Spring 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 more than 5,600 participants including over 1,500 *BRCA1/2* carriers and more than 1,000 other inherited cancer gene carriers. ICARE participants represent all 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 see if you might want to participate in our efforts.

Follow us @inheritedcancer

Welcome Message

Discoveries relevant to those with or at risk for inherited cancers continue to progress at a rapid pace. Studies to which we, as part of ICARE-related efforts, have contributed or led include a study outlining cancer risks in older females with a *BRCA* mutation;[1] a research letter about risk-reducing mastectomies among female ICARE participants which suggests possible overtreatment in some cases;[2] and testing a web-based inherited cancer educational tool to provide education about inherited cancers in young Black females with breast cancer.[3] Additional studies currently available through participating in ICARE include a clinical trial to test free online resources to improve care in those with inherited cancer gene mutations (additional details available at https://inheritedcancer.net/impact-study). We are also studying breast cancers in women with *BRCA1*, *BRCA2*, *PALB2, ATM*, and *CHEK2* mutations by conducting free genomic testing in breast tumor samples. We have already completed testing in ~100 tumors and are halfway to reaching our goal of testing 200 samples. This study is a step to better understand how these tumors develop and to help identify additional treatment options in the future.

We also encourage you to check out our YouTube channel (youtube.com/@inheritedcancer), where we have posted many talks from inherited cancer experts who have generously shared their expertise with us. This includes a recent talk on the CanRisk tool, given by Dr. Antonis Antoniou from Cambridge University in the United Kingdom (youtube.com/watch?v=yBLeaUBWkmo). CanRisk is a publicly available web-based tool to generate personalized breast and ovarian cancer risks based on personal and family history and genetic test results (canrisk.org/canrisk_tool/).

Finally, 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 ICARE participants an automatically generated family tree after they complete the family history questions. 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 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

[1]*Metcalfe et al. Cancer. 2023;129(6):901-907. PMID: 36571512.* [2]*Reid et al. JAMA Oncol. 2023;9(1):143-145. PMID: 36326735. Social media post December 8th, 2022. Available at: https://tinyurl.com/post1282022.* [3]*Pal et al. Genet Test Mol Biomarkers. 2023;27(1):1-4. PMID: 36719977.*

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, Pancreatic

January 10th, 2023 (*Version 2.2023*) focused on male *BRCA* carriers:

- Consider annual mammograms (particularly in *BRCA2* carriers) starting at age 50 or 10 years before the earliest male breast cancer in the family (whichever comes first)

February 13th, 2023 (*Version 3.2023*)

- To release the annual update of the discussions section, which is a tremendous source of background information, to provide information upon which the updates to the guidelines were based

Genetic/Familial High-Risk Assessment: Colorectal

December 7th, 2022 Update (*Version 2.2022*)

- Lynch Syndrome: No clear data exist to support surveillance for gastric, duodenal, and more distal small bowel cancer
- Familial Adenomatous Polyposis: Surveillance, after *APC* positive, bullet revised: High-quality colonoscopy (preferred) every 12 months beginning at age 10–15; explanation provided in footnote: Colonoscopy is preferred due to the possibility of missing early transverse colon and right-sided polyps when limiting to sigmoidoscopy. However, based on patient and family preference or clinical judgment, sigmoidoscopy may also be considered.
- Gene/Syndrome tables extensively revised and updated, specifically pages GENE-3 through GENE-19

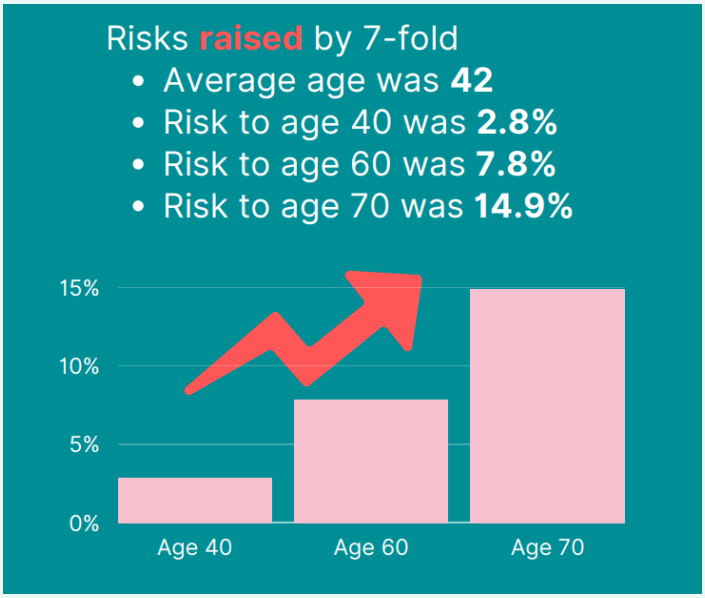
Inherited Cancer Content in Other NCCN Guidelines (*aside from the Genetic/Familial already listed*)

