REGISTRY NEWSLETTER

Welcome back to another Registry newsletter! As 2025 begins, we are celebrating connection and collaboration.

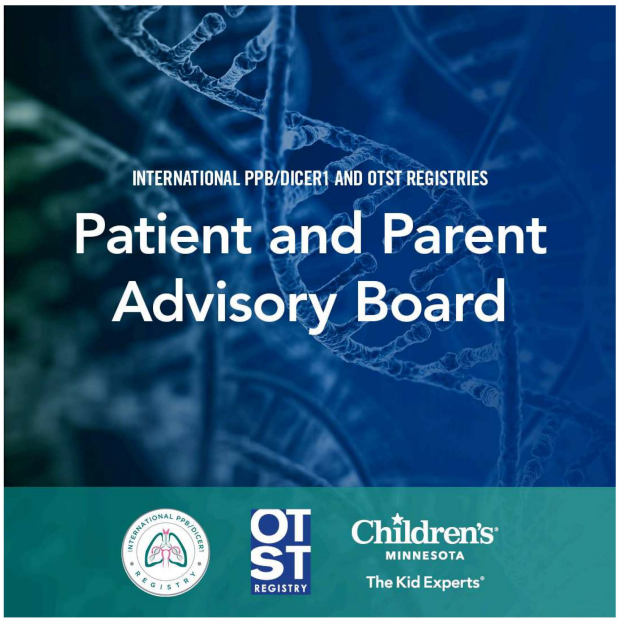
At last year's *DICER1* Scientific Symposium and PPB/*DICER1*/OTST Family Meeting, we had the honor of connecting with over 150 healthcare professionals and researchers and over 135 patients and families from around the world, including but not limited to Australia, Belarus, Brazil, Chile, Czech Republic, Denmark, Egypt, France, Germany, Honduras, India, Indonesia, Ireland, Israel, Netherlands, New Zealand, Oman, Pakistan, Papua New Guinea, Peru, Russia, Spain, Turkey, United Arab Emirates, United Kingdom, and many Canadian provinces and U.S. states. We have also had the opportunity to host a series of Registry Patient/Parent Advisory Board meetings. We appreciate the many insights shared by this group and look forward to learning more together in 2025!

Additionally, we had an exciting year of advancing and/or completing existing projects and starting new endeavors including biomarker testing and analysis, tumor sequencing, intronic germline testing, PDX model development, and organoid development. All of these projects are designed to optimize early detection and the development of novel therapies for individuals with *DICER1*-related conditions.

The Registry recently published updated *DICER1* surveillance guidelines in the journal of *Clinical Cancer Research*. As we often say, "knowledge is power," therefore to summarize these findings, we developed a patient education document, which we would love to share with you. We hope these documents are useful tools for you, your families, and your care teams.

This year, we look forward to merging our *DICER1* Scientific Symposium and PPB/*DICER1*/OTST Family Meeting into one event to bring patients, families, healthcare professionals, and researchers together to discuss the updated *DICER1* surveillance guidelines. We hope you will join us virtually for the 2025 *DICER1* Symposium and Family Meeting on May 6th, when we will discuss *DICER1* surveillance, testing, and novel approaches.

Opportunities to Connect



Register Here

Request Meeting Link

DICER1 Surveillance

What is *DICER1*?

DICER1 is a gene in our body. Each person has two copies of this gene, which is used to produce the protein Dicer. The Dicer protein regulates gene expression, which impacts a cell's ability to multiply, mature, and perform programmed cell death - which helps dispose of damaged and potentially harmful cells.

What is a *DICER1* variant?

DICER1 is located on chromosome 14 and consist of thousands of units of genetic code. When there is a variation in the genetic code of *DICER1*, this is known as a *DICER1* variant. There are numerous conditions, cancerous and non-cancerous, that have been found to be linked to variants in *DICER1*. These conditions are called *DICER1*-associated conditions.

It is not always clear if a *DICER1* variant truly affects the function of Dicer. Therefore, genetic variants have different classifications. A variant can be classified as pathogenetic, likely pathogenic,

Efforts are currently underway to further understand variants of unknown significance so that we can better determine how these individuals should be monitored.

What is *DICER1* Surveillance?

Individuals are diagnosed with *DICER1* tumor predisposition when they are found to have a pathogenic or likely pathogenic variant in the *DICER1* gene. While many individuals with *DICER1* variants are healthy, due to increased risk of tumor development, it is recommended that these individuals have routine monitoring. *DICER1* surveillance consists of routine radiographic imaging (Ex: X-ray, ultrasound, CT, etc.) at specific time points based on the individual's age. The goal of surveillance is to catch *DICER1*-associated conditions in their earliest and most curable form.

