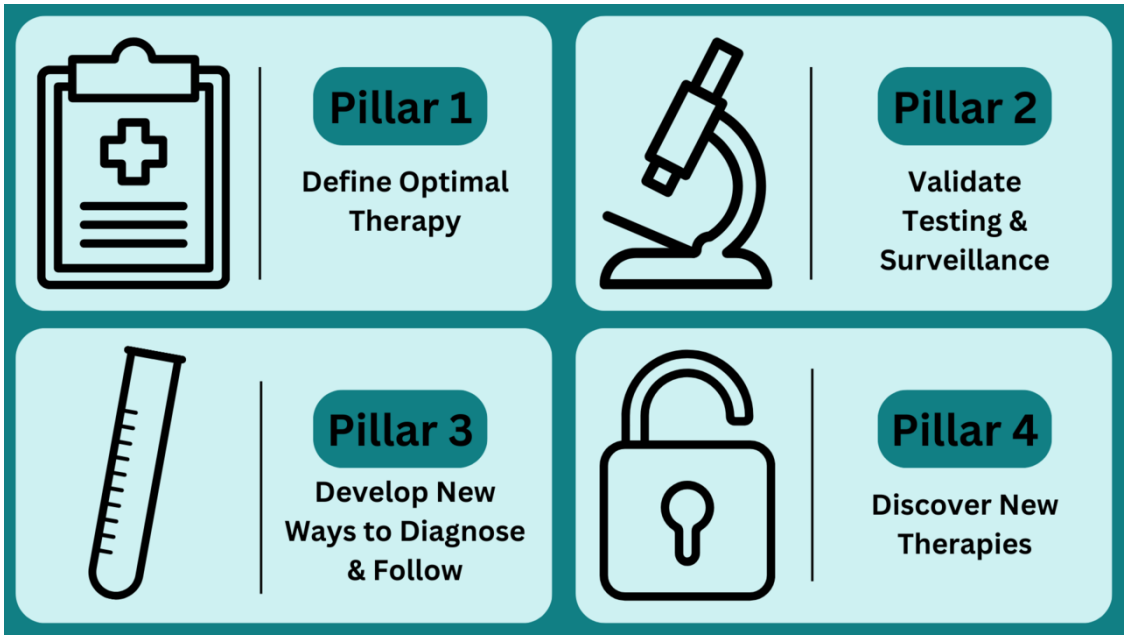
REGISTRY NEWSLETTER

Thank you for joining us for another issue of the International Pleuropulmonary Blastoma (PPB)/*DICER1* and Ovarian and Testicular Stromal Tumor (OTST) Registries newsletter. The mission of the PPB/*DICER1* Registry is to improve outcomes for children and adults with PPB, and other *DICER1*-related cancers through four strategic pillars:



Through the participation of many patients and families as well as collaborations with numerous researchers and clinicians worldwide, we've been grateful to have made strides forward in each pillar this past year.

Pillar #1, define optimal therapy: We published a manuscript reporting outcomes in the largest-ever cohort of children with Types I and Ir PPB in 2023. We also hosted the Registry's first-ever Pathology Conference in April 2023, a round table discussion focused on the pathologic differences between Types I and Ir PPB. Additionally, we published a report pertaining to the role of PET and bone scintigraphy imaging in Types II and III PPB. Thank you to the 205 kids and families with Type I or Ir PPB and to the 133 kids and families with Type II or III PPB that made these advances possible!

Pillar #2, validate testing for children and adults with germline *DICER1* variation: By studying blood samples from patients and families with *DICER1*-related cancers yet negative germline genetic testing, the Registry and collaborators were able to show that variants deep in the intronic (noncoding) region of the *DICER1* gene can lead to tumor development. These are variants not previously detectable by typical germline testing and may have implications for other patients and families. If you or your loved one has had a *DICER1*-related tumor and negative germline testing, it may be reasonable to consider updated testing based on this new information. Also, we are now analyzing data from all of the enrolled individuals with germline *DICER1* with plans to use this information to optimize the current surveillance recommendations. Join us at the August 2024 Family Meeting, registration link below, to hear the results of these analyses and the latest updates to the surveillance guidelines!

