

# ICARE NEWSLETTER



• SUMMER 2016 •

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### ICARE Recruitment and Participation Update

Participation in the ICARE initiative continues to expand through referrals, events, and active outreach efforts. As of August 2016, there are 2059 participants, including 1029 individuals from families with *BRCA* mutations, enrolled in the registry. Participants in ICARE represent 46 U.S. states and the District of Columbia, and 11 countries worldwide. We appreciate the time our participants have taken to complete their initial and follow-up questionnaires, and assist us in collecting their three-generation family trees and documentation of genetic test results (as applicable).

Your participation directly contributes to learning more about how to identify, evaluate, and manage those with inherited cancer. If you have not completed your initial or follow-up questionnaire and would like to be sent an additional paper copy or electronic link, please contact the study team via phone (813-745-6446) or email ([ICARE@InheritedCancer.net](mailto:ICARE@InheritedCancer.net)).

## Welcome Message

As ICARE continues to grow, we remain grateful to our participants and partner providers for their involvement and support as we strive to meet our mission to “end the cycle of inherited cancer through research, education, and outreach.” As part of our expansion efforts, we have transitioned to becoming a fully bilingual registry in English and Spanish, with enrollment materials, website, and newsletters in both languages. We are also excited to announce that in addition to the paper enrollment option, we now have the option of completing all enrollment materials online. We hope that this addition will make it even easier to participate in ICARE, for those who may be interested.

In this newsletter, we have outlined some of the exciting new discoveries to guide us in advising and managing individuals with inherited cancers as follows: updates to national practice guidelines, cancer risks and management for newer and established inherited cancer risk genes, and the importance of genetic testing among men with advanced prostate cancer. We hope this new information is useful to you. We are always looking to you for feedback, so please let us know if you have other topics you would like to see in future newsletters.

Sincerely,

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

### Community Spotlight

When I was diagnosed with cancer the first time at age 38, my sister (a breast cancer survivor since the age of 29) was positive we had a *BRCA* gene mutation. However, after we both had genetic testing done in 2006 the results showed we didn't. Doctors said they were surprised we did not have a mutation in one of the *BRCA* genes, but believed we probably had another gene mutation that was not yet identified. In 2011, we were asked to participate in a genetic study called *Whole Genome Analysis of High Risk Cancer Families* through the Genetics Program at the University of North Carolina at Chapel Hill. We both had our DNA sequenced and were found to have a mutation in the *PALB2* gene. The genetic study asked if other family members would be willing to be tested and out of the 19 members tested, 18 were positive for *PALB2*. Since my second battle with breast cancer this past year, I am more committed to help in whatever way I can help find a cure and find answers as to how our genes play a crucial role with cancer. – Cynthia Cardenas Schweitzer, ICARE participant



### Effort Focused on *PALB2* Mutation Carriers through ICARE

Together with Dr. Marc Tischkowitz, a leading expert on *PALB2*, Drs. Steven Narod, Kelly Metcalfe, and Tuya Pal are recruiting 500 women with a *PALB2* mutation to determine breast cancer characteristics and outcomes. Only through these types of research efforts will we be able to learn more about this gene and figure out how to help those with mutations. If you are a *PALB2* carrier, have a relative with a *PALB2* mutation, or are a healthcare provider with a *PALB2* positive patient, please contact us via our website ([InheritedCancer.net](http://InheritedCancer.net)), email ([ICARE@inheritedcancer.net](mailto:ICARE@inheritedcancer.net)), or phone (813-745-6446).

Please note for those with a *PALB2* mutation who are already enrolled in ICARE, we have collected much of the information needed from you to contribute to this focused effort. We will inform you of additional information that may be needed for this focused effort.

