Fall 2025

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, reaching nearly 7800 participants, including over 1800 individuals with *BRCA1/2* mutations and more than 2500 individuals with other inherited cancer gene mutations. ICARE participants represent 50 U.S. states, the District of Columbia, the U.S. Virgin Islands, and 30 other countries worldwide. If you have been affected by inherited cancer or are a provider caring for those affected by inherited cancer, visit our website (InheritedCancer.net) to learn more about how participating may benefit you.

Follow us @inheritedcancer

Welcome Message

As always, we thank you for your ongoing support and partnership. In honor of National Family History Month, a number of articles in this newsletter are focused on ways to help family members get tested (often called "cascade testing"). In fact, a recent study looking at 18 inherited cancer genes estimated that if an individual tests positive for a mutation and 70% of their relatives got tested (including first-, second-, and third-degree relatives), all 4 million individuals in the United States with mutations in one of these genes would be found in less than 10 years! Yet even though we are now about 30 years out from the discovery of the *BRCA1* and *BRCA2* genes, only ~10-20% of the adult United States population with a mutation in these genes knows they have it. In this issue of our newsletter, we draw upon the knowledge of colleague, Dr. Brian Shirts, founder of a non-for-profit called ConnectMyVariant, to tell us more about the process of family communication and testing. Our participant spotlight is Kathy Baker, founder of the non-profit called My Faulty Gene, who has led the development of real patient testimonials to educate about the importance of family testing (available at familygeneshare.org). We hope you find the information in this newsletter both informative and helpful, and we welcome you sharing information about ICARE with your family members, so they too might considering participating. As always, we thank you for your interest in our efforts…it is because of you that we have been able to contribute to ending "*the cycle of inherited cancer through research, education, and engagement.*"

With our sincere gratitude,
Tuya Pal, MD, FACMG on behalf of the ICARE Team

Offit, et al. J Clin Oncol. 2020;38(13):1398-1408. PMID: 31922925. Article available at https://pubmed.ncbi.nlm.nih.gov/31922925/

National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment Guideline Updates

Select updates outlined below. Check out the full guidelines by creating a FREE account at https://www.nccn.org/guidelines/category_2

Colorectal, Endometrial, & Gastric Cancer

V1.2025 – Released June 13th, 2025

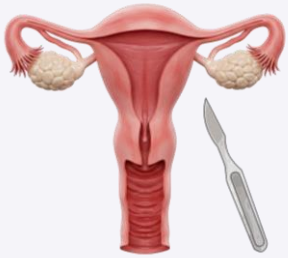
- ***MSH2* & *EPCAM* (LS-C 1 of 5 – Page 50)**: Added row for sarcoma risk, primarily for *MSH2*, but indicated there is no clear evidence to support surveillance at this time.
- ***PMS2* (LS-E 1 of 5 – Page 60)**: Removed cancer risks for ovarian, renal pelvis and ureter, bladder, gastric, small bowel, pancreas, biliary tract, prostate, breast (female), brain, and skin to reflect that association with these cancers is unclear.
  - Replaced with: *While other LS-associated cancers have been observed in individuals with PMS2 LS, it is unclear whether PMS2 LS carriers have increased risk for these cancers* (thus, should be individualized based on personal and family cancer history and clinical judgment)
- ***CDH1* (HGAST-A – Page 97)**:
  - Stomach cancer – now limited to diffuse in table (signet ring removed)
  - HGAST-B 4 of 5: Footnote c added: *if there are **mucosal abnormalities**, recommend a referral to an expert center for discussion of surgery.*
- ***TP53* (GENE-15 – Page 117)**:
  - Risks: Colon cancer absolute risk: 5-20% (changed from >20%)
  - Management: Colonoscopy and upper endoscopy every 2-5 years starting at **age 20-25** (changed from age 25) or 5 years before earliest colorectal cancer in the family.

