Spring 2026

ICARE NEWSLETTER

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

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About ICARE

ICARE continues to grow rapidly, with nearly 8200 participants, including almost 1900 *BRCA1/2* carriers and over 2800 individuals with other inherited cancer gene mutations. Participants represent 50 U.S. states, the District of Columbia, the U.S. Virgin Islands, and 31 other countries worldwide. If you have been affected by inherited cancer or care for those affected by inherited cancer, visit InheritedCancer.net to learn more about how participating in our efforts may benefit you. We also encourage you to follow @inheritedcancer for the latest clinical and research updates.

NCCN Guidelines Insights Article

JNCCN released an article in the February issue with insights on:

Prostate cancer screening:

› Review of genes/risks: *BRCA1/2*, *HOXB13*, *ATM*, *CHEK2*, *MSH2*, *PALB2*, and *TP53*

› Prostate MRI recommended screening is done in experienced high-volume centers after an in-depth discussion

Pancreatic cancer screening:

› Screening without need for family history: *CDKN2A*, *STK11*, *ATM*, *BRCA2*

› Family history needed: *BRCA1*, *MSH2*, *MLH1*, *MSH6*, *EPCAM*, *PALB2*, *TP53*

Testing for non-epithelial ovarian cancer:

› SCCOHT: test for *DICER1*

› SCTAT: test for *STK11* (Peutz-Jeghers)

› Given rarity, consultation with expert may be considered

Cheng, et al. J Natl Compr Cancer Netw. 2026:24(2):2-10. PMID: 41671423.Article available at: https://jnccn.org/view/journals/jnccn/24/2/article-p2.xml. Social media post available at: https://www.facebook.com/share/p/1Rk6tvn2AB/

Welcome Message

We are excited to share ongoing progress relevant to inherited cancer predisposition, ranging from refining risks to guiding treatments, with the goal of improving care. In partnership with ConnectMyVariant (led by our colleague, Dr. Brian Shirts), we are trying to help refine *BRCA1/2* variant-specific risks, particularly among variants suspected to confer lower risks. We are doing this through working with ConnectMyVariant by building out more families. Family members can be tested for free through the lab of Dr. Marie-Claire King (who named the *BRCA1* gene, after discovering its location on chromosome 17 to show that inherited breast and ovarian cancer genes existed) and can also get free ancestry testing. These types of efforts are important to provide information about cancer risks for specific variants. Additionally, we have included new research about hormone replacement therapy-related risks in *BRCA1/2* carriers in our 'Ask the Expert' section; and highlighted additional research advances focused on refining risks and guiding care. Finally, we recently report on our study of breast cancers among *BRCA1/2, PALB2, ATM,* and *CHEK2* carriers, with some interesting results that we hope will contribute to figuring out the best treatments (see Page 4). These efforts are ongoing and only made possible through the willingness of our ICARE participants to enroll in this registry, for which we remain tremendously grateful. We hope you find the information in this newsletter both informative and helpful, and 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

National Comprehensive Cancer Network (NCCN) Guideline Update

Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, & Prostate

Select updates are outlined below. Check out the full guidelines by creating a FREE account at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

Version 2.2026 focused on adding comprehensive prostate cancer information and revising the name of the guidelines to encompass prostate cancer. Updates included:

- Recommendations (*BRCA2*) and considerations (*ATM*, *BRCA1*, *CHEK2*, *HOXB13*, *PALB2*, and *TP53*) for prostate cancer screening which are meant to be annual.
- Adding *HOXB13* in gene table, indicating an absolute prostate cancer risk: ~33-60% by age 80, predominantly based on the p.G84E variant. More recently, the X285K variant has been identified in males of African ancestry. Overall, *HOXB12* is not associated with aggressive disease, based on the majority of studies to date.
- Among *BRCA1/2* carriers, prostate cancer screening may also include a baseline mpMRI by age 50 or 10 years younger than age at prostate cancer in the family, which should be done on clinical trial and in experienced high-volume centers. Moreover, screening should be done through a shared decision-making model, with discussion of potential limitations, including cost, high incidence of benign or indeterminate abnormalities, and uncertainties about the potential benefits

Version 3.2026 encompassed updates to the discussion section.

