Spring 2022

ICARE Newsletter

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

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About ICARE

ICARE continues to grow rapidly, reaching almost 5,000 participants, including more than 1,350 individuals with *BRCA1/2* mutations and more than 1,300 individuals with other inherited cancer gene mutations. ICARE participants represent 50 U.S. states, the District of Columbia, and 24 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.

Join ICARE to Participate in New Research Efforts!

We have research efforts to:

- Improve the delivery of follow-up care for those with inherited cancer gene mutations by conducting a trial through which we provide FREE online resources.
- Better understand breast cancer development in those with *PALB2*, *ATM, CHEK2, BRCA1* and *BRCA2* mutations by performing MORE genomic testing on breast cancer tumors and saliva samples.

Join ICARE to be screened for these focused efforts!

Welcome Message

In these challenging times, we hope you and your loved ones are faring well – while the worst of the pandemic may be behind us, we remain unsettled as worldwide conflicts ensue and we hope for both peace and justice for those experiencing such unfair turmoil. The disparities experienced by populations worldwide have remained a consistent focus of our efforts, becoming more widely acknowledged across populations. In fact, a recent study reported the development of a model in Asians to more accurately predict the chance of a *BRCA* mutation.[1] Another study reported the development of a new model to predict breast cancer risk in Black women in the United States.[2] This is in contrast to prior models, which were developed in White women, yet used in Black women (which underpredicted risks). As we strive towards health equity across populations, I recently wrote an editorial to highlight the importance of promoting diversity in genomics research.[3] This is an ethical issue to ensure that all populations may benefit equally from genomic advances, such as predicting risks based on polygenic risk scores. Moreover, we need to ensure diversity in clinical trials participation, again to ensure that the results from these trials benefit us all, as highlighted by an editorial led by my colleague, Dr. Sonya Reid.[4]

ICARE has enabled us to conduct research focused on inherited cancers (*highlighted in the box to the left*). One of our studies is a trial that offers free online resources with the goal of improving care for those with inherited cancer (additional details available at https://inheritedcancer.net/impact-study). We and colleagues also continue to focus on *PALB2* research efforts to better understand breast cancer risks and outcomes. We have recently expanded these efforts to perform additional genomic studies on breast cancer tumors and germline DNA to learn more about breast cancer development in *PALB2*, *ATM, CHEK2, BRCA1* and *BRCA2* carriers. We hope that this type of work will lead to a better understanding of tumor development among those with inherited cancer and contribute to improving outcomes.

We sincerely thank our participants and providers for their ongoing support and partnership as we strive ***"To end the cycle of inherited cancer through research, education, and engagement"***. We regularly post newly released information on social media and have included links to our posts throughout this newsletter (*see references*), for anyone interested in checking these out!

With our sincere gratitude,

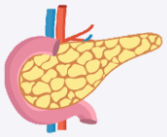
Tuya Pal, MD, FACMG on behalf of the ICARE Team

[1]Hong Ang et al. J Clin Oncol. 2022 Feb. PMID: 35143328. Social media post March 25th, 2022. Available at: https://tinyurl.com/post32522; [2]Palmer et al. J Clin Oncol. 2021 Dec. PMID: 34623926. Social media post December 23rd, 2021. Available at: https://tinyurl.com/post122321; [3]Pal. Genet Med. 2021 Nov. PMID: 34906472. Social media post January 18th, 2022. Available at: https://tinyurl.com/post011822; [4]Reid et al. ASCO Daily News. 2021 April. Available at: https://dailynews.ascopubs.org/do/10.1200/ADN.21.200499/full/.

ATM and Pancreatic Cancer

A new article reported that pancreatic cancer risks are more than 6-fold higher in individuals with an *ATM* mutation. Pancreatic cancer risks by age were:

- 1.1% by age 50
- 6.3% by age 70
- 9.5% by age 80



Hsu, et al. JAMA Oncol. 2021 Sep. PMID: 34529012. Social media post October 1st, 2021. Available at: https://tinyurl.com/post100121.

CDH1 and Stomach Cancer

A recent study of women with hereditary lobular breast cancer due to *CDH1* mutations found high rates of undetected stomach cancer (with signet ring features). The findings suggested that among *CDH1* carriers, there were very high risks for stomach cancer, even when family history of stomach cancer was absent.

