

# The Inherited Cancer Registry (ICARE) Initiative: An Academic-Community Partnership for Patients and Providers



**G**enetic testing for inherited cancer predisposition can reduce cancer associated morbidity and mortality.<sup>1-3</sup> Given that 5 to 15 percent of cancer may be due to inherited predisposition,<sup>4-9</sup> identification and management of those with inherited cancer predisposition offers the opportunity to refine cancer risks and personalize cancer prevention and treatment.<sup>10-16</sup> In fact, testing for inherited cancer to guide cancer treatment is becoming increasingly important to identify among cancer patients, with the recent U.S. Food and Drug Administration approvals for drug eligibility based on presence of inherited cancer predisposition due to germline DNA changes.<sup>17-21</sup> Moreover, the increasing use of tumor DNA testing to guide treatment has tremendous potential to identify individuals predisposed to inherited cancers if the changes are confirmed to be present in the germline.<sup>22</sup>

For individuals to benefit from cancer genetic risk assessment services (i.e., genetic counseling and testing), they must first be identified as at-risk, offered appropriate testing, receive accurate interpretation of their genetic test results, and access risk-appropriate cancer screening and prevention options. Yet data from us and others suggest limited knowledge about cancer genetics services among providers,<sup>23-27</sup> which is required to fully maximize the benefits of genetic testing for inherited cancer susceptibility. Furthermore, many physicians report a lack of confidence regarding their ability to interpret genetic test results, with a recent study suggesting that some patients receive non-guideline-adherent care recommendations, particularly among those with uncertain genetic test results.<sup>28</sup> This is particularly concerning given that the advances in sequencing technology and the availability of multigene panels have led to additional complexities with higher rates of uncertain

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#### **About Our Program**

The Inherited Cancer Registry (ICARE) represents an academic-community partnership among healthcare providers, researchers, and individuals at an increased risk for inherited cancer. Through these partnerships, ICARE strives to fulfill its mission of ending the cycle of inherited cancer through research, education, and engagement. Established in the summer of 2010, ICARE has grown into one of the largest registries focused on individuals with inherited cancer predisposition, with more than 2,500 participants including 1,100 *BRCA1/2* carriers and nearly 500 carriers of other inherited cancer genes. Provider and participant engagement has remained a key component that underlies the success of ICARE's ongoing efforts.

results and testing for genes with variable cancer risks, spectrum, penetrance, and evidence-based management guidelines.<sup>27,29-31</sup> Amidst the issues of quality and competency in the provision of genetic services, availability and access to cancer genetic risk assessment services through certified and credentialed genetics professionals is limited, particularly in rural areas,<sup>32,33</sup> certain states, and community oncology practices.<sup>34-36</sup> Consequently, healthcare providers with limited genetics proficiency and training order most genetic tests for inherited cancer susceptibility, which may result in guideline-discordant care.<sup>23,24,26-28,37-39</sup> Yet, restricting the provision of genetic services to only those with specialized training in clinical cancer genetics has raised concerns that this may reduce utilization of genetic services,<sup>40</sup> thus making it important to explore novel service delivery models through academic-community partnerships.

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In an effort to broadly share clinical cancer genetics expertise, the ICARE initiative was launched in 2010 along with the ICARE genetics case conference. Through engaging healthcare providers who offer genetic testing for inherited cancer predisposition, a community-academic partnership was formed. Healthcare professionals across the country were offered free educational resources, including access to the web-based genetics case conferences as well as regular newsletters outlining clinical and research updates pertaining to inherited cancers. The ICARE provider network has experienced ongoing expansion and encompasses genetic counselors, nurse practitioners, nurses, physician assistants, physicians, and other healthcare professionals (further referred to as provider partners). These provider partners refer their high-risk patients to participate in ICARE, which has resulted in its rapid growth. ICARE participants are also provided with regular clinical and research updates and opportunities, which has fostered their ongoing engagement in this initiative. From the outset, the ICARE initiative has simultaneously focused on research, education, and engagement, with details and accomplishments for each of these areas outlined in the ensuing sections.

