Fall 2023

ICARE NEWSLETTER

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

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About ICARE

ICARE has continued to grow rapidly, with over 6,000 participants, including over 1,500 *BRCA1/2* carriers and more than 1,200 other inherited cancer gene carriers. ICARE participants represent all 50 U.S. states, the District of Columbia, Puerto Rico, and 28 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 see if you may want to participate in our efforts.

Follow us @inheritedcancer

Welcome Message

We have many interesting updates to share with you, and sincerely thank you for your partnership with us, whether as a participant or a provider. We continue to contribute to advances in the field of inherited cancer because of your support and have outlined some of the recent research studies in which ICARE participants were included within this newsletter.

Additionally, we all know that family history is very important in refining care – to make it easier to collect and update family history, we have developed a family history drawing tool, through which we can email an automatically generated family tree after our family history questionnaire is completed. Please reach out to us if this may be of interest to you and we will send you a direct link to complete the questions, after which we will automatically draw out and send you your updated family tree.

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."*

With our sincere gratitude,

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

National Comprehensive Cancer Network (NCCN) Guidelines Updates

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

Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Cancer

Released August 28th, 2023 (V1.2024)

- Transgender, Non-Binary, and Gender Diverse Individuals: NEW section on care (Page 63-66, TNBGD-1 to 4)
- Li-Fraumeni Syndrome: Significant updates to content (risks and care) (Pages 57-60, LIFR-A): Table added to guide work up and management, based on etiology; colonoscopy recommendation revised; PSA screening (prostate) added; and pediatric cancer screening recommendations added
- *PTEN:* Mammogram age for females changed from 35 to 30 (Page 61, COWD-A 1 of 2)

GENE-A Table (Pages 38-46)

- *ATM/CHEK2* Male Carriers: Added consideration of prostate cancer screening starting at age 40
- *CHEK2* I157T: Stated that additional cancer risk management solely based on this variant is NOT recommended
- *PALB2:* Age at which to consider removing ovaries and fallopian tubes (risk-reducing salpingo-oophorectomy) changed from 45 to 45-50; added that for males, consider screening for breast cancer similar to *BRCA1* (consider annual mammograms at age 50); and range of pancreatic cancer risk revised to 2-5%

Genetic/Familial High-Risk Assessment: Colorectal Cancer

Released May 30th, 2023 (V1.2023)

- At a minimum, the following colorectal cancer genes should be included on multi-gene panel testing: *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *BMPR1A*, *SMAD4*, *PTEN*, *STK11*, & *TP53*
- Addition of MSI/IHC concordance data (*see table below*)

CRC: MSI vs IHC – High Concordance HIGH (99.1%)	MSI	IHC
Sensitivity	92.9%	88.9-92.4%
% time limited by small tumor size	14%	0.3%

- Addition of NEW gene/syndrome: ***MBD4*-associated neoplasia syndrome**

NTHL1 tumor syndrome (biallelic)

- Breast cancer risks modified: Revised text to indicate risk may be elevated; however, there is not enough data yet to support increased breast cancer surveillance
- Removed: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 (now aligns with Breast, Ovarian, and Pancreatic guidelines)
- For duodenal cancer: Added baseline upper endoscopy (including complete visualization of the ampulla of Vater) beginning at age 30–35

Mammograms: New U.S. Preventive Services Task Force (USPSTF) Recommendations

On May 9th, 2023, the USPSTF published a new draft recommendation for all cisgender women and those assigned female sex at birth to do mammograms from ages **40** to 74, every **two** years, for those at average (population) risk for breast cancer. This change in recommendation is due to recent troubling trends, including an increase in the number of cancers diagnosed before age 50, as well as a failure to narrow the gap in survival in younger Black women who die of breast cancer twice as often as White women of the same age.

U.S. Preventive Services Task Force. Breast Cancer: Screening. Accessed May 9th, 2023. Available at https://tinyurl.com/USPSTFbreastcancerscreening. Social media post May 10th, 2023. Available at https://tinyurl.com/post5102023.