- In the Genetics/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic guidelines, there is now a table added at the end of the guidelines to summarize inherited cancer content across ALL NCCN guidelines, including a live link to table of contents and name of section heading in table of contents with this content. Table on page 55 of 148 (starting on SUMM-1 page)

Melanoma Risk in Li-Fraumeni Syndrome

A recently published cohort study of 483 individuals with Li-Fraumeni Syndrome (LFS) identified 113 skin cancers. The cumulative incidence of a diagnosis of any skin cancer was 36.3% by the age of 70. Specifically for melanoma, the median age at diagnosis was 42 with a 7-fold increased incidence (SIR 7.28, 95% CI 4.50-11.13) compared with the general population and a risk to age 70 of almost 15% (**Figure 1**). The incidence of other types of skin cancer (i.e., squamous cell and basal cell carcinoma) were similar to those in the general population.

Figure 1: Li-Fraumeni Syndrome Melanoma Risk by Age



Currently, there is an international study being conducted to learn more about LFS, called the LiftUp Study – to learn more or participate in these efforts directly, visit https://liftupstudy.org.

Hatton et al. J Invest Dermatol. 2022;142(9):2534-2537. PMID: 35183552. Social media post March 3rd, 2023. Available at: https://tinyurl.com/post332023.

Lynch Syndrome: Colorectal Cancer Risks Revisited

A study of 381 individuals with Lynch Syndrome in New Zealand (98 with Lynch Syndrome-associated variants in *MLH1*, 159 in *MSH2*, 103 in *MSH6*, and 21 in *PMS2*) found that risks for colorectal cancer were lower in *MSH6* and *PMS2* carriers, suggesting that it might be possible to spread out colonoscopy intervals for these individuals.[1] Findings also indicated that not removing the polyps completely were responsible for 1/3 of surveillance-detected colorectal cancers.

In people with Lynch Syndrome, the risk of getting a second (also called 'metachronous') colorectal cancer is higher. In a recent study, risk factors for getting a metachronous colorectal cancer included a history of colorectal polyps and having an *MLH1* or *MSH2* mutation, while protective factors included female sex and extended surgical resection.[2] This highlights the importance of genetic testing and counseling for Lynch Syndrome prior to surgery, which can influence surgical strategy and lead to better outcomes.

[1]Lamba et al. Clin Gastroenterol Hepatol. 2020;18(12):2768-2774. PMID: 32240831. Social media post March 13th, 2023. Available at https://tinyurl.com/post3132023. [2]Signoroni et al. Int J Clin Oncol. 2020;25(9):1644-1652. PMID: 32430733. Social media post March 19th, 2023. Available at https://tinyurl.com/post3192023.

Inherited Breast Cancer: Contralateral Breast Cancer Risks

While higher risks for contralateral breast cancer (CBC) have been known for *BRCA1* and *BRCA2*, a newly published study demonstrated that the risk of CBC is also higher for female *PALB2* and *CHEK2* carriers; however, no elevated risks were found for *ATM* carriers (**Table 1**).[1] This information is important to study, as it may be used to guide cancer screening and risk reduction strategies.

Table 1: Contralateral Breast Cancer Risks by Gene

Gene	10-year Cumulative Incidence of Contralateral Breast Cancer
BRCA1	33%
BRCA2	27%
CHEK2	13%
PALB2 (only ER- cancers)	35%
ATM	No increased risk

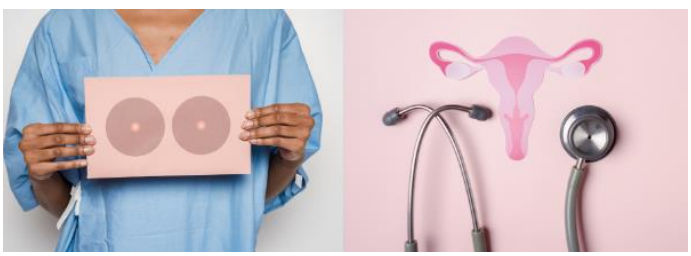
Risks of CBC may be further personalized in *BRCA1* and *BRCA2* carriers, with a recent study showing that risks were higher when the first breast cancer happened at a younger age, when there were close family members with breast and/or ovarian cancer, and when the mutation was located near the 3' region of the gene.[2] In contrast, risks were lower with endocrine therapy.

