Fall 2022

ICARE NEWSLETTER

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

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Table of Contents

About ICARE

ICARE continues to grow rapidly, with almost 5,200 participants, including more than 1,400 individuals with *BRCA1/2* mutations and more than 1,000 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.

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Welcome Message

We are excited to share several updates relevant to those at risk for inherited cancer. In this issue, we highlight efforts which have included data from ICARE participants. For instance, we have contributed to one of the largest studies to figure out which genes raise breast cancer risk (*outlined on page 2*)[1] and contributed to a study focused on breast cancer risks after oophorectomy (*outlined on page 2*).[2] We have also reviewed care updates in the latest NCCN guidelines (*outlined below*), which include: 1) revisions to make more individuals eligible for genetic testing; 2) removing content or practices that lack robust supporting evidence; and 3) adding a table highlighting inherited cancer content across all NCCN guidelines.

ICARE has served as a platform to launch efforts focused on inherited cancers, including a clinical trial, through which we offer free resources to improve guideline-adherent care (*details available at inheritedcancer.net/impact-study*). We are also conducting studies to better understand breast cancer characteristics, treatments, and outcomes among *PALB2, ATM*, and *CHEK2* carriers. These studies are related to another effort through which we are doing free genomic testing on breast cancers in *BRCA1*, *BRCA2*, *PALB2*, *ATM*, and *CHEK2* carriers to better understand how these tumors develop. Through this type of work, we hope to identify additional treatment options to contribute to improving outcomes in the future. Lastly, recognizing the importance of family history, we have developed a family history drawing tool for ICARE participants, through which we can email an automatically generated family tree, after the family history questionnaire is completed – we hope you will check this new feature out! 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 – *Released September 7th, 2022*

- Testing eligibility based on personal history of any type of breast cancer in females was updated from age ≤45 to ≤50 making more females with breast cancer eligible for testing regardless of family history or type of breast cancer.
- *BRCA1/2*: Removed ovarian cancer screening consideration from care guidelines given the lack of evidence to support that screening is useful to reliably detect ovarian cancer early.
- *BRCA1/2*: Clarified that hormone replacement therapy (HRT) is a consideration in pre-menopausal patients without breast cancer or other contraindications for HRT. Perioperative menopause management consultation was also included as a consideration.
- *CHEK2/ATM*: Age to start breast MRI screening in females was reduced from age 40 to 30-35 making more females eligible for screening at an earlier age.
- *PALB2*: Added consideration of risk-reducing salpingo-oophorectomy at age >45.
- Added a table at the end of the guidelines (*see page 54 on the SUMM-1 page*) to summarize inherited cancer content across **all** NCCN guidelines, including live links to the guidelines and sections referenced.

Genetic/Familial High-Risk Assessment: Colorectal – *Released June 8th, 2022*

- Testing criteria was expanded to offer germline multi-gene panel testing to **all** individuals diagnosed with colorectal cancer below age 50; and to consider testing for all others, particularly those with a family history or evidence of mismatch repair deficiency (but not restricted to just these patients).

[1]*Hu et al. N Engl J Med. 2021;384(5):440-451. PMID: 33471974;* [2]*Kotsopoulos et al. Cancer Epidemiol Biomarkers Prev. 2022;31(7):1351-1358. PMID: 35477169. Social media post September 25th, 2022. Available at: https://tinyurl.com/post9252022.*

BRCA1/2 Cancer Risk Updates

During preventive surgery to remove the ovaries and fallopian tubes (called a risk-reducing salpingo-oophorectomy or RRSO), a new study found that the detection of tubal intraepithelial carcinoma predicts the risk of later peritoneal cancer.[1] These findings show the importance of timely RRSO and the need to do a careful pathology exam of the ovaries and fallopian tubes to detect cancer. More research is needed to figure out how to best treat patients with isolated serous tubal intraepithelial carcinoma.