Recommendations for Inherited Ovarian Cancer Genes: United Kingdom (UK)

Through consensus, management recommendations were developed in the UK for females with pathogenic variants in the following inherited ovarian cancer genes: *RAD51C*, *RAD51D*, *BRIP1*, and *PALB2*.

Hanson, et al. J Med Genet. 2023;60(5):417-429. PMID: 36411032. Social media post September 26th, 2023. Available at https://tinyurl.com/post9262023.

BRCA1 and *BRCA2* Carriers: Cancer Risks with Oral Contraceptive Use

Among female *BRCA1* and *BRCA2* carriers, a recent study found that oral contraceptive use is associated with:

- Raised risk of breast cancer, but only in those using for over 5 years (relative risk: 1.25)
- Lower risk of ovarian cancer (nearly cut in half)

Park, et al. Carcinogenesis. 2022;43(3):231-242. PMID: 34958358. Social media post July 6th, 2023. Available at https://tinyurl.com/post7062023.

Tamoxifen and Breast Cancer Risk in Women with a *BRCA1* or *BRCA2* Mutation

In a study of female *BRCA* carriers, **including ICARE participants**, those that used tamoxifen and/or raloxifene were compared to those that did not. After an average follow-up time of almost 7 years, 10.9% of those in the tamoxifen/raloxifene group were diagnosed with breast cancer, compared to 14.3% in the group that did not use these drugs. This study suggests that chemoprevention through use of tamoxifen and/or raloxifene may work to reduce risks for breast cancer in *BRCA* carriers, but more studies with longer follow-up are necessary.

Kotsopoulos, et al. Breast Cancer Res Treat. 2023;201(2):257-264. PMID: 37432545.

Newly Released ACMG Clinical Practice Resource on *CHEK2* Developed Through a Group of Worldwide Experts!

A person with a pathogenic variant in the *CHEK2* gene may be at an increased risk for developing breast and other cancers. This ACMG Clinical Practice Resource, published in ACMG's flagship journal, *Genetics in Medicine*, provides valuable information for healthcare providers caring for individuals with pathogenic variants in the *CHEK2* gene.

This new ACMG Practice Resource points out that while *CHEK2* has largely been considered a "moderate risk" breast cancer gene, the distinction is blurred with risk being on a continuum, ranging from low to moderate to high risk. It states that the association of cancer risk with *CHEK2* variants is also complex and is influenced by a number of factors, including the specific variant, family history, non-*CHEK2* genetic background, and other factors. Therefore, personalized (rather than generalized) risk must be assessed by a specialist in cancer genetics and take into account family and personal history, the specific variant(s), and other risk factors. Early cancer detection, surveillance, prevention, and clinical decisions should then be guided by these personalized risk estimates and shared decision making. Seeking consultation with a healthcare provider with expertise in cancer genetics and genetic counseling is recommended.

Hanson, et al. Genet Med. 2023:100870. PMID: 37490054. Social medica post September 27th, 2023. Available at https://tinyurl.com/post9272023. Read the ACMG press release at: https://tinyurl.com/yvammhzt

Fertility Treatment in *BRCA* Carriers: Breast Cancer Risk

A recent study among female *BRCA* carriers showed risk of breast cancer was not significantly raised through fertility treatment, which is reassuring. There remains a need to further study this question in more detail, for associations with breast cancers across different breast cancer subtypes, including breast cancers that are hormone-related and breast cancers that are hormone receptor-positive.

Liu, et al. Front Endocrinol (Lausanne). 2022;13:986477. PMID: 36176466. Social medica post August 7th, 2023. Available at https://tinyurl.com/post8072023.

Are *BRCA2* Carriers at Higher Risk for Melanoma?

At present, we are not sure because results from different studies have been inconsistent[1]. For instance, one study among 173 families with a *BRCA2* mutation found a 2.6-fold risk of developing melanoma[2]; however, another study of 139 Dutch families with a *BRCA2* mutation revealed a lower than general population risk for melanoma[3]. These inconsistent findings emphasize the need for additional research on melanoma risk among *BRCA2* carriers.