Introducing the NCCN Guidelines Navigator™

Explore this new interactive, color-coded platform designed to simplify navigation of NCCN's Genetics/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate cancer guidelines. Whether you're a clinician, researcher, or advocate, this tool helps you stay informed and make confident decisions in cancer care. To read more, create a FREE account at: https://www.nccn.org/guidelines/nccn-guidelines-navigator

BRCA Carriers: High Risk for Ovarian Cancer After Breast Cancer Diagnosis

A new study of >2,000 *BRCA1/2* carriers found 71 cases of ovarian/fallopian tube carcinoma following a breast cancer diagnosis. Of these 71 cases, 66 were among *BRCA1* carriers and 5 were among *BRCA2* carriers. *BRCA1* carriers had a 5-fold higher risk of ovarian cancer compared to *BRCA2* carriers. The risk of ovarian/fallopian tube cancer at 15 years in women WITH versus WITHOUT a prior history of breast cancer was 10.8% and 25.9%, respectively. These findings show that preventive removal of the ovaries and fallopian tubes (i.e., preventive surgery) remains strongly recommended for *BRCA1/2* mutation carriers regardless of whether they have a history of breast cancer.

Apostol, et al. Gynecol Oncol. 2025;201:44-52. PMID: 40784323. Article available at: https://pubmed.ncbi.nlm.nih.gov/40784323/. Social media post available at: https://www.facebook.com/share/p/1DyBkt1wn1/

How Does Family History of Breast Cancers Affect Risk?

In a new study of almost 70,000 women, including those with hereditary forms of breast cancer, breast cancer risk was higher in those with a family history of breast cancer. Interestingly, family history raised breast cancer risks the least in *BRCA1* carriers and the most in *PALB2* carriers. Additionally, the effect of other risk factors on breast cancer risk also varied across genes. This type of information to personalize risk estimates can help women to guide screening and prevention decisions. See table for additional details.

Gene	N	Family History of Breast Cancer	Additional Non-Genetic Risk Factors*
BRCA1	374	Minimal	Some influence
BRCA2	574	++ Influence	Minimal influence
CHEK2	531	++ Influence	Some influence
PALB2	211	+++ Influence	Minimal influence
ATM	405	++ Influence	Some influence
BARD1	89	++ Influence	Some influence
RAD51C	81	+ Influence, but only at later ages	Seemed to have influence at both early and later ages

**age, height, age at menarche, parity, age at first term, pregnancy, BMI, alcohol use, oral contraceptive use, age at menopause, and hormone therapy use*

O'Brien, et al. JAMA Oncol. 2025;11(12):1458-1469. PMID: 41066089.
Article available at: https://pubmed.ncbi.nlm.nih.gov/41066089/.
Social media post available at: https://www.facebook.com/share/p/1N2Y76tFWT/

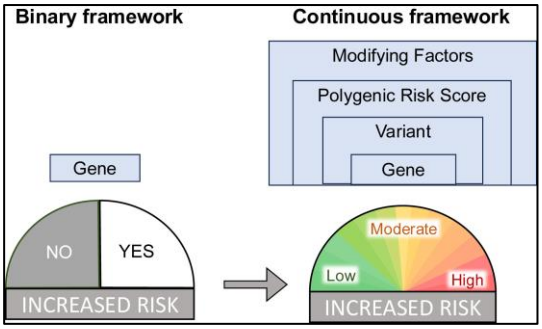
HOXB13 and Prostate Cancer

In a recently published study based on the VA's Million Veteran Program, men with the *HOXB13* p.G84E variant (the common variant in European populations, upon which much of the data is based) had a higher risk of prostate cancer, a slightly earlier age at diagnosis, and did not tend to develop more aggressive disease.

