Fall 2024

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, reaching over 6800 participants, including almost 1700 individuals with *BRCA1/2* mutations and more than 2000 individuals with other inherited cancer gene mutations. ICARE participants represent 50 U.S. states, the District of Columbia, the U.S. Virgin Islands, and 26 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

As we continue to experience a tremendous pace of discovery in the field of inherited cancers, we have many interesting updates to share with you. There are a number of recently published research studies that have included data from ICARE participants, such as a study through which we looked at specific *CHEK2* carriers and saw that those with the I157T variant may be getting more cancer risk management than they need;[1] a study to outline melanoma risks in *BRCA1/2* carriers (as detailed on Page 2);[2] and a study in *BRCA1/2* carriers looking at peritoneal cancer risks after preventive salpingo-oophorectomy (removal of the ovaries and fallopian tubes; as detailed on Page 2).[3] Additionally, we continue to recruit for our IMPACT study, focused on testing strategies to improve follow-up care in those with inherited cancer risk (*if you are interested in participating, see the last page of this newsletter for more details*). We are also continuing to conduct our study among *BRCA1/2*, *PALB2*, *CHEK2*, and *ATM* carriers with breast cancer through which we send tumor specimens for additional genomic testing to better understand pathways to tumor development and to contribute to personalized cancer treatments. As always, we sincerely thank our participants and provider contributors 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]*Garmendia, et al. Genes (Basel). 2024; 15(7):881. PMID: 39062660. Social media post Aug 5th, 2024. Available at: https://tinyurl.com/post80524;*
[2]*Narod, et al. Hered Cancer Clin Pract. 2024;22(1):7. PMID: 38741145. Social media post Aug 26th, 2024. Available at: https://tinyurl.com/post82624;*
[3]*Narod, et al. J Natl Cancer Inst. 2024:djae151. PMID: 38937272. Social media post Aug 25th, 2024. Available at: https://tinyurl.com/post82524.*

National Comprehensive Cancer Network (NCCN) Guideline Updates

Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Cancer – *Released September 11th, 2024 (V1.2025)*

Check out the full guidelines by creating a FREE account at www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

Testing Updates:

- Clarified that it is appropriate to test unaffected family members if they meet testing criteria (even if they are not the "best testable")
- Testing in female breast cancer patients: Consider testing for high penetrance genes in those diagnosed at age 65 or younger (used to be younger than age 60)
- Added guidance about minimal recommended elements to be discussed during 'Point-of-Care' testing (as outlined in Eval-A 10 of 11 on Page 17 of the guidelines), in those with active cancer diagnoses and previous history, when testing is performed outside of specialty genetics setting

Gene Updates:

- *ATM*: Colorectal cancer risk added as an emerging risk; Consider pancreatic cancer screening beginning at age 50 (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier), regardless of family history (i.e., family history criteria removed)
- *BRCA2*: Consider pancreatic cancer screening beginning at age 50 (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier), regardless of family history (i.e., family history criteria removed)
- *CHEK2*: Colorectal cancer risk removed

Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric Cancer – *Released August 8th, 2024 (V1.2024)*

Check out the full guidelines by creating a FREE account at https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

Guideline name expanded from Colorectal Cancer → Colorectal, Endometrial, and Gastric Cancer

- Endometrial cancer recommendations included throughout
- Hereditary Diffuse Gastric Cancer section added (HGAST-1)
- Gynecologic risk and preventive surgery considerations for those with Lynch Syndrome added
- Use of hormone replacement treatment following premature surgical menopause from risk-reducing oophorectomy added
- *CHEK2*: Absolute colon cancer risk revised to "NO INCREASED RISK"; thus, general population screening is appropriate for these individuals

Risks of Cancer in Individuals with TWO *CHEK2* Mutations (called "Bi-Allelic" Mutations)

A new study found that risks may be higher for multiple types of cancer, including breast cancer, in both females and males who have two *CHEK2* mutations:

- Females more frequently developed 2 or more cancers at younger ages
- Males more frequently developed more than 1 cancer

Additionally, findings showed that the type of mutation may be important to guide level of risk (e.g., truncating 1100delC homozygotes being at a higher risk than compound heterozygotes with truncating mutation along with the established lower risk I157T mutation).

Hinić, et al. Genet Med. 2024;26(5):101101. PMID: 38362852. Social media post May 28th, 2024. Available at: https://tinyurl.com/post52824.