[1]Gumaste, et al. Br J Dermatol. 2015;172(6):1498-1506. PMID: 25524463. [2]Breast Cancer Linkage Consortium. J Natl Cancer Inst. 1999;91(15):1310-6. PMID: 10433620. [3]van Asperen, et al. J Med Genet. 2005;42(9):711-9. PMID: 16141007.

Genes Associated with Aggressive Prostate Cancer

A new study of almost 18,000 men with prostate cancer showed that inherited mutations in the *BRCA2*, *ATM*, and *NBN* genes were strongly associated with aggressive prostate cancer. Less strong associations were seen for inherited mutations in the *MSH2*, *XRCC2*, and *MRE11A* genes. The findings of this study suggest that knowing about inherited genes that raise the risk for prostate cancer can help guide treatment, because even men with non-aggressive prostate cancer who have these inherited mutations are at higher risk to develop advanced disease.

Darst, et al. JAMA Oncol. 2023. Online ahead of print. PMID: 37733366.

Germline *EGFR* Mutations and Familial Lung Cancer

A study, in which our Vanderbilt colleagues Georgia Wiesner, MD, MS (geneticist) and Kelly Taylor, MS, LCGC (genetic counselor) participated, was recently published about the inherited T790M *EGFR* mutation. Mutations in this gene lead to a higher risk of lung cancer and were found to be more common in the Southeast United States where there was shown to be a 'founder effect' (meaning that the mutation was more common because it came from a common ancestor hundreds of years ago and became more common in the population over time). Over half of individuals with this mutation were affected with lung cancer. This study demonstrates the importance of this *EGFR* mutation to lead to both a higher risk of lung cancer, as well as lung nodules. These findings also highlight the importance of identifying individuals and their family members to investigate lung cancer screening (through CT scans) in these individuals.

Oxnard, et al. J Clin Oncol. 2023. Online ahead of print. PMID: 37579253.

Healthcare Delivery

A recent study, **based on ICARE participants**, found that getting care according to guidelines depends on what the healthcare provider recommends, as well as how much trust the patient has in their care. This study shows us how important it is to find ways to improve knowledge among healthcare providers and trust in care among patients!

Dean, et al. Genet Med. 2023;100945. PMID: 37515473. Social medica post August 4th, 2023. Available at https://tinyurl.com/post8042023.

BRCA-associated Prostate Cancers

On April 28th, 2023, the FDA approved olaparib plus abiraterone acetate for first line treatment for metastatic castration-resistant prostate cancer, but only in patients whose tumors have *BRCA* mutations. Although a broad indication for the combination therapy was desired, concerns about the trial design were raised, and the phase III results did not explicitly show that patients without a *BRCA* mutation would benefit.[1]

On August 11th, 2023, the FDA approved the use of niraparib and abiraterone acetate with prednisone in treating patients with *BRCA*-mutated castration-resistant prostate cancer. The green light comes backed by the robust efficacy data from the MAGNITUDE trial.[2]

[1]U.S. Food and Drug Administration (FDA). FDA Briefing Document: NDA 208558/Supplement 25. 2023. Available at www.fda.gov/media/167483/download. Social medica post June 16th, 2023. Available at https://tinyurl.com/post6162023; [2]Chi, et al. J Clin Oncol. 2023;41(18):3339-3351. PMID: 36952634. Social medica post August 24th, 2023. Available at https://tinyurl.com/post8242023.

Ask the Expert


Kelly Taylor, MS, LCGC

This question was addressed by Kelly Taylor, MS, LCGC, a licensed and certified genetic counselor with expertise in research genetics and hereditary cancers at the Vanderbilt Hereditary Cancer Clinic. If you have a question you would like addressed, please email the ICARE team at ICARE@vumc.org for consideration in future newsletters.

