



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

Phone: (615) 875-2444 | Email: ICARE@vumc.org | Website: InheritedCancer.net

Table of Contents

Guideline, Cancer Risk, & Genetics Updates.....	2
Research & Clinical Updates.....	3
Ask the Expert.....	3
Community Spotlight, Research, & Resources.....	4

About ICARE

ICARE continues to grow rapidly, reaching over 8,500 participants, including almost 2,000 individuals with *BRCA1/2* mutations and more than 2,000 individuals with other inherited cancer gene mutations. ICARE participants represent 50 U.S. states, the District of Columbia, the 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, visit InheritedCancer.net to learn more about ICARE and how participating may benefit you.

Welcome Message

We are excited to provide you with several updates related to inherited cancer. Notably, there have been some exciting updates to two inherited cancer-focused practice guidelines through the National Comprehensive Cancer Network (NCCN) as outlined below. We have also been busy continuing to publish our work, made possible by our ICARE participants, including some exciting results of our clinic trial focused on sharing genetic test results,¹ as well as our study evaluating tumor genomics from women with hereditary breast cancer due to *BRCA1*, *BRCA2*, *PALB2*, *ATM*, and *CHEK2* mutations.² We hope you find these newsletter updates interesting and informative. We are only able to contribute to ending *"the cycle of inherited cancer through research, education, and engagement"* because of your continued interest to participate in our efforts.

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

¹ Cragun, et al. *Genet Med*. 2026;28(10):102694. PMID: 42626853. Article: <https://pubmed.ncbi.nlm.nih.gov/42626853/>. Social media post: <https://inheritedcancer.net/post91826/>; ² Yadav, et al. *J Natl Cancer Inst*. 2026;118(8):1416-1424. PMID: 41832987. Article: <https://pubmed.ncbi.nlm.nih.gov/41832987/>. Social media post: <https://inheritedcancer.net/post032526/>

National Comprehensive Cancer Network (NCCN) Guidelines Update

Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, & Prostate (Version 1.2027)

Released August 31st, 2026: https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

GENE TABLES EXPANDED

- New summary table to show you where to find your specific gene (**GENE-A**)
- Each gene has its own page (**GENE-A (1-19)**)
- *SMARCA4* added (**GENE-A (16 of 19)**)

GENETIC TESTING

- Testing may be appropriate for some individuals with a close family member who meets testing criteria but has **not** had genetic testing. This helps expand access to testing for families seeking answers (**CRIT-2 & 6**), while acknowledging that testing the affected family member is most informative (**CRIT-2, 4, 6A, 7, & 8**)

PRINCIPLES SECTION

- If you've had an allogeneic bone marrow or stem cell transplant, blood or saliva genetic testing may **not** accurately reflect your own inherited DNA because donor cells can affect results (**EVAL-A (2 of 11)**)
- Research is promising, but experts currently recommend caution and do not support using polygenic risk scores (PRS) alone to guide medical management outside of clinical trials (**EVAL-A (3 of 11)**)
- At-home, direct-to-consumer genetic tests can provide interesting information about your ancestry and health, but they are **not** designed to replace medical genetic testing. Results may be incomplete or inaccurate, so findings should be confirmed through a clinical lab before making healthcare decisions (**EVAL-A (4 of 11)**)
- Added section of atypical risk pathogenic/likely pathogenic variants to highlight the importance of looking beyond the gene name alone and considering the specific variant and family history when assessing risk and discussing cancer screening and prevention options (**EVAL-A (6 of 11)**)
- For negative results, added "eligibility for emerging therapies" as an indication for updated testing (**EVAL-A (8 of 11)**). Even if past genetic testing was negative, advances in cancer treatment may create new reasons to revisit testing. Updated genetic testing may help determine whether someone could benefit from newer targeted therapies, such as PARP inhibitors.