BRCA2-Associated Prostate Cancer

A new study found that males with a *BRCA2* mutation and metastatic hormone-sensitive prostate cancer face poorer outcomes. *BRCA2* carriers were also found to have a higher risk of progression to castration-resistant prostate cancer. These findings highlight the importance of evaluating germline mutations among prostate cancer patients.

Custodio-Cabello, et al. Urol Oncol. 2024;42(10):331.e13-331.e24. PMID: 38926076. Social media post Sept 30th, 2024. Available at https://tinyurl.com/post93024.

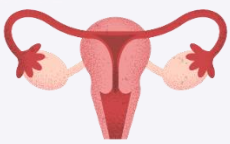
Risk of Melanoma in *BRCA1/2* Carriers

Over the last few years, there has been mixed information about the risk of melanoma in *BRCA1/2* carriers – while earlier studies had suggested an association,[1,2] other studies showed no association.[3,4] Thus, based on current evidence, it is unclear if *BRCA1* and/or *BRCA2* pathogenic variants increase melanoma risk based on the current evidence.[5,6] However, more recently, a study, **which included ICARE participants**, reported that compared to 1.5% in the general population, the risk of melanoma may be slightly higher in *BRCA1* carriers (2.5%) and *BRCA2* carriers (2.3%).[7] Ultimately, given it is reasonable to do a regular skin exam in the general population, this suggestion certainly holds in individuals with a *BRCA1* or *BRCA2* mutation as well.

[1]Breast Cancer Linkage Consortium. J Natl Cancer Inst. 1999;91(15):1310-6. PMID: 10433620; [2]Moran, et al. Fam Cancer. 2012;11(2):235-42. PMID: 22187320; [3]van Asperen, et al. J Med Genet. 2005;42(9):711-9. PMID: 16141007; [4]Kadouri, et al. Fam Cancer. 2009;8(1):29-32. PMID: 18679827; [5]Gumaste, et al. Br J Dermatol. 2015;172(6):1498-506. PMID: 25524463; [6]Johansson, et al. Melanoma Res. 2019;29(5):483-490. PMID: 31464824; [7]Narod, et al. Hered Cancer Clin Pract. 2024;22(1):7. PMID: 38741145. Social media post Aug 26th, 2024. Available at: https://tinyurl.com/post82624.

BRCA1/2 Carriers: Risk of Peritoneal Cancer After Bilateral Oophorectomy

A recent study among *BRCA1* and *BRCA2* carriers, **which included ICARE participants**, found that the risk for peritoneal cancer following a preventive bilateral oophorectomy was higher among *BRCA1* carriers than *BRCA2* carriers. Specifically, among 6310 females, the annual risk of peritoneal cancer was 0.14% for *BRCA1* carriers and 0.06% for *BRCA2* carriers, and the 20-year cumulative risk of peritoneal cancer from the date of oophorectomy was 2.7% for *BRCA1* carriers and 0.9% for *BRCA2* carriers. This information shows that removing the ovaries not only greatly lowers cancer risks for ovarian cancer, but also the remaining risk to develop peritoneal cancer is very low.



Narod, et al. J Natl Cancer Inst. 2024:djae151. PMID: 38937272. Social media post Aug 25th, 2024. Available at: https://tinyurl.com/post82524.

BRCA1/2 Carriers and Pregnancy-Related Risks

A recent study reported that **pregnancy after breast cancer** was safe for both mother and baby.[1] Specifically, the researchers found that pregnancy after breast cancer was not associated with adverse maternal prognosis or fetal outcomes. Another study reported that **breast cancer after pregnancy** could be associated with poorer outcomes. Specifically, breast cancer diagnosed within 10 years of having a child was associated with a higher risk of mortality, especially in *BRCA1* carriers.[2] This information could be important for genetic counseling, prevention, and treatment strategies in *BRCA1/2* carriers.

[1]Newman, et al. JAMA Surg. 2024;159(5):482-483. PMID: 38536201. Social media post June 3rd, 2024. Available at: https://tinyurl.com/post60324; [2]Zhang, et al. JAMA Netw Open. 2024;7(4):e247421. PMID: 38639936. Social media post June 6th, 2024. Available at: https://tinyurl.com/post60624.