Pillar #3, develop new ways to diagnose and follow children with *DICER1*-related cancers: We are continuing to collect both blood samples and clinical data for the development of new ways to diagnose and follow these tumors through our biomarker project, described in our last newsletter, linked here>>. Through this project, we continue expanding our knowledge of ctDNA and its potential uses for detecting these rare tumors in their earliest form.

Pillar #4, discover new therapies for *DICER1*-related cancers: We have expanded our fresh and frozen tissue collection efforts, which in collaboration with our laboratory partners, have led to the development of patient-derived xenograft (PDX) models. Thank you to all those who have contributed tumor samples to this effort. We hope to use these models to test novel treatments.

In 2024, we look forward to continuing work in each of these areas to help provide better resources for you and your families and the rare tumor community.

Research Updates & Publications

What are the different types of PPB?

Pleuropulmonary blastoma (PPB) is the most common type of lung cancer for infants and young children. There are four main types of PPB:

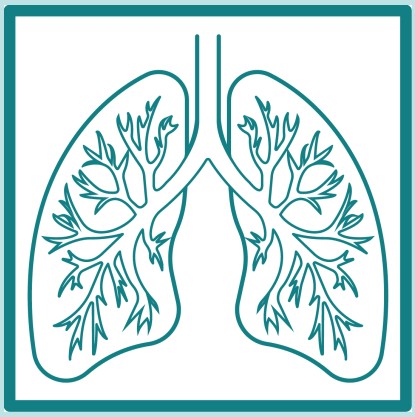
- **Type I PPB:** Purely cystic tumor

- **Type II PPB:** Mixed cystic and solid tumor

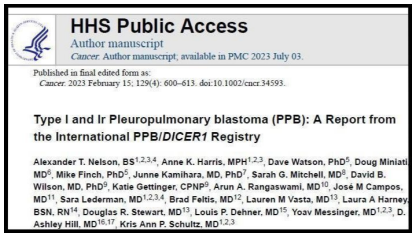
- **Type III PPB**: Purely solid tumor

- **Type Ir PPB:** Purely cystic lesion, not containing any malignant cells. Instead, this type is considered a regressed or non-progressed form of PPB.

Learn more here>>



Type I and Ir Pleuropulmonary blastoma (PPB)



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Type I and Ir Pleuropulmonary blastoma (PPB): A Report from the International PPB/*DICER1* Registry

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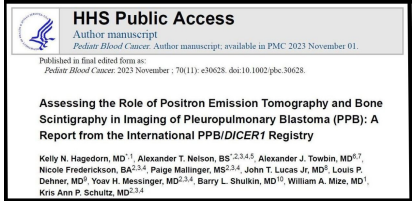
In February 2023, the Registry published a report in *Cancer*, a journal of the American Cancer Society, that analyzed a cohort of 205 participants enrolled in the PPB/*DICER1* Registry with a diagnosis of Type I or Ir PPB centrally reviewed between 2006 and 2022. Findings include information on differentiating between these similar diagnoses, optimal treatment considerations for each diagnosis, and areas for future work to continue better defining the optimal therapy for these diagnoses.

Knowing the difference between a diagnosis of Type I and Ir PPB is important for understanding what treatment is needed. Through imaging (CT/MRI/US) Types I and Ir PPB both look purely cystic and can be difficult to tell apart from one another. Our report describes how the age of the patient and the size of the cyst can help decide if the cyst could be Type I or Ir PPB. Thank you to the 205 kids and their families who made this research possible!

The report is available here>>.

Assessing the Role of Positron Emission Tomography and Bone Scintigraphy in Imaging of Pleuropulmonary Blastoma (PPB)



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Assessing the Role of Positron Emission Tomography and Bone Scintigraphy in Imaging of Pleuropulmonary Blastoma (PPB): A Report from the International PPB/*DICER1* Registry

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In August 2023, the Registry published a report in *Pediatric Blood & Cancer* that retrospectively analyzed nuclear medicine imaging, PET and/or planar bone scintigraphy, from 133 Registry participants with centrally reviewed diagnoses of Type II or III PPB.