[1]Yadav et al. J Clin Oncol. 2023;41(9):1703-1713. PMID: 36623243. Social media post February 1st, 2023. Available at: https://tinyurl.com/post212023. [2]Sun et al. J Clin Oncol. 2023;41(5):991-999. PMID: 36480783. Social media post January 14th, 2023. Available at: https://tinyurl.com/post1142023.

Cancer Risks in Older Female *BRCA* Carriers

While there are higher cancer risks in *BRCA* mutation carriers starting in the mid-20s, a recent study focused on studying cancer risks in older females aged 50-75. Of the over 2000 females in the study, **which included ICARE participants**, 379 cancers were found between age 50 to 75 with risks of 49% in *BRCA1* carriers and 43% in *BRCA2* carriers. The most common cancers were breast (n=186) and ovarian (n=45) cancer. In those with risk-reducing surgery for both breasts and ovaries, the risk was 9%. This study shows that older female *BRCA* carriers still have high cancer risks and should be counseled appropriately.

Metcalfe et al. Cancer. 2022;129(60:901-907. PMID: 36571512.



Breast Cancer Screening in Male *BRCA1/2* Carriers

Generally, males with breast cancer present with advanced stage disease, thought to be due to a lack of screening. While data to determine performance of breast screening through mammograms for males at inherited risk is limited, recent studies suggest that the detection rate is similar or better than for females at general population risk.[1,2,3] In one study, the cancer detection rate (CDR) in males with screening mammograms due to a personal or family history of breast cancer or genetic predisposition was 18 per 1000 exams, with detection of five node negative cancers.[1] In comparison, the CDR among symptomatic males was 20 per 1000 exams, of which 2/3 measured 2.1 cm on average and most had nodal metastases. Mammographic screening sensitivity, specificity, and positive predictive value (PPV) of biopsy were 100%, 95% and 50% respectively. In another cohort of males at increased risk for breast cancer based on a personal and/or family history of breast cancer or genetic predisposition with screening mammograms, the CDR was reported as 4.9 per 1000, which is similar to screening mammography in females (5.4 per 1000).[2] Collectively, these studies suggest that screening mammography may be useful to detect breast cancer among males at increased risk. Of note, gynecomastia may be common in males (particularly at certain ages) and is not a risk factor for breast cancer, thus should not impact the decision to screen.

[1]Gao et al. Radiology. 2019;293(2):282-291. PMID: 31526252. [2]Marino et al. Breast Cancer Res Treat. 2019;177(3):705-711. PMID: 31280425. [3]Campos et al. Cancers (Basel). 2021;13(14):3535. PMID: 34298749.

Breast Cancer Treatment Updates

Findings from a Phase II study to evaluate the use of talazoparib (a PARP inhibitor) in individuals with advanced *PALB2*-mutation breast cancer showed that it appeared effective in certain patients and appeared safe (with similar adverse events as those previously reported with this drug).[1]

There are several Phase II trials to evaluate PARP inhibitors in *PALB2* carriers (as well as *BRCA1* and *BRCA2* carriers) with breast cancer at Vanderbilt and other locations across the country as outlined below:

1) Niraparib with Dostarlimab Therapy as Neoadjuvant Treatment for Patients with *BRCA*-Mutated Breast Cancer (NCT04584255). Additional details available at: https://vanderbilt.trialstoday.org/trial/NCT04584255
- **Brief Eligibility Criteria**: Documented germline *PALB2*, *BRCA1*, or *BRCA2* mutation; stage 1 to 3 invasive breast cancer ≥ 1.5 cm in size; HER2 negative tumor; inflammatory breast cancer not eligible

2) Niraparib in the Treatment of Patients with Advanced *PALB2*-Mutated Tumors (NCT05169437). Additional details available at: https://vanderbilt.trialstoday.org/trial/NCT05169437
- **Brief Eligibility Criteria**: Documented tumor *PALB2* mutation; locally advanced or metastatic tumors

[1]Gruber et al. Nat Cancer. 2022;3(10):1181-1191. PMID: 36253484. Social media post March 27th, 2023. Available at https://tinyurl.com/post3272023.