Breast cancer risk following preventive RRSO was studied in three recent reports, which varied in their results as outlined in the table below.[2,3,4] Overall, these studies consistently suggest that RRSO may reduce breast cancer risk, particularly in *BRCA2* carriers, in the 5 years following surgery. The data is less consistent for *BRCA1* carriers, where a subsequent study (which included ICARE participants), focused on breast cancer risk following preventive removal of the ovaries, reported decreased breast cancer risks in those with prior breast cancer yet no protective effect of RRSO was seen in those without a prior diagnosis of breast cancer.[5] Authors concluded that RRSO does not reduce breast cancer risk in *BRCA1* carriers. This study showed how various sources of bias can influence results in studies involving individuals with either a genetic predisposition or strong family history of disease, which in turn may erroneously influence clinical care recommendations. Authors also reiterated that regardless of these results, *BRCA1* carriers should be offered RRSO at age 35 to reduce the risk of ovarian and fallopian tube cancer. In those that have preventive removal of their ovaries, a frequent concern is the side effects of premature menopause and use of hormone replacement therapy (HRT). Several studies have suggested this to be safe, including a recent study which showed that HRT is reasonable to offer to *BRCA1/2* carriers after preventive removal of the ovaries.[6]

"…RRSO may reduce breast cancer risk, particularly in *BRCA2* carriers, in the 5 years following surgery."

In addition to preventive RRSO, which is currently the most effective strategy to reduce risks for these cancers, other strategies such as oral contraceptives and implants have also been studied. A recently published study suggests oral contraceptives and implants significantly lower risk of ovarian cancer in *BRCA1/2* carriers.[7] Similar findings were seen with injectables, but results did not reach statistical significance.

Finally, it is known that adult weight gain is a risk factor for ovarian cancer in the general population; however, a recent study showed this to also be the case in *BRCA1/2* carriers.[8] These findings highlight the importance for *BRCA1/2* carriers to maintain a healthy body weight throughout adulthood.

Inherited Cancer Genes: New Associations

A new study led by colleagues at Vanderbilt University Medical Center, including our clinical geneticist colleague, Dr. Georgia Wiesner, evaluated 23 hereditary cancer genes and found 19 new gene associations, including 7 new associations with cancer and 12 new associations with non-cancer diseases. The associations with cancer versus other conditions is included in the table.

	Gene	Association
Cancer	*ATM*	Stomach
	CHEK2	Leukemia, Plasma cell
	MSH6	Bladder
	MUTYH (bi-allelic)	Kidney
Non-Cancer	*APC*	Gastritis, Duodenitis
	BRCA1/2	Ovarian Cysts
	MEN1	Acute Pancreatitis
	PTEN	Chronic Gastritis

Zeng et al. JAMA Oncol. 2022;8(6):835-844. PMID: 35446370. Social media post June 1st, 2022. Available at: https://tinyurl.com/post6012022

Which Genes Are Confirmed as 'Inherited Breast Cancer Genes'?

There were two large studies published early last year that evaluated which genes raise risks for breast cancer, including breast cancer patients from many centers worldwide, representing the largest available datasets to look at this question. These efforts were led by the worldwide Breast Cancer Association Consortium (BCAC)[1] and the United States-based CARRIERS consortium.[2] The BCAC study was based on 113,000 women tested for 34 inherited cancer genes, while CARRIERS reported on 64,000 women tested for 28 inherited cancer genes. Significant associations were reported for 8 genes in both studies (*BRCA1, BRCA2, PALB2, BARD1, RAD51C, RAD51D, ATM*, and *CHEK2*), while only the BCAC study reported an association with *MSH6* and only CARRIERS reported an association with *CDH1*. Both *TP53* and *PTEN*, which are established breast cancer predisposing genes, did not have significant associations presumably because the mutation prevalence for each of the genes is so low. *[1]Breast Cancer Association Consortium et al. N Engl J Med. 2021; 384(5):428-439. PMID: 33471991; [2]Hu et al. N Engl J Med. 2021;384(5):440-451. PMID: 33471974.*

Articles	*BRCA1*	*BRCA2*
Mavaddat et al. 2020[2]	No lowering of breast cancer risk	Possible reduction in breast cancer risks 5 years after RRSO
Choi et al. 2021[3]	Reduction in breast cancer risks 5 years after RRSO, and even beyond 5 years	Reduction in breast cancer risks 5 years after RRSO
Wang et al. 2022[4]	Reduction in breast cancer risks, particularly 5 years after RRSO, and especially in younger females	Reduction in breast cancer risks, particularly 5 years after RRSO, and especially in younger females

RRSO: Risk-reducing salpingo-oophorectomy (removal of the ovaries and fallopian tubes to prevent cancer)

