ICARE NEWSLETTER

SUMMER 2018

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About ICARE

ICARE provides individuals interested in participating in inherited cancer research studies the opportunity to enroll in a research registry. As of August 2018, there are 2789 participants, including 1142 *BRCA* carriers, enrolled in ICARE. These participants represent 47 U.S. states, the District of Columbia, and 16 other countries worldwide.

For those affected by inherited cancer, please visit InheritedCancer.net or call 615-875-2444 to learn more about participating. For providers treating or testing patients with inherited cancer, please call 615-875-2444 to learn more about how referring to ICARE may benefit you and your patients.

Welcome Message

We remain tremendously grateful to our ICARE participants as well as our healthcare provider partners for contributing to the continued growth of our registry. The ongoing data collected from ICARE participants has contributed to several recent articles as follows: *BRCA1* carriers may consider risk-reducing salpingo-oophorectomy before age 40, and ideally by age 35, while *BRCA2* carriers should consider this surgery by age 45;[1] among *BRCA1* and *BRCA2* carriers, breast cancer risk is not influenced by age at first birth,[2] body size,[3] or having a first-degree relative with breast cancer (versus not),[4] while tobacco smoking modestly increases cancer risks;[5] among *BRCA1* carriers, estrogen after oophorectomy may not increase breast cancer risk.[6] Data on other gene carriers are being analyzed, and will be the subject of additional focused efforts. Additionally, we have initiated a study to learn more about cancer risk management and family sharing among those with inherited cancer predisposition and *BRCA* variants of uncertain significance, and thank many of our ICARE participants for their interest in these efforts. In the current newsletter, we have highlighted some of the recent advances relevant to those with inherited cancer predisposition, including new gene associations and discoveries, as well as advances in cancer risks and treatments among those with mutations in inherited breast, colorectal, leukemia, and other genes. Wishing you the very best as we continue to expand our efforts and contribute to our mission to: *end the cycle of inherited cancer through research, education, and engagement.*

Sincerely,

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

[1]Kotsopoulos J, et al. Gynecol Oncol. 2018 Jul. PMID: 29793803. [2]Kotsopoulos J, et al. Breast Cancer Res Treat. 2018 Sep. PMID: 29774471. [3]Kim SJ, et al. Int J Epidemiol. 2018 Mar 13. PMID: 29547931. [4]Metcalfe KA, et al. Clin Genet. 2018 May. PMID: 29206279. [5]Ko KP, et al. Int J Cancer. 2018 Jun 1. PMID: 29330845. [6]Kotsopoulos J, et al. JAMA Oncol. 2018 Aug 1. PMID: 29710224.

Updates to NCCN Genetic/Familial High Risk Assessment:

Breast and Ovarian Guidelines (*Version 1.2019, posted July 11, 2018*)

- Regardless of family history, some individuals with a hereditary breast- and ovarian-related cancer may benefit from genetic testing to determine eligibility for targeted treatment
- The multi-gene testing section table was updated with:
  - A potential association of *ATM* with ovarian cancer risk
  - Potential increased risk of *BARD1* with breast cancer
  - Risk of breast cancer in *BRIP1* was changed from no increased risk to unknown/insufficient evidence

Colorectal Guidelines (*Version 1.2018, posted July 12, 2018*)

For Individuals with Lynch Syndrome:

- Surveillance for gastric and small bowel cancer now indicates there is no clear data to support this, but surveillance can be performed every 3-5 years starting at age 40
- Lack of evidence to make a recommendation for pancreatic or prostate cancer screening, beyond those already recommended through other NCCN Guideline panels
- Increased breast cancer risk was acknowledged, however there is not enough evidence to support increased screening above what is recommended for the general population

In the multi-gene testing section:

- New genes added for colorectal cancer risk included *NTHL1* and *MSH3* ('biallelic' mutations)
- Indicated lack of data to determine screening recommendations among those with single (heterozygous) mutation in *MUTYH* and a second degree relative with colorectal cancer