Gamble et al. JAMA Surg. 2021 Oct. PMID: 34643667. Social media post January 11th, 2022. Available at: https://tinyurl.com/post11122.

Li-Fraumeni Syndrome and Cancer Risks

A new study reported on differences in the *TP53* mutations between patients who met vs those who did not meet Li-Fraumeni Syndrome (LFS) testing criteria. Several variants were identified multiple times in those who did and did not meet LFS clinical criteria: p.R175, p.G245, p.R248, p.R273, and p.R282. Other variants were exclusively found in those in the LFS group: p.M133T, p.P152L, p.C275Y, p.C275*, p.R337C, p.R342*, and p.R342P. One variant was exclusively found in patients with attenuated (meaning less cancers seen) LFS: p.R110L. Those who met LFS genetic testing criteria were more likely to have early adrenal, brain, connective tissue, and bone tumors; in contrast, those who did not meet the criteria were more likely to have breast and other cancers (including lung, ovarian, kidney, and pancreatic cancers), with almost half of the cancers occurring after the age of 45.

Kratz, et al. JAMA Oncol. 2021 Dec. PMID: 34709361. Social media post December 21st, 2021. Available at: https://tinyurl.com/post122121.

Polygenic Risk Scores and Inherited Breast Cancer Genes: *BRCA1/2, PALB2, CHEK2, & ATM*

Breast MRIs are advised in women with >20% lifetime risk of breast cancer. A new study showed that breast cancer risks in *BRCA1*, *BRCA2* and *PALB2* carriers remained higher than 20%, regardless of whether polygenic risk scores (PRS) were done, suggesting this is of limited help in refining screening. In contrast, PRS downgraded breast cancer risks to <20% in about 1/3 of *CHEK2* carriers and almost half of *ATM* carriers, meaning screening may not be needed. This information may be used in the future to prevent over-screening and refine cancer risk management.

Gao et al. J Clin Oncol. 2021 Aug. PMID: 34101481. Social media post February 8th, 2022. Available at: https://tinyurl.com/post20822.

Lynch Syndrome and Prostate Cancer

A new study suggests men with certain *MSH2* and *MSH6* mutations have higher risks of prostate cancer and may be candidates for PSA screening.

Bancroft et al. Lancet Oncol. 2021 Nov. PMID: 34678156. Social media post December 17th, 2021. Available at: https://tinyurl.com/post121721.

BRCA1/2 and Male Cancer Risks

A recent international study found that male *BRCA1* and *BRCA2* carriers have a higher risk for breast, pancreatic, and stomach cancer. Additionally, male *BRCA2* carriers were found to have higher risks for prostate cancer. See the below table for the specific risk levels:

Cancer Type	*BRCA1*		*BRCA2*	
	Relative Risk	Absolute Risk to Age 80	Relative Risk	Absolute Risk to Age 80
Male Breast	4.3 fold	0.4%	44 fold	3.8%
Pancreatic	2.4 fold	2.9%	3.3 fold	3.0%
Stomach	2.2 fold	1.6%	3.7 fold	3.5%
Prostate	~	~	2.2 fold	27%

Li et al. J Clin Oncol. 2022 Jan. PMID: 35077220. Social media post January 28th, 2022. Available at: https://tinyurl.com/post12822.

BRCA1/2: Oral Contraceptives and Breast Cancer

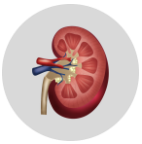
A new study found that among *BRCA1/2* carriers, oral contraceptive use strongly lowered cancer risk over one's lifetime, even though at first, they raise risks of breast, ovarian, and endometrial cancer.

Schrijver et al. J Natl Cancer Inst. 2022 Jan. PMID: 35048954. Social media post February 15th, 2022. Available at: https://tinyurl.com/post21522.