Crawford, et al. J Natl Compr Canc Netw. 2025;23(10):e257055. PMID: 40953603.
Article available at: https://pubmed.ncbi.nlm.nih.gov/40953603/.
Social media post available at: https://www.facebook.com/share/p/18M2wxUqy3/

Consideration of Inherited Cancer Risk on a Continuum

Historically, heritable cancer risk was generally considered binary, based on the presence or absence of a germline pathogenic or likely pathogenic variant (GPV) in a known inherited cancer susceptibility gene (CSG). However, it has become clear that risk is more complex and presents on a continuum based on specific GPVs, in conjunction with interactions with additional genomic risk modifiers, and many hormonal, lifestyle, and other environmental risk factors. Each of these factors have a variable contribution to risk in an individual with a CSG GPV and can be dynamic over a lifetime. In this article, the key concepts and considerations underpinning the paradigm shift in our understanding of inherited cancer risk is presented. Key concepts outlined in the article:



- GPVs in CSGs vary in their penetrance across organ sites and resultant influence on clinical management.
- Overall cancer risk in an individual with a CSG GPV can vary widely due to contributions from genetic factors such as the specific variant, wider genomic context (e.g., common risk alleles comprising polygenic risk scores), and modifiable and non-modifiable factors, including but not limited to, family history, age, environment, lifestyle, and hormonal factors.
- Cancer risk perception for an individual can be influenced by factors such as personal context, experience of hereditary cancer risk, and subjective experience of risk.
- The threshold for clinical intervention to either reduce cancer risk or initiate cancer surveillance requires assimilation of all contributing risk factors, consideration of medical context (i.e., other competing risks such as co-morbidities) and personalized counseling to enable individualized cancer risk management.

Preview our new article, which highlights key concepts in consideration of inherited cancer risk on a continuum at: https://www.gimjournal.org/article/S1098-3600(25)00306-5/fulltext

Pal, et al. Genet Med. 2026;28(3):101659. PMID: 41618953.
Article available at: https://pubmed.ncbi.nlm.nih.gov/41618953/.
Social media post available at: https://www.facebook.com/share/p/1D4coZ7jnz/

VANDERBILT HEALTH

BRCA1/2: PARP Inhibitors

According to a new study, 50% of men in the U.S. with *BRCA1/2* and metastatic castration-resistant prostate cancer receive PARP inhibitor treatment.[1] This study also found that PARP inhibitor treatment differed by insurance coverage, with PARP inhibitors among commercially insured LESS LIKELY than those covered by government-issued insurance.

Similarly, a U.S.-based study of adults with HER2-negative breast cancer showed that from 2018 onwards (i.e., the year both Olaparib and Talazoparib were approved for use in metastatic breast cancer in *BRCA1/2*-positive patients), less than 50% of *BRCA1/2* carriers received PARP inhibitors.[2] These findings suggest that even though we have life-prolonging treatment for these individuals (PARP inhibitors), many are not receiving it. It remains important to improve awareness regarding data to support using PARP inhibitors and ensure access to these agents.

[1]*Ostrowski, et al. JAMA Netw Open. 2025;8(10):e2534968. PMID: 41037269. Article available at: https://pubmed.ncbi.nlm.nih.gov/41037269/. Social media post available at: https://www.facebook.com/share/p/1G9tHiA2Gp/;* [2]*Yadav S, et al. JCO Precis Oncol. 2025:e2400814. PMID: 40669020. Article available at: https://pubmed.ncbi.nlm.nih.gov/40669020/.*

New Gene Alert: *SMARCAL1*

A new study found the *SMARCAL1* gene predisposes to a specific type of bone cancer (osteosarcoma) in children and young adults.

Oak, et al. J Clin Oncol. 2025;43(36):3833-3843. PMID: 41066719. Article available at: https://pubmed.ncbi.nlm.nih.gov/41066719/. Social media post available at: https://www.facebook.com/share/v/1GZ2GdNU69/

BRCA1/2: Preventive Bilateral Mastectomy Can Save Lives

A new study that combined the results of prior studies (through a systematic review/meta-analysis) including a total of over 6,000 *BRCA1/2* carriers showed that preventive bilateral mastectomy lowered overall deaths as well as deaths from breast cancer, compared to not having this done. This information is important as women with *BRCA1/2* mutations are deciding on their health options. Keep in mind, breast cancer screenings (through mammograms and MRIs) are recommended for these women, and have also been shown to save lives; however, these screenings were not the focus of this study.

