Winter 2021

ICARE NEWSLETTER

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

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

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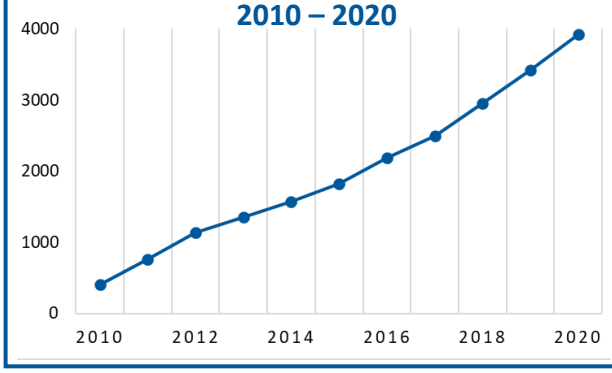
About ICARE

ICARE growth continued without pause over the past year, reaching almost 4,000 participants, including more than 1,200 individuals with *BRCA1/2* mutations and more than 1,000 individuals with other inherited cancer gene mutations. ICARE participants represent 50 U.S. states, the District of Columbia, and 20 other countries worldwide. Please visit our website (InheritedCancer.net) to learn more about ICARE and how participating in our efforts may benefit you.

ICARE Participant Growth 2010 – 2020



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Welcome Message

Since ICARE launched over a decade ago in 2010, unprecedented advances in technologies, policies, and treatments have led to many practice and paradigm shifts for those with inherited cancer. To grow our ability to provide updates beyond our bi-annual newsletter, we regularly post on multiple social media platforms. As we reflect on the past decade, we are thankful and indebted to our ICARE participants, provider partners, and team members who have worked on ICARE over the years. Recently, we put together a brief video to show ICARE growth in the context of changes in the national landscape, available at: https://tinyurl.com/ICAREdecadeinreview.

We also wanted to share some of the efforts in which we have participated, which are included in articles within this newsletter.[1,2] Based on information we collected through ICARE,[3,4,5] we recently launched the IMPACT study to develop and test strategies to improve both cancer risk management and family sharing practices among those with inherited cancer gene mutations. We will be reaching out to some of our ICARE participants for their interest in participating in this effort, which is entirely web-based and can be done in the comfort of one's home – additional details are available at: https://inheritedcancer.net/impact-study/.

We hope you and your loved ones have stayed safe in these unprecedented and challenging times. Wishing you the very best in 2021!

Sincerely,

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

[1]Palmer, et al. J Natl Cancer Inst. 2020 Dec. PMID: 32427313. [2]Kotsopoulos, et al. Gynecol Oncol. 2020 Dec. PMID: 33010967. [3]Dean, et al. Patient Educ Couns. 2021 Jan. PMID: 33455826. [4]Cragun, et al. J Genet Couns. 2020 Nov. PMID: 33174380. [5]Cragun, et al. Breast Cancer Res Treat. 2020 Jul. PMID: 32445176.

Updates to National Comprehensive Cancer Network (NCCN) Guidelines Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Released September 8th, 2020:

Genetic testing criteria by cancer type:

Breast Cancer:

- Broadened to include relatives with ALL grades of prostate cancer (not just high-grade)
- Having multiple breast cancer diagnoses no longer depends on whether the diagnoses were on two different breasts

Prostate Cancer:

- Now includes cribriform histology and ANY risk group (not just high-grade prostate cancer)
- Only first-degree relatives should be offered genetic testing

Pancreatic Cancer:

- Only first-degree relatives should be offered genetic testing

Released September 8th, 2020:

Breast cancer risk management recommendations by gene:

- *NBN*: high-risk breast screening was **removed** as there is insufficient evidence to support high breast cancer risks
- *BARD1*: **added** consideration for high-risk breast screening starting at age 40
- *RAD51C* & *RAD51D*: risks for triple-negative breast cancer were broadened to include potential increase in female breast cancer risk
- *BRCA1/2*: in men with gynecomastia, added consideration for annual mammogram at age 50 (or 10 years before earliest male breast cancer diagnosis in the family)

Released November 20th, 2020:

Inherited cancer gene tables expanded to include more detailed risk information, level of risk, and strength of evidence