Inherited Cancer Treatment Updates

Lynch Syndrome Carriers with Advanced Uterine Cancer: Treatment with Pembrolizumab

Women with Lynch Syndrome are at high risk for uterine cancer. The type of uterine cancer they develop has the tumor characteristic of being 'MSI-H'. A new study indicated treatment with pembrolizumab (Keytruda) resulted in benefit in patients with MSI-H advanced uterine cancer.[1]

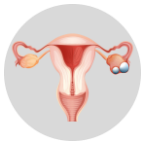


Von Hippel-Lindau Patients: Treatment of Tumors with Belzutifan

On August 13th, 2021, the U.S. Food and Drug Administration (FDA) approved belzutifan (Welireg), for adult patients with von Hippel-Lindau (VHL) disease who need to be treated for renal cell cancer, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumors not requiring immediate surgery. A recent study reported that belzutifan was a useful treatment in patients with renal cell carcinoma who have VHL disease.[2]

BRCA1/2 Carriers with Early-Stage Breast Cancer: Treatment with Olaparib

On November 30th, 2021, the FDA granted priority review to olaparib for adjuvant treatment of certain patients with high-risk breast cancer. This applies to the use of the agent by patients with *BRCA*-mutated, HER2-negative, high-risk early breast cancer who received chemotherapy before or after surgery.[3]



BRCA1/2 Carriers with Ovarian Cancer: Maintenance with Olaparib

A new study suggests that olaparib (PARP-inhibitor) for maintenance therapy for 2 years in *BRCA* carriers with newly diagnosed advanced ovarian cancer extended survival as follows - median progression-free survival in the olaparib group was 56.0 months compared to the placebo group where it was 13.8 months.[4]

[1]O'Malley et al. J Clin Oncol. 2022 Jan. PMID: 34990208. Social media post March 1st, 2022. Available at: https://tinyurl.com/post30122; [2]Jonasch, et al. N Engl J Med. 2021 Nov. PMID: 34818478. Social media post January 21st, 2022. Available at https://tinyurl.com/post12122; [3]Social media post December 6th, 2021. Available at: https://tinyurl.com/post120621; [4]Banerjee et al. Lancet Oncol. 2021 Dec. PMID: 34715071. Social media post January 4th, 2022. Available at: https://tinyurl.com/post10422.

Ask the Expert

The below question was addressed by ICARE Founder, Dr. Tuya Pal, and her oncology colleague, Dr. Sonya Reid. Dr. Pal is a Professor of Genetic Medicine, Ingram Professor of Cancer Research, and the Associate Director for Cancer Health Disparities at Vanderbilt-Ingram Cancer Center. Dr. Reid is an Assistant Professor of Hematology/Oncology at Vanderbilt University Medical Center. Drs. Pal and Reid work in collaboration to better understand inherited breast cancer and cancer health disparities.

Tuya Pal, MD, FACMG

Sonya Reid, MD, MPH

What specific types of breast cancer occur in inherited breast cancers? Does having an inherited form of breast cancer affect survival?

For a long time, we have known that most breast cancers in *BRCA1* carriers are triple negative, which are also more common in *BRCA2* and *PALB2* carriers, even though they do not make up most breast cancers in these women. A recent international study showed that breast cancer pathology and other clinical features differ by inherited breast cancer gene,[1] as shown in the table.

Gene	Breast Cancer Characteristic
RAD51C *RAD51D* *BARD1*	Associated with triple-negative breast cancer (TNBC)
CHEK2	Less often associated with TNBC
BRCA1	Higher risks of TNBC
BRCA2 *PALB2*	All breast cancer subtypes seen, with slight over-representation of TNBC
ATM	Associated with high-grade triple-positive breast cancer
CHEK2	Associated with hormone receptor negative, HER2-positive disease
TP53	Associated with HER2-positive disease, with or without hormone receptor positivity

We have also been looking at this question in ICARE participants, and have found similar results, which we presented at the Annual American College of Medical Genetics (ACMG) Meeting.[2] Beyond the tumor characteristics, we are trying to better understand the genomics of tumors in individuals with breast cancer and an inherited breast cancer gene and are in the process of conducting a study to learn more about these cancers. This information could tell us more about how these tumors develop and give us more clues about how to best treat them. **We are grateful to our ICARE participants, who have made these efforts possible!**

Regarding survival for inherited forms of breast cancer, most studies to date have suggested that outcomes of these women do not differ from women with sporadic breast cancer. Most recently, a study found there were BETTER short-term outcomes among women with triple-negative breast cancer and *BRCA1* or *BRCA2* mutations (which was also seen in those with ovarian cancer and *BRCA2*, *BRIP1*, *RAD51C*, or *ATM* mutations). These findings may be reassuring to individuals with inherited gene mutations related to breast and ovarian cancer.[3]

[1]Breast Cancer Association Consortium. JAMA Oncol. 2022 Jan. PMID: 35084436. Social media post February 1st, 2022. Available at: https://tinyurl.com/post20122; [2]Shah et al. Breast Cancer Characteristics Among Women with Hereditary Breast Cancer. 2022 ACMG Annual Clinical Genetics Meeting, Nashville, TN. Abstract available at https://tinyurl.com/ACMGeP059; [3]Kurian et al. J Natl Cancer Inst. 2021 Aug. PMID: 34373918. Social media post February 18th, 2022. Available at: https://tinyurl.com/post21822.

