ICARE NEWSLETTER

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About ICARE

ICARE provides individuals interested in inherited cancer research studies the opportunity to enroll in a research registry. Participation in ICARE continues to expand through referrals, events, and active engagement efforts. As of July 2019, there are over 3,200 participants enrolled in ICARE, including more than 1,100 individuals from families with *BRCA1/2* mutations. ICARE participants represent 49 U.S. states, the District of Columbia, and 16 other countries worldwide.

If you have been affected by inherited cancer or are a provider managing patients with inherited cancer, please visit our website to learn more about ICARE and how participating in our efforts may benefit you.

Welcome Message

Thanks to our ICARE participants and provider partners, our efforts have continued to grow. We have recently revitalized our information sharing media and are making additional efforts to highlight resources we have developed on the ICARE website. For example, we have created an interactive video to briefly explain the importance of sharing test results with family members. This effort was the result of feedback received from many ICARE participants who expressed that having additional resources and ways to explain family sharing to their relatives would be helpful. These resources are available at GeneSHARE.net. Please feel free to share these broadly with anyone who might find these helpful.

With the speed at which new information becomes available, we are actively broadening the ways we share information, including through the ICARE website (InheritedCancer.net), Facebook (@inheritedcancer), Twitter (@inheritedcancer), Instagram (@inheritedcancer), and LinkedIn (linkedin.com/company/inherited-cancer-registry/). Please follow us on your favorite social media platform to obtain regular clinical and research updates pertaining to inherited cancer predisposition.

In the current newsletter edition, we have highlighted some of the recent clinical and research advances that are relevant to those with inherited cancer risk. These include new information about cancer risks, advances in cancer treatment, and updates to national practice guidelines, including NCCN inherited colorectal cancer guidelines, as well as the U.S. Preventive Services Task Force guidelines for *BRCA1/2* testing and care.

Wishing you the very best as we strive together *to end the cycle of inherited cancer through research, education, and engagement*.

Sincerely,

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

Updates to National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment: Colorectal Guidelines (*Version 1.2019, posted July 3, 2019*)

For Individuals with **Lynch Syndrome**:

- The cancer risk table was updated:
  - Addition of new cancer risks by specific genes: breast and bladder cancers
  - Updates of cancer risks by specific genes: ovarian, prostate, gastric, pancreatic, urothelial, small bowel, and brain/CNS cancers
  - Removal of reference to sebaceous neoplasms
- Recommendations for cancer risk management were updated for colon, gastric, small bowel, urothelial, and prostate cancers:
  - For *MSH6* carriers: consideration of colonoscopy at age 30 or 10 years younger than age of any relative with colorectal cancer
  - Initiation of gastric and small bowel cancer surveillance was updated to age 40
  - Surveillance for urothelial cancer may be considered in individuals with a family history of urothelial cancer or *MSH2* mutations (especially males)

For Individuals with **Attenuated Familial Adenomatous Polyposis (AFAP) and *MUTYH*-Associated Polyposis**:

- Colonoscopy frequency was increased to every 1-2 years

For the complete updated versions of the NCCN Guidelines, please visit NCCN.org

Cancer Treatment Advances for *BRCA1/2* Carriers

Over the past six months, treatment of inherited cancers has continued to progress, as outlined below:

Prostate Cancer: There is now information to suggest that identifying inherited mutations in DNA repair genes, such as *BRCA1/2* and other genes, in men with metastatic prostate cancer may open doors for other treatment options. Results of a phase 2 clinical trial among men with metastatic and heavily pre-treated prostate cancer were presented at the American Society of Clinical Oncology 2019 meeting.[1] Mateo and colleagues found that treatment with a PARP inhibitor (olaparib) was promising among those with *BRCA1/2* mutations (24 of 30 patients) and *PALB2* mutations (4 of 7 patients), while patients with other inherited genes also showed some response.[1] Another recent study suggested that men with metastatic prostate cancer and a *BRCA2* mutation who received androgen blockers for their initial treatment had better outcomes compared with those who received taxanes.[2] This suggests that *BRCA2* status may guide initial treatments among metastatic prostate cancer patients.[2]

Pancreatic Cancer: Results from a clinical trial of individuals with a *BRCA1/2* mutation and pancreatic cancer showed that patients who received a PARP inhibitor (olaparib) for maintenance treatment had almost half the risk of their disease progressing when compared to receiving a placebo.[3] In fact, after 2 years, 22.1% of patients who received olaparib had no disease progression compared to 9.6% of those receiving a placebo.[3] In October 2018, Lynparza (olaparib) received orphan drug designation for pancreatic cancer through the U.S. Food and Drug Administration. Another study of a PARP inhibitor called rucaparib, presented at the 2019 AACR meeting, showed that *BRCA1/2* or *PALB2* carriers with advanced, platinum-sensitive, pancreatic cancer seemed to benefit from this maintenance treatment.[4] In fact, of the 19 patients assessed so far, one had a complete response, and six had a partial response to the treatment.[4] These results remain preliminary and require more proof that they are true, but represent another possible treatment advance for those with pancreatic cancer and *BRCA1/2* or *PALB2* mutations. These results also highlight the importance for both germline (inherited) and tumor (somatic) testing among patients with pancreatic cancer.

