Spring 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 almost 6,500 participants, including more than 1,600 *BRCA1/2* carriers and more than 1,500 other inherited cancer gene carriers. ICARE participants currently represent all 50 U.S. states, the District of Columbia, the Virgin Islands, and 25 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

The pace of discovery in the field of inherited cancers continues to progress quickly, so we have many interesting updates to share with you. A number of recently published research studies have **included ICARE participants**, such as a study that found promising results of a behavioral phone intervention delivered by genetic counselors that may raise the uptake of risk-reducing surgery of the ovaries and fallopian tubes in *BRCA1* and *BRCA2* carriers.[1] This study highlights the value of testing strategies to improve follow-up care in those with inherited cancer risk, and is in line with the IMPACT trial we are currently conducting among those with inherited cancer gene mutations (*if interested in participating, see the last page of this newsletter for details*). Other studies among *BRCA* carriers which **included information from ICARE participants** shows the low risks of both developing and dying from breast cancer after preventive mastectomy,[2] lower risk of death from any cause after removing both ovaries and fallopian tubes,[3] and lower risk of breast cancer-specific death with MRI Screening.[4] We want to again take the opportunity to sincerely thank our participants and providers 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]*Metcalfe, et al. Cancer Med. 2023;12(17):18246-18257. PMID:37602539. Social media post Oct 12th, 2023. Available at https://tinyurl.com/post101223;* [2]*Metcalfe, et al. Br J Cancer. 2024;130(2):269-274. PMID:38030749. Social media post Feb 27th, 2024. Available at https://tinyurl.com/post22724;* [3]*Kotsopoulos, et al. JAMA Oncol. 2024;Online ahead of print. PMID:38421677. Social media post March 5th, 2024. Available at https://tinyurl.com/post3524;* [4]*Lubinski, et al. JAMA Oncol. 2024;Online ahead of print. PMID:38421676. Social media post March 5th, 2024. Available at https://tinyurl.com/post3524.*

National Comprehensive Cancer Network (NCCN) Guideline Updates

Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Cancer – *Released February 12th, 2024 (V3.2024)*

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

Contralateral breast cancer risks in these updated guidelines:

Gene	Contralateral Breast Cancer Cumulative Risk	Strength of Evidence
ATM	10-year risk: 4%	Limited
BRCA1	20-year risk: 30-40% 15-year risk in premenopausal women: >20%	Strong
BRCA2	20-year risk: 25% 15-year risk in premenopausal women: >20%	Strong
CHEK2	10-year risk: 6-8%	Limited
PALB2	10-year risk: 5-8%	Limited
RAD51C	10-year risk: <2% [a]	Limited
RAD51D	10-year risk: <2% [a]	Limited
TP53	10-year risk: 18-49%	Strong

[a] Same as sporadic breast cancer

Expanded guidance about gynecologic cancers in *BRCA1*/2 carriers:

- Reproductive considerations
- Non-surgical and surgical risk reduction
- Salpingectomy
- Hysterectomy considerations
- Hormone replacement therapy (HRT) after risk-reducing removal of the ovaries

Some highlights related to HRT include:

- Premature menopause due to risk-reducing removal of the ovaries and fallopian tubes can cause detriments to quality-of-life, as well as bone, cardiovascular, psychosocial, neurologic, and sexual health.
- HRT can reduce these risks and is generally **not** contraindicated.
- Thus, HRT should be discussed with premenopausal patients who do **not** have a personal history of breast cancer.

Genetic/Familial High-Risk Assessment: Colorectal Cancer – *Released October 30th, 2023 (V2.2023)*

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

- Test Selection modified: Germline panel testing should include at a minimum the following colorectal cancer risk-associated genes: *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *BMPR1A*, *SMAD4*, *PTEN*, *STK11*, *TP53*
- *MUTYH* monoallelic pathogenic variant/heterozygotes (carrier): revised to indicate "No increased risk."
- Criteria for the Evaluation of Lynch Syndrome Based on Personal or Family History of Cancer were expanded from personal history of colorectal and/or endometrial cancer to any Lynch Syndrome-related cancer.
- Please see guidelines for many additional revisions based on tumor screening results; and refinement in care based on having an inherited colorectal cancer predisposing gene.