MANAGEMENT

- Added principles of breast cancer risk management (**GENE-B (1-2)**) & principles of ovarian cancer risk management (**GENE-C (1-2)**)
- *BRCA1/2* management update to indicate that there is limited data suggesting benefit from Tamoxifen, particularly for *BRCA2* carriers (**BRCA-A (1 of 5)**)
- Pancreatic cancer screening updated to reflect a strong family history may be enough for some people to qualify for screening, even if no inherited genetic mutation has been identified. New criteria has also been added to start screening at age 50-55 or earlier based on the youngest diagnosis in the family (**PANC-A (2 of 2)**)
- Whole-body MRI is an important screening tool for Li-Fraumeni Syndrome patients, but there is currently no single standardized way it is performed. Some areas of the body may **not** be fully included depending on the imaging protocol used (**LIFR-A (4A of 6)**)

National Comprehensive Cancer Network (NCCN) Guidelines Update

Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, Esophageal, and Gastric (Version 1.2026)

Released June 16th, 2026: https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceeg.pdf

- Esophageal cancer added to name of this guideline, with a section added on hereditary esophageal cancer (**HESOPH-1 & 2**)
- One of the biggest changes was recommendation for genetic testing for all colorectal, endometrial, and gastric cancers
- Tumor screening for MMR deficiency recommended for the following cancers: sebaceous neoplasms, small bowel, biliary tract, brain, bladder/urothelial, and adrenocortical cancers
- The panel set a specific minimal set of genes to test for colorectal, endometrial, and gastric cancer:

COLORECTAL CANCER GENES

(including genes that predispose to polyps)

- **Recommend:** *APC* (Familial Adenomatous Polyposis), Juvenile Polyposis genes (*BMPT1A* & *SMAD4*), Lynch Syndrome genes (*MLH1*, *MSH2*, *EPCAM*, *MSH6*, *PMS2*), biallelic *MUTYH*, *PTEN* (Cowden), *STK11* (Peutz-Jeghers), and *TP53* (Li-Fraumeni).
 - **Consider:** *AXIN2*, *GREM1*, *POLE*, *POLD1*, and biallelic mutations in *MSH3*, *MLH3*, *MBD4*, and *NTHL1*.
 - Additional genes that sometimes get included: *ATM*, *BLM*, *CHEK2*, *GALNT12*, *RNF43*, and *RPS20*.
- Test selection and decision to retest including additional genes beyond these minimal sets should be based on considerations such as: age at presentation, type of polyps, personal and family history of cancer, and patient and provider preference

ENDOMETRIAL (UTERINE) CANCER GENES

- **Recommend:** *BRCA1/2*, *PTEN*, and Lynch Syndrome genes (*MLH1*, *MSH2*, *EPCAM*, *MSH6*, *PMS2*).
- **Consider:** *POLD1* and *POLE*.

GASTRIC CANCER GENES

- **Recommend:** *APC* (including *APC* promoter 1B), *ATM*, Juvenile Polyposis genes (*BMPT1A* & *SMAD4*), *BRCA1/2*, *PALB2*, Hereditary Gastric Cancer genes (*CDH1* & *CTNNA1*), Lynch Syndrome genes (*MLH1*, *MSH2*, *EPCAM*, *MSH6*), *STK11* (Peutz-Jeghers), and *TP53* (Li-Fraumeni).

Check out the full NCCN guidelines by creating a FREE account at [nccn.org](https://www.nccn.org)

For additional instructions on accessing and navigating NCCN guidelines, scan the following QR code:



ACMG Points-to-Consider: Variants of Uncertain Significance

A new ACMG Points-to-Consider article provides advice for clinicians and genetic testing labs regarding reporting of Variants of Uncertain Significance (VUS) to better balance the potential benefits and harms of reporting such variants, offer suggestions for following up on genetic test reports, and consider adopting VUS subclasses and updating reports when variant classifications change. They outlined that all VUS results are not equal! Thus, they suggested a subcategorization system which included: VUS-low (lowest concern), VUS-mid (uncertain), and VUS-high (higher concern). They also suggested VUS results should be reported in symptomatic genetic testing when results relate to the patient's condition. On the flip side, they suggested not to report a VUS in population/screening testing for disease risk. This matters because over 90% of clinicians, genetic counselors, lab directors, AND patients surveyed agree that clearer reporting helps guide better follow-up care. This guidance helps labs prioritize which variants are most likely to explain a patient's symptoms and reduce unnecessary follow-up on unlikely findings. We expect that an updated sequence variant classification standard (SVC v4.0) will come out soon, to make this approach standard across all genetic testing labs. These recommendations put patients first—ensuring results are clear, actionable, and personalized to individual cases.

Mighton, et al. Genet Med. 2026;102583. PMID: 42287277. Article: <https://pubmed.ncbi.nlm.nih.gov/42287277/>. Social media post: <https://inheritedcancer.net/post070726/>

AACR Cancer Disparities Report

The AACR Cancer Disparities Progress Report was just released in June 2026! This new report highlights the need to advance policies to expand access to genetic testing, which is important in achieving health equity (see pages 202 and 207 of report for more details). In particular, they reviewed HR.4752/S.2760: Reducing Hereditary Cancers Act and explained the importance of this proposed bill. The purpose of this bill (which has bipartisan support) is to expand Medicare coverage for genetic counseling and testing, as well as screening for those without cancer but with family history or known hereditary mutations

It is important to recognize that Medicare covers genetic testing only AFTER a cancer diagnosis, which leaves millions of Americans unable to act on inherited cancer risk until it is too late (and they already have cancer). This bill would fix this gap coverage for Medicare patients, so those without cancer would have the following paid for:

- Genetic testing in those eligible (because of family cancer history or a known mutation in the family)
- Recommended screening or prevention for cancer (in those with inherited cancer gene mutations)

Read the report at:

https://cancerprogressreport.aacr.org/wp-content/uploads/sites/2/2026/06/AACR_CDPR_2026.pdf

More Melanomas Are Due to Inherited Mutations Than Previously Thought

New research shows that inherited melanomas are more common than previously realized. Specifically, in a study of almost 700,000 people, about 1 in 100-200 individuals had a mutation in a melanoma risk gene. Many of the mutations detected were in the *MITF* gene (E318K variant), and the overall prevalence of gene mutations was over 2.5%. These findings suggest that more people may benefit from genetic testing and skin cancer screening. If you might be at risk, talk to your healthcare provider.

Goldstein, et al. *JAMA Dermatol.* 2026;e261305. PMID: 42201696. Article: <https://pubmed.ncbi.nlm.nih.gov/42201696/>. Social media post: <https://inheritedcancer.net/post92926/>

Ovarian Cancer Survivors

A new study shows that women with high grade serous ovarian cancer who remain cancer free for 7 years or more had nearly the same mortality risk as the general U.S. population. Of note, most of the women in this study had stage 3 ovarian cancer. Those with homologous repair deficiency (HRD) ovarian tumors (which is present in *BRCA1/2* carriers) had substantially higher survival than those without HRD, both at 5 and 10 years out from their diagnosis:

- Event-Free Survival at 5 years (24.3% vs. 14.7%) and 10 years (15.5% vs. 8.9%)
- Overall Survival at 5 years (54.6% vs. 34.9%) and 10 years (28.4% vs. 16.8%)

This means that once an ovarian cancer survivor has reached the 7 year mark and is cancer free, their mortality rates are similar to that of the U.S. general population.

De Vitis, et al. *JCO Oncol Adv.* 2026;3(1):e2500142. PMID: 41918500. Article: <https://pmc.ncbi.nlm.nih.gov/articles/PMC13035374/>. Social media post: <https://inheritedcancer.net/post50526/>

Results Disclosure and Follow-up Communication with Family

We are excited to share our latest publication which included ICARE participants. Our results showed that GeneSHARE, an online family communication intervention, significantly increased the sharing of hereditary cancer genetic test results with at-risk relatives, highlighting the importance of providing practical tools and timely resources to support family communication after testing.