Breast, Ovarian, Pancreatic, & Prostate Cancer

V1.2026 – Released July 10th, 2025

- **Testing: Ovarian Cancer Susceptibility (CRIT-4)**: expanded to include testing of non-epithelial ovarian tumors - sex-cord tumors with annular tubules (SCTAT) and small cell carcinoma of the ovary (hypercalcemic type) (SCCOHT) at any age. Consider testing for those with serous tubal intraepithelial carcinoma (STIC).
- ***CHEK2***: Revised comment to reflect that risks in the table are for frameshift and missense pathogenic/likely pathogenic (P/LP) variants (other than missense ***Ile157Thr, Ser428Phe, and Thr476Met***). Specifically, indicated that there is emerging evidence that **not all missense P/LP variants are low penetrance**.
- ***PALB2* & *TP53***: Added **prostate cancer** risks and screening (starting at age 40).
- ***BRCA* Management: BRCA-A (1 of 5)**: Sub-bullet added: Screening with clinical breast exam should continue after risk-reducing mastectomy. Routine screening with mammogram and breast MRI are not indicated.

BRCA1/2 Carriers with Breast Cancer: Removal of Ovaries and Fallopian Tubes Lowers Risk of Death



A new study among *BRCA1*/2 carriers with breast cancer showed that the **overall risk of death was 48% lower** for those that removed their ovaries and fallopian tubes. Specifically, these women had lower risks of all-cause mortality, breast cancer-specific mortality, and second non-breast cancer development. Removing the ovaries leads to menopause which has other health risks – however, study results showed that benefits were seen without a higher risk of other adverse long-term health outcomes, such as heart diseases. This information may give *BRCA1/2* carriers with breast cancer added information about the health benefits of removing their ovaries; and reassure them about other possible health-related side effects.

Hassan, et al. Lancet Oncol. 2025;26(6):771-780. PMID: 40347974. Article available at: https://pubmed.ncbi.nlm.nih.gov/40347974/. Social media post available at: https://www.facebook.com/share/p/1J7kcvPZuW/

Ovarian Cancer: 1 in 4 Cases Could Have Been Prevented!

A new study of 1877 ovarian cancer patients showed almost 25% of patients had 'missed opportunities' for salpingectomy (removal of fallopian tubes) when they had another surgery or procedure before their ovarian cancer diagnosis. Additionally, 6% of patients had a close relative with ovarian cancer, and almost 20% had a mutation in an ovarian cancer gene, only found after an ovarian cancer diagnosis. Most common genes were *BRCA1* and *BRCA2*, followed by *ATM, BRIP1, MLH1/MSH2, PALB2, RAD51C*, and *RAD51D*. This study shows the importance of preventing ovarian cancer, and how genetic testing and preventive care can lower risks. Ultimately, we as a community must try harder to find women at high risk, and offer them genetic testing, before they get ovarian cancer.

"…almost 20% had a mutation in an ovarian cancer gene, only found after an ovarian cancer diagnosis."

Moufarrj, et al. JAMA Surg. 2025:e252810. PMID: 40802262. Article available at: https://pubmed.ncbi.nlm.nih.gov/40802262/. Social media post available at: https://www.facebook.com/share/p/1MLT9n2Psj/

BRCA2 Gene: Mutation Type & Location Matter

A new study found that compared to those with *BRCA2* mutations outside exon 11, those with exon 11 mutations had a lower breast cancer risk, higher risk for ER-negative breast cancer, and later age at diagnosis. These findings suggest that taking mutation type and location into account in cancer risk models may improve the ability to predict individualized breast cancer risks. Ultimately, this information could be used to guide care.

