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; among BRCA1 and BRCA2 carriers, breast cancer risk is not influenced by age at first birth; body size; or having a first-degree relative with breast cancer (versus not), while tobacco smoking modestly increases cancer risks; among BRCA1 carriers, estrogen after oophorectomy may not increase breast cancer risk. 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

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.

Table of Contents
Welcome Message..............................1
NCCN Guideline Update ........................1
Clinical & Research Updates ...............2
Advances in Treatment ........................3
Ask the Expert.....................................3
Community Spotlight..........................4

Updates to NCCN Genetic/Familial High Risk Assessment:

- 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

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 MLH1. 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.\(^3\)


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.


Refraining 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 increased 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. \(^1\)


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.\(^2\)


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. \(^1\)

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.
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


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

Phone: 615-875-2444  |  Email: ICARE@InheritedCancer.net  |  Website: InheritedCancer.net

Follow or like us on Facebook: www.facebook.com/ICARERegistry