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

Inherited Breast Cancer Genes: Two New Important Articles Just Released

Results of a United States (U.S.)-based study[1] and an international study[2] were released in January in the *New England Journal of Medicine* and provide a much clearer picture about the role of inherited breast cancer genes in women without a family history of cancer, and how common these genes may be in the general population. In both the U.S. study (**to which ICARE contributed**) and the international study, 8 genes — *BRCA1, BRCA2, PALB2, BARD1, RAD51C, RAD51D, ATM*, and *CHEK2* — had a significant association with breast cancer risk. In addition, for *MSH6* variants this significant association was only observed in the international study; and for *CDH1* variants only in the U.S. study. As outlined in the excellent accompanying editorial written by Dr. Steven Narod,[3] the majority of mutations among those with breast cancer were in *BRCA1, BRCA2*, and *PALB2*, whereas among those without, the majority were in *CHEK2* and *ATM* (according to Table 1 of the article by Dorling et al.[2] and Table 2 of the article by Hu et al.[1]). This is a big difference because it clearly shows that risks are much higher for *BRCA1, BRCA2*, and *PALB2*; whereas with *CHEK2* and *ATM*, the risks are lower, yet these gene mutations are much more common in the general population. Ultimately, these studies help establish genes that do versus do not confer breast cancer risks. *[1]Hu, et al. N Engl J Med. 2021 Jan. PMID 33471974. [2]Dorling, et al. N Engl J Med. 2021 Jan. PMID 33471991. [3]Narod. N Engl J Med. 2021 Jan. DOI: 10.1056/NEJMe2035083.*

Assessing How Pregnancy and Breastfeeding May Affect Cancer Risks in *BRCA* Carriers

Results of a recently published study suggested that pregnancy after breast cancer in *BRCA* carriers does not lead to a worse outcome in women or their fetuses.[1] This information is reassuring for *BRCA* carriers who have had a prior diagnosis of breast cancer and are considering having children. In another study among female *BRCA* carriers **which included ICARE participants**, breastfeeding reduced the risk of ovarian cancer.[2] The risk reduction was highest in those who breastfed for 7 months or longer and completed childbearing by age 35. *[1]Lambertini, et al. J Clin Oncol. 2020 Sep. PMID: 32673153. [2]Kotsopoulos, et al. Gynecol Oncol. 2020 Dec. PMID: 33010967.*

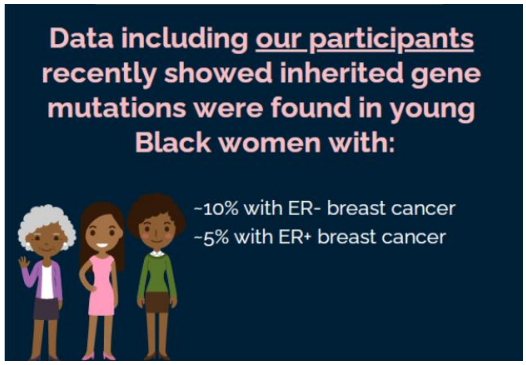
CHEK2 is NOT a Li-Fraumeni Syndrome Gene

An old study back in 1999 suggested that *CHEK2* may be a Li-Fraumeni Syndrome gene.[1] However, a subsequent report in 2002 clearly refuted this original assertion, and based on additional data and analysis concluded that "*… it is very unlikely that CHEK2 is an alternative Li-Fraumeni Syndrome susceptibility gene*."[2] Another subsequent report in 2008 based on additional information concluded that "*… it is no longer reasonable to consider CHEK2 mutations to be a cause of Li-Fraumeni Syndrome*."[3] Based on this information, *CHEK2* is absolutely not considered a gene that causes Li-Fraumeni Syndrome. *[1]Bell, et al. Science. 1999 Dec. PMID: 10617473. [2]Sodha, et al. Hum Mutat. 2002 Dec. PMID: 12442270. [3]Evans, et al. J Med Genet. 2008 Jan. PMID: 18178638.*

Exploring Disparities Among Those with Inherited Cancers

It has never been more urgent to ensure that advances in genomic technologies do not further widen existing cancer health disparities. In the fall of 2020, the American Association for Cancer Research (AACR) put forth a report focused on cancer health disparities, in which they highlighted several issues.[1] Notably, disparities in inherited cancer care were included throughout the report, including that there is inadequate representation and a lack of data in genomic studies from other racial and ethnic minorities, such as African Americans and Hispanics. Consequently, our current knowledge of cancer genetics cannot be applied to all populations, limiting our understanding of inherited cancer risks in racial and ethnic minorities.