# Clinical and Research Updates

## Practice Guideline Updates for NCCN Genetic/Familial High-Risk Assessment

The National Comprehensive Cancer Network (NCCN) is a network of oncology healthcare providers who work together to develop best practice guidelines for the delivery of cancer care. Given the increasing use of testing for mutations in several inherited cancer genes at one time (called “multi-gene panel testing”), the Breast/Ovarian and Colorectal Panels sought to provide medical management guidance when using this testing approach. To access current NCCN guidelines, visit: [https://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](https://www.nccn.org/professionals/physician_gls/f_guidelines.asp)

### Breast and Ovarian (v2.2016)

Cancer risk management recommendations for some of the newer inherited breast and ovarian cancer genes were recently added. Based on emerging data, risk-reducing salpingo-oophorectomy became a consideration for women with mutations in *BRIP1*, *RAD51C* and *RAD51D*. Also, risk-reducing mastectomy became a consideration for women with a *PALB2* mutation.

### Colorectal (v1.2016)

The current version was significantly changed to include risk level and recommended management for several newer genes associated with colorectal cancer risk as outlined below:

#### 1) High-Risk Colorectal Cancer Genes (*GREM1*, *POLD1*, *POLE*):

Begin colonoscopy between age 25-30 and repeat every 2-3 years if normal. If polyps are found, repeat colonoscopy every 1-2 years. Surgical consideration if polyp number becomes unmanageable.

#### 2) Low/Moderate-Risk Colorectal Cancer Genes (*APC* (I1307K variant), *BLM* (single carrier), *CHEK2*, *GALNT12*, *MUTYH* (single carrier)):

For carriers without a personal history of colon cancer who have a first-degree relative (parent, sibling, child) with colorectal cancer: colonoscopy every 5 years beginning at age 40 or 10 years prior to the earliest diagnosis of colon cancer in the first-degree relative. For patients without a personal history of colon cancer who do not have a first-degree relative with colorectal cancer: colonoscopy every 5 years beginning at age 40.

#### 3) Lynch Syndrome (LS) (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*):

Begin colorectal screening at the same age and interval regardless of which of the five LS genes has a mutation. This is an important update for individuals with LS to share with at-risk family members as this may help to inform the age at which relatives may consider predictive testing for a known familial mutation. The updated NCCN colorectal cancer screening guidelines for LS are as follows:

LS Genes	Colorectal Cancer Risk by Age 70	Updated Colorectal Cancer Screening
▪ <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> , <i>EPCAM</i>	▪ <i>MLH1/MSH2</i> : 52-82% ▪ <i>MSH6</i> : 10-22% ▪ <i>PMS2</i> : 15-20%	▪ Begin colonoscopy at 20-25 years old or 2-5 years prior to the earliest colon cancer in the family if diagnosed < age 25 ▪ Repeat every 1-2 years

### An Approach to Making Risk Management Recommendations for Newer Inherited Cancer Genes

A recent article sought to develop an approach to cancer risk management among individuals with mutations in newer inherited cancer genes, many of which result in a moderate (rather than ‘high’) cancer risk.<sup>1</sup> Overall, the investigators suggest a framework that takes the age-specific, lifetime, and absolute cancer risks into account for inherited cancer genes where there is a proven association with cancer predisposition based on published data. They then suggest that cancer risk management should be initiated in women with pathogenic mutations in these inherited genes at the age when their 5-year cancer risk would approach that at which screening would routinely be initiated in women in the general population (which in the U.S. is approximately 1% for breast cancer). Given the lack of data on many of these newer genes to inform best surveillance strategies, investigators offer management suggestions with the hope of providing assistance to clinicians in managing patients as more definitive data emerges. The need to collect data among those with mutations in these newer genes (such as *ATM*, *CHEK2*, *NBN*, *PALB2*, *BRIP1*, *RAD51C*, and *RAD51D*) highlights the importance of participating in research registry efforts such as ICARE.

<sup>1</sup>Tung N, et al. Nat Rev Clin Oncol. 2016 Jun 14. PMID: 27296296.