[1]Steenbeek et al. J Clin Oncol. 2022;40(17):1879-1891. PMID: 35302882. Social media post May 24th, 2022. Available at: https://tinyurl.com/post5242022; [2]Mavaddat et al. Breast Cancer Res. 2020;22(1):8. PMID: 31948486. Social media post September 27th, 2022. Available at: https://tinyurl.com/post9272022; [3]Choi et al. JAMA Oncol. 2021;7(4):585-592. PMID: 33630024. Social media post September 27th, 2022. Available at: https://tinyurl.com/post9272022; [4]Wang et al. Eur J Surg Oncol. 2022;48(6):1209-1216. PMID: 35216860. Social media post September 27th, 2022. Available at: https://tinyurl.com/post9272022; [5]Kotsopoulos et al. Cancer Epidemiol Biomarkers Prev. 2022;31(7):1351-1358. PMID: 35477169. Social media post September 25th, 2022. Available at: https://tinyurl.com/post9252022; [6]Mills et al. Gynecol Oncol. 2020;157(3):706-710. PMID: 32143914. Social media post September 26th, 2022. Available at: https://tinyurl.com/post9262022; [7]Xia et al. Gynecol Oncol. 2022;164(3):514-521. PMID: 35063280. Social media post September 21st, 2022. Available at: https://tinyurl.com/post9212022; [8]Kim et al. Cancer Epidemiol Biomarkers Prev. 2021;30(11):2038-2043. PMID: 34426412. Social media post October 1st, 2022. Available at: https://tinyurl.com/post10012022.

Screening & Treatment Updates

Pancreatic Cancer: A recent small study suggests that immunotherapy may benefit patients with refractory pancreatic or biliary cancer who have inherited a mutation in the homologous recombination deficiency (HRD) genes, *BRCA1*, *BRCA2*, and *RAD51C*.[1] Another new study reported that in *BRCA1/2* carriers with pancreatic cancer, maintenance treatment with Olaparib may be of benefit.[2] Findings showed that with Olaparib, long-term survival was more common and time to subsequent therapy was prolonged. *[1]Terrero et al. JAMA Oncol. 2022;8(6):1-3. PMID: 35446342. Social media post June 13th, 2022. Available at: https://tinyurl.com/post6132022; [2]Kindler et al. J Clin Oncol. 2022;JCO2101604. PMID: 35834777. Social media post August 5th, 2022. Available at: https://tinyurl.com/post8052022*

New Modeling Analysis About Breast Cancer Screening in *ATM* and *CHEK2* Carriers: Using information from twelve prior population-based studies, a modeling analysis was done to look at when to start mammography and breast MRI in females with inherited mutations in genes including *ATM* and *CHEK2*. Overall, findings showed that starting annual MRI screening between age 30 to 35 and mammography at age 40 may lower death from breast cancer by more than half in female *CHEK2* and *ATM* carriers. Since this report was published earlier this year, the NCCN guidelines were changed to recommend starting breast MRI screening in female *CHEK2* and *ATM* carriers between age 30 to 35. These findings highlight how new research is used to update national practice guidelines. *Lowry et al. JAMA Oncol. 2022;8(4):587-596. PMID: 35175286. Social media post April 1st, 2022. Available at: https://tinyurl.com/post4012022*

ATM-associated Cancer Risks

Female *ATM* carriers have approximately a 2-fold risk, on average, for developing breast cancer, which was confirmed through two large studies that reported risks (odds ratio) as 2.10 (95% CI, 1.71–2.57)[1] and 1.82 (95% CI, 1.46–2.27).[2] Both studies reported an association with ER+ tumors. Another recent study estimated breast cancer risks to be 13% by age 80, but suggested that these risks may vary based on the specific mutation type and location.[3] A similar breast cancer risk (odds ratio) of 2.03 (95% CI, 1.89–2.19) was estimated through a commercial lab-based study of 4607 *ATM* carriers.[4] This study reported higher breast cancer risks in female carriers with the c.7271T>G missense variant (OR, 3.76; 95% CI, 2.76–5.12) compared to other missense and truncating *ATM* mutations. Risk (odds ratio) reported for ovarian cancer in this study was 1.57 (95% CI, 1.35–1.83) and for pancreatic cancer was 4.21 (95% CI, 3.24–5.47). Estimates of cumulative risk for pancreatic cancer risk through another study of 130 pancreatic cancer kindreds with a pathogenic germline *ATM* variant were reported to be 1.1% (95% CI, 0.8%–1.3%) by age 50; 6.3% (95% CI, 3.9%–8.7%) by age 70; and 9.5% (95% CI, 5.0%–14.0%) by age 80.[5] Overall, the relative risk of pancreatic cancer was 6.5 (95% CI, 4.5–9.5) in *ATM* carriers compared with noncarriers, and the average age at diagnosis was 64 (range 31-98). Finally, risks for the association of *ATM* mutations with prostate cancer have been mixed, with the recent commercial lab-based study reporting a risk (odds ratio) of 2.58 (95% CI, 1.93–3.44).[4]