Another important study **to which the ICARE effort contributed** is the largest study evaluating inherited gene mutations in Black women with breast cancer.[2] Results showed inherited gene mutations were found in young Black women, including ~10% with ER- breast cancer and ~5% with ER+ breast cancer. These findings reinforce that it is important to test for inherited cancer genes across all populations. In another study in which a group of diverse patients received genetic counseling before testing, results showed that race/ethnicity did not influence levels of distress and uncertainty experienced by patients.[3] While these results are reassuring, it is important to recognize that many individuals receive genetic testing without counseling, highlighting the need to conduct additional studies like this across different healthcare settings. *[1]American Association for Cancer Research (AACR). AACR Cancer Disparities Progress Report 2020. Available at: tinyurl.com/AACRCDPR. [2]Palmer, et al. J Natl Cancer Inst. 2020 Dec. PMID: 32427313. [3]Culver, et al. Cancer. 2020 Dec. PMID: 33320347.*



Learning You Have a Mutation in an Inherited Cancer Gene: What's Next?

The benefits achieved through genetic testing for inherited cancer only happen by acting upon the results. This can be through guiding cancer treatment, receiving appropriate cancer risk management strategies, and sharing results with at-risk family members so they too can benefit from this information. We recently reported on results of our study, **made possible through ICARE participants**, about sharing genetic test results with family members.[1,2] Our results showed that many of the challenges experienced with sharing genetic test information are similar across the various inherited cancer genes. Participants thought the information was complex to share and had concerns about family members' reactions, yet they also felt informational resources would be helpful. Keeping up with appropriate cancer risk management is also important, yet there are many who do not keep up with ongoing strategies to detect cancers early or prevent them.[3] This is truly a missed opportunity, as a recent report showed women who are identified with inherited cancer before they have any symptoms have better outcomes.[4]

We recently opened a study to test strategies to help those with inherited cancers to make sure they have the latest information about how to manage cancer risks and share results with family members. **If you are interested in learning more about this study, please go to** https://inheritedcancer.net/impact-study/.

[1]Dean, et al. Patient Educ Couns. 2021 Jan. PMID: 33455826. [2]Cragun, et al. J Genet Couns. 2020 Nov. PMID: 33174380. [3]Ter-Minassian, et al. JCO Oncol Pract. 2021 Jan. PMID: 33428469. [4]Hadar, et al. JAMA Oncol. 2020 Sep. PMID: 32644100.

Inherited Cancer Treatment: Updates and Relevant Policies

Over the last several months, the American Society of Clinical Oncology published a number of guidelines related to the use of PARP inhibitors among those with *BRCA*-associated cancers, including guidelines focused on ovarian cancer,[1] metastatic pancreatic cancer,[2] and breast cancer.[3] Additionally, costs of drugs also have great potential to influence policy, highlighting the importance of studies that suggest cost effectiveness when using PARP inhibitors to treat *BRCA*-associated pancreatic[4] and ovarian cancer.[5]

[1]Tew, et al. J Clin Oncol. 2020 Oct. PMID: 32790492. [2]Sohal, et al. J Clin Oncol. 2020 Aug. PMID: 32755482. [3]Tung, et al. J Clin Oncol. 2020 Jun. PMID: 32243226. [4]Wu, et al. J Natl Compr Canc Netw. 2020 Nov. PMID: 33152708. [5]Muston, et al. Gynecol Oncol. 2020 Nov. PMID: 32951894.

Study Suggests Low Yield of MRI Surveillance After Bilateral Mastectomy

A study of 159 women, including *BRCA1/2* carriers, who had a bilateral mastectomy with reconstruction and underwent breast MRI screening, showed few women had detection of breast cancer through MRI after their bilateral mastectomy. These results support the recommendation that *BRCA1/2* carriers with or without breast cancer who have a bilateral mastectomy with reconstruction do not need breast MRIs for screening.

Golan, et al. Breast Cancer Res Treat. 2019 Apr. PMID: 30511241.

Ask the Expert

In each newsletter, we give participants the opportunity to have their questions addressed by experts in the field. This question was addressed by Rebecca Smith, PhD, Laboratory Director at Genetics Associates, Inc. with over 20 years of experience in biomedical research and 7 years of experience in clinical laboratory diagnostics. If you have a question you would like addressed, please email ICARE@inheritedcancer.net for consideration in future newsletters.

Q. How is a genetic variation (or DNA change) classified as pathogenic or benign?

A. Genetic variation, or DNA changes between people, is a normal part of being human. Each person's DNA contains roughly 4 to 5 million normal genetic variations (sometimes referred to as 'single nucleotide polymorphisms'). Humans are 99.9% alike, with only ~0.1% variation. Genetic testing labs interpret an individual's DNA change by comparison to a reference sequence, and then figure out if the change is harmful versus harmless.