### Surveillance among Individuals with Li-Fraumeni Syndrome (LFS): An 11 year Follow-up Study

Results from the original screening protocol for LFS<sup>1</sup> were recently updated following collection of 11 years of follow-up data.<sup>2</sup> Through this study, 89 patients with LFS were given the option of a clinical surveillance protocol consisting of a physical examination as well as frequent biochemical and imaging studies. Forty asymptomatic tumors were detected in 32% of the *TP53* mutation carriers who chose clinical surveillance. Overall survival was much higher in the surveillance group (almost 90%) compared to the non-surveillance group (~60%). These data imply benefits from ongoing comprehensive cancer surveillance with early detection of tumors with suggestions that overall survival may be improved.

<sup>1</sup>Villani et al. Lancet Oncol. 2011 June. PMID: 21601526. <sup>2</sup>Villani et al. Lancet Oncol. 2016 Aug 5. PMID: 27501770.

## ***Inherited Cancer Genes and Metastatic Prostate Cancer***

Several prior studies have suggested that men with a *BRCA* mutation (primarily *BRCA2*) tend to develop an aggressive form of prostate cancer that is more likely to metastasize. These findings were recently extended through a new study published in the *New England Journal of Medicine*.<sup>1</sup> In this study, almost 700 men with metastatic prostate cancer, unselected for strong family history or young age, were tested for mutations in 20 inherited cancer risk genes involved in repairing DNA damage. Germline (inherited) mutations were identified in 82 men (11.8%), of which the most frequently mutated gene was *BRCA2* (5.3%). Mutation frequency among those with metastatic prostate cancer was substantially higher than those with localized disease where only 4.6% were identified to have a mutation ( $p < 0.001$ ). Notably, unpublished findings presented during the 2016 American Urological Association Meeting suggested that among men with prostate cancer, *BRCA* mutations were significantly more common among African Americans (7.2%) compared to Caucasians (2.1%), with borderline significant results ( $p = 0.052$ ) of a shorter time to metastasis among African Americans.<sup>2</sup>

Taken together, the much higher than expected frequency of inherited mutations identified among men with metastatic prostate cancer regardless of age or family history (even more so among those who are African American) in conjunction with potential relevance to targeted treatments suggest that it may be appropriate to offer genetic testing for inherited cancer genes involved in DNA repair to all men with metastatic prostate cancer.

***“...it may be appropriate to offer genetic testing for inherited cancer genes involved in DNA repair to all men with metastatic prostate cancer.”***

<sup>1</sup>Pritchard CC, et al. *N Engl J Med*. 2016 Jul 6. PMID: 27433846. <sup>2</sup>Petrovics G., et al. *Higher Frequency of Germline BRCA1 and BRCA2 Mutations in African American Prostate Cancer*. Presented at the 2016 American Urological Association as Abstract #MP39-18.

## ***CHEK2 \*1100delC Mutation Carriers: Breast Cancer Risk by Age and Tumor Type and Other Associated Cancer Risks***

The *CHEK2* \*1100delC mutation is the most common “truncating” mutation (causing a shortened protein) in the *CHEK2* gene among Europeans, with lifetime breast cancer risk in the range of 20-30% among female carriers. Results of data pooled from over 30 studies which included 40,000 breast cancer cases and 40,000 controls, showed that estrogen receptor (ER) positive breast cancer was significantly (i.e., 2.5-fold) more common for *CHEK2* \*1100delC carriers compared to non-carriers.<sup>1</sup> Furthermore, breast cancer risk decreased with advancing age. *CHEK2* mutation status and other familial risk factors may now be taken into account through a publically available risk model, called BOADICEA, to provide women with a more precise estimate of their lifetime breast cancer risk.<sup>2</sup> Another recent Dutch study<sup>3</sup> reported

***“...BOADICEA may provide women with a more precise estimate of their lifetime breast cancer risk...”***

that risks of developing cancers other than breast cancer among *CHEK2* \*1100delC mutation carriers was 15% to 82% higher than non-carriers; however, the exact risks by cancer type could not be calculated. Although these results are based on the \*1100delC mutation, it is possible that this information may be applied to those with other truncating mutations in the *CHEK2* gene. This type of data is crucial to help refine the level of cancer risk and the types of associated cancers among those with mutations in moderate risk genes as well as newer genes to best guide cancer risk management strategies.