Breast Cancer After Ovarian Cancer in *BRCA1/2* Carriers

A recently published study reported that among females with ovarian cancer who received chemotherapy, their risk for breast cancer was lower for the next 5 years. Specifically, incidence rates were lower at 2 years (1.18%) and between 2 to 5 years (1.13%); however, incidence rates rose thereafter for *BRCA1* carriers (>4% annually post 10 years). This study shows that the chance of getting breast cancer after an ovarian cancer diagnosis is relatively low. However, it now looks like the rates rise again, especially after 10 years.

Evans, et al. Genet Med. 2024;26(9):101172. PMID: 38847192.

American Society of Clinical Oncology (ASCO) Guideline Update: Selecting Genetic Tests in Patients with Various Cancers

What elements are most important in the collection of family history?

› Cancer details in first- and second-degree relatives and the patient's ethnicity.

When and how to use multigene panel testing when indicated?

› When more than one gene is relevant based on personal and/or family history, multigene panel testing should be offered.

Which genes should be tested based on cancer type?

› Table 1 outlines genes based on cancer type, including those more versus less strongly recommended.

Among patients with tumor testing, who should be offered germline testing?

› Any patient who meets criteria for germline genetic testing should be offered germline testing regardless of results from tumor testing.

› Even those not meeting criteria based on personal or family history who have a mutation identified through tumor testing in a gene listed in Table 2 under the outlined circumstances should be offered germline testing.

For a full list of recommendations in this guideline, the article is available at: https://ascopubs.org/doi/10.1200/JCO.24.00662

Tung, et al. J Clin Oncol. 2024;42(21):2599-2615. PMID: 38759122. Social media post May 21st, 2024. Available at: https://tinyurl.com/post52124.

BRCA1/2 Carriers: Treatment Advances

Among *BRCA1/2* carriers with advanced breast cancer, PARP inhibitors showed some activity even in patients with platinum resistant/unresponsive disease. However, the optimal delivery of platinum agents and PARP inhibitors was not clear.[1] In another study of *BRCA1/2* carriers with breast cancer (OlympiAD Trial), PARP inhibitors were compared to chemotherapy Treatment of Physician's Choice (TPC), with 25.7 months follow up, and the following results were generated:[2]

	PARP	TPC
Overall Survival	18.9 months	15.5 months
Alive at 3 Years	40.8%	12.8%

Of note, the effect was greatest in those receiving Olaparib for first line treatment (22.6 months) compared to not first line (14.7 months). Furthermore, benefit was seen regardless of hormone receptor status, *BRCA* status (*BRCA1* versus *BRCA2*), site of metastasis, amount of prior treatment, and stage of disease progression.[3]

[1]Valenza, et al. Eur J Cancer. 2023;190:112944. PMID: 37437366; [2]Robson, et al. Eur J Cancer. 2023;184:39-47. PMID: 36893711; [3]Senkus, et al. Int J Cancer. 2023;153(4):803-814. PMID: 36971103.

New Study to Evaluate Pancreatic Cancer Screening

A recent study among high-risk patients found that pancreatic cancer screening through endoscopic ultrasound and/or MRI-based tests led to detection of smaller and earlier-stage cancers, and overall, seemed to result in longer survival. Patients with an inherited gene mutation that predisposes to pancreatic cancer and/or a family history of pancreatic cancer were considered to be high risk. This study contributes to the growing body of literature to show the possible benefits of pancreatic cancer screening to detect cancer early, when it is more treatable.

Blackford, et al. JAMA Oncol. 2024;10(8):1087-1096. PMID: 38959011.

Double Mastectomy Not Linked to Survival Advantage

A recent study found that in females with unilateral breast cancer (meaning breast cancer on one side) who decided to have a double mastectomy had similar mortality rates to those treated with lumpectomy or unilateral mastectomy (meaning double mastectomy did NOT lead to longer survival). Findings showed that while bilateral mastectomy greatly lowered the risk of breast cancer in the other (contralateral) breast, this more extensive surgery (bilateral mastectomy) did not lower the risk of dying from breast cancer. This is very important information for females to know as they make decisions about breast cancer surgery.

Giannakeas, et al. JAMA Oncol. 2024:e242212. PMID: 39052262.

