Spring 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 rapidly, reaching nearly 7500 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 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

Therapeutic Clinical Trials for *BRCA1* and *BRCA2* Carriers

We are also excited to introduce a new initiative to help match *BRCA1* and *BRCA2* carriers to novel treatment trials for which they may be eligible. If you are interested, please scan the QR code or go to https://redcap.link/ICAREcontactform where you may also provide more details about your history and ask any specific questions you may have.

Welcome Message

We are excited to share updates with you, as we strive *"To end the cycle of inherited cancer through research, education, and engagement."* We continue to work with colleagues across the globe to contribute to research studies that include data from ICARE participants, such as a recently published study about pancreatic cancer risks among *BRCA* carriers (as detailed on Page 3).[1] Our team has also contributed to several guideline updates, including NCCN (detailed below); a newly published *ATM* practice resource (as detailed on Page 2);[2] and a recently published study of specific *BRCA1* and *BRCA2* mutations that lead to lower breast cancer risks (~25% lifetime risk) than "typical" mutations that lead to breast cancer risks in the range of 60-70%.[3] As always, we sincerely thank our participants and provider contributors for their ongoing support and partnership as our efforts would not be possible without all of you.

With our sincere gratitude,

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

[1]*Katona, et al. Cancer. 2025;131(1):e35666. PMID: 39611336. Article available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC11694537/. Social media post available at: https://tinyurl.com/post12122024;* [2]*Pal, et al. Genet Med. 2025;27(1):101243. PMID: 39636577. Article available at: https://www.gimjournal.org/article/S1098-3600(24)00177-1/fulltext. Social media post available at: https://tinyurl.com/post12052024;* [3]*Pal, et al. NPJ Precis Oncol. 2024;8(1):247. PMID: 39488595. Article available at: https://www.nature.com/articles/s41698-024-00741-4. Social media post available at: https://tinyurl.com/post11112024.*

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

Breast, Ovarian, Pancreatic, and Prostate Cancer

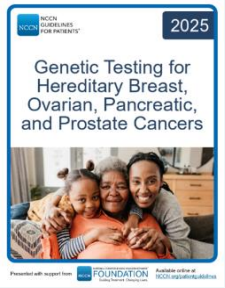
- **Version 2.2025** (*Released November 7th, 2024*): Added "prostate" to the name and the relevant content to improve consistency of information.
- **Version 3.2025** (*Released March 6th, 2025*): Updated the discussion (starting on Page 74 of the PDF) based on the current guidelines.
- *Check out the full guidelines by creating a FREE account at* www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

Colorectal, Endometrial, and Gastric Cancer

- **Version 2.2024** (*Released October 31st, 2024*): Age at which to consider gynecologic risk-reducing surgery (to lower risks for uterine and/or ovarian cancer) revised based on specific Lynch syndrome gene in which mutation is present (i.e., *MLH1*, *MSH2*, *EPCAM* and *MSH6*)
- **Version 4.2024** (*Released April 2nd, 2025*): Discussion updated (starting on Page 74 of the PDF) based on the current guidelines.
- *Check out the full guidelines by creating a FREE account at* www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

New 2025 NCCN Guidelines for Patients

We are excited to announce the release of the newly created 2025 NCCN Guidelines **for Patients**: Genetic Testing for Hereditary Breast, Ovarian, Pancreatic, and Prostate Cancers. These comprehensive guidelines provide valuable insights and information for patients navigating genetic testing. You can view and download a free copy of the guidelines by visiting: www.nccn.org/patients/guidelines/content/PDF/genetics-patient.pdf



ACMG Guidelines Focused on Risks and Care Among *ATM* Carriers

A panel of worldwide experts recently published recommendations for people with an *ATM* mutation, which raises the risk for breast, pancreatic, and prostate cancers.

Among women

› Breast cancer: Recommend starting annual breast magnetic resonance imaging (MRI) between age 30 to 35 and adding mammograms at age 40. Routine consideration of risk-reducing mastectomy is not supported by evidence. In women diagnosed with breast cancer, shared decision-making about bilateral mastectomy should be made estimating individual risks based on the age, tumor size, stage, grade, receptor status and family history.

› Ovarian cancer: Generally, the risk threshold to consider removing the ovaries and fallopian tubes is not met; however, family history of ovarian cancer can be considered and shared decision-making remains important. Screening is not advised since no reliable methods to detect ovarian cancer early are known.

Check out an overview by Drs. Tischkowitz and Pal, who co-led this *ATM* effort, at: https://youtu.be/T76iGtn8_Do

Among men

› Prostate cancer: Prostate-specific antigen (PSA) testing should begin at age 40 on an annual basis. A digital rectal exam may be useful to guide interpretation of PSA findings.