Community Spotlight

Stefanie Curtiss & Meghan Durrick

Genetic testing sounded like a futuristic concept when it originally came to our attention. It sounded something to the likes of cloning. We didn't really understand what it was and why it was important, but rather thought it sounded like something out of science fiction. Thankfully, our medical providers and genetic counselors stuck with us until we understood the benefit.

Growing up, our family was blessed and untouched by cancer. We didn't have any immediate family members treated for or diagnosed with cancer in our childhoods. We were familiar with the term cancer but didn't know what it MEANT. That all changed in our early 20s when our mother was diagnosed with uterine cancer. She had already been through menopause and therefore knew when she had bleeding that something was wrong. We often wonder what would have happened if she had been younger when the cancer occurred, and she didn't have that indicator?

Thankfully, our mother was an employee at Vanderbilt, where she was referred to the genetic department for genetic counseling and testing and was diagnosed with Lynch syndrome due to an *MSH6* mutation. We met with the genetic counselor at that time who did a great job in explaining what it meant if we had a mutation and encouraged us to get tested. This was in the early 2000s, when testing was thousands of dollars; and we were also worried that if we had the mutation, it could be considered a pre-existing condition for insurance companies. These concerns and being frightened to hear we were potentially predisposed to cancer led to our decision to not move forward with testing.

Our mother battled her uterine cancer and recovered. Later, she was diagnosed with kidney cancer and even later still melanoma. This temporarily caused us to bury our heads in the sand even further. However, eventually as our 20s turned into our 30s we realized this was something we shouldn't ignore. Insurance now covers the testing. Law states that you can't consider it a pre-existing condition. Our excuses were being removed and we decided it was time to move forward and see if we also had the mutation. Stefanie was the first to meet with the genetic counselor. Testing was so easy, they used saliva, so no blood was even needed to be drawn. Shortly after, the results came in that Stefanie had inherited the *MSH6* gene mutation from our mother. Being identical twins, Meghan knew she also had this mutation, even before she was tested mainly as a formality.

Although the initial diagnosis of having an *MSH6* mutation was scary, we realize it is scarier not to know. Since the diagnosis, we are now screened every year with colonoscopies and kidney screenings because of our family history. We both recently had our uterus and ovaries removed preventatively. We have an older sister who recently decided she also wants to get tested. We are so grateful and feel at peace that we can be prepared to minimize the impact any potential cancer diagnosis has on our lives thanks to our doctor's monitoring and care. If cancer shows up, we are now READY!

› **Stefanie Curtiss & Meghan Durrick**

Stefanie now has two workshops a year on the benefits of genetic testing. Meghan now acts as an advocate for those who don't have access to affordable healthcare and/or are afraid to explore their medical needs.

Reducing Hereditary Cancer Act of 2022

On February 16th, 2022, the ***Reducing Hereditary Cancer Act*** (S.3656) was introduced to the U.S. Senate with the goal of ensuring Medicare beneficiaries have coverage for potentially life-saving inherited cancer genetic counseling and testing as well as recommended screening and risk-reducing procedures, when medically necessary and appropriate. Currently, Medicare only covers genetic testing for beneficiaries *already diagnosed with cancer*, regardless of whether there is cancer or a known genetic mutation in the family. Therefore, if someone without cancer is found to have an inherited mutation that increases cancer risk (e.g., *BRCA1/2*), Medicare may not cover the recommended cancer screenings and/or risk-reducing surgeries.

Help ensure these life-saving services are accessible to Medicare patients by emailing members of Congress to ask them to support this important bill at https://tinyurl.com/RHCACQ. For more information about this bill, please visit https://tinyurl.com/BillS3656 and https://tinyurl.com/FORCERHCA.

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…

Provides summaries about inherited cancers, written and maintained by a multi-disciplinary Editorial Board of experts in genetics, oncology, and other specialties

Summaries updated monthly and are currently available on multiple cancer types, with additional summaries under development

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