New Guidelines Released Through ASCO-Society of Surgical Oncology: Germline Testing in Patients with Breast Cancer

In January 2024, the American Society of Clinical Oncology (ASCO) in conjunction with the Society of Surgical Oncology released new guidelines for germline testing in patients with breast cancer, which include the following:

- Offer *BRCA1/2* testing to all patients diagnosed with breast cancer at or below age 65.
- For those getting *BRCA1/2* testing, testing for other hereditary cancer genes should also be offered based on their personal or family history.

- Testing for other **HIGH** penetrance genes, such as *PALB2*, *TP53*, *PTEN*, *STK11*, and *CDH1* should be offered to appropriate patients, as mutations in these genes could inform medical treatment, influence surgical decision making, refine estimates of second primary cancer risks, and inform family risk assessment.

- Testing for **MODERATE** penetrance genes, such as *ATM*, *CHEK2*, *RAD51C*, *RAD51D*, and *BARD1*, may be offered to appropriate patients who are undergoing *BRCA1/2* testing. While mutations in these genes may inform risks of second primary cancer or family risk assessment, they currently offer no treatment benefits for breast cancer patients.

- When deciding on which specific multigene panel test to order, providers should take the patient's personal and family history into account. Consequently, a provider experienced in clinical cancer genetics can be helpful in selecting a specific panel or interpreting results. Furthermore, the patient should be provided with sufficient information before testing is ordered, in order for them to provide INFORMED CONSENT for testing.

> "When deciding on which specific multigene panel test to order, providers should take the patient's personal and family history into account…"

- \+ Individuals with **POSITIVE** test results should be given individualized post-test genetic counseling and offered a referral to a provider experienced in clinical cancer genetics.
- ? Individuals with a Variant of Uncertain Significance (**VUS**) test result should be advised that the result should not alter management. Additionally, patients should be made aware that VUS results may be reclassified in the future and there is a need for periodic follow-up.
- – Individuals with **NEGATIVE** test results may still benefit from genetic counseling if there is a significant family history of cancer. If this is the case, referral to a provider experienced in clinical cancer genetics is recommended.

For a full list of recommendations in this guideline, the article is available at: https://ascopubs.org/doi/10.1200/JCO.23.02225

Bedrosian, et al. J Clin Oncol. 2024;42(5):584-604. PMID:38175972. Social media post Jan 5th, 2024. Available at https://tinyurl.com/post1524.

Aerobic Exercise May Reduce Risk of Colorectal Cancer in Patients with Lynch Syndrome

A new research study among individuals with Lynch Syndrome reported that regular and intense aerobic exercise may lower the risk of colorectal cancer by improving the immune system's ability to detect and remove potentially harmful cells. Specifically, the researchers enrolled 21 patients with Lynch Syndrome either to an 1) exercise group (45 minute cycling classes three times per week) or 2) usual care group (a one-time exercise counseling session). Biomarkers measured in both groups showed that the exercise group had reduced levels of inflammatory markers in their colon and blood, compared to the usual care group. These data suggest that exercise may be a strategy to intercept cancers in those with Lynch Syndrome, and for the first time, show the possible biological effects of exercise on the immune system of the colon in patients at risk for colon cancer. Therefore, this study suggests regular, intense aerobic exercise may lower colorectal cancer risk in Lynch Syndrome patients, although additional studies with larger samples are needed to confirm and expand upon these findings.

Deng, et al. Clin Cancer Res. 2023;29(21):4361-4372. PMID:37724990. Social media post Nov 15th, 2023. Available at https://tinyurl.com/post111523.

How Well Do Cancer Risk Management Strategies Work Among *BRCA* Carriers?