Among both women and men

› Pancreatic cancer: Surveillance through annual endoscopic ultrasound (EUS) or MRI cholangiopancreatography (MRI/MRCP) may be considered, though recommendations vary greatly across countries. Surveillance should be done at medical centers with appropriate expertise. The panel of experts noted that more research is needed, ideally as part of a clinical trial.

Pal T, et al. Genet Med. 2025;27(1):101243. PMID: 39636577. Article available at: https://tinyurl.com/atmarticle. Social media post available at: https://tinyurl.com/post12052024.

Lynch Syndrome: Personalizing Risks

Check out a recent presentation by Dr. Yurgelun, who helped develop MyLynch, at: https://youtu.be/5l3GLYtDN_E

MyLynch is a resource for Lynch syndrome patients that provides personal cancer risks, education on interventions, and adjusted risk estimates, depending on the intervention(s) the patient chooses to pursue. If you have Lynch syndrome, go to https://hereditarycancer.dfci.harvard.edu/mylynch/ to get your personalized risk estimate.

Knapp, et al. Cancers (Basel). 2023;15(2):391. PMID: 36672340. Article available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC9856567/. Social media post available at: https://tinyurl.com/post442025.

Working Towards Defining a New Category of Reduced Penetrance *BRCA1/2* Variants

We recently published a study that brings attention to "reduced penetrance" *BRCA1* and *BRCA2* (*BRCA*) mutations, which lead to LOWER breast cancer risks than "typical" *BRCA* mutations.[1] Specifically, these mutations lead to a lifetime breast cancer risk of 20-30%, similar to moderate penetrance breast cancer genes such as *CHEK2* or *ATM*. This level of risk does not typically warrant the option for risk-reducing mastectomy, although high-risk screening with breast MRI and mammograms would continue to be recommended. The specific variants included in this paper are outlined in **Table 1** below (also posted to our social media accounts **@inheritedcancer**). This work, done by our team at Vanderbilt, Moffitt, and Mayo, in collaboration with our commercial laboratory colleagues at Ambry and Myriad, is ongoing and just the beginning. More variants like this will be identified, and it is important to define and clarify this new class of variants in order to refine risks and contribute to improving patient care.

Table 1: Specific *BRCA1* and *BRCA2* Variants

BRCA1	*BRCA2*
c.5096G>A	c.658_659delGT
c.671-1delins6	c.9672dupA
c.671-2A>T	c.9699_9702delTATG
c.671-2A>G	c.7878G>C
c.671-2A>C	c.7878G>T
c.671-1G>T	c.9302T>G
c.671-1G>C	c.8488-1G>A
c.671-1G>A	c.8488-1G>T

Another subsequently published article led by the team at Mayo tried to classify over 6000 *BRCA2* missense variants (meaning a change in the amino acid that does not typically shorten the protein and can often lead to a Variant of Uncertain Significance (VUS) classification) using various databases and laboratory studies.[2] Because VUS results are not useful in directing care, better strategies to characterize these results are needed. The team was able to classify 91% of 6960 variants. This is important to improve risk assessment and management in those with a variant in *BRCA2*.

Check out an overview of this missense variant work by Dr. Couch at: https://youtu.be/HpTDRRJ3c4U

[1]Pal, et al. NPJ Precis Oncol. 2024;8(1):247. PMID: 39488595. Article available at: https://tinyurl.com/39488595. Social media post available at: https://tinyurl.com/post11112024. An overview by Dr. Tuya Pal is available on our ICARE YouTube channel at: https://youtu.be/CZI46jH3DJY; [2]Huang, et al. Nature. 2025;638(8050):528-537. PMID: 39779857. Article available at: https://tinyurl.com/39779857. Social media post available at: https://tinyurl.com/post2132025.

BRCA1/2: Second Primary Cancers After Breast Cancer

Through linking test results to electronic health records in England from 1995 to 2019, researchers estimated risks of a second primary cancer after breast cancer for *BRCA1/2* carriers (**Table 1**) as well as risks over 10 years (**Table 2**). This study gives us more generalizable information about cancer risks to help guide risk assessment and management.