## Research

The ICARE initiative houses a research registry for individuals at high risk for inherited cancer predisposition. The registry has experienced continued growth as a result of provider partners referring their high-risk patients to the registry (Figure 1, right), thereby providing them with a research link as well as an opportunity to receive ongoing clinical and research updates. The registry consists of men and women interested in participating in studies about inherited cancer, including those with inherited cancer predisposition based on their genetic test result(s) or family history. Enrollment in the registry involves completing a consent form, through a traditional paper-based consenting method or online through the ICARE website (InheritedCancer.net). Participants are also asked to complete a baseline questionnaire and periodic follow-up questionnaires. To date, more than 2,500 high-risk patients have enrolled into ICARE, including more than 1,100 *BRCA* mutation carriers and nearly 500 participants with mutations in 40 other inherited cancer genes (Figure 2, right). Registry participants have been recruited throughout the United States and internationally (Figure 3, page 58), with participants representing 47 U.S. states, the District of Columbia, and 15 countries worldwide.

The data collected through the registry have enabled research efforts to broadly study the delivery of clinical cancer genetic services across diverse providers and settings. Such efforts include data suggesting that there is a higher uptake of cancer risk management options among *BRCA* carriers with longer genetic counseling sessions and when testing was performed by a genetics professional.<sup>41</sup> Furthermore, despite the existence of cancer genetic risk assessment standards put forth through multiple national organizations,<sup>42-47</sup> our data indicated higher adherence to nationally recommended genetic counseling practices and potential reduction in *BRCA* testing costs when services were delivered by genetics professionals.<sup>39</sup>

These registry participant-reported data (i.e., patient-level data) are consistent with provider-level data collected through surveying providers in Florida who order hereditary cancer genetic testing. Specifically, survey data was collected in 2010<sup>24,48,49</sup> and 2013<sup>25</sup> to better understand service delivery models, management practices, and educational needs across providers who order *BRCA* testing. Comparisons were made between those with certifications and/or credentials in genetics (called genetics professionals) to those without any formal training in genetics (called non-genetics professionals). Results of the 2010 provider survey showed that genetics professionals were significantly more likely to discuss the standard pre-test genetic counseling elements, accurately interpret test results, and recommend guideline-concordant management compared to providers without credentials or certifications in genetics.<sup>24</sup> Furthermore, survey respondents indicated both the need for and interest in ongoing educational opportunities and resources focused on clinical cancer genetics.<sup>48</sup> Data from the subsequent 2013

(continued on page 58)