Several important studies were published recently on the effectiveness of risk management strategies in *BRCA* carriers. Specifically, a recently published study **in which ICARE participants were included** suggested that preventive bilateral mastectomy for *BRCA* carriers greatly reduced the risk of developing breast cancer by 80%.[1] Additionally, study findings showed that after preventive mastectomy, the chance of dying from breast cancer was less than 1%. Another very recently published study in *BRCA1* carriers **in which ICARE participants were also included** is the FIRST to show that screening through MRI greatly lowered the risk of death from breast cancer (hazard ratio of 0.23) with a 'statistically significant' reduction seen for *BRCA1* (but not *BRCA2*) carriers.[2]

Looking at studies about preventive removal of the ovaries and fallopian tubes (called bilateral salpingo-oophorectomy or BSO) in *BRCA* carriers, a recently published study **also including ICARE participants**, showed that removing both ovaries and fallopian tubes lowered the risk of death from any cause ('all-cause mortality').[3] The age-adjusted hazard ratio for *BRCA1* was 0.28 and for *BRCA2* was 0.43. Another study showed that BSO after surgery for breast cancer in *BRCA* carriers lowered the risk of death.[4] Specifically, among almost 500 *BRCA* carriers treated at a single center in Italy, BSO significantly lowered the risk of death (hazard ratio [HR], 0.40; 95% CI, 0.25-0.64; $P < .001$), with the strongest effect in *BRCA1* carriers (HR, 0.35; 95% CI, 0.20-0.63; $P = .001$), those with triple-negative disease (HR, 0.21; 95% CI, 0.09-0.46; $P = .002$), and those with invasive ductal carcinoma (HR, 0.51; 95% CI, 0.31-0.84; $P = .008$). These findings highlight the potential importance of considering BSO, specifically in *BRCA* carriers with a breast cancer diagnosis.

> "…in *BRCA* carriers…removing both ovaries and fallopian tubes lowered the risk of death from any cause…"

As highlighted in the recently updated gynecologic section of the NCCN Familial/Genetic Breast, Ovarian, and Pancreatic Cancer Guidelines, it is important to consider BSO in *BRCA* carriers, but BSO leads to surgical menopause in those who are pre-menopausal. A new study showed declining cancer worry over time in most *BRCA* carriers who had preventive removal of their ovaries and fallopian tubes.[5] However, there was a subset of patients who had concerns, and these patients are important to identify and try to offer additional support to. Furthermore, as we have highlighted in the guideline update, and our 'Ask the Expert' section (*see below*), hormone replacement treatment may be a consideration to reduce symptoms of menopause following removal of the ovaries among premenopausal *BRCA* carriers without a history of breast cancer or any other contraindications.

[1]Metcalfe, et al. Br J Cancer. 2024;130(2):269-274. PMID:38030749. Social media post Feb 27th, 2024. Available at https://tinyurl.com/post22724; [2]Lubinski, et al. JAMA Oncol. 2024;Online ahead of print. PMID:38421676. Social media post March 5th, 2024. Available at https://tinyurl.com/post3524; [3]Kotsopoulos, et al. JAMA Oncol. 2024;Online ahead of print. PMID:38421677. Social media post March 5th, 2024. Available at https://tinyurl.com/post3524; [4]Martelli, et al. JAMA Surg. 2023;158(12):1275-1284. PMID:37792368. Social media post Dec 13th, 2023. Available at https://tinyurl.com/post121323; [5]van Bommel, et al. Support Care Cancer. 2022;30(4):3409-3418. PMID:34997316. Social media post Oct 20th, 2023. Available at https://tinyurl.com/post102023.

Ask the Expert

This question was addressed by Ronald D. Alvarez, MD, MBA, Professor and Chairman of the Department of Obstetrics and Gynecology at the Vanderbilt University Medical Center in Nashville, Tennessee. He is also the current vice chair of the National Comprehensive Cancer Network (NCCN) Ovarian Cancer Treatment Guidelines and has served in multiple leadership roles in both national and international organizations in various capacities. If you have a question you would like addressed, email ICARE@vumc.org for consideration in future newsletters.

Ronald D. Alvarez, MD, MBA

Q: I am 40 years old with a *BRCA1* mutation and no history of cancer. I had my ovaries preventively removed last year at the recommendation of my doctor, but now I am having severe symptoms from menopause. Is hormone replacement treatment (HRT) an option for me, and would this further raise my risk of breast cancer?