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

Differences in Breast Cancer Risks among Women with Lynch Syndrome

Breast cancer risks were recently reported among a sample of 423 women with mutations in one of the Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*).[1] Results indicated that breast cancer risks were substantially higher among those with *MSH6* and *PMS2* mutations, compared to *MLH1* and *MSH2* mutations. In fact, breast cancer risk to age 60 was 37.7% for *PMS2*, 31.1% for *MSH6*, 16.1% for *MSH2*, and 15.5% for *MHL1*. These findings are consistent with another recent study of 528 patients with Lynch syndrome gene mutation (including *MLH1*, *MSH2*, *MSH6*, *PMS2,* and *EPCAM*) in which *PMS2* and *MSH6* mutations were much more frequent among those with only breast cancer, whereas *MLH1* and *MSH2* mutations were much more frequent among those with only colorectal cancer.[2] These studies highlight how the risk profile among patients with Lynch syndrome is continuing to evolve as more individuals are tested through multi-gene panel testing, with particular focus on the complexities of the *PMS2* mutation carrier phenotype.[3] *[1]Roberts ME, et al. Genet Med. 2018 Jan 18. PMID: 29345684. [2]Espenschied CR, et al. J Clin Oncol. 2017 Aug 1. PMID: 28514183. [3]Blount J, et al. Clin Genet. 2018 Jul. PMID: 29286535.*

The Role of Inherited Genes Increasingly Recognized in Pancreatic Cancer

A number of recent studies have suggested that a substantial number of individuals with pancreatic cancer have a mutation in an inherited cancer gene. In a study of over 300 patients with pancreatic cancer (and with one or two family members with pancreatic cancer), 12% were found to have a mutation in 1 of 11 genes, most commonly *BRCA2* and *ATM*.[1] In a subsequently published study of 274 patients with pancreatic cancer (unselected for family history), almost 9% had a mutation in an inherited cancer gene.[2] Through another large study of over 3000 pancreatic cancer patients, mutations in 6 genes associated with pancreatic cancer were found in 5.5% of these patients (including 7.9% and 5.2% of patients with and without a family history of pancreatic cancer).[3] Most recently, ~10% of almost 300 unselected pancreatic cancer patients were found to have a mutation in an inherited cancer gene, most of which were genes known to be associated with pancreatic cancer.[4] Many of these individuals did not meet current clinical criteria to warrant testing. Taken together, these findings highlight the importance of broadly considering testing for inherited cancer genes among individuals with pancreatic cancer, which is particularly important given the advances in targeted therapeutics. *[1]Chaffee KG, et al. Genet Med. 2018 Jan. PMID: 28726808. [2]Young EL, et al. BMC Cancer. 2018 Jun 27. PMID: 29945567. [3]Hu C, et al. JAMA. 2018 Jun 19. PMID:29922827. [4]Brand R, et al, Cancer.2018 Aug 1. PMID: 30067863.*

Refining Cancer Risks among Individuals with Lynch Syndrome

Over the past year, multiple studies have refined risks and types of cancer among individuals with Lynch syndrome. Through a Scandinavian study, risks for 13 types of cancer (with colorectal cancers being excluded), were reported to be elevated with differences related to gender, age, and the gene in which mutation was present. Incidence rates of cancer peaked by age as follows: between age 30-49, ovarian cancer; between age 50-69, endometrial, breast, renal cell and brain cancers; after age 70, urothelial, small bowel, stomach, pancreatic cancer and skin tumors. This is yet another study that may eventually be used to individualize cancer risk management among patients. *Therkildsen C, et al. Br J Cancer. 2017 Nov 21. PMID: 29065108.*

NTHL1: A New Gene for Inherited Colorectal Cancers

In a study of 51 individuals with multiple colon polyps drawn from 48 families, genetic testing through whole-exome sequencing identified 7 individuals (from 3 unrelated families) to have a mutation in both copies of their *NTHL1* gene, and pedigree structure was consistent with autosomal recessive inheritance.[1] All these individuals had colorectal cancer and a large number of adenomas (ranging from 8-50), and none of the 8 cancers or adenomas tested showed microsatellite instability. There were also individuals who developed endometrial and duodenal cancer. A subsequent study of over 2400 families confirmed the association between this gene and colorectal cancer risk.[2] *[1]Weren RD, et al. Nat Genet. 2015 Jun. PMID: 25938944. [2]Broderick P, et al. Gastroenterology. 2017 Jan. PMID: 27713038.*