[1]Breast Cancer Association Consortium et al. N Engl J Med. 2021; 384(5):428-439. PMID: 33471991; [2]Hu et al. N Engl J Med. 2021;384(5):440-451. PMID: 33471974; [3]Renault et al. Breast Cancer Res. 2022;24(1):24. PMID: 35365198. Social media post September 19th, 2022. Available at: https://tinyurl.com/post9192022; [4]Hall et al. Cancer Prev Res (Phila). 2021;14(4):433-440. PMID: 33509806. Social media post June 21st, 2022. Available at: https://tinyurl.com/post6212022; [5]Hsu et al. JAMA Oncol. 2021;7(11):1664-1668. PMID: 34529012. Social media post October 1st, 2021. Available at: https://tinyurl.com/post10012021

Ask the Expert

The below question was addressed by Dr. Kamran Idrees, Chief of the Division of Surgical Oncology & Endocrine Surgery, Associate Professor of Surgery, Ingram Associate Professor of Cancer Research, and Director of Pancreatic and Gastro-Intestinal Surgical Oncology at Vanderbilt-Ingram Cancer Center. Dr. Idrees' research has focused on colorectal cancer, liver metastases, and pancreatic cancer treatments. Dr. Indrees also leads the Vanderbilt Pancreas Center, which performs high-risk pancreatic cancer surveillance. Learn more at https://www.vanderbilthealth.com/service/high-risk-pancreatic-cancer-surveillance.

If you have a question you would like addressed, please email the ICARE team at ICARE@vumc.org for consideration in future newsletters.

Kamran Idrees, MD

Q: I am 58 years old and have a *BRCA2* mutation – should I get pancreatic cancer screening?

A: Per national and international practice guidelines,[1,2] you are eligible for screening if you have at least one close relative (defined as a first- or second-degree relative, meaning parents, siblings, children, aunts, uncles, etc.) from the same side of the family the mutation is thought to be coming from. Screening is done each year starting at age 50 through MRI/MRCP alternating with endoscopic ultrasound. Recently, a new study evaluated pancreatic cancer screening in high-risk individuals defined based on family history and/or inherited gene mutation (*BRCA1, BRCA2, CDKN2A*, Lynch Syndrome genes, *PALB2, ATM*, and *STK11*).[3] Findings showed that screening led to diagnosis at an earlier stage and improved survival. Specifically, in the entire sample of 1,731 high-risk patients, 26 pancreatic cancers were diagnosed. Of these, there were 10 in the surveillance group, of whom the majority (57.9%) had stage 1 disease and 5.2% had stage IV disease. In contrast, of the 7 in the group outside of surveillance, the majority (85.7%) had stage IV disease. Survival of patients in the screen-detected group was 73.3% at 5 years, with a median overall survival of 9.8 years compared to 1.5 years in those diagnosed outside of surveillance (hazard ratio 0.13; 95% CI, 0.03–0.50; P = .003). These findings highlight the potential value of screening in those at high risk of pancreatic cancer, through MRI/MRCP and endoscopic ultrasound. When thinking about where to go for screening, it is important to go to a center with experience in these specialized tests. To that end, at Vanderbilt University Medical Center, we have recently expanded our high-risk pancreatic cancer clinic to follow those with inherited cancers through the nationally recommended screening modalities. If you or a family member think you may be at risk, please call the nurse navigator at (615) 473-1930 to schedule an appointment. *[1]NCCN Genetic/Familial Risk Assessment: Breast, Ovarian and Pancreatic. V1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf; [2]Goggins et al. Gut. 2020;69(1):7-17. PMID: 31672839. Social media post February 4th, 2020. Available at: https://tinyurl.com/post2042020; [3]Dbouk et al. J Clin Oncol. 2022:JCO2200298. PMID: 35704792. Social media post July 26th, 2022. Available at: https://tinyurl.com/post7262022*