A: HRT should be considered in women without a history of breast cancer who go into menopause prematurely due to preventive removal of their ovaries and do not have any other reasons they should not take HRT. In fact, premature menopause can be harmful to bone, cardiovascular, psychosocial, neurologic, and sexual health, as well as generalized quality-of-life, and HRT can reduce these side effects. It is important to discuss menopausal management with a gynecologist or other qualified healthcare professional with expertise in this area, as recently outlined in the NCCN Familial/Genetic Breast, Ovarian and Pancreatic Cancer Guidelines, Version 3.2024.

While there has historically been concern that HRT may raise the risk of breast cancer among those already at higher risk for breast cancer (e.g., *BRCA1* and *BRCA2 (BRCA)* carriers), findings through observational and retrospective studies are reassuring. Specifically, research studies have not shown that *BRCA* carriers without a history of breast cancer who are given HRT had a higher risk for breast cancer.[1-3] Furthermore, studies have shown that HRT use in *BRCA* carriers may reduce the side effects from menopause,[4] similar to that observed in the general population.[5] Therefore, while it would be ideal to confirm these findings through a randomized clinical trial, current information is reassuring that HRT does not raise breast cancer risk in *BRCA* carriers.[6]

[1]Rebbeck, et al. J Clin Oncol. 2005;23(31):7804-10. PMID:16219936; [2]Eisen, et al. J Natl Cancer Inst. 2008;100(19):1361-7. PMID:18812548; [3]Kotsopoulos, et al. Breast Cancer Res Treat. 2016;155(2):365-73. PMID:26780555.; [4]Vermeulen et al. Eur J Cancer. 2017;84:159-167. PMID:28818705; [5]Mielke, et al. Menopause. 2023;30(11):1090-1097. PMID:37699239; [6]Chlebowski RT, Prentice RL. J Natl Cancer Inst. 2008;100(19):1341-3. PMID:18812547.

BRCA-Associated Prostate Cancer Treatment Updates

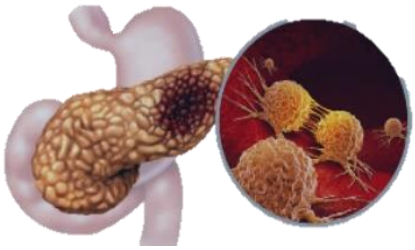
New studies to guide treatment strategies in men with prostate cancer and a *BRCA* mutation were recently published. Specifically, a recent study suggested that platinum-based chemotherapy may be as effective as PARP inhibitors for individuals with *BRCA*-positive metastatic castration-resistant prostate cancer.[1] The study sheds light on treatment options for advanced prostate cancer patients. More recently, another study of men with *BRCA*-associated metastatic castration-resistant prostate cancer treated with a PARP inhibitor (Olaparib) had improved survival regardless of whether the mutation was germline or somatic.[2] This highlights the importance of tumor testing to help guide cancer treatment.

> "…platinum-based chemotherapy may be as effective as PARP inhibitors for individuals with *BRCA*-positive metastatic castration-resistant prostate cancer …"

[1]*Fazekas, et al. Eur Urol Oncol. 2023:S2588-9311(23)00174-8. PMID:37722977. Social media post Jan 3rd, 2024. Available at https://tinyurl.com/post1324;* [2]*Mateo, et al. J Clin Oncol. 2024;42(5):571-583. PMID:37963304. Social media post Feb 20th, 2024. Available at https://tinyurl.com/post22024.*

Inherited Risk in Patients with Pancreatic Acinar Cell Carcinoma

In a study of a rare type of pancreatic cancer, called pancreatic acinar cell cancer (PACC), over one third (36.7%) of a total of 49 patients with PACC had a mutation in an inherited cancer gene. The most commonly mutated gene was *BRCA2* (12), and other genes included *BRCA1* (1), *PALB2* (2), *ATM* (2), and *CHEK2* (1). Of note, patients with PACC generally do better than patients with the more common pancreatic ductal cell carcinoma. These findings suggest that all patients with PACC should get genetic testing, which may guide treatment and screening strategies. Furthermore, study authors suggested that PACC should be considered one of the cancer types that are related to *BRCA* mutations.



