]Stjepanovic, et al. Breast Cancer Res Treat. 2021 Jun. PMID: 33423179.

Modifying Risks in *BRCA* Carriers

Breast cancer risks*:* A risk-reducing salpingo-oophorectomy (i.e., removal of both ovaries and fallopian tubes) in *BRCA* carriers was associated with a reduced risk of breast cancer within five years after surgery, with evidence of longer-term risk reduction among those with *BRCA1* variants.[1]

Ovarian cancer risks*:* A new study reported that the use of oral contraceptives reduced ovarian cancer risk in *BRCA* carriers,[2] with less frequent oral contraceptive use reported among carriers who were diagnosed with ovarian cancer. Specifically, 58.6% of *BRCA1* and 53.5% of *BRCA2* carriers who were diagnosed with ovarian cancer had ever used oral contraceptives, as compared to 88.9% and 80.7% of *BRCA1* and *BRCA2* carriers, respectively, who were not diagnosed with ovarian cancer. Additionally, those who developed ovarian cancer had used oral contraceptives for a shorter duration (median of 7 years) compared to those who did not develop ovarian cancer (median of 9 and 8 years for *BRCA1* and *BRCA2*, respectively).

[1]Choi, et al. JAMA Oncol. 2021 Apr. PMID: 33630024. [2]Schrijver, et al. Am J Obstet Gynecol. 2021 Jul. PMID: 33493488.

Inherited Cancer Treatment Updates

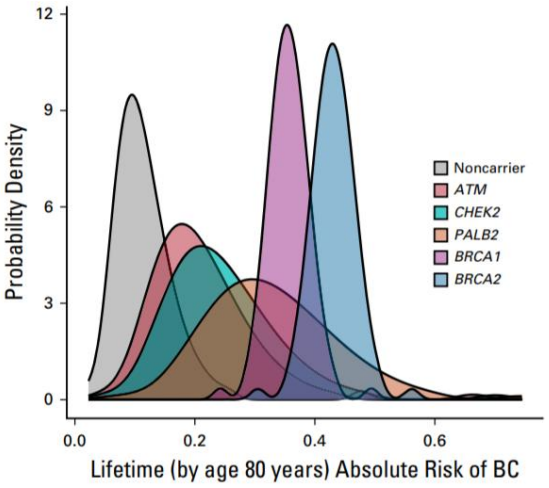
Early-stage, high-risk breast cancer in *BRCA* carriers: Results of the highly awaited phase 3 OlympiA trial showed promising results for EARLY STAGE (i.e., localized Stage 2-3) high-risk breast cancer patients with a *BRCA* mutation who were treated with a PARP inhibitor (olaparib) in the adjuvant setting (i.e., AFTER surgery).[1] Early-stage breast cancer in this trial was defined as those with at least Stage 2 triple negative disease or Stage 3 hormone receptor positive disease (with 4+ lymph nodes). Specifically, among women and men with early-stage breast cancer and a *BRCA* mutation who were given olaparib for 1 year after surgery, survival was better (86%) compared to those given placebo (77%) after 3 years of follow up. Based on this information, the American Society of Clinical Oncology (ASCO) released a rapid guidelines recommendation update for certain patients with hereditary breast cancer based on the research supporting the use of adjuvant olaparib in patients with early-stage, high-risk HER2-negative breast cancer and germline *BRCA* mutations.[2]

Ovarian cancers in *RAD51C* and *RAD51D* carriers: Results of a new phase 2 study suggest that *RAD51C* and *RAD51D* carriers with ovarian cancer may respond to a PARP inhibitor (rucaparib).[3]

Pancreatic cancer in *BRCA1*, *BRCA2*, or *PALB2* carriers: Results of a Phase 2 trial of a PARP inhibitor (rucaparib) for platinum-sensitive advanced pancreatic cancer showed potential benefit in those with either a germline or somatic mutation in *BRCA1*, *BRCA2*, or *PALB2*.[4]

[1]Tutt, et al. N Engl J Med. 2021 Jun. PMID: 34081848. [2]Tung, et al. J Clin Oncol. 2021 Aug. PMID: 34343058. [3]Swisher, et al. Nat Commun. 2021 May. PMID: 33941784. [4]Reiss, et al. J Clin Oncol. 2021 Aug. PMID: 33970687.