Ovarian Cancer: A recently reported study of women with ovarian cancer and homologous recombination deficiency (HRD) who received a PARP inhibitor (niraparib) as fourth-line or later treatment showed potential clinical benefit.[5] Specifically, median overall survival after treatment was 19 months in the HRD-positive group (including those with *BRCA1/2* mutations) compared to 15.5 months in the HRD-negative group.[5] In fact, the subgroup with *BRCA1/2* mutations had a median overall survival of 26 months. These results suggest possible expansion for use of this class of drugs beyond those with *BRCA1/2* mutations to a broader patient population with HRD-positive ovarian cancer.

[1]Mateo, et al. *J Clin Oncol*. 2019 May. DOI: 10.1200/JCO.2019.37.15_suppl.5005. [2]Castro, et al. *J Clin Oncol*. 2019 Feb. PMID 30625039. [3]Golan, et al. *N Engl J Med*. 2019 July. PMID 31157963. [4]Reiss Binder, et al. Abstract CT234. AACR Annual Meeting, presented 2019 April. [5]Moore, et al. *Lancet Oncol*. 2019 May. PMID 30948273.

Expansion of Criteria for *BRCA1/2* Testing through the USPSTF

The U.S. Preventive Services Task Force (USPSTF) came out with new genetic testing guidelines for the *BRCA1/2* genes, which has garnered substantial media attention.[1] This task force consists of a team of primary care and preventive medicine healthcare experts to lower the chance of a conflict of interest (which is also the reason that subspecialty providers who practice in the area of clinical cancer genetics were excluded from this group, but who may be consulted to provide input). For the current guideline, essentially a three-step process was included: 1) a brief risk assessment for *BRCA1/2* risk by primary care providers with a validated tool; 2) referral to genetic counseling if positive; and 3) *BRCA1/2* testing if indicated.

A **substantial update** to the guideline is that it now covers more women at-risk for a *BRCA1/2* mutation. Specifically, guidelines now include women with a history of breast, ovarian, fallopian tube, and peritoneal cancer who are disease-free, as well as those with ancestry prone to *BRCA1/2* mutations, such as Ashkenazi Jewish women. Some of the **items that were not addressed** include: 1) other cancers associated with the *BRCA1/2* genes, including male breast cancer, prostate cancer, or pancreatic cancer; 2) other inherited breast or ovarian cancer genes (this is especially relevant as most providers are not just testing for the *BRCA1/2* genes, but other genes as well through multi-gene panel tests); 3) existing disparities in testing across racial/ethnic groups, and how these new guidelines may affect existing disparities; and 4) lack of accounting for some of the subtle nuances of treating those with a *BRCA1 or BRCA2* mutation by outlining the differences in type of breast cancer that each primarily predisposes someone to (i.e., triple negative breast cancer) and providing evidence to support hormone receptor blockers for prevention.

"A substantial update to the guidelines is that it now covers more women at-risk for a BRCA1/2 mutation."

[1]US Preventive Services Task Force, Owens et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2019 Aug. PMID: 31429903. Available at: https://jamanetwork.com/journals/jama/fullarticle/2748515

VANDERBILT-INGRAM CANCER CENTER

New Information About Cancer Risks for Inherited Cancer Genes

Among BRCA1/2 carriers*: Looking at pregnancy history and breast cancer risk*, a recent study of almost 8,000 women with *BRCA1/2* mutations evaluated breast cancer risks related to pregnancy.[1] Findings suggested the overall number of pregnancies was not associated with breast cancer risk in *BRCA1* carriers; however, *BRCA1* carriers with one pregnancy were at higher risk for breast cancer when compared to those with no pregnancies or more than one pregnancy. In contrast, among *BRCA2* carriers, more pregnancies were associated with a lower breast cancer risk. Additionally, longer duration of breastfeeding in *BRCA1* carriers lowered breast cancer risks. *Looking at risks of contralateral breast cancer after removal of the ovaries*, in a study of over 2,000 women with a *BRCA1* or *BRCA2* mutation and almost 10 years of follow-up, results suggested that removal of the ovaries did not reduce the chance of developing a second new breast cancer.[2] This finding did not change with type of *BRCA1/2* mutation or age at diagnosis of the first breast cancer. Overall, these findings suggest that removing the ovaries in *BRCA1/2* carriers with breast cancer may not reduce their risk for developing another breast cancer. *Looking at Non-Hodgkin lymphoma risks*, in a study of pediatric cancer survivors, results suggested that children and adolescents with a *BRCA2* mutation may have a higher risk for non-Hodgkin lymphoma, with a significant association (Odds Ratio of 5; 95% Confidence Interval: 2.1-10.2).[3] These findings contribute to refining cancer risks among those with *BRCA1/2* mutations and require confirmation through other studies.