Akamandisa, et al. Ann Oncol. 2025;36(8):954-963. PMID: 40288678. Article available at: https://pubmed.ncbi.nlm.nih.gov/40288678/. Social media post available at: https://www.facebook.com/share/p/1AzV2gpmer/

BRCA1/2 Carriers: High Risk of Breast Implant-Associated Lymphoma

In a new study of female *BRCA1*/2 carriers who had breast cancer, there was a 16-fold higher risk of anaplastic large-cell lymphoma associated with breast implants. This occurred in *BRCA1*/2 carriers who received textured breast implants as part of breast reconstruction. This is important information for *BRCA1*/2 carriers to know about to guide breast reconstruction options, including:

1) those thinking about breast reconstruction options
2) those who already had reconstruction and have textured implants in place.

Ghione, et al. Blood Advl. 2025;9(17):4436-4443. PMID: 40512039. Article available at: https://pubmed.ncbi.nlm.nih.gov/40512039/. Social media post available at: https://www.facebook.com/share/p/17JP5qxFrx/

BRIP1: Third Most Common Gene for Inherited Ovarian Cancer

In a new study of unselected women with ovarian cancer, *BRIP1* was the third most common gene for inherited ovarian cancer at a frequency of 1.1%, following *BRCA1/2* which were found in 14.8%. Other inherited ovarian cancer genes included *PALB2* (0.8%), *RAD51C* (0.4%), and *RAD51D* (0.4%). Beyond *BRCA1*/2 testing, additional testing through inherited cancer multi-gene panel tests detected mutations in an additional 2% to 3% of patients.

Morgan, et al. Genet Med. 2024;26(10):101230. PMID: 39096152. Article available at: https://pubmed.ncbi.nlm.nih.gov/39096152/. Social media post available at: https://www.facebook.com/share/p/1B6soiHPUF/

ATM, CHEK2, & *PALB2* Carriers: Are There Differences in Cancer-Associated Mortality?

A new study of *ATM*, *CHEK2*, and *PALB2* carriers compared to non-carriers showed similar mortality from breast cancer, pancreatic cancer, and colorectal cancer. Other findings among *BRCA1/2* carriers and Lynch Syndrome patients showed: 1) *BRCA1/2* carriers had lower mortality from triple-negative breast cancer; and 2) Lynch Syndrome patients had lower mortality from colorectal cancer. Ultimately, these results may be reassuring for *ATM*, *CHEK2*, and *PALB2* carriers, and provide additional useful information when discussing cancer prognosis with them.

Veenstra, et al. J Clin Oncol. 2025;43(13):1587-1596. PMID: 40020204. Article available at: https://pubmed.ncbi.nlm.nih.gov/40020204/. Social media post available at: https://www.facebook.com/share/p/1EemCwseZp/

Lynch Syndrome: Showing the Importance of Family Testing

Cascade testing refers to testing family members for a gene mutation after another family member is found to have a mutation. Once family members get cascade testing, they can also benefit from screening, cancer prevention, and early detection strategies. A study conducted a microsimulation model to look at the cost effectiveness of cascade testing of all close (first-degree) relatives. Results showed that cascade testing: lowered colorectal cancer cases by 61.0%, lowered deaths from colorectal cancer by 78.5%, and on average, led to 11 more colonoscopies in someone's lifetime. These findings provide a number to how much cascade testing can help family members of patients with Lynch Syndrome newly diagnosed with colorectal cancer. Furthermore, showing the value of cascade testing in lowering the rates of colorectal cancer across generations may help patients talk with their family, and ultimately help family members see why they may want to move forward with genetic testing.

Rustgi, et al. Clin Gastroenterol Hepatol. 2025;23(10):1834-1845.e4. PMID: 40010417. Article available at: https://pubmed.ncbi.nlm.nih.gov/40010417/. Social media post available at: https://www.facebook.com/share/p/1AVoJ3eGU2/

Breast Cancer Treatment: *BRCA1/2* Carriers

A new randomized controlled trial among *BRCA1/2* carriers comparing neoadjuvant chemotherapy with olaparib versus chemotherapy alone found:

- No improvement in pathological complete response (64.1% with olaparib versus 69.8% with chemotherapy alone)
- Yet significant improvement in overall survival (100% at 3 years with olaparib versus 88.2% with chemotherapy alone)
- Superior event-free and breast cancer specific survival

These findings suggest that adding olaparib may benefit survival for *BRCA1/2* carriers, even if this is not apparent when looking at pathologic response.