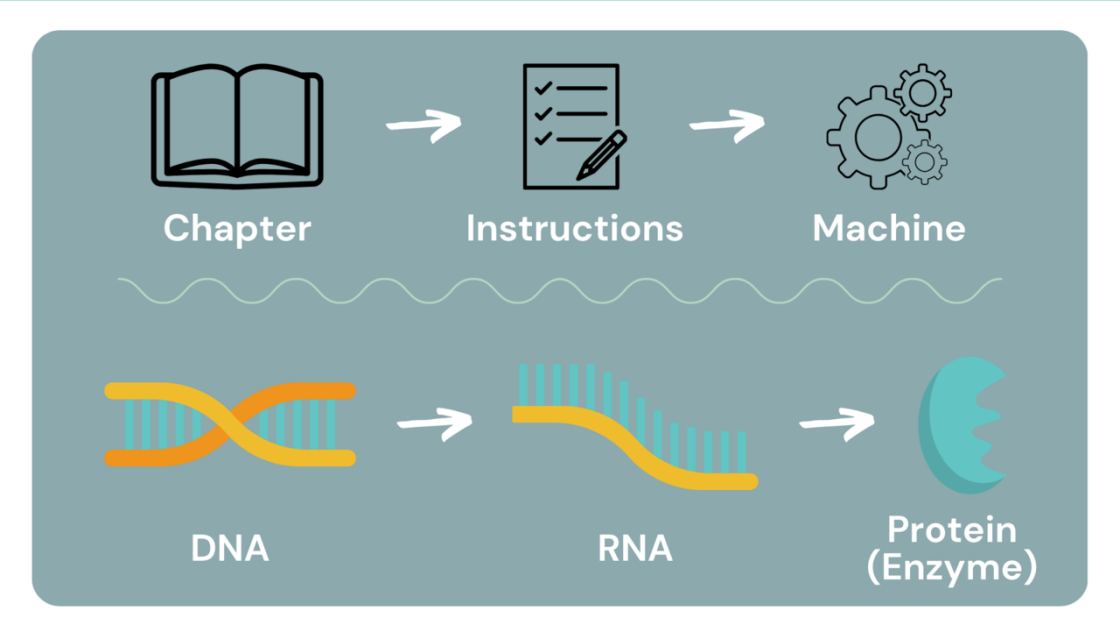
This report talks about how PET scans might be helpful during chemotherapy and before and after surgery. We found that having a PET scan during chemotherapy, but before surgery, sometimes showed that the chemotherapy could be working. We also found that PET scans were better at finding bone metastases than a bone scan only (planar bone scintigraphy). PET scans did not always find brain metastases. MRI scans are recommended to look for brain metastases. We must continue researching if PET scans are helpful in seeing chemotherapy results in patients with Type II or III PPB.

The report is available here>>.

What is a *DICER1* variant?

DICER1 is a gene, that codes for the enzyme DICER1. An enzyme is a type of protein that helps cells carry out specific reactions. To make enzymes, a gene (a section of DNA) is used to make RNA and then the RNA is used to make proteins (enzymes).

The process of DNA to RNA to protein is similar to a specific chapter from a massive book being used to create a sheet of instructions which is then used to make tiny machines. A series of processes take place to edit the instruction sheet (RNA). One of these processes is removing information that is no longer needed (splicing). Splicing is when certain regions of the pre-mRNA are cut out (introns), and other regions (exons) are kept and pasted together to create the final instruction sheet (messenger RNA or mRNA). The mRNA is then read to build the tiny machine (enzyme).

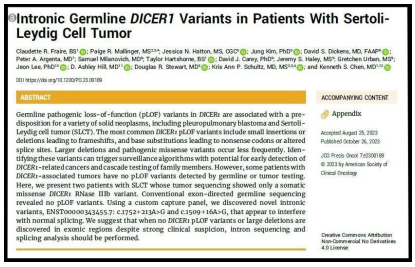


When there is a change in the genetic code of a gene, this is known as a variant. A variant can be pathogenic (negatively affects the function of the enzyme), benign (has no influence on the enzyme's function), or be a variant of unknown significance (VUS, the effects are not yet known).