Trained laboratory geneticists interpret DNA changes through various sources, including review of several databases. This is like a detective working to find enough evidence to "make a case" that the variant is "harmful" or "harmless." All sources of evidence are not equal and can be scored as supporting, moderate, strong, very strong, or stand-alone. Types of information to classify variants include: type of change (e.g., truncating, missense, splicing, etc.), predictions made through computer programs, whether the DNA change tracks with the occurrence of cancer in family members (referred to as 'family segregation studies'), whether the variant is seen in many unrelated patients with the same disease, and how common it is in the population (i.e., more common suggests it may not be harmful). For example, a genetic variant found in more than 5% of the general population can be assigned stand-alone benign (harmless) evidence.

After researching all the available information for a variant, the evidence scores are added up to determine the variant's final classification. A five-tier classification system has been developed, ranging from "pathogenic", "likely pathogenic", "uncertain significance", "likely benign", and "benign".[1] Insufficient or conflicting evidence may result in classifying a change as a variant of uncertain significance (VUS).

While the identification of genetic variants has been simplified through advances in technology and the use of automated tools, the interpretation of changes remains a challenge. However, sharing classification evidence across databases and making this information publicly available improves our ability to interpret changes which in turn helps us to better counsel and treat patients.

[1]Richards, et al. Genet Med. 2015 May. PMID: 25741868.

Community Spotlight

My genes don't define me. I am AliveAndKickn. Pretty bold statement. AliveAndKickn is more than just a name. It's a way of life. I joke that Lynch Syndrome is the genetic predisposition to colon cancer, endometrial cancer, other cancers…and soccer. But that's just me. Besides half a dozen surgeries since 1997, I have and still play and coach the game I love. You may find your own game, or hobby, or solace in something that can help you in your day. Lynch Syndrome, other hereditary cancers, even other disorders are difficult to absorb and overcome. Having your first colon cancer at 29 is not easy. Surviving (thus far) to a point where your oldest son who has inherited your mutation is 25 is also stressful. The fact that my father, grandfather, and brother have all lived long fruitful lives post-cancers is comforting to both me and my family. Knowledge is power. By knowing you have Lynch, you can stay ahead of your cancer.

As co-founder of AliveAndKickn, I've had the good fortune of being able to share our message with a number of outlets, including the Forbes Healthcare Summit and the Biden Cancer Initiative, and more. AliveAndKickn has co-signed on a number of grant applications for studies, and has had posters at ASCO, NSGC, CGA and other professional conferences. AliveAndKickn is here for you. We are looking to make a difference for you and others, both current and future with hereditary cancer. Part of that is helping navigate the system, offer insights into options, share a smile, look for research trials, but most importantly, aggregate pertinent data to research potential cures. Genetics is taking huge strides almost every day. Precision medicine, immunotherapy and gene sequencing are the future. We thank you for being a part of our lives. I'm humbled to be part of yours. Be resilient. Be AliveAndKickn!

– Dave Dubin, co-founder of AliveAndKickn in Haworth, NJ

For more information about AliveAndKickn, please visit: https://www.aliveandkickn.org/

Featured Highlights

Since our last newsletter, we have featured many informational posts on social media. We are grateful to our followers for their support and encourage you to consider liking or following ICARE on your favorite social media platform to obtain regular updates on treatment advances, cancer risks, and inherited cancer screening guidelines.

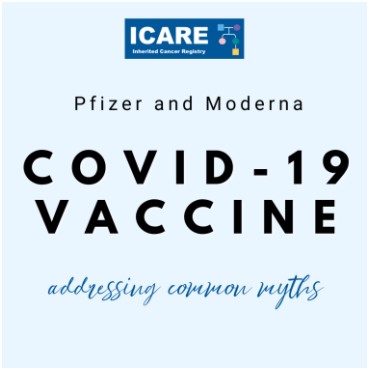
Below we have highlighted a few of our recent social media posts:

@INHERITEDCANCER

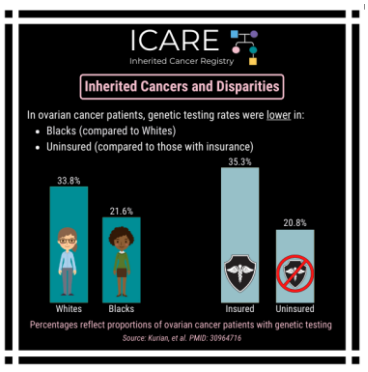
DECADE IN REVIEW

NEW ARTICLES

COVID VACCINE



CANCER DISPARITIES



All social media posts and newsletter articles can be searched on our ICARE website:
https://inheritedcancer.net/category/newsletter-articles/