Community Spotlight

Monique Tiffany

When I was just 8 years old my mother was diagnosed with a very aggressive breast cancer. I didn't really understand the concept of cancer at that age, but I knew what was happening was terrible. After many surgeries and treatments, she passed away 2 years later at the age of 35. There was no hereditary cancer testing in the 1980's, but somehow the message came through to me that I too could be at risk. I began having mammograms sometime during my 20's, even before guidelines were established, and I attempted self-breast exams regularly even though no one really taught me how to. In 2001, at the age of 31, I felt a hard lump in my breast and even before the biopsy came back as cancer, I knew that it was. I was diagnosed with a stage II triple-negative breast cancer (TNBC). Luckily, by this time testing for *BRCA1*/2 had become available and thankfully my medical oncologist was savvy enough to know that I needed to be tested. My result came back positive for a *BRCA1* mutation, which is associated with a high risk of breast cancer among several other cancers. This changed my world overnight, but also led me to make medical decisions that ultimately saved my life, which is why 21 years later I can write about it here. Unfortunately, I have lost too many close family members to *BRCA1*-related cancers, but I decided that I am still here for a reason. I decided to go to nursing school to pursue oncology and ended up becoming the lead nurse in a high-risk cancer program in 2009. I enrolled in the ICARE study while attending my first FORCE conference in 2010 and quickly realized that my participation in this study was helping to further research for many other families just like mine. Over the past 8 years I have been working as a Regional Medical Specialist and Nurse Planner for continuing education at Myriad Genetics. I regularly share ICARE research and publications with the healthcare professionals that I work with along with the opportunity to enroll their patients in the study. I love how the newsletters highlight the publications that come from updates from study participants, including my own. I may be just one person but because I attended the right conference at the right time and made the right decision to take a proactive role in helping others with hereditary cancer, I have been able to affect thousands of patients. That has given me an amazing sense of purpose with a disease that seems so purposeless. **– Monique Tiffany, MSN, RN, CGRA, BHCN**

Inherited Cancer Research Efforts

Please continue to refer your patients to ICARE to be considered for these and other targeted efforts!

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*.

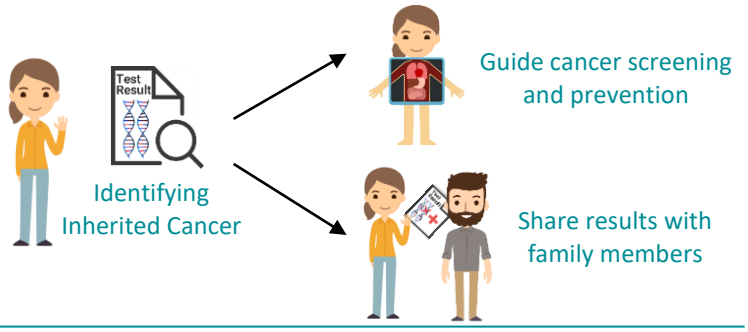
Progress: Almost 100 breast cancer tumors from ICARE participants have been sent for additional genomic analyses.

IMProving Care After Inherited Cancer Testing (IMPACT) Study

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

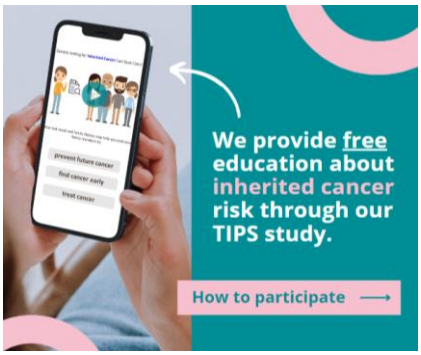
Eligibility: Mutation in an inherited cancer predisposing gene.

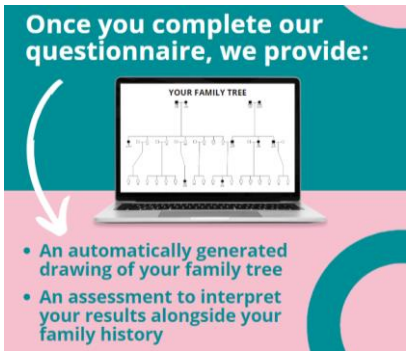
Progress: Hundreds of ICARE participants have been invited to participate, the trial has started, and we are actively enrolling!



Tool for Inherited Cancer Predisposition Counseling and Testing Study (TIPS)

Enroll today to receive free education and assessment about inherited cancer risk!





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