Abraham, et al. Nat Commun. 2025;16(1):4269. PMID: 40360463. Article available at: https://pubmed.ncbi.nlm.nih.gov/40360463/. Social media post available at: https://www.facebook.com/share/p/1CRyyzRq1e/

Inherited Prostate Cancer: PARP Inhibitors

A new study combined the results of prior studies of PARP inhibitors in patients with metastatic castration-resistant prostate cancer and an inherited gene mutation through a meta-analysis. The results showed that PARP inhibitors provided the greatest benefit in *BRCA1/2* carriers and there was a strong signal of benefit in *PALB2* or CDK12 alterations. However, there was no benefit observed in those with *ATM* or *CHEK2* alterations.

Naqvi, et al. Eur Urol. 2025;87(6):626-640. PMID: 39848867. Article available at: https://pubmed.ncbi.nlm.nih.gov/39848867/. Social media post available at: https://www.facebook.com/share/p/1EaQ3dKG3H/

Ask the Expert

Brian Shirts, MD, PhD

The question was addressed by Brian Shirts, MD, PhD, President of ConnectMyVariant and Service Medical Director of the Molecular Genetics Laboratories at Vanderbilt University Medical Center. If you have a question you would like addressed, email ICARE@vumc.org for consideration in future newsletters.

Q: Why do you think cascade testing has not happened as much as we would like, and how do you think we can do better?

A: Talking to relatives about a genetic variant that may change their lives is hard! From a health care provider perspective, we should not be surprised when it does not happen as much as we would like. This is not the type of thing that comes easily for most people. Working with hundreds of people through ConnectMyVariant, I have seen a few things that make family communication about hereditary cancer genetics easier. **1) Find your team**. Find people who you can work with and encourage each other. Successful families often have more than one person working together. It might be a sister, aunt, cousin, or spouse who works with you to contact relatives. It could be a volunteer Family Outreach Navigator at ConnectMyVariant that you can go to for ideas and positive feedback. **2) Don't give up.** Sometimes relatives are not ready to get genetic testing. That is OK. Give them more than one opportunity to hear the information and understand the benefits of testing. Don't nag but let them know that you still care. **3) Seek a bigger community to see how it makes a difference.** People who have the same variant have a 90% chance of having a common ancestor. When people connect with others and start working together to explore distant family connections, miracles can happen. People may find a whole group of others to work with. They share stories and encourage each other. I have seen groups build huge family trees over a few years and help hundreds of others get genetic testing and cancer prevention. Understanding genetics beyond their immediate family helps people see that, even if their brother refuses to get testing, they can be part of a bigger cause that makes a difference for many others.

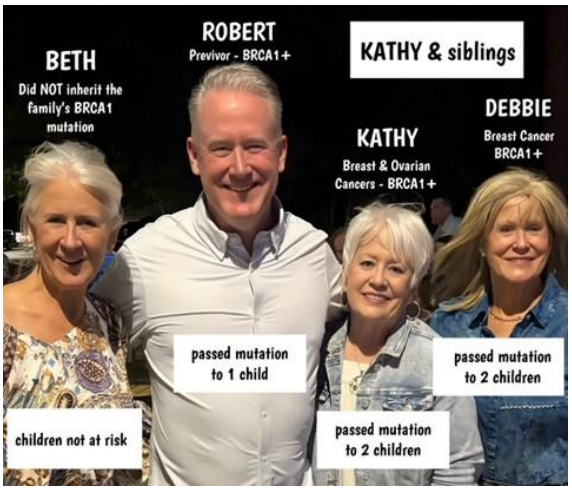
ConnectMy VARIANT

Discover Your Genetic Connections with ConnectMyVariant

A powerful resource designed to help those with inherited cancer risk connect with family, share genetic information, and build supportive communities. By signing up, you'll help advance research and support others on similar journeys. Check it out at https://connectmyvariant.org/signup-form/icare