Polygenic Risk Scores and Breast Cancer Risks: *BRCA1/2*, *PALB2*, *CHEK2*, *ATM*, and beyond!



A recent study found use of a polygenic risk score (PRS) modified the estimated risk of breast cancer among both carriers and non-carriers of inherited breast cancer predisposition genes. Taking PRS into account, more than 95% of *BRCA1*, *BRCA2*, and *PALB2* carriers had greater than 20% lifetime risks of breast cancer. In contrast, among *ATM* and *CHEK2* carriers without a first-degree relative with breast cancer, proportions with a 20% or higher lifetime risk were 52.5% and 69.7%, respectively, whereas higher proportions with a 20% or higher risk were seen in those with a first-degree relative with breast cancer (78.8% and 89.9%, respectively). The authors suggest that incorporating PRS into breast cancer risk estimation may help identify greater than 30% of *CHEK2* and nearly half of *ATM* carriers who have less than a 20% lifetime risk for breast cancer and in whom breast MRI may not be needed. This suggests the **addition of PRS may prevent over screening** and enable personalized risk management approaches.

Gao, et al. J Clin Oncol. 2021 Aug. PMID: 34101481.

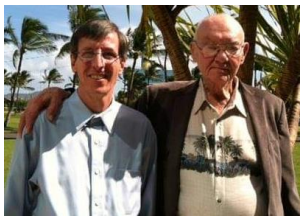
Ask the Expert

In each newsletter, we give participants the opportunity to have their questions addressed by experts in the field. This question was addressed by Kerry Schaffer, MD, medical oncologist at Vanderbilt University Medical Center with a focus on urological cancers.

Q. Is there enough information to consider using PARP inhibitors to treat inherited forms of prostate cancer?

A. Over the last few years, many studies have reported on the use of PARP inhibitors (PARPi) in advanced prostate cancer,[1,2,3] including men with inherited cancer gene mutations, but there still remains a need for larger more definitive studies. At the moment, the strongest data to support the use of PARPi is for *BRCA2* carriers; the data also support use in *BRCA1* and *PALB2* carriers. Finally, use may be considered in some of the other DNA repair genes, although conclusions about the impact of PARPi for these other genes remain preliminary[4] – these genes include *ATM*, *RAD51C*, *RAD51D*, *BARD1*, and *CHEK2*. These findings highlight the need for patients with prostate cancer to participate in clinical trials, so that over time we can better understand what treatments will work best for them. *[1]Adiba, et al. J Clin Oncol. 2020 Nov. PMID: 32795228. [2]de Bono, et al. N Engl J Med. 2020 May. PMID: 32343890. [3]Mateo, et al. Lancet Oncol. 2020 Jan. PMID: 31806540. [4]Abida, et al. Clin Cancer Res. 2020 Jun. PMID: 32086346.*

Community Spotlight



At the age of 51, my first and only colonoscopy revealed 100 polyps in my colon, rectum, and anus even though I had no symptoms or family history. I was immediately referred to a Certified Genetic Counselor at Tripler Army Medical Center in Hawai'i. Germline DNA testing revealed I had attenuated familial adenomatous polyposis (AFAP), due to an autosomal dominant germline mutation. After reading about AFAP to better prepare myself and learn the facts of AFAP, I wanted to have the surgery to remove my colon.