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 Study

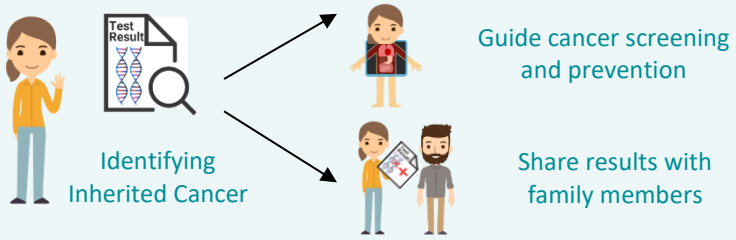
Goal: To perform genomic analyses to better understand how breast cancers develop and identify additional treatment options to improve outcomes in those with a positive result in *BRCA1*/2, *PALB2*, *ATM*, and/or *CHEK2*.

Progress: Almost 300 breast cancer tumors from ICARE participants have been sent for additional tumor genomic analyses.

IMProving Care After Inherited Cancer Testing (IMPACT) Study

Goal: To improve follow-up care after genetic testing for those with a positive result in an inherited cancer predisposing gene.

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



The Patient *and* the Researcher Shares Her Uncertain Future and Lessons She's Learned

By Marleah Dean Kruzel, PhD, *BRCA2* Previvor

When I was eight years old, my mother found a lump in her breast – *barely noticeable*. For a few years, I watched her undergo chemotherapy, radiation, and a prophylactic mastectomy and reconstruction. Since then, my maternal aunt and grandmother also fought breast cancer, and we learned my great-grandmother died of breast cancer at 35 years old.

From a young age, I assumed I would get cancer. That is what happened to women in my family. But those childhood experiences also propelled my desire to give back to the medical community who saved my mom's life. I earned my PhD and now conduct research to understand and improve communication of cancer and genetic risk information across patients, families, and clinicians.

During my doctoral work, I thought about getting tested. For a year, the test kit sat in my closet because I knew if I tested positive, it would change my life, so I wanted to be absolutely sure I was ready to receive the results. Finally, after my mom and aunt tested positive for a *BRCA2* mutation, I did the testing.

After testing positive, I began surveillance, rotating between breast MRIs and mammograms every six months, a regimen I continue. But for over a decade, I have struggled with my uncertain future. One particularly difficult moment was my first MRI after having my son. It had been over a year and a half since I had been screened because I was pregnant and then breastfeeding. The radiologist found something "suspicious," and I had a biopsy. While I was not diagnosed with cancer, it was in that moment I realized my uncertainty was not going to *ever* go away. No amount of information would reduce it. No amount of social support would make me feel less alone. So, I did the only other thing I could: I embraced it.

My journey with hereditary cancer has made me realize life IS uncertain. Yet, it isn't just those with mutations who feel this, but other patients too—a cousin with diabetes, a father with heart disease, a grandmother living with Alzheimer's. All humans—in all areas of life. But it is in the uncertainty of our lives we learn and grow. Embracing uncertainty means identifying it and moving forward anyways, knowing we will never have all the information to make a decision.

As I reflect on this past decade, in my roles as a patient *and* a researcher, I can share lessons I've learned which help me in my journey. Maybe they will help you, too:

1. Information is powerful, but more information isn't always better. Trustworthy and credible resources are important to find.
2. Information changes. We live in an era of evolving cancer information. While this is exciting as a researcher, this also means that as a patient, I must continually reassess and talk to my clinicians.
3. Actively participate in medical encounters. Ask questions even when we are embarrassed and bring information to our appointments even when we found them online.
4. Emotions are part of the journey with hereditary cancer. Not only must we manage our own emotions, but our family members' emotions may also influence us. We don't always know what someone is going through, so we cut our family slack.
5. Sharing genetic risk information is not a "one and done conversation." Effective communication with family members requires multiple conversations over years. While we can't control how our family members react, we can share information in stages to help reduce information overload and to help continue our relationships.

I hope these lessons are helpful and encouraging. May we embrace our uncertainty each day and remember what my mother always says, "We make the best decisions we can with the information we have…at that time."

Please join us and invite any of your interested family members or friends for our….

Online Patient Forum: Inherited Breast Cancers in Men

October 29th, 2024 (6:30pm-8:00pm CT)

Ask questions and get feedback from our expert panelists!

Harvey Singer
Co-Founder, HIS Breast Cancer Awareness

Vicki Wolf
Co-Founder, HIS Breast Cancer Awareness

Ben Park, MD, PhD
Director, Vanderbilt-Ingram Cancer Center

Register today at **https://tinyurl.com/OctoberPatientForum** or by scanning the QR code.