Table 1: Second Primary Cancer Risks in *BRCA1* and *BRCA2* Carriers

Second Primary Cancer Type	*BRCA1*		*BRCA2*	
	SIR	HR	SIR	HR
Contralateral breast	15.6	3.6	7.7	2.4
Ovarian	44	33	16.8	12
Combined non-breast or ovarian	2.18	1.45	1.68	
Colorectal	4.8	2.93		
Endometrial	2.92			
Pancreatic			5.72	3.56
Male breast				13.1
Prostate				5.61

SIR: Standardized Incidence Ratio (represents comparison with population-level incidences); HR: Hazard Ratio (represents comparison with non-carriers); A blank cell represents insignificant data.

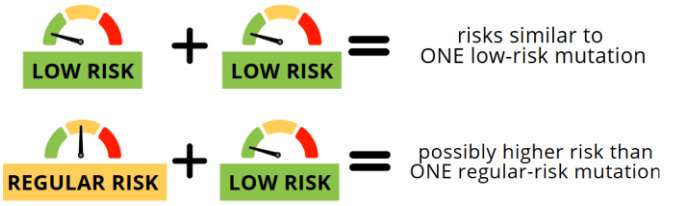
Table 2: Cancer Risks Over 10 Years

Cancer Type	*BRCA1*	*BRCA2*	Non-Carriers
Contralateral breast	16.0%	12.0%	3.6%
Ovarian	6.3%	3.0%	0.4%
Combined non-breast or ovarian	7.8%	6.2%	4.9%

Allen, et al. J Clin Oncol. 2025;43(6):651-661. PMID: 39475295. Article available at: https://ascopubs.org/doi/10.1200/JCO.24.01146. Social media post available at: https://tinyurl.com/post1282025.

Refining Specific *CHEK2* Mutation Risks

A recent editorial highlighted three common low-risk *CHEK2* mutations (p.I157T, p.S428F, and p.T476M) that lead to a breast cancer risk of <1.4 fold (compared to "typical" *CHEK2* mutations where the risk is over 2-fold).[1] This is important because the level of risk for these mutations does not warrant high-risk screening. Another study on these three low-risk mutations showed how combinations of low- and regular-risk *CHEK2* mutations may affect breast cancer risk.[2] Results showed differing risks for various combinations of variants as shown below.



An accompanying editorial highlights the importance of contextualizing cancer risks for these low-risk variants based on the second allele ('mutation').[3] While biallelism (meaning having two mutations) does not occur that often, this work shows the importance of discussion at the VARIANT alleles level to guide cancer risk and care.

[1]Hernandez et al. Oncotarget. 2024:15:459-460. PMID: 38985133. Article available at: https://tinyurl.com/fullarticle28604. Social media post available at: https://tinyurl.com/post10312024; [2]Bychkovsky, et al. JAMA Netw Open. 2025;8(1):e2451361. PMID: 39745704. Article available at: https://tinyurl.com/fullarticle2828642; Social media post available at: https://tinyurl.com/post2102025; [3]Rajagopal. JAMA Netw Open. 2025;8(1):e2451303. PMID: 39745708. Article available at: https://tinyurl.com/fullarticle2828646. Social media post available at: https://tinyurl.com/post2102025.

BRCA1/2: Pancreatic Cancer Risks in Women

A new international study in over 8000 *BRCA1/2* carriers, which **included data from ICARE participants**, showed risk of pancreatic cancer to age 80 in *BRCA1* was 2.2% (95% CI: 1.1%-4.3%) and in *BRCA2* was 2.7% (95% CI: 1.3%-5.2%). Of the 34 *BRCA1/2* carriers with pancreatic cancer, only 2 had a close (first-degree) relative with pancreatic cancer, suggesting that family history didn't predict who would get these cancers. Of those with pancreatic cancer, less than 10% were alive after 5 years, showing the urgency to find strategies for prevention and early detection.

Katona, et al. Cancer. 2025;131(1):e35666. PMID: 39611336. Article available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC11694537/. Social media post available at: https://tinyurl.com/post12122024.

New ASCO Guideline: Advanced Stage Ovarian, Fallopian Tube, and Peritoneal Cancer

A new guideline from the American Society of Clinical Oncology (ASCO) was released January 22nd, 2025, updating care for women with advanced-stage ovarian, fallopian tube, or primary peritoneal cancer. Recommendations included that these patients should be evaluated by a gynecologic oncologist before starting treatment to determine if they are candidates for primary cytoreductive surgery (meaning surgery to remove as much tumor as possible before starting treatment). They also recommended that germline and somatic testing for *BRCA1* and *BRCA2* as well as germline testing for other ovarian cancer susceptibility genes should be done. These updates reinforce the importance of genetic testing and specialized evaluation in treatment planning, ensuring patients receive the most effective and personalized care.