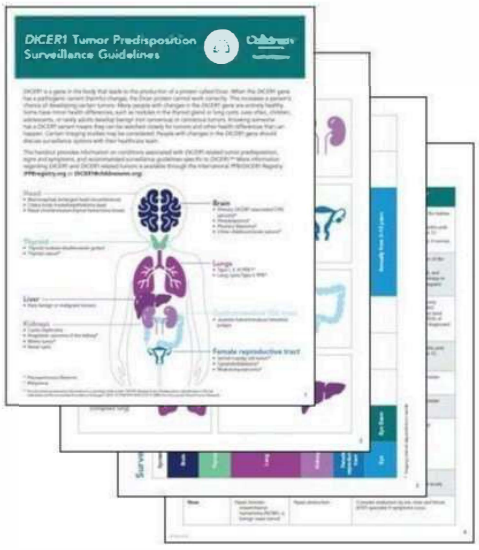
Individuals with likely benign or benign variants are not typically considered to have *DICER1* tumor predisposition since there is not a clear indication that their variant affects the function of Dicer. For individuals with variants of unknown significance (VUS), it is not clear if there is increased cancer risk so management is generally individualized based on personal and family history. Talking with your healthcare provider and genetic counselor is recommended to help determine the best *DICER1* testing and surveillance for you and your family members.

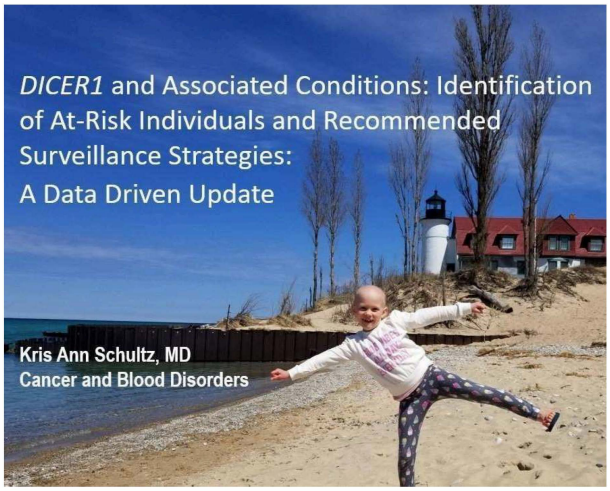
Updated Surveillance Guidelines

In 2018, the International PPB/*DICER1* Registry published imaging-based surveillance guidelines for individuals with *DICER1* tumor predisposition. In 2024, the Registry published an updated article in *Clinical Cancer Research*.

The article highlights the need for earlier female pelvic surveillance. Previously, pelvic ultrasounds were recommended starting at age 8 years. Based on new research, the Registry guidelines now recommend that pelvic ultrasounds begin as soon as a pathogenic or likely pathogenic (P/LP) *DICER1* variant is identified. This recently published article also includes updates for other aspects of surveillance and considerations for *DICER1* testing and/or additional testing.

The findings included in this article are summarized in the Registry's *DICER1* Tumor Predisposition Surveillance Guidelines Patient Education document. Additionally, at the 2024 PPB/*DICER1*/OTST Family Meeting, our Registry team shared these updates in the presentation linked below.



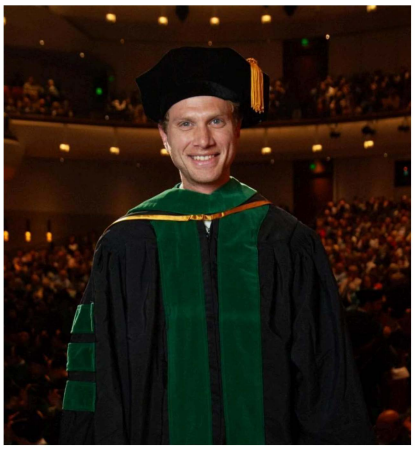


Request Ed Doc

View Presentation

Updated guidelines, such as those included in this report, are made possible by each and every one of you. You are the reason our research moves forward, and we are honored to be partners with you in advancing *DICER1* care. Thank you for letting us be a part of your journey.

Outcomes in Ovarian Sertoli-Leydig Cell Tumor



In 2024, the Registry analyzed outcomes in individuals with Sertoli-Leydig cell tumor (SLCT), a rare type of ovarian tumor usually associated with *DICER1*. This analysis, led by Dr. Alexander Nelson, highlights the role of surveillance in identifying asymptomatic SLCT at its earliest stage. Additionally, in this analysis, mesenchymal heterologous elements were identified as a poor prognostic feature of SLCT regardless of stage, which indicates the need for strong consideration of treating with chemotherapy in these cases.

Thanks to each person who participated in this research which is already improving care for girls and young women with this rare tumor, and thank you, Dr. Nelson, for leading this important effort.

Dr. Nelson is also leading an analysis of the impact of germline *DICER1* variants versus tumor-confined variants for SLCT - stay tuned for more information!

Retesting: Getting the Surveillance You Need

Surveillance is recommended for individuals diagnosed with a pathogenic or likely pathogenic (P/LP) germline *DICER1* variant. Accurate genetic testing is essential since *DICER1* surveillance recommendations rely on the results of the test. Genetic testing is complex - it is important to know what types of variants a test would or would not detect.

Deletions/Duplications:

Older genetic testing techniques did not always analyze genes for deletions or duplications (del/dup testing). Individuals with a tumor history who received a *DICER1* germline negative result and did not have del/dup analysis included in their original test may wish to consider additional testing.