I embraced this diagnosis from the onset and have since joined various registries focused on inherited cancers, participated in live-case presentations, and have been selected to serve on advisory boards. Sharing my journey and being a source of inspiration is important to me. Shortly after my diagnosis, I created my mantra: *Always Forge Ahead with a Purpose*. This is a positive spin on a bleak diagnosis. My mindset is not to think of things I'm unable to control, such as medical conditions, but what I can control is my positive attitude. My vision is to establish national legislature jurisdiction designating the 4th week of March as Hereditary Colon Cancer Awareness Week. As of this year, Texas is the only state to designate this Awareness Week.

My purpose in life now is to educate the world about AFAP and the importance of early detection in hopes of saving lives, continuing the legacy of Dr. Henry T. Lynch.

- **Dan Dry Dock Shockley** (*pictured above on left with Dr. Lynch on right*)
  Retired U.S. Navy; Operation Desert Storm; Enduring & Iraqi Freedom veteran and 9-year hereditary colon cancer WARRIOR

Reducing Hereditary Cancer Act of 2021

Under current Medicare guidelines, only those with "signs, symptoms, complaints, or personal histories of disease" meet the criteria for medical services coverage. Thus, genetic testing is only covered for those already diagnosed with cancer, regardless of family history. If someone without cancer has an inherited mutation that increases cancer risk (e.g., *BRCA1/2*), Medicare may not cover recommended high-risk cancer screenings or risk-reducing procedures. While Medicare now covers certain cancer screenings for the "average risk" population, those at high-risk do not have recommended screening or prevention covered through Medicare.

The ***Reducing Hereditary Cancer Act*** was recently proposed to fix this problem and ensure Medicare beneficiaries have access to inherited cancer genetic testing as well as recommended screening and risk-reducing procedures, when medically necessary and appropriate. The bill was introduced in the House by Rep. Debbie Wasserman Schultz (D-FL-23) on June 23rd, 2021 and has secured bipartisan support.

For more information about this bill, please visit https://tinyurl.com/HR4110 and https://tinyurl.com/force-rhca2021. You may also watch FORCE's Community & Stakeholder Advocacy Briefing at https://tinyurl.com/force-rhca2021-briefing. Lastly, we encourage you to ask your elected representatives to support this important legislation! Find your representative at https://tinyurl.com/find-your-representatives.

Direct-to-Consumer (DTC) Tests: Not Reliable to Detect *BRCA1/2* Mutations

Researchers reported that single nucleotide polymorphism (SNP) tests, which are used by DTC tests such as 23andMe, are not reliable in identifying the majority of *BRCA1*/2 mutations or other inherited cancer gene mutations. The SNP test used by many DTC ancestry and DNA companies is designed to detect common traits many people share. However, when this test is used to identify rare mutations that contribute to disease (e.g., *BRCA1*/2 mutations), the study found it identified only 16% of nearly 5,000 rare mutations that could be confirmed by more stringent DNA testing/sequencing tools.

Authors of this study concluded:

- SNP-based tests are very unreliable to detect rare mutations
- These test results need to be confirmed in a clinical lab before being used to guide health decisions

To raise awareness about this topic, the team at Vanderbilt (Tuya Pal and Katie Lang) have partnered with MusiCares to host a free virtual educational session open to the public entitled 23 and Why Me, on **Wednesday, October 6th** at 1:30pm CT (11:30am PT, 2:30pm ET). During this 1-hour session, they will debunk myths related to DTC testing and other inherited cancer-related topics. Register for this free event at https://tinyurl.com/MusiCaresOct2021.

Weedon, et al. BMJ. 2021 Mar. PMID: 33589468.

RESOURCE SPOTLIGHT: National Cancer Institute's Cancer Genetics PDQ®

Looking for a place to get the latest curated information about inherited cancers? Look no further…

- Provide evidence-based summaries about inherited cancer genetics for health professionals and patients
- Summaries updated based on monthly review of published literature
- Written and maintained by a multidisciplinary Editorial Board of experts in medical genetics, oncology, and related specialties

Visit https://tinyurl.com/NCIPDQ and https://www.cancer.gov/publications/pdq/editorial-boards/genetics for more information

VANDERBILT-INGRAM CANCER CENTER

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