Figure 1. ICARE Provider Partner Recruitment by Year

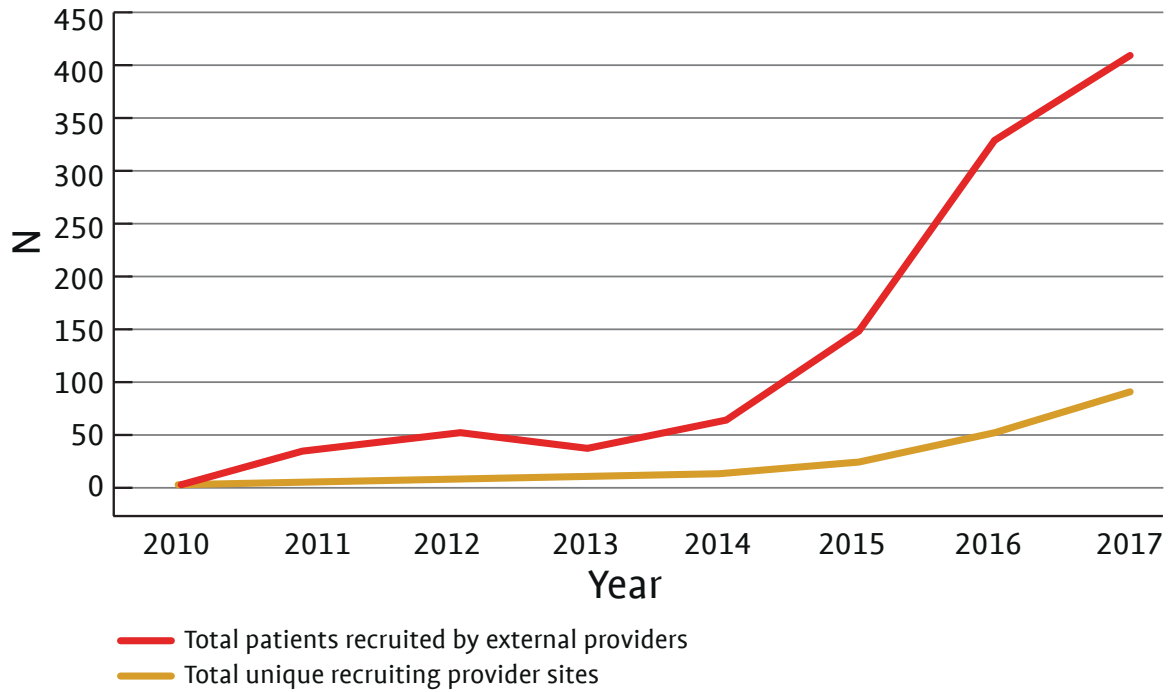


Figure 2. ICARE Carrier Count by Gene

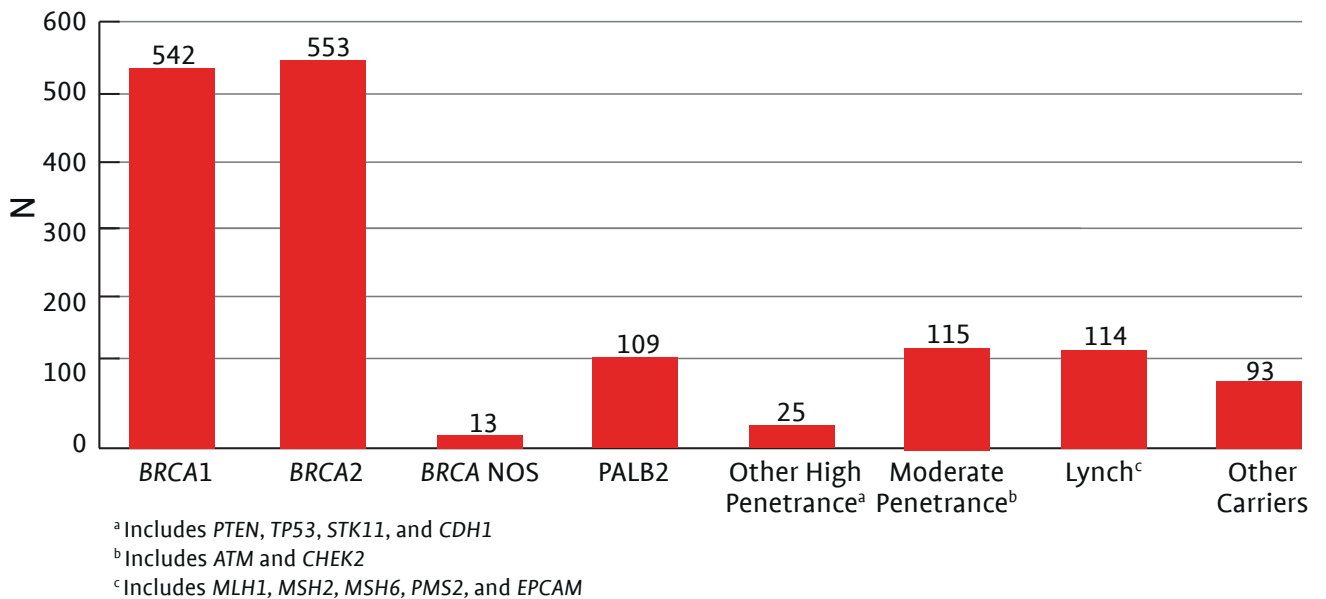
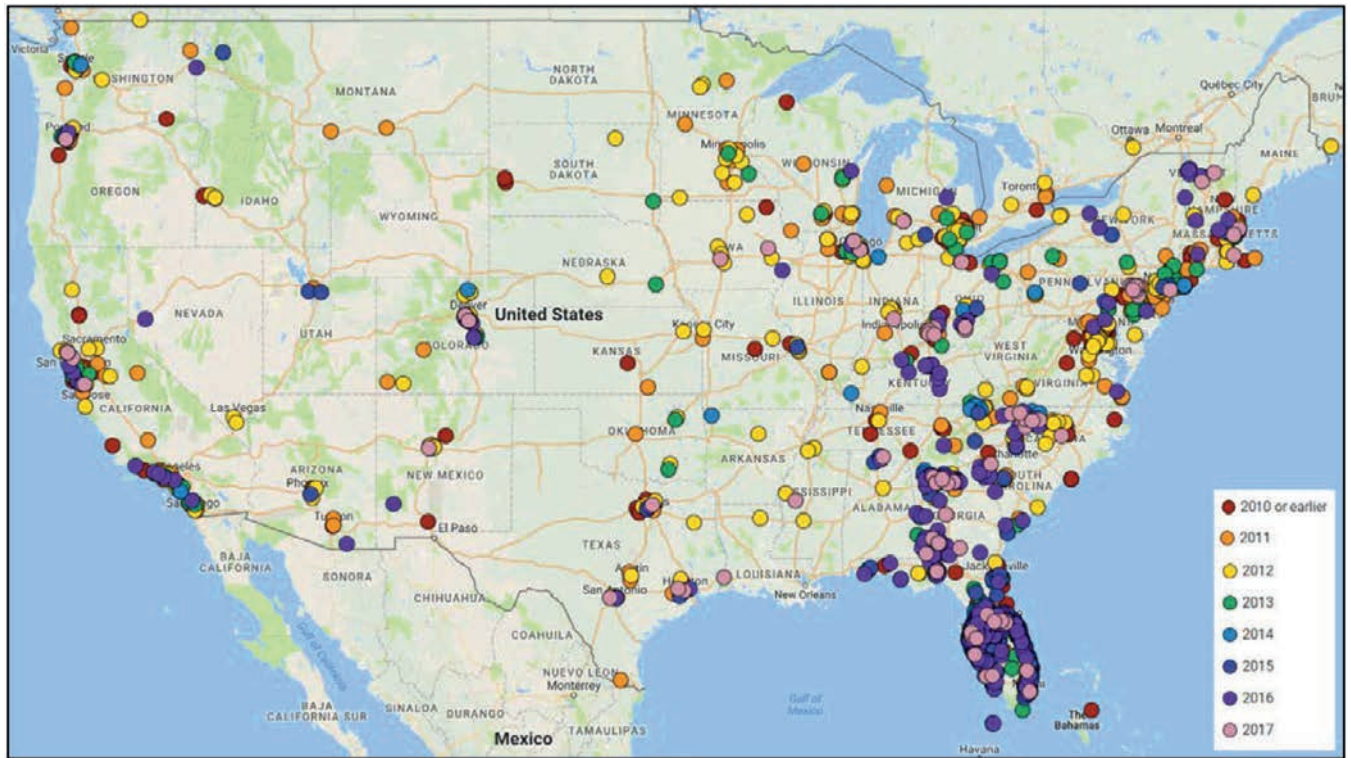


Figure 3. Location of ICARE Registry Participants



(continued from page 56)

provider survey were consistent with the prior 2010 survey data, revealing significantly higher knowledge and guideline-adherent testing and cancer risk management recommendations among genetics professionals compared to non-genetics professionals.<sup>25</sup> Furthermore, genetics professionals had a greater awareness of recent changes in genetic testing and policies, particularly given that the 2013 survey was conducted after the fall of the *BRCA* patent and as multigene panel testing became more widely available. Overall, these efforts have confirmed both the benefits of and interest in the formation of academic-community partnerships where the expertise of genetics professionals may be maximally leveraged for patient benefit.