Intronic Regions:

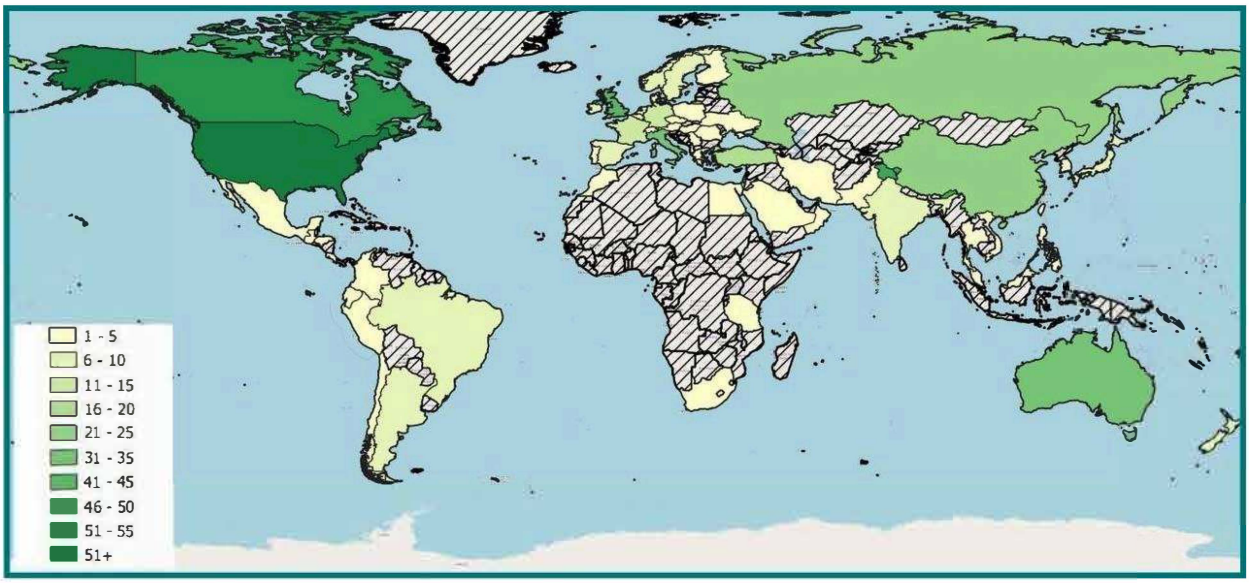
As discussed in our previous newsletter, linked here, genes contain both exons and intronic regions. Recent Registry research identified variants associated with tumor risk deep in an intronic region of the *DICER1* gene, an area not generally analyzed by clinical testing. Additional testing to analyze this region may be indicated in select circumstances.

The goal of retesting is to look for *DICER1* variants that the first type of testing may have missed. Talking with your primary care physician or genetic counselor can be a great first step in determining if you or a loved one may benefit from additional testing. Figure 3 in the Registry's updated surveillance guidelines article presents a framework for *DICER1* germline testing/retesting.

Opportunities to Participate

More than 1650 participants have enrolled in the Registries. The reach of Registry participation continues to grow, with participants joining the Registries from 49 U.S. states and 65 countries.

Did you know that a current *DICER1*-associated diagnosis is not the only way to be eligible to participate in the Registry? In fact, there are many ways to be eligible for Registry participation and every participant helps move research forward.



REGISTRY Q&A

Q Can individuals with a germline *DICER1* variant but no history of a *DICER1*-associated condition enroll in the Registry?

A Yes, we welcome anyone with a *DICER1* variant to enroll whether or not they've been diagnosed with a *DICER1*-associated condition.

Q How do *DICER1* only participants contribute to the research of the Registry?

A Including all individuals with *DICER1*-realted conditions and/or *DICER1* variants provides a more complete understanding of this rare condition.

Q If my *DICER1*-associated condition was diagnosed a long time ago, would my enrollment still be beneficial to the Registry's research?

A Absolutely! The majority of the Registry's research is retrospective (gathering information from the past), so whether you have a current diagnosis or were diagnosed years ago, every person's journey is helpful in the effort to learn more.

For more information about participation, you can visit us at the links below.

PPB/*DICER1* Registry

OTST Registry

Registry Team Update

Congratulations, Anna!

Anna has been a part of the Registry team since 2021. While working full time, she pursued a Master of Public Health (MPH) degree. In December 2024, Anna graduated with her MPH in epidemiology with an emphasis in biostatistics from Kent State University.

Over her time at the Registry, Anna has led many projects, including the Registry's quality of life (QoL) project. She greatly enjoys the opportunity to connect with each of you who make this research possible. This past year, Anna paired her passion for connection with her biostatistics skills at the International PPB/*DICER1*/OTST Family Meeting when she presented Registry thyroid data, which she had gathered and analyzed.

We are grateful for all of the ways that Anna contributes to the Registry's research and are excited for her to continue sharing her biostatistics skills with us, now as a research coordinator on the team. Congratulations on your graduation, Anna!