The variant can be found in the intron or exon regions of the DNA. Typically, *DICER1* variants are found in the exon regions of the *DICER1* gene. Since exon regions are kept in the final version of mRNA, some of these variants can affect the function of the enzyme that's assembled from the incorrect instructions. We now know that variants can also be found in the intronic regions of the DNA. If an intronic variant is in an area where it affects the splicing process, this can also affect the function of the enzyme since the mRNA's message is changed.

Learn more about *DICER1* mutations and *DICER1*-associated conditions here>>.

Intronic Germline *DICER1* Variants in Patients with Sertoli-Leydig Cell Tumor



Intronic Germline *DICER1* Variants in Patients With Sertoli-Leydig Cell Tumor

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ABSTRACT

Germline pathogenic loss-of-function (pLOF) variants in *DICER1* are associated with a predisposition for a variety of solid neoplasms, including pleuropulmonary blastoma and Sertoli-Leydig cell tumor (SLCT). The most common *DICER1* pLOF variants include small insertions or deletions leading to frameshifts, and base substitutions leading to nonsense codons or altered splice sites. Larger deletions and pathogenic missense variants occur less frequently. Identifying these variants can trigger surveillance algorithms with potential for early detection of *DICER1*–related cancers and cascade testing of family members. However, some patients with *DICER1*–associated tumors have no pLOF variants detected by germline or tumor testing. Here, we present two patients with SLCT whose tumor sequencing showed only a somatic missense *DICER1* RNase IIIb variant. Conventional exon-directed germline sequencing revealed no pLOF variants. Using a custom capture panel, we discovered novel intronic variants, ENST00000343455.7: c.1752+23A>G and c.1509+16A>G, that appear to interfere with normal splicing. We suggest that when no *DICER1* pLOF variants or large deletions are discovered in exonic regions despite strong clinical suspicion, intron sequencing and splicing analysis should be performed.

ACCOMPANYING CONTENT

Appendix

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JCO Precis Oncol 7:e2300189

In October 2023, this article was published in the *Journal of Clinical Oncology: Precision Oncology* and describes finding two new intronic *DICER1* variants.

Two patients, one with a history of a *DICER1*-related chest tumor and the other with a history of SLCT, were both found to have intronic *DICER1* variants, each of which change the splicing process. These variants were not found by their previous testing.

These findings show that, in some situations, follow-up testing for a person with a history of *DICER1*-associated conditions should be considered when the original testing does not show a germline *DICER1* change.

The report is available here>>.

Ways to Get Involved

2024 Family Meeting

To learn more about PPB, *DICER1*, and OTST research, we invite you to join us in-person or virtually for the 2024 International PPB/*DICER1*/OTST Registries Family Meeting on Thursday, August 1st.

The Registries will be hosting this hybrid Family Meeting from St. Paul, MN for those gathering in-person; those joining virtually are invited to join via Zoom.

All attendees, virtual and in-person, can register by clicking the button below. You can reach us by email at DICER1@childrensmn.org or by calling 612-813-7121 if you have any questions.

Register Here

Following the hybrid Family Meeting, there will be a further opportunity to connect at an evening Meet-&-Greet with food, kids' arts and crafts, and, we hope, some Minnesota summer sunshine. More details and registration for the Meet-&-Greet will be available as the event draws closer.

Connect with us online

International OTST Registry:

Facebook | Website

International PPB/*DICER1* Registry:

Facebook | Website | Instagram | X (Twitter)

Registry Participation

All individuals with Sertoli cell tumor, Leydig cell tumor, juvenile granulosa cell tumor, or any undifferentiated stromal tumor are welcome to enroll in the International OTST Registry. To learn more about the Registry and inquire about enrollment, please click the button below or call 612-813-7121.

Inquire about OTST Enrollment

All individuals with PPB, Sertoli-Leydig cell tumor (SLCT), *DICER1* variants or *DICER1*-related conditions (such as cystic nephroma, pituitary blastoma, pineoblastoma, and others) are