<sup>1</sup>Schmidt, MK, et al. *J Clin Oncol*. 2016 Aug 10;34(23):2750-60. PMID: 27269948. <sup>2</sup>Lee, A et al. *Genet Med*. 2016 Apr 14. PMID: 27464310. <sup>3</sup>Näslund-Koch, C., et al. *J Clin Oncol*. 2016 Apr 10;34(11):1208-16. PMID: 26884562.

## ***Cancer Chemoprevention in Individuals with Familial Adenomatous Polyposis (FAP)***

Prior research has demonstrated that NSAIDs significantly reduce colonic and rectal polyp burden among individuals with FAP although their impact on outcomes remains to be determined.<sup>1,2</sup> Recent data extended these results to the small intestine through completion of a randomized clinical trial among patients with FAP which demonstrated that use of sulindac and erlotinib compared with placebo led to lower duodenal (part of the small intestine) polyp burden at six months.<sup>3</sup> However, grade 1 or 2 adverse events (i.e., side effects) were more common in the group that received the drug (the majority of which included an acne-like rash) which may limit use of these medications at the doses given in this study. Given results of this preliminary study, it is important to evaluate these drugs in a larger population of patients with FAP with a longer follow-up period to determine if these observations lead to improved clinical outcomes among these individuals.

<sup>1</sup>Giardiello FM, et al. *N Engl J Med*. 1993;328(18):1313-1316. PMID: 8385741. <sup>2</sup>Giardiello FM, et al. *N Engl J Med*. 2002;346(14):1054-1059. PMID: 11932472. <sup>3</sup>Samadder NJ, et al. *JAMA*. 2016 Mar 22-29;315(12):1266-75. PMID: 27002448.

## ***Risk of Second Cancers among those with PTEN Mutations***

A recently published study to evaluate the risk of second cancers among *PTEN* mutation carriers showed that women with breast cancer had a 10-year second breast cancer cumulative risk of almost 30%.<sup>1</sup> Overall, the risk of second primary cancers was almost 8-fold that of the general population, primarily due to the higher risks of cancer of the breast (almost 9-fold), thyroid (almost 6-fold), and uterus (14-fold). These findings reiterate the importance of cancer risk management options among *PTEN* mutation carriers in order to detect cancers early or prevent them altogether.

<sup>1</sup>Ngeow J, et al. *J Clin Oncol*. 2014 Jun 10;32(17):1818-24. PMID: 24778394.

## What are the Endometrial Cancer Risks among BRCA Carriers?

Although *BRCA* mutations confer increased risk for ovarian, fallopian tube, and primary peritoneal cancer, there have been limited and conflicting risks reported for endometrial cancer. Consequently, current practice guidelines only recommend the removal of the fallopian tubes and ovaries as a risk-reducing option for *BRCA* carriers.<sup>1</sup> Specifically, through a prospective study of 4500 women with a *BRCA* mutation, there were 17 women identified with endometrial cancers (13 in *BRCA1* and 4 in *BRCA2*) with an average follow-up time of 5.7 years.<sup>2</sup> This suggested an overall endometrial cancer risk of 2-fold; although risks were higher (~4-fold) in those who received tamoxifen. The incidence of endometrial cancer was 2% at 10-years among those treated with tamoxifen. A subsequent study by the same group suggested the increased endometrial cancer risks among those with a history of tamoxifen use was associated with progesterone-only hormone replacement therapy, which warrants further study.<sup>3</sup> These findings suggest that tamoxifen contributed substantially to the endometrial cancers seen among *BRCA1* mutation carriers, although the actual risk is still fairly small. Consequently, in those considering tamoxifen, it may be important to discuss hysterectomy at the time of risk-reducing salpingo-oophorectomy (RRSO).