In addition to pursuing our own efforts focused on better understanding the delivery of cancer genetic risk assessment services, the research registry has enabled the contribution of data to international research efforts focused on optimizing management among *BRCA* carriers (as regularly updated on our website: [inheritedcancer.net/publications](http://inheritedcancer.net/publications)). For example, findings from studies in which *BRCA* carriers from ICARE were included have shown that an oophorectomy may prevent premenopausal

breast cancer in *BRCA2* but not *BRCA1* mutation carriers<sup>50</sup>; breastfeeding and oral contraceptive may be useful for the primary prevention of ovarian cancer among *BRCA* carriers<sup>51</sup>; and infertility treatment does not significantly increase the risk of ovarian cancer among *BRCA* carriers.<sup>52</sup>

In addition to efforts among *BRCA* carriers, it has become increasingly important to study patients who are carriers of other inherited cancer genes, including genes with moderate or uncertain levels of cancer risk and that lack evidence-based management options. These individuals have been increasingly identified with the expanded use of multigene cancer panels, which has also raised the complexity of testing and results interpretation.<sup>53</sup> There are currently almost 500 registry participants with mutations (i.e., pathogenic or likely pathogenic variants) in inherited cancer predisposing genes other than *BRCA1* or *BRCA2* (Figure 2), with ongoing efforts to study cancer risks and management practices among these individuals. These include focused efforts to study breast cancer outcomes among *PALB2* carriers in collaboration with colleagues from the University of Toronto ([inheritedcancer.net/palb2-study](http://inheritedcancer.net/palb2-study)), which has resulted in the recruitment of more than 100 *PALB2* carriers to ICARE. We have also

recently reported on *TP53* carriers in ICARE identified through multigene panel tests.<sup>54</sup> Our findings indicated that many of these individuals did not meet clinical diagnostic criteria for Li-Fraumeni syndrome, highlighting the substantial variations in clinical phenotypes among *TP53* carriers that may be taken into account when making cancer risk management recommendations.

Ultimately, the expanding indications for *BRCA* testing, in conjunction with testing for genes with uncertain or moderate levels of cancer risk through multigene panel tests highlight the importance of data collected through registries such as ICARE. Furthermore, data collected through registries such as ICARE have reinforced evidence-based care and the benefits of genetic testing and family history to help guide cancer care, primarily among high-risk individuals and families. These types of efforts are needed to generate observational and often longitudinal data to refine cancer risks and optimize management of patients at high risk for inherited cancer. They may also serve as the platform upon which interventional trials may be based.

### Education

Educational efforts through the ICARE initiative have encompassed the dissemination of research findings and clinical updates to both provider partners and registry participants. Our published research results (as outlined previously) suggest limited proficiency in genetics among many testing providers<sup>24,25</sup> who are interested in educational opportunities,<sup>48</sup> reinforcing the need for our educational efforts. These ongoing efforts have been achieved through 1) regular web-based genetics case conferences for our provider partners and 2) biannual newsletters for both provider partners and registry participants through which clinical and research updates are provided and other research opportunities are highlighted.

### ICARE Case Conference

The ICARE genetics case conference was initiated in June 2010 and initially hosted quarterly; however, the frequency increased to bimonthly in March 2011 and then to monthly since September 2015 to accommodate requests from provider partners. These virtually-hosted case conferences consist of clinicians who present interesting and challenging patient cases with inherited cancer predisposition, followed by a discussion and feedback about the case by a multidisciplinary group of attendees. These case conferences take place on a weekday during regular working hours and last for one hour.

Case conference attendance has continued to grow annually, as reflected in Figure 4 (page 60), with providers participating across the country and beyond. The diversity of attendees has fostered a unique forum for healthcare providers to network and communicate, as well as obtain feedback on complex cases. Many of the conferences focus on a particular inherited cancer predisposition topic, with past topics including uninformative negative test results, families with *PALB2* mutations, and the identification of germline findings through somatic testing. For some topics, a guest expert attends to provide deeper insight, such as presentation of unpublished clinical data and case commentary. A complete

list of upcoming ICARE case conference dates and topics is made available and updated regularly on the ICARE website ([inheritedcancer.net/case-conferences](http://inheritedcancer.net/case-conferences)).

### ICARE Newsletters

ICARE newsletters are developed and disseminated biannually to registry participants and provider partners and made freely available on the website ([inheritedcancer.net/newsletters](http://inheritedcancer.net/newsletters)). The newsletters are a means by which new information is widely disseminated to these groups. Newsletters include clinical and research updates relevant to clinical cancer genetics and highlight other research and clinical trial opportunities for individuals with inherited cancer.