Cragun, et al. *GenetMed.* 2026;28(10):102694. PMID: 42626853. Article: <https://pubmed.ncbi.nlm.nih.gov/42626853/>. Social media post: <https://inheritedcancer.net/post91826/>

BRCA1: Hormone Replacement Therapy After Ovary Removal

A new study shows that estrogen-only hormone replacement therapy (HRT) after ovary removal can LOWER breast cancer risk in cancer-free women carrying the *BRCA1* genetic mutation.

This study showed that women using HRT had many fewer cases of breast cancer compared to those that did not use HRT (11% vs 19%). The longer women used estrogen-only HRT, the greater the protection, with every additional year of use lowering risk by about 10%. This is another study to show that HRT appears safe to take in *BRCA1* carriers after removing their ovaries (i.e., surgical menopause). We know that estrogen is important in premenopausal women for bone health, cardiovascular health, etc. If you have *BRCA1* or *BRCA2* mutations, talk to your doctor about what options might be right for you.

Regev-Sadeh, et al. *JAMA Netw Open.* 2026;9(4):e265648. PMID: 41949865. Article: <https://pubmed.ncbi.nlm.nih.gov/41949865/>. Social media post: <https://inheritedcancer.net/post60226/>

NHS Galleri Trial: Blood Test for Cancer Detection

A new study (NHS-Galleri trial) tested whether a simple blood test could catch more cancers early. Bottom line: Stage 3 and 4 cancers (together) were not lowered by this study, so this test is NOT ready for prime time yet! A small silver lining is that when looking at stage 4 cancers alone, there was a 14% reduction, which MIGHT be promising.

We know that the key to effective screening tests is to find cancers at an early rather than late stage. Basically, this study tells us that more work is needed before blood tests become routine screening.

Kuznar, W. (n.d.). Multicancer early detection test fails to reduce cancers detected at late stages: However, an increase in the detection of stage I/II cancers was observed. *MedPage Today*. Full story: <https://www.medpagetoday.com/meetingcoverage/asco/121498>. Learn more about the NHS-Galleri trial: <https://clinicaltrials.gov/study/NCT05611632>

Ask the Expert

The following question was addressed by Sheila Rajagopal, MD, MSc, MPH, a board-certified medical oncologist and bioinformatician, who recently joined us at Vanderbilt University Medical Center.

Q: In people with hereditary cancers, why might genetic testing in the tumor be important to guide treatment?

A: You may hear about two types of "genetic testing" – (1) testing for inherited cancer risk, which uses saliva, blood, or skin, to find genetic changes you were born with, and (2) testing on tumor tissue, which looks for possible changes arising only in the cancer and not the rest of the body. Depending on what type of cancer and at what stage, you may undergo one or both types of testing, so it is important to know what type of genetic testing you underwent.

Testing for inherited cancer risk can help guide some treatment options. For example, patients who have a known *BRCA1/2* alteration may be aware of or have received PARP inhibitor therapy.

Testing on tumor tissue is different. For one thing, this testing often looks at hundreds more genes, which may change only in the cancer but not the rest of the body. For another thing, we may look for (1) overall changes across the tumor, such as tumor mutation burden, (2) in the actual gene sequences (DNA changes), or (3) in how genes are expressed (gene expression assays or RNA). When clinically indicated (meaning results of research have shown benefit to patients), testing for tumors can provide important information to guide treatment options that kill cancer cells in specific cancer types.



Sheila Rajagopal,
MD, MSc, MPH

Community Spotlight: Krista Brown



My mom was diagnosed with breast cancer at 48 and tested negative for *BRCA1/2*, which were the only genes they were testing for at that time. Twelve years later, she had expanded panel testing. Shortly before she passed away, she learned she carried an *ATM* mutation (c.7271T>G), which leads to higher risks of breast cancer than typical *ATM* mutations. Once I learned about her *ATM* result, I got tested too. I was 38 years old when I learned I had inherited her *ATM* mutation.