Q: I have Lynch Syndrome and an *MLH1* mutation. I saw a blood test to detect cancer early on TikTok. Are you familiar with this test and can you give me advice on if this is something I could have?

A: A ctDNA test is a test that looks for circulating tumor DNA in a person's blood. If a person has cancer, as cancer cells go through their life cycle, pieces of the DNA from the cancer cells can enter a person's blood. A ctDNA test looks for these pieces of DNA in a person's blood. Testing can be done for different reasons. It can be done to see if a person who has already been diagnosed with a cancer to see if their cancer may have returned or may have spread. It can be done in a person who has not been diagnosed with cancer to see if they might have cancer.

This type of test is not approved by the FDA for people who have not been diagnosed with cancer. More research is needed before this type of test can be used for people who have not had cancer. The test can have false negatives – meaning the test is normal, but the person does in fact have a cancer. If the person is not having standard cancer screening, like colonoscopies, then a cancer could be missed. The test can also have false positives – meaning the test is positive, but the person does not have cancer. This could lead to follow-up tests that are not needed such as x-rays or scans that might not be covered by insurance; and to anxiety about the possibility of having cancer, even when scans are not able to find anything.

At this time, insurance is unlikely to pay for this test since it would be considered experimental, so you would most likely have to pay for this out of pocket. Even if a patient has the test and pays for it themselves, insurance may not pay for follow-up after a positive test. Regardless of what you decide, it is important that you continue to have the standard recommended screening for Lynch Syndrome (like colonoscopies).

Additional readings that may be helpful include: [1]Carr DJ, Welch HG. JAMA Intern Med. 2023;183(10):1144-1151. PMID: 37639262; [2]Connal S, Cameron JM, Sala A, Brennan PM, Palmer DS, Palmer JD, Perlow H, Baker MJ. J Transl Med. 2023;21(1):118. PMID: 36774504; [3]Ignatiadis M, Sledge GW, Jeffrey SS. Nat Rev Clin Oncol. 2021;18(5):297-312. PMID: 33473219.

Community Spotlight

Cheryl Livingston

My paternal grandparents were my heroes. Wise beyond their time, they relished teaching our family that knowledge is power, health is everything, and love is unconditional. Back then, *Prevention* health magazine and vitamin supplements filled their mailbox and 1960's exercise guru Jack LaLane, and health food advocate Euell Gibbons, beckoned new followers from a talking picture box in the living room. Eavesdropping on adult conversations around their Sunday dinner table was a sport. When their voices lowered, and their eyes bowed, I'd freeze, waiting to hear the word "CANCER" whispered from their tight lips, followed by the name of a person somehow acquainted.

In a blink, my paternal grandpa, who had been a poster child of a life led healthy and clean, was dead from melanoma. Pancreatic cancer swiftly stole the life from my paternal grandma, just a few years later. Looking back at our family tree, both the maternal and paternal branches quivered under the weight of serious cancers – great-grandparents, four grandparents, great uncles, great aunts, father, mother, sister, uncles, aunts, first and second cousins. Cancer had rotted our family tree to the core.

At age 40, my sister (*I'm the oldest of four girls*), and later my mother, were each diagnosed with lobular breast cancer. Six months after mom's diagnosis she was gone, having unexpectedly flatlined in the ER, from an unknown cause. One less loved one to break the news to that, only days before, I was inducted into the "you have cancer" club, specifically early-stage ductal breast cancer. Now what? My mind hadn't considered that my type of breast cancer would be different from theirs. Hoping for better insight, I paid a visit to Vanderbilt's Hereditary Cancer Clinic.

There, they tested me for many inherited cancer genes, but no *BRCA* gene mutation was found nor were mutations found in any other genes at this time that would explain the cancers in my family. My sister, who also beat her breast cancer, was proven *BRCA* negative, back in the day. It's been suggested she be retested, even for the *BRCA* mutations again, as much has changed in the past 20+ years, but she has chosen not to test again. There is a weight to knowing some things. Once we've opened that proverbial envelope of test results, for better or worse, we are responsible for management and stewardship of caring for that knowledge, for the rest of our lives. So, with much respect, I want to emphasize choosing not to know is also power…and my grandparents would be proud their teachings had not been lost on us.