Gaillard, et al. J Clin Oncol. 2025;43(7):868-891. PMID: 39841949. Article available at: https://ascopubs.org/doi/10.1200/JCO-24-02589. Social media post available at: https://tinyurl.com/post2072025.

PARP Inhibitor: Relapsed *BRCA*-Mutated Ovarian Cancer

A new study (phase 3 ARIEL4 trial) to evaluate rucaparib (PARP inhibitor) versus standard-of-care chemotherapy among patients with relapsed *BRCA*-mutated ovarian cancer showed that median overall survival in the rucaparib group was 19.4 months versus 25.4 months in the chemotherapy group. This shows that more research is needed to figure out the most appropriate treatment options for patients who progressed on a PARP inhibitor.

Oza, et al. Lacet Oncol. 2025;26(2):249-264. PMID. 39914419. Article available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(24)00674-0/abstract. Social media post available at: https://tinyurl.com/post32425.

ICARE Community Spotlight: Sara Kavanaugh

As someone with two inherited cancer gene mutations—*MSH6* (Lynch syndrome) and *CHEK2* — I know firsthand the emotional and practical complexities of navigating hereditary cancer risk. My journey began without what many might consider "classic" red flags — just a few scattered cancer cases in my family, none of which seemed connected at the time. However, my breast specialist, who takes a conservative approach to patient care, recommended genetic testing to rule out additional risk factors, as I was already considered high risk due to my extremely dense breasts.

That single recommendation opened the door to a journey filled with its share of ups and downs — preventative surgeries, extra screenings, and moments of uncertainty — but ultimately, I am grateful that there have been more ups than downs. Most importantly, it connected me with one of the most supportive communities I've ever encountered.

Through it all, I've found that curiosity has been my greatest source of strength. The more I've learned about my genetic risks, the more confident and in control I've felt— with ICARE providing support along the way. What once felt overwhelming now feels purposeful as I manage my care and help others do the same, all thanks to ICARE's reliable and easy-to-understand resources.

Since joining ICARE, I have been invited to and have participated in the IMPACT Study, which aims to improve how care is delivered after receiving genetic test results. Through ICARE, I've contributed to focused research efforts like the IMPACT Study while staying connected to valuable updates that help me — and others — make informed decisions about our health.

One notable example of how this has helped me personally was receiving gene-specific updates when NCCN revised screening guidelines for my *CHEK2* variant—a powerful reminder of how critical it is to stay engaged and informed as research evolves. Additionally, the information is so well laid out that I was able to send it to my family members who are interested in learning more while they consider genetic testing.

As a hereditary cancer Previvor, I am honored to support ICARE's mission, which includes amplifying awareness through my podcast, *The Positive Gene Podcast.* This platform has allowed me to reach out to others and share important information about hereditary cancer risk, including ICARE's work. For instance, I recently hosted Dr. Tuya Pal (who founded and leads ICARE) on my podcast, discussing ICARE's mission to make cancer genetics expertise more accessible—especially for those who might not otherwise have it.

Participating in ICARE is about more than staying ahead of cancer—it's about working together to empower others. As a podcast host and advocate, one of my roles is to help share valuable resources from organizations like ICARE, so more people feel informed and supported on their journeys. I'm grateful to ICARE for the meaningful work they do every day, and I encourage them to keep going. I carry this spirit into every podcast closing: stay proactive, stay informed, and remember, you are never alone on this journey.

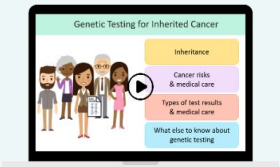
Research Efforts and Resources

FamilyGeneShare: Testimonials from People Affected with Inherited Cancers

We invite you to explore short videos of personal stories from people with inherited cancer due to specific genes (e.g., *BRCA1*, *BRCA2*, *PALB2*, Lynch Syndrome, and other genes), produced by My Faulty Gene. You may watch these videos at https://familygeneshare.org. Sharing these videos with family members may be an effective way to explain the importance of genetic testing to them.

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

Have you already had genetic testing for inherited cancer and want more information about your results? Or are you considering getting tested and want information and guidance before getting tested? Enroll in TIPS to receive free education about inherited cancer and a personalized inherited cancer risk assessment at https://redcap.link/TIPS or by scanning the QR code below.



Inherited Cancer Registry (ICARE)

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

Did you know that by participating in ICARE, you can be a part of new focused research efforts, get care updates personalized to you, and find out about other studies you may be eligible for? Learn more about participating in ICARE by visiting https://inheritedcancer.net/. You may also enroll into ICARE online at https://redcap.link/ICAREconsent or by scanning the QR code below.

VANDERBILT-INGRAM CANCER CENTER

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