Initially, it was overwhelming to learn I had an increased risk of cancer. But as I learned more, genetic information began to feel less like something that was taking choices away from me and more like information that gave me options. I began high-risk breast screening, alternating mammograms and MRIs every six months. While bilateral mastectomy is not generally recommended solely based on having an *ATM* mutation, my *ATM* mutation leads to much higher lifetime risks of breast cancer (~60%) compared to typical *ATM* mutations (~25%). For this reason, paired with my family history, I decided to have a risk-reducing bilateral mastectomy.

While I was waiting for surgery, a breast MRI showed an abnormality that led to further testing and, ultimately, a breast cancer diagnosis—just two weeks before my scheduled preventive surgery. In what felt like an instant, everything changed. Suddenly, I was no longer asking, “Do I really need to do this?” Instead, I was asking, “What are we dealing with, and how far has it spread?” Surgical pathology confirmed stage 1A breast cancer. In that moment, I truly understood what a gift genetic testing had been to me. Without knowing about my cancer risk, the breast cancer may have been detected at a later, more difficult-to-treat stage.

Today I work as an oncology nurse navigator and have the unique experience of sitting on both sides of the healthcare conversation—as a patient and as a nurse. I use that perspective in my work and advocacy every day, helping patients understand hereditary cancer risk, screening, risk reduction, survivorship, and the importance of using their voice to advocate for personalized care through my social media platform [@cancerpreventionrn](https://twitter.com/cancerpreventionrn). Knowing I carry an *ATM* pathogenic variant means my three daughters and other family members now have information about their own potential hereditary cancer risk. If they are found to carry the familial variant, they will have the opportunity to make informed decisions about screening and risk reduction. That is also why my participation in ICARE is so meaningful to me. Through research I hope to help create better information for the people who come after me, including my daughters and future generations of families navigating hereditary cancer risk. Knowledge doesn't eliminate cancer risk, but it does provide us with options and opportunities that can change the trajectory of our lives for the better.

New ESMO Recommendations About Genetic Testing

The European Society of Medical Oncology (ESMO) evaluated breast cancer susceptibility genes on the basis of cancer-related mortality to help guide which genes should be included in genetic testing for inherited breast cancer. They indicated that those that may lead to patients living longer included: *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, *RAD51D*, *TP53* (for breast cancer diagnosed < age 40), and *BRIP1* (possibly). Other genes that might help estimate risks, although uncertain they lead to patients living longer, included: *CHEK2* and *ATM*. The group recommended strongly against inclusion of 'syndromic' genes such as *STK11*, *PTEN*, *NF1*, and *CDH1*, when considering testing at a population level.

Turnbull, et al. *Ann Oncol*. 2025;36(8):853-865. PMID: 40523834. Article: <https://pubmed.ncbi.nlm.nih.gov/40523834/>. Social media post: <https://inheritedcancer.net/post42826/>

Research Efforts and Resources

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 online at <https://redcap.link/ICAREconsent> or by scanning the QR code below.



Initiative in Partnership with ConnectMyVariant

We are working to improve *BRCA1* and *BRCA2* cancer risk estimates through helping family members get free genetic testing (as well as optional free ancestry testing). By participating, you'll help advance research and support other families affected by inherited cancer. Learn more and sign up at <https://connectmyvariant.org/signup-form/icare>



INSTAGRAM LIVE

UPDATES IN GENETIC TESTING & MANAGEMENT FOR HEREDITARY BREAST CANCER

WEDNESDAY, OCTOBER 7TH
5 PM MT | 6 PM CT | 7 PM ET

Tanya Patel, MD
Clinical Geneticist

Kathy Baker
Founder of My Faulty Gene

Krista Brown, MS, RN
Oncology Nurse Navigator

Sonya Reid, MD, MPH
Breast Medical Oncologist

Sheila Rajagopal, MD
Medical Oncologist

Join us @inheritedcancer