– Cheryl Livingston

Inherited Cancer Research Efforts

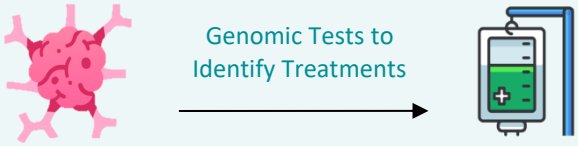
Enroll in ICARE if you are interested in being considered for the below studies and many other current efforts!
*Participation is easy and can be completed online at **https://redcap.link/ICAREconsent** or by scanning the QR code.*

Genomic Characterization of Breast Cancer: *BRCA1/2, PALB2, ATM,* and *CHEK2*

Objective: Perform genomic analyses to better understand how breast cancer tumors develop to identify additional treatment options and improve health outcomes.

Eligibility: Invasive breast cancer and a confirmed positive result in *BRCA1*/2, *PALB2*, *ATM*, and/or *CHEK2*.

Progress: Over 150 breast cancer tumors from ICARE participants have been sent for additional tumor genomic analyses.

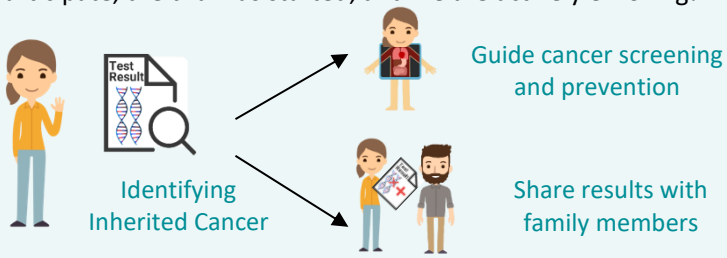


IMProving Care After Inherited Cancer Testing (IMPACT) Study

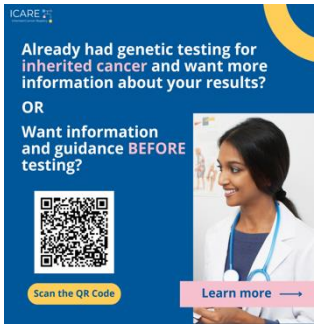
Objective: To improve follow-up care after genetic testing for those with a positive result.

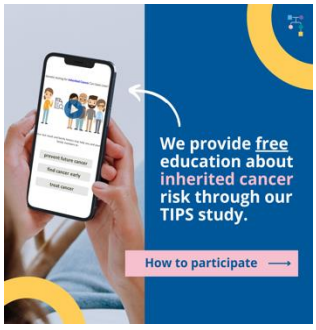
Eligibility: Mutation in an inherited cancer predisposing gene.

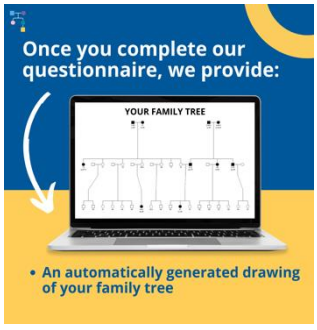
Progress: Hundreds of ICARE participants have been invited to participate, the trial has started, and we are actively enrolling!

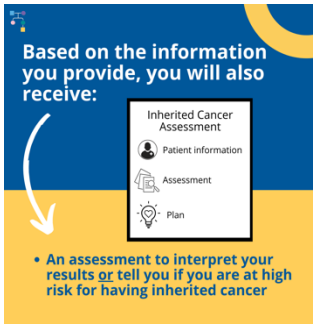


*Enroll in TIPS to receive free education and assessment about inherited cancer risk by scanning the QR code or visiting **https://redcap.link/TIPS***









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