New Data to Suggest Additional Genes Associated with Breast and Ovarian Cancer

A recent study reported on cancer risks among over 10,000 cancer patients across the United States who had genetic testing. Findings suggest breast cancer risks were associated with *ATM*, *CHEK2,* and *PALB2*, as expected; but an association was also found with *MSH6* (in line with other recently published data, as outlined in another article in this newsletter). Regarding ovarian cancer risks, associations were found with *MSH6* and *RAD51C*, as previously reported; however, risks were also reported with *TP53* and *ATM*. These data provide new insight on both previously confirmed well-established breast and ovarian cancer genes, while implicating additional genes not currently established to be associated with these cancers. *Lu H, et al. JAMA Oncol. 2018 Aug 16. PMID: 30128536.*

Another PARP-Inhibitor Trial among *BRCA* Carriers with Advanced Breast Cancer

In a Phase 3 clinical trial among *BRCA* carriers with advanced breast cancer, an oral PARP Inhibitor (talazoparib) was compared to standard chemotherapy. Among those who received the PARP inhibitor, risk of disease progression or death was 46% lower, and the response rate was double. Furthermore, the side effect profile, quality-of-life measures, and breast cancer symptoms were more favorable in the PARP inhibitor group. These findings indicate that talazoparib among this group of patients results in longer progression-free survival than standard chemotherapy, with better patient-reported outcomes.

"…risk of disease progression or death was 46% lower, and the response rate was double."

Litton JK, et al.. N Engl J Med. 2018 Aug 15. PMID: 30110579.

Prevention of Colorectal Cancer among Individuals with Familial Adenomatous Polyposis (FAP)

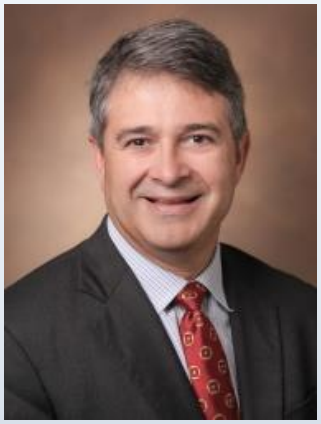
Through a randomized trial, patients with FAP were treated with sulindac and erlotinib versus placebo for 6 months. Results of the study showed that those treated with sulindac and erlotinib had 70% fewer polyps than those in the placebo group. The lower number of polyps was seen in both those with an intact colorectum and those who had had their colon removed and only had a rectal pouch or rectum. However, there was a high rate of side effects, most commonly skin and oral mucosal findings, which may limit the use of these medications at the doses used in the current study. Additional research is needed to follow patients for a longer time period to determine the effect of these medications on patient outcomes.

"…those treated with sulindac and erlotinib had 70% fewer polyps than those in the placebo group."

Samadder NJ, et al. JAMA Oncol. 2018 May 1. PMID: 29423501.

Ask the Expert

Through each newsletter, we give our participants an opportunity to have their genetics and research questions answered by experts. If you have a question you would like addressed, please email the study team at ICARE@InheritedCancer.net so we may include responses in future newsletters. The following question was addressed by Ronald D. Alvarez, MD, MBA who is Professor, Chairman, and Clinical Service Chief of the Department of Obstetrics and Gynecology at Vanderbilt University Medical Center in Nashville, Tennessee. Dr. Alvarez has been the recipient of several National Cancer Institute (NCI) and other industry funded grants in support of his research in gene therapeutics for ovarian cancer. He has served on the editorial board of *Gynecologic Oncology* and currently serves as Director of the Gynecologic Oncology Division for the American Board of Obstetrics and Gynecology.



Q. After an ovarian cancer diagnosis, should women with a *BRCA* mutation consider a risk-reducing mastectomy?

A. Among women with ovarian cancer who are found to have a *BRCA1* or *BRCA2* mutation, there is a lack of clear guidance as to when and in whom to consider risk-reducing mastectomy. In a study based on *BRCA* carriers (which included ICARE participants), 4% of these women developed breast cancer ten years following the ovarian cancer diagnosis. However, benefits of mastectomy (as well as breast MRI for early breast cancer detection) were primarily seen among women who had survived 10 years following their ovarian cancer diagnosis (without any disease recurrence) or had early stage (stage I or II) ovarian cancer. Consequently, risk-reducing mastectomy or breast MRI may be considered among *BRCA* carriers with ovarian cancer without a personal history of breast cancer and no evidence for recurrence for 10 years, as well as among those with early stage disease.

McGee J, et al. Gynecol Oncol. 2017 May. PMID: 28314588.