Mandelker, et al. J Clin Oncol. 2023:41(33):5151-5162. PMID:37607324. Social media post Oct 29th, 2023. Available at https://tinyurl.com/post102923.

Inherited Cancer Research Efforts

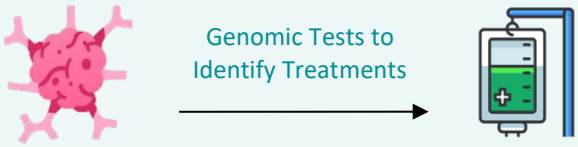
Enroll in ICARE if you are interested in being considered for the below studies and many other current efforts! Participation is easy and can be completed online at ***https://redcap.link/ICAREconsent*** *or by scanning the QR code.*

Genomic Characterization of Breast Cancer: *BRCA1/2*, *PALB2*, *ATM*, and *CHEK2*

Objective: Perform genomic analyses to better understand how breast cancer tumors develop to identify additional treatment options and improve health outcomes.

Eligibility: Invasive breast cancer and a confirmed positive result in *BRCA1*/2, *PALB2*, *ATM*, and/or *CHEK2*.

Progress: Over 200 breast cancer tumors from ICARE participants have been sent for additional tumor genomic analyses.

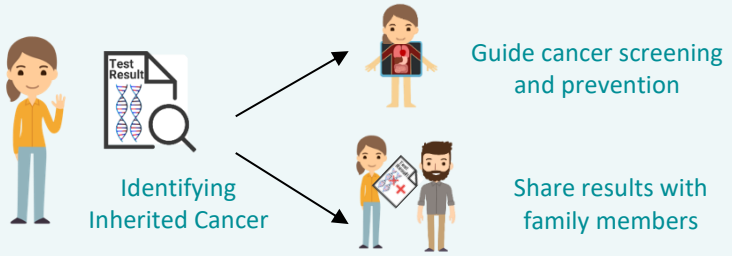


IMProving Care After Inherited Cancer Testing (IMPACT) Study

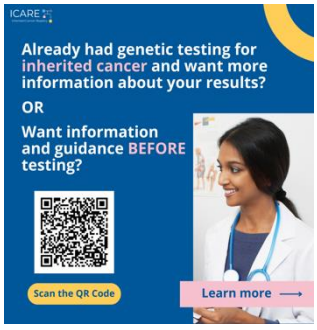
Objective: To improve follow-up care after genetic testing for those with a positive result.

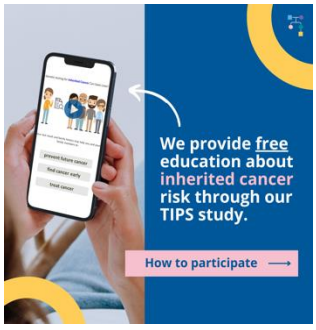
Eligibility: Mutation in an inherited cancer predisposing gene.

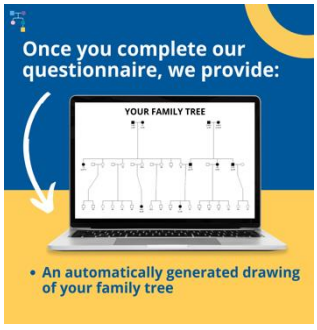
Progress: Hundreds of ICARE participants have been invited to participate, the trial has started, and we are actively enrolling!

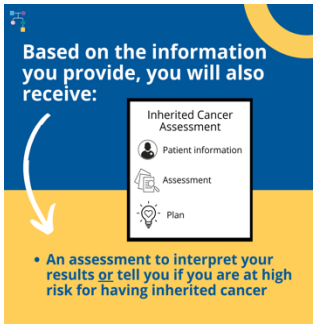


Enroll in TIPS to receive free education and assessment about inherited cancer risk by scanning the QR code or visiting ***https://redcap.link/TIPS***









VANDERBILT-INGRAM CANCER CENTER

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