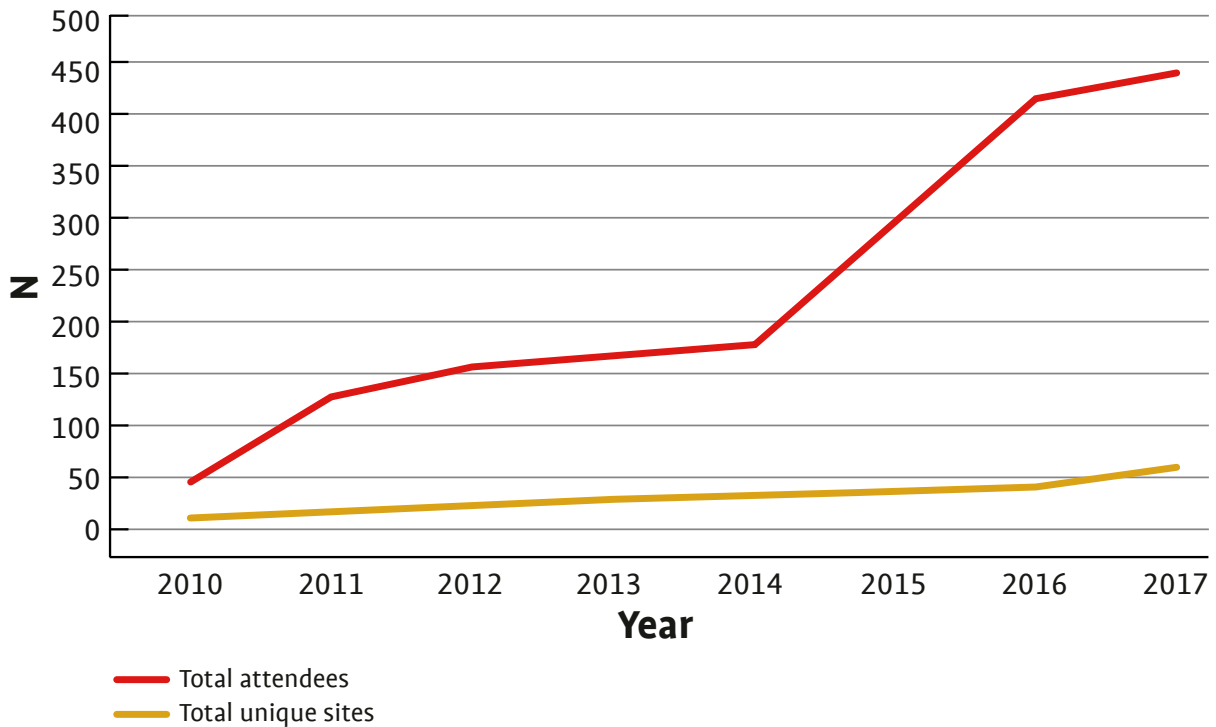
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These efforts have served to provide registry participants and provider partners with clinically relevant and practice-changing updates that may be pertinent to them. These include data on newer genes, clinical trials, U.S. Food and Drug Administration approvals for new drug treatments, updates to national practice guidelines, as well as new research to guide testing or management of individuals with inherited cancer predisposition. A community spotlight piece is featured in each newsletter, providing ICARE participants the opportunity to share their stories of navigating cancer prevention, screening, and treatment options for themselves and their families. Additionally, updates about the continued growth of the registry, published efforts in which our registry data were included, and information about new research and clinical updates are included in each newsletter. Overall, this effort has been met with much enthusiasm. Each ICARE newsletter dissemination effort is typically followed by an influx of questions and comments from registry participants and provider partners who email or call the study team. Moreover, with the rapid pace at which new information is generated, these newsletters have been welcomed by ICARE provider partners given that these function as a mechanism by which to deliver targeted information to this high-risk population. Over the past seven years, ICARE has developed 13 newsletters and disseminated more than 15,000 copies.