Prostate Cancer Treatment Updates

A study to test niraparib (a PARP inhibitor) in males with metastatic prostate cancer showed that those with an inherited *BRCA1* or *BRCA2 (BRCA)* mutation lived longer on average compared to those without a *BRCA* mutation. Side effects from niraparib were similar to those previously reported with PARP inhibitors.[1]

Another PARP inhibitor trial tested an oral drug (talazoparib) in metastatic castration-resistant prostate cancer and showed that it improved progression-free survival compared to standard of care (which was an androgen receptor inhibitor) regardless of *BRCA* mutation status.[2] However, in males with a *BRCA* or other DNA repair gene mutation, the benefit was the greatest.

[1]Smith et al. Lancet Oncol. 2022;23(3):362-373. PMID: 35131040. [2]Bono et al. Lancet Oncol. 2021;22(9):1250-1264. PMID: 34388386.

Ask the Expert

The below question was addressed by Ben Ho Park, MD, PhD, who is the Director of the Vanderbilt-Ingram Cancer Center and a Professor of Medicine in the Division of Hematology and Oncology. If you have a question you would like addressed, please email the ICARE team at ICARE@vumc.org for consideration in future newsletters.

Dr. Ben Ho Park

Q: As a 35-year-old woman with a *BRCA1* mutation, I get breast MRIs and mammograms every year. I heard about additional blood tests that might be used to detect cancers early. Is this something that may be important for me to do?

A: These blood tests generally are talking about circulating tumor DNA (ctDNA) which comes from cancer cells and is released into the bloodstream. This is because as tumors get bigger, new cells grow as other cells die and get broken down, releasing their DNA into the bloodstream (meaning the ctDNA). For people at higher risk for cancer due to a mutation in an inherited cancer risk gene, the value of using ctDNA to screen for a new cancer is currently not known and should only be offered in the setting of prospective clinical trials. This is because the sensitivity, false-positive rates, false negative rates, and the positive predictive and negative predictive values of ctDNA tests for early-stage disease, are not yet well-established, particularly the negative predictive value, meaning if the test is negative, does this mean the patient is free of cancer? Moreover, even though the positive predictive value for some tests is quite good (meaning if the test is positive there is a good chance there is cancer somewhere), what we do not have is any data suggesting that acting on this information affords better outcomes. That's the difference between what we call clinical validation (in this case positive predictive value has been validated) versus clinical utility, that is, knowing this is not helpful until we show that we can do something useful with this information.[1-4] Additionally, the psychological impact of ctDNA testing also remains unknown. Currently, these types of tests have been shown to be useful in helping to diagnose certain tumors, guiding and monitoring tumor-specific treatment, and monitoring tumor-free periods.

[1]Duffy et al. Clin Chem Lab Med. 2021;59(8):1353-1361. PMID: 33856748. [2]Offit et al. J Clin Oncol. 2023;41(1):11-21. PMID: 35944238. [3]Hackshaw et al. Cancer Cell. 2022;40(2):109-113. PMID: 35120599. [4]Raoof et al. Cancer Epidemiol Biomarkers Prev. 2022;31(6):1139-1145. PMID: 35320352.

Community Spotlight

The Campbells

In 1997 when I was a junior in college, my mom called to let me know that my father had been diagnosed with prostate cancer. Luckily for him, Prostate Specific Antigen (PSA) testing had recently started which resulted in early detection and subsequent prostatectomy. Due to his diagnosis and knowing prostate cancer is an inherited cancer, my paternal uncle and paternal grandfather began monitoring their PSA levels closely. Over the next several years, both were diagnosed with prostate cancer. As I got older, I knew that I would need to have annual physicals to monitor my PSA levels.

Over the past several years, my PSA level consistently stayed at zero until August 2021, when my PSA jumped to 4.7. To confirm this drastic increase, my primary care physician requested a second PSA. The next day, he called me to let me know that it was 6. Knowing my family history, I felt a sense of fear, but knew there were more steps to be taken before a cancer diagnosis was confirmed. In November 2021, my urologist performed a biopsy that determined a cancer diagnosis. Even though I was destined for this diagnosis because of prostate cancer's inherited characteristics, my wife Jeana and I were in shock because I was only 47 at the time. Surgery with Dr. Sam Chang took place at Vanderbilt on January 11th, 2022, which resulted in a successful removal of my prostate and a cancer free diagnosis.