Refining cancer risks in other inherited cancer genes, as outlined below:

***Among CHEK2 carriers*:** In a study of inherited mutations in the *CHEK2* gene, findings suggest there were two specific mutations that could predispose men to testicular germ cell tumors (TGCT).[4] Specifically, 205 men with these tumors were tested for 48 DNA repair genes, and findings were then tested in other patient populations. These findings suggest that *CHEK2* mutations might predispose to TGCT, and also identify new avenues to explore treatments.

Among DICER1 carriers: In a study of over 100 individuals with a *DICER1* mutation, findings suggest that 5.3% of individuals had developed cancer by age 10, and 19.3% by age 50.[5] After age 10, cancer risks for women were higher compared to men. Specific cancers for which risks were high included gynecologic and thyroid cancers. These findings are important to characterize cancers and natural history of the condition among those with *DICER1* mutations, which is tremendously important for genetic counseling, risk counseling, and follow-up care.

New Ovarian Cancer Genes*:* Through a study of over 13,000 patients with serous ovarian cancers and almost 41,000 controls, 34 genes that raise the risk for ovarian cancer were identified.[6] Additional laboratory studies were conducted to further characterize some of these genes, suggesting that three of these new genes may be essential (*HAUS6*, *KANLS1*, and *PRC1*). This study has expanded the list of genes that raise the risk for ovarian cancer, and this information may eventually be used to identify those at highest risk for the disease.

[1]Terry, et al. *JNCI Cancer Spectr*. 2018 Dec. PMID: 30873510. [2]Kotsopoulos, et al. *Breast Cancer Res Treat*. 2019 Jun. PMID: 30756284. [3]Wang, et al. *JAMA Oncol*. 2019 Jul. PMID: 31343663. [4]AlDubayan, et al. *JAMA Oncol*. 2019 Apr. PMID: 30676620. [5]Stewart, et al. *J Clin Oncol*. 2019 March. PMID: 30715996. [6]Gusev, et al. *Nat Genet* 2019 May. PMID: 31043753

Ask the Expert

Through each newsletter, we give our participants an opportunity to have their questions answered by experts. If you have a question you would like addressed, please email the study team at ICARE@InheritedCancer.net for consideration in future newsletters. The following question was addressed by Gillian Hooker, PhD, ScM, LCGC, who is the president-elect for the National Society of Genetic Counselors, Adjunct Associate Professor in the Division of Genetic Medicine at the Vanderbilt University Medical Center, and the Vice President of Clinical Development for Concert Genetics in Nashville, TN.

Q. Why was the BRCA1/2 mutation detected through genetic testing ordered by my healthcare provider but not found on my 23andMe® genetic test?

A. This is not unexpected. There are thousands of different mutations in the *BRCA1* and *BRCA2* (*BRCA1/2*) genes found among families with inherited cancers. When testing is ordered by a healthcare provider, the vast majority of mutations in these genes can be detected if they are there. However, *BRCA1/2* at-home genetic testing done by 23andMe® looks for only 3 specific mutations in the *BRCA1/2* genes found mostly in people of Ashkenazi Jewish descent. This testing does not look for the thousands of other mutations that have been found in the *BRCA1/2* genes. In fact, a study published last year looked at 49 different patients who learned from at-home testing that they had mutations.[1] When these samples were tested again after a healthcare provider ordered the test, 40% of the mutations were not found (i.e., they were 'false positives'). Other "mutations" were present, but turned out to be benign, non-harmful genetic changes after further inspection. These findings highlight the shortcomings of at-home genetic testing, and the potential for miscommunication, misinformation, and distress as eloquently articulated in a recent article by Dorothy Pomerantz.[2] We recommend reaching out to your doctor or a genetic counselor if you have questions about these tests. [1]Tandy-Connors, et al. *Genet Med.* 2018 Dec. PMID: 29565420. [2]Pomerantz D. "23andMe had devastating news about my health. I wish a person had delivered it." Stat News, available at: https://www.statnews.com/2019/08/08/23andme-genetic-test-revealed-high-cancer-risk/