ICARE Community Spotlight: Kathy Baker

I was only 30 when my 32-year-old sister was diagnosed with breast cancer. A couple years later, when a mobile mammography bus showed up at my law school offering free mammograms, I decided it couldn't hurt to be screened. When my mammogram was normal, I made plans to wait until age 50 for my next mammogram. But at age 42, a lump in my breast was detected during an exam, which turned out to be breast cancer. Thankfully, after a lumpectomy and many months of chemotherapy and radiation, I was declared to have no evidence of disease. At this point, my oncologist began recommending genetic testing due to my family's history of cancer.



For nine years, at every checkup my oncologist would once again bring up the subject of genetic testing. My response was always the same: "I'll think about it." But I didn't. Finally, in 2009, my sister and I agreed to the testing when our mother was nearing the end of her own battle with cancer. We both tested positive for a *BRCA1* mutation, and I knew I needed to have two risk-reducing surgeries, a double mastectomy and a complete hysterectomy. However, because I was self-employed, I did not have the time to take off work for two separate major surgeries, so my oncologist worked with me to make sure my one "big" surgery happened. After over 10 hours of surgery, I was stunned to learn the surgeon had unexpectedly discovered I already had early ovarian cancer! I firmly believe that I am alive today because of genetic testing. Had I not learned about MY FAULTY GENE through genetic testing and chosen risk-reducing surgeries, my cancer would have gone undetected until it was too late. I count every year since as a miracle year!

In 2020, I founded the non-profit My Faulty Gene (https://myfaultygene.org) as a way to "pay it forward" for being given the gift of life as a result of my genetic testing. My Faulty Gene is dedicated to helping ensure that everyone who needs genetic testing due to a suspected inherited gene mutation has access to it, because there is power in knowledge! After realizing that patient testimonials are a powerful way to share information, I went forward with a related effort, called Family Gene Share (https://familygeneshare.org), to create short professional videos focused on stories from individuals impacted by hereditary cancers. These videos are gene-specific and were created to help share genetic test results with family members and educate them about the importance of testing and care if they have an inherited cancer gene mutation.

Because educating about hereditary cancer risks is very important to me, I often reshare ICARE's excellent gene-specific content on My Faulty Gene's social media platforms. I am also personally enrolled in ICARE and encourage others to join, since I know research is the key to understanding inherited cancer risks and improving patient outcomes. With two of my children having inherited my *BRCA1* mutation and with grandchildren at a 50% risk of having the mutation, there's nothing more important to me.

Research Efforts and Resources

Real Pink Podcast: Decoding Genetic Testing

We're proud to highlight an episode from the Susan G. Komen's *Real Pink* podcast in which ICARE's Principal Investigator, Dr. Tuya Pal, discussed the critical role of genetic testing, how inherited gene mutations can increase cancer risk, and why early detection and education are key to saving lives. Listen to the full episode at https://tinyurl.com/realpink or by scanning the QR code below.

Genomic Characterization of Breast Cancer Study

Through ICARE, we are performing genomic analyses to better understand how breast cancers develop and identify additional treatment options to improve health outcomes in *BRCA1*/2, *PALB2*, *ATM*, and *CHEK2* carriers. Learn more about ICARE at https://inheritedcancer.net/. You may also enroll into ICARE directly online at https://redcap.link/ICAREconsent or by scanning the QR code below.

Expansion of Recommendation for Hereditary Cancers

Watch an exciting presentation from the NCCN 2025 Annual Conference, during which several inherited cancer experts discuss genes related to prostate, endometrial, and gastric cancers as well as the expanded NCCN Guidelines for Genetic/Familial High-Risk Assessment. Watch at https://tinyurl.com/nccnpres or read the full article at https://tinyurl.com/nccnpaper.

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