O'Reilly, et al. JAMA Surg. 2026;161(3):260-267. PMID: 41499127. Article available at: https://pubmed.ncbi.nlm.nih.gov/41499127/. Social media post available at: https://www.facebook.com/share/p/18U3T3v6D7/

BRCA1/2: Preventive Mastectomy vs. Screening

A new study shows similar rates of death from breast cancer when comparing 460 women who had a mastectomy with 745 women who chose surveillance (screening). For women choosing surveillance, these results are reassuring that survival is not likely to be compromised. Keep in mind, the goal of surveillance is to detect cancer early if it develops (i.e., the goal is early detection of a cancer diagnosis), whereas the goal of a risk-reducing mastectomy is to prevent a cancer diagnosis altogether (i.e., the goal is no cancer diagnosis). Not surprisingly, breast cancer incidence was greatly lowered in the mastectomy group compared to the surveillance group. Specifically, mastectomy lowered breast cancer risk by 94% with a 2% rate of occult cancer after mastectomy.

Gandhi, et al. J Clin Oncol. 2026:JCO2500834. PMID: 41637687. Article available at: https://pubmed.ncbi.nlm.nih.gov/41637687/. Social media post available at: https://www.facebook.com/share/p/1CQKBwr8yH/

Ask the Expert

The following question was addressed by Joanne Kotsopoulos, PhD, who is a scientist at Women's College Hospital in Toronto, Canada, with a longstanding interest in researching hormonal and other risk factors among those with inherited forms of breast cancer.

Joanne Kotsopoulos, PhD

Q: What is the latest information about risks of taking hormone replacement therapy (HRT) in *BRCA1/2* carriers without a past diagnosis of breast cancer?

A: The information we have is reassuring that HRT does not further raise the risks of breast cancer in pre-menopausal *BRCA1/2* carriers following risk-reducing salpingo-oophorectomy. We recently published a study among *BRCA1/2* carriers without a prior breast cancer diagnosis (**which included ICARE participants**) and showed that HRT use (either estrogen plus progesterone OR estrogen alone) did NOT lead to a significant increase in breast cancer risk and that estrogen alone HRT may actually be protective (meaning this may actually lower risk).[1] Findings were similar regardless of the type of estrogen or how the HRT was given (whether it was oral, injected, or absorbed through the skin). It is important to remember that estrogen alone is not given in someone who has their uterus, as it can then raise the risk of uterine (also referred to as endometrial) cancer. This is important information for women with *BRCA1/2* mutations as well as their healthcare providers. Given their high risk of ovarian (or fallopian tube) cancer, these women are strongly encouraged to remove their ovaries and tubes at an early age leading to early surgical menopause. HRT is the most effective way to mitigate the health issues that go along with early menopause that may include vasomotor symptoms, a decline in quality of life and other side effects. Importantly, this study shows that HRT can be used safely in this population. Prior research studies have also shown that among *BRCA* carriers without a history of breast cancer, HRT does not further raise the risk for breast cancer.[2-5]

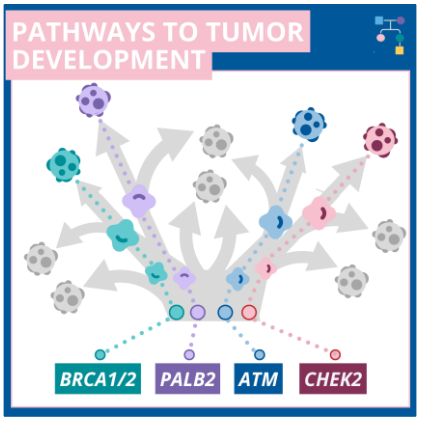
[1]*Kotsopoulos, et al. J Natl Cancer Inst. 2025:djaf363. PMID: 41403285. Article available at: https://pubmed.ncbi.nlm.nih.gov/41403285/;* [2]*Rebbeck, et al. J Clin Oncol. 2005;23(31):7804-10. PMID:16219936. Article available at: https://pubmed.ncbi.nlm.nih.gov/16219936/;* [3]*Eisen, et al. J Natl Cancer Inst. 2008;100(19):1361-7. PMID:18812548. Article available at: https://pubmed.ncbi.nlm.nih.gov/18812548/;* [4]*Kotsopoulos, et al. Breast Cancer Res Treat. 2016;155(2):365-73. PMID:26780555. Article available at: https://pubmed.ncbi.nlm.nih.gov/26780555/;* [5]*Mills KA, et al. Gynecol Oncol. 2020 Jun;157(3):706-710. PMID: 32143914. Article available at: https://pubmed.ncbi.nlm.nih.gov/32143914/*