Expanding Our Thinking About Cancer Risks in *TP53* Mutations and Li-Fraumeni Syndrome

Since expanded genetic testing has become available through multigene panel tests, studies have suggested that many people identified to have *TP53* mutations do not have a typical personal or family history, which is usually seen with Li-Fraumeni syndrome (LFS). A recent study looking at over 300 individuals with *TP53* mutations (identified through multi-gene panel testing) suggested that the level of cancer risks was dependent on the type of mutations within the *TP53* gene.[1] Specifically, those with a loss-of-function mutation (i.e., causing the protein produced from the *TP53* gene to lose its function) tended to have stronger, more classic family histories suggestive of LFS, compared to those with other types of mutations (i.e., dominant-negative missense, other missense, splice site, or in-frame deletion). Although these findings require confirmation through other studies, this type of information may eventually become very helpful for genetic counseling by refining cancer risks and guiding follow-up care among individuals with *TP53* mutations.

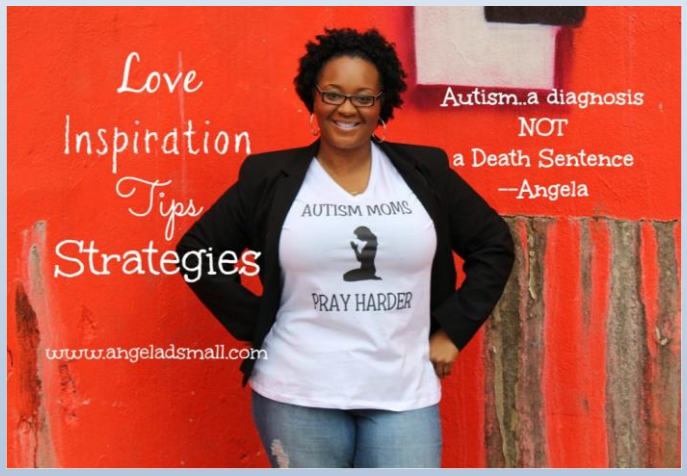
[1]Rana, et al. *Genet Med.* 2019 May. PMID: 31105275.

Community Spotlight

Life was great at 45. I had nothing more than a few headaches and was a tad overweight. After a friend was diagnosed with breast cancer, I realized I had not had a mammogram in a couple of years, so I scheduled an appointment. One mass was found, but it was benign and nothing to worry about. The mass continued to grow, and again, a biopsy confirmed it was benign. The mass was removed, and I went on with my life. A few months later, I returned for a follow-up appointment. It felt like a blow to my chest as the doctor confirmed I had a rare malignant phyllodes tumor in one breast. Because of the rarity of this type of cancer, I was offered genetic testing. A few months later, I was diagnosed with Li-Fraumeni syndrome (due to a *TP53* mutation), a rare condition that greatly increases the risk for many types of cancers.

I have three children ages 11, 22, and 27. My 11-year-old was diagnosed with autism at age 3, which has prepared me to advocate like no other. Although there is so much more to my story, when faced with challenges, I prefer to come through and share the answers I have collected throughout my journey. I'm just starting, but here are a few tips I have used to cope:

1. Brainstorm your thoughts in a journal. I have learned there are so many things I can't control, but so many more that I can.
2. Get your life in order and encourage your family and friends to do the same. With or without Li-Fraumeni syndrome, we are all guaranteed a death which can happen at any moment. As crazy as it sounds, while journaling, I realized that death was not my real fear. My real fear was leaving my son, and what his life would look like if I was not here to take care of him. Insurance policies, wills, trusts, and written expectations for my son are no longer something just on a to-do list.
3. Get organized. I'm still figuring this out, but the appointments and test results can take over your life quite literally. Getting a calendar and establishing systems that work for you is a must.
4. Research solutions and take an active role in your care. Ask questions no matter how silly they may seem. Always ask, "Is that the best we can do, and what are my other options?"
5. Take your time when making decisions. Never allow anyone to pressure you into making a decision. Sometimes you have to take a step back and seek wise counsel.
6. Create a "worry" section in your journal. As things pop up in my mind, I write them in the "worry" section of my journal and tell those thoughts that we can talk about them later during my worry time. "Worry time" is time I set aside to worry so that my day is not consumed with worry, which helps me stay focused on positive things. Typically, by the time "worry time" comes around, I have either found a solution, or I'm over it!
7. This probably should have been number 1 on the list but seek therapy. A few weeks in I realized the thoughts about "what if" were consuming me. Depression is real. Get a good therapist. It may take several sessions with several therapists but talking it out can be a game changer.



Hope this helps because I'm out of space. Sending great vibes and love your way!

—ICARE participant, Angela Watson, from Memphis, Tennessee