With my strong family history of prostate cancer, Dr. Chang suggested that I provide a blood sample for genetic testing. Jeana and I have two daughters, Suzanna, age 17, and Elizabeth, age 12, so we assumed that they would be spared an inherited cancer diagnosis being females. However, after completing my genetic testing and discussing with Dr. Pal, it was discovered that I had a *CHEK2* mutation, which can present as breast or colon cancer. We are so grateful to have this important information so we can determine if early testing is right for our daughters.

My father will be participating in testing on April 7th, 2023. He is a retired pediatrician and is eager to be a part of this process to paint a better picture for our family and to help others learn more. My family is so thankful that the Inherited Cancer Registry exists to gather information to assist with cancer research and diagnosis, and ultimately treatment. – **Adam Campbell**

Inherited Cancer Research Efforts

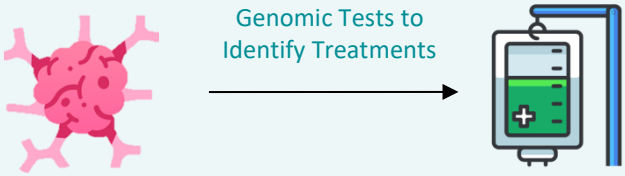
*Enroll in ICARE if you are interested in being considered for the below studies and many other current efforts. Participation is easy and can be completed online at **https://redcap.link/ICAREconsent** or by scanning the QR code.*

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: Almost 100 breast cancer tumors from ICARE participants have been sent for additional tumor genomic analyses.

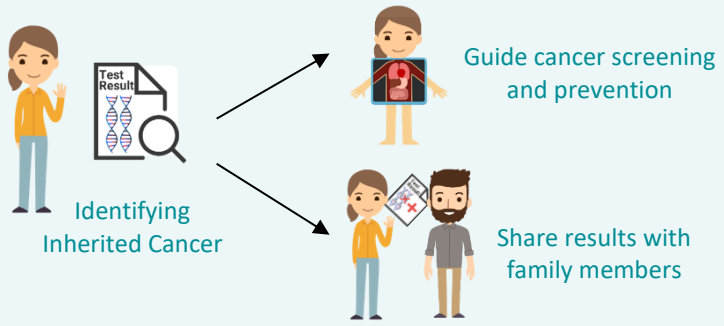


IMProving Care After Inherited Cancer Testing (IMPACT) Study

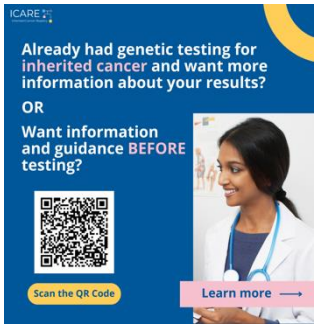
Objective: To improve follow-up care after genetic testing for those with a positive result.

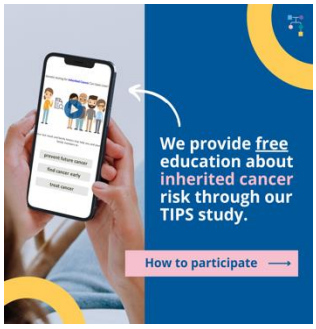
Eligibility: Mutation in an inherited cancer predisposing gene.

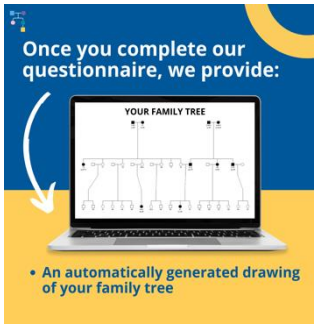
Progress: Hundreds of ICARE participants have been invited to participate, the trial has started, and we are actively enrolling!

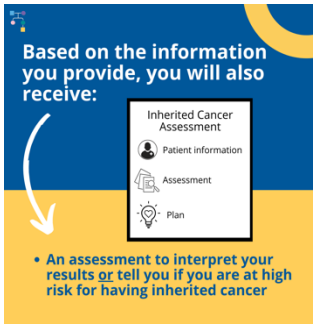


*Enroll in TIPS to receive free education and assessment about inherited cancer risk by scanning the QR code or visiting **https://redcap.link/TIPS***









VANDERBILT-INGRAM CANCER CENTER

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