More recently, a prospective study of almost 1100 *BRCA* carriers who had previously undergone removal of their tubes and ovaries, demonstrated an increased risk in *BRCA1* carriers for a type of endometrial cancer called serous/serous-like. In this study, 8 women with endometrial cancer (of which 5 were serous/serous-like) were identified over an average follow-up time of 5.1 years.<sup>4</sup> This suggested an overall elevation in endometrial cancer risk of almost 2-fold. The association of serous/serous-like endometrial cancer is particularly relevant as it only accounts for approximately 10% of endometrial cancer cases in the general population and is typically associated with aggressive disease and poor prognosis. As eloquently reviewed in the Leath et al editorial for this article,<sup>5</sup> *the risk of serous endometrial cancer among BRCA1 carriers may warrant a discussion of the potential risks and benefits of hysterectomy at the time of RRSO as well as a discussion about the limitations of our current knowledge in order for patients to make an individualized decision.* In fact, a recent report of cancer risks among relatives of over 1000 *BRCA* mutation carriers detected no increased risk of endometrial cancer,<sup>6</sup> highlighting the limited (if any) elevation of endometrial cancer risk. Taken together, these findings emphasize the need for further studies to refine risks and determine the need for hysterectomy both at time of RRSO as well as the role (if any) of risk-reducing hysterectomy among those who have already had an RRSO (as the risk of a second surgery may be greater than the risk of endometrial cancer).

*“...risk of endometrial cancer among BRCA1 carriers may warrant discussion of the potential risks and benefits of hysterectomy at the time of RRSO...”*

<sup>1</sup>National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Genetic Familial High-Risk Assessment: Breast and Ovarian. Version 1.2016. Retrieved from: [www.nccn.org](http://www.nccn.org).  
<sup>2</sup>Segev Y, et al. *Gynecol Oncol.* 2013 Jul;130(1):127-31. PMID: 23562522. <sup>3</sup>Segev Y, et al. *Fam Cancer.* 2015 Sep;14(3):383-91. PMID: 25838159. <sup>4</sup>Shu CA, et al. *JAMA Oncol.* 2016 Jun 30. PMID: 27367496. <sup>5</sup>Leath CA, et al. *JAMA Oncol.* 2016 Jun 30. PMID: 27367041. <sup>6</sup>Streff H, et al. *Oncologist.* 2016 Jul;21(7):869-74. PMID: 27306910.

### Ask the Expert

Through each newsletter, we give our participants an opportunity to have their genetics and research questions answered by experts. Please send your questions to [ICARE@InheritedCancer.net](mailto:ICARE@InheritedCancer.net) so that we may include responses in future newsletter editions. The following question was addressed by Dr. Christine Laronga at the Moffitt Cancer Center:



**Q.** *How should bone health be monitored in women with a BRCA mutation after removal of the ovaries (i.e., risk-reducing salpingo-oophorectomy (RRSO))?*

**A.** Women with a *BRCA* mutation have a substantially high risk to develop ovarian cancer in their lifetime, yet there is currently no reliable screening method to detect ovarian cancer before it spreads beyond the ovaries. Consequently, RRSO among *BRCA* carriers is generally recommended around age 35-40, recognizing that childbearing plans are a consideration when deciding on age at which to have this surgery. However, this surgery also leads to early menopause which affects bone health. A recent study looked at women with a *BRCA* mutation who had undergone RRSO and showed that only 44% of these women had gotten at least one DXA scan (which is a radiological test that measures bone density). Of these women, 32% had normal results, 55.6% had osteopenia (reduced bone density), and 12.1% had osteoporosis. Additionally, 4% of women had a fracture (not related to trauma) after surgery. Low bone density was not related to age, breast cancer history, prior chemotherapy, or hormone receptor blocker treatment, suggesting that this was mainly due to removal of the ovaries. These findings suggest that RRSO in *BRCA* carriers is a strong risk factor for bone loss – as a result, it may be prudent to offer these women screening for bone health following RRSO to allow for timely intervention. Furthermore, although there is a lack of data regarding the best interval for bone density screening among carriers following RRSO, obtaining a baseline DXA and then screening every two years is reasonable to consider in these women.

<sup>1</sup>Garcia C, et al. *Gynecol Oncol.* 2015 Sep;138(3):723-6. PMID: 26086567.

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