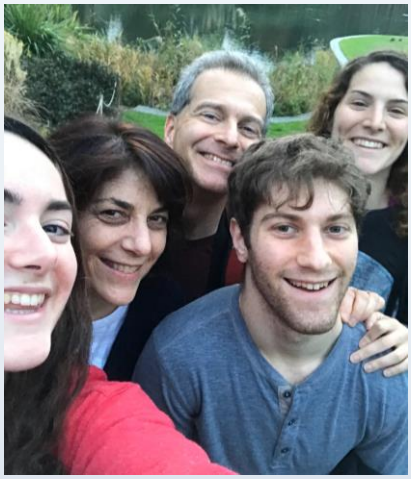
Inherited Leukemias:
The Importance of *TP53*/Li-Fraumeni Syndrome and Other Genes

It has long been established that the risk for developing leukemia in childhood is high among individuals with Li-Fraumeni Syndrome; however, better understanding the characteristics of leukemia among these individuals is important to guide treatment approaches. In a study of children with Acute Lymphocytic Leukemia (ALL), those with a germline *TP53* mutation (compared to those without a mutation) were older (median age of 15.5 years, compared to 7.3 years), were at a much higher risk of second cancers (25.1% versus 0.7%), and were more likely to have hypodiploid ALL (65.4% versus 1.2%), with poorer outcomes.[1] This information may be important to guide treatment among these individuals, including type and timing of treatment.

In addition to Li-Fraumeni Syndrome, there are several other conditions that are associated with inherited susceptibility to leukemia among individuals of all ages, including those associated with bone marrow failure syndromes, those in which myelodysplastic syndrome is seen before the onset of leukemia, and those with primarily a leukemia risk.[2] Patients with inherited hematologic malignancy syndromes may present without classic clinical signs of a particular familial syndrome or even a family history.[3] As more patients with inherited forms are diagnosed, there remains a need for developing evidence-based recommendations because current recommendations are primarily based on expert consensus.[4]

[1]Qian M, et al. J Clin Oncol. 2018 Feb 20. PMID: 29300620. [2]McReynolds LJ, et al. Hematology Am Soc Hematol Educ Program. 2017 Dec 8. PMID:29222262. [3]Furutani et al. J Clin Oncol. 2017 Mar 20. PMID: 28297620. [4]Godley LA, et al. Blood. 2017 Jul 27. PMID: 28600339.

Community Spotlight



I was aware from a very young age that breast cancer was part of our family. I knew that my great-grandmother (whom I never met) had breast cancer and my grandmother was diagnosed in her 50's. While I didn't grow up being afraid of the disease, I was far more aware of it than were any of my friends. My mom was diagnosed with a uterine sarcoma in her mid-40's and breast cancer at age 48, and again at age 54. She underwent a few grueling surgeries, but was spared chemotherapy and radiation. She also had her ovaries removed prophylactically, years before it was considered a "viable" option. My grandmother died in her 70's from complications of ovarian cancer, and my mom lived until she was 81 when she succumbed to Alzheimer's disease.

When I learned about genetic testing for the *BRCA* genes in spring of 2000, my mother and I had testing through Vanderbilt's genetic counseling program and learned we were both *BRCA2* positive; my two sisters tested negative. After much research—I met with numerous oncologists, surgeons, and plastic surgeons, and learned everything I could about possible insurance ramifications to any decisions I might make—I decided to have a complete hysterectomy and a prophylactic bilateral mastectomy with reconstruction.

During this time, I turned to FORCE (Facing Our Risk of Cancer Empowered) for much of my research and critical emotional support. My family was extremely supportive; my husband was "all in" despite having no prior experience with cancer. I felt lucky to have three healthy children (ages 3, 6, and 9 at the time) and was ready to undergo these surgeries to lower my cancer risks. The surgeries didn't scare me because I had watched my mother successfully undergo tough surgeries. Primarily, I was afraid of the unknown.

It's been 17 years since then, and I have no regrets. I'm eternally grateful for the research dedicated to hereditary cancers, the familial support I received, and the peace of mind my surgeries brought. I participate in ICARE and other related activities in hopes that continued research will positively impact all of us with hereditary cancers, and especially my three children who are now young adults. From my mom, I gleaned two thoughts I hope I've passed on to my children: live every day to the fullest; and knowledge is power. Because of my mother's legacy and willingness to tackle this very tough issue, my kids are armed with information they can use as they grapple with difficult decisions in the years ahead.

– ICARE Participant, Patricia Blumenthal (*pictured above with her husband and three children*)

VANDERBILT-INGRAM CANCER CENTER

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