Genomics of Breast Cancers Among *BRCA1/2*, *PALB2*, *CHEK2*, and *ATM* Carriers

We recently published a study which included information from over 200 *BRCA1, BRCA2, PALB2, CHEK2* and *ATM* carriers in ICARE who had breast cancer (mostly early-stage) combined with data from over 200 carriers (predominantly with metastatic breast cancer) who had clinical tumor testing. We pursued this research because we believe that distinct genomic changes in tumors from these carriers can uncover distinct pathways by which these tumors develop. This in turn can give us information about best treatments, and may also refine prognostic and predictive markers, as well as inform treatment targets. Of note, women with early-stage breast cancer are not generally offered sequencing of their tumors, as it is not clinically indicated. This means that current information about tumor sequencing is from mostly tumors of women with metastatic breast cancer. **Consequently, recruitment through ICARE was instrumental in being able to include early-stage cases, which is essential to see what changes occur at early versus later stages in these tumors.** This information is important in figuring out how tumors develop and how best to treat them.

For ICARE participants, we collected their breast tumor specimens and conducted both DNA and RNA sequencing studies through Tempus labs. Our findings showed that even in *BRCA1* carriers with HR+/HER2- disease, almost half still had basal subtypes (which may not respond to hormone receptor blockers). Other interesting findings included that *TP53* somatic mutations are enriched in *BRCA1* carriers, regardless of subtype, yet not observed in *BRCA2* carriers. This suggests that despite playing similar roles in DNA repair, the evolution of *BRCA1* versus *BRCA2*-associated breast tumors are distinct. *PIK3CA* mutations are increased in *ATM* and *CHEK2* carriers across locoregional and metastatic HR+ cases.

Finally, *ESR1* mutations are increased in *ATM* carriers, but only in metastatic cases. These findings suggest that GPVs in *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, and *PALB2* are associated with distinct intrinsic breast cancer subtypes and somatic genomic alterations, which could enhance precision in risk stratification and eventually be used to guide treatment.



Yadav, et al. J Natl Cancer Inst. 2026:djag070. PMID: 41832987. Article available at: https://pubmed.ncbi.nlm.nih.gov/41832987/. Social media post available at: https://www.facebook.com/share/p/1EPvRoA6aY/

Research Efforts and Resources

New Initiative in Partnership with ConnectMyVariant

ConnectMyVariant is a powerful resource designed to help those with inherited cancer risk connect with family, share genetic information, and build supportive communities. This new initiative through ICARE, in partnership with ConnectMyVariant, aims to give more accurate risks to families based on the specific *BRCA1* or *BRCA2* variant they have. This is done through helping family members get free genetic testing (as well as optional free ancestry testing) to be able to come up with mutation-specific risks. In particular, there are specific *BRCA1* and *BRCA2* variants that may actually be lower risk than what we usually think of. Through having more family members tested, we will get much needed information to better predict risks for these variants. By signing up, you'll help advance research and support others on similar journeys. Check it out at https://connectmyvariant.org/signup-form/icare

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.

ACMG Clinical Practice Resource on *RAD51C*, *RAD51D*, and *BRIP1*

Alongside worldwide colleagues, we recently released the ACMG Clinical Practice Resource on *RAD51C*, *RAD51D*, and *BRIP1*, to guide risks and care based on what we currently know about these genes. Check it out at https://www.sciencedirect.com/science/article/pii/S1098360025002047 or by scanning the QR code below.

Genetic Risk Models in Breast Cancer: Overview & Impact

Don't miss this summary of **ICARE Principal Investigator**, Dr. Tuya Pal's SABCS 2025 presentation, highlighting how genetic risk models can transform breast cancer prevention and care. Check it out now at the following link https://tinyurl.com/BreastCancerRiskModels or by scanning the QR code below.

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