Figure 4. Genetics Case Conference Attendance by Year



Recognizing that it takes effort on the part of provider partners to refer patients, as well as the patients to enroll in the registry, we continuously strive to share information about publications and presentations made possible through their involvement.

### Engagement

In conjunction with our educational efforts, we have actively promoted the engagement of provider partners and registry participants in our efforts, which we believe has been instrumental in expanding our provider network and registry growth. This engagement has been at the core of the ICARE initiative from the beginning and has served as a means to constantly reassess, reengage, and realign research and educational efforts to meet the evolving landscape of cancer genetic risk assessment services and the needs of provider partners and registry participants. For


example, days and times for ICARE case conferences were guided through surveying provider partners to enhance broad attendance. Additionally, provider partners were surveyed to determine specific topics that may be of interest to them for a case conference, which guides upcoming case conference themes.

Registry participant and provider partner engagement works in synergy with both research and educational endeavors with the ICARE website serving as a centralized hub to keep registry participants and provider partners informed. Recognizing that it takes effort on the part of provider partners to refer patients, as well as the patients to enroll in the registry, we continuously strive to share information about publications and presentations made possible through their involvement. We include this type of information in our biannual newsletters in order for registry participants and provider partners to be aware that their efforts are contributing to research advances to guide care among those with inherited cancer or at risk for inherited cancer. Our website also includes up-to-date information on other educational and research-based initiatives that are in development or currently in practice within various professional and patient-based cancer communities or through ICARE. A public forum that may be viewed by provider partners and registry participants enables transparency in ICARE efforts and validates participation in ICARE is being used toward ICARE's mission.

Other avenues to enhance engagement in ICARE-focused efforts have included the implementation of a dedicated telephone line and e-mail address to provide centralized and ongoing access to the ICARE study team for both provider partners and registry participants. For provider partners, the ICARE team is available to provide guidance about general clinical, research, and recruitment questions and help connect providers to appropriate resources for their patients. Furthermore, registry participants recruited through provider partners are tracked, and this information is shared with the providers. Participants often contact the ICARE team with clinical questions (ranging from questions about other mutation-focused studies to questions about clarification on additional genetic testing or screening based on prior results), which are funneled back to the referring provider partner, underscoring the value of maintaining the link between participants and their referring healthcare providers within the ICARE database. For example, when gene panels became clinically available, the newsletter provided an update about new genetic tests being available. We received inquiries from participants about these tests and were able to refer them back to their provider for update testing. By constantly engaging with provider partners, the ICARE team has tailored its research and educational objectives to meet the needs of healthcare providers actively involved in the provision of cancer genetic risk assessment services. Similar to engagement with the providers, ICARE participants are kept informed about clinical and research updates via ICARE's website and biannual newsletter. Data from the research registry have facilitated patient participation in translational studies and multi-institutional consortia, and participants are able to track progress of these types of efforts through the website, newsletter updates, and individual inquiries to our study phone line or email.

## Summary

The ICARE initiative is a novel program that provides research opportunities, education, and engagement about inherited cancers to patients and healthcare providers. It has experienced a tremen-

dous growth trajectory for both registry participation and provider partnerships spanning across the United States and internationally since its foundation in 2010. The infrastructure and success of the ICARE initiative has resulted in the study team's ability to conduct its own hypothesis-driven research, participate in a number of grants, and contribute de-identified data to international efforts. Over the years, the development of a collaborative network of hundreds of unique healthcare providers has culminated in the recruitment of more than 2,500 participants to the research registry, who continue to be followed over time. These efforts will continue to enable ongoing information dissemination to healthcare providers, researchers, registry participants, and members of the general population, while providing an infrastructure to conduct clinical and translational research studies to achieve a mission—to end the cycle of inherited cancer through research, education, and engagement. 

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### Get Involved

To learn more about how referring to ICARE may benefit you and your patients, please visit [InheritedCancer.net](http://InheritedCancer.net) or call 615-875-2444. There is no cost to participate.

### Who Can Enroll in ICARE?

- Men and women
- Aged 18 or older
- Carries a gene mutation linked to an inherited cancer syndrome
- Gene status negative or unknown but personal and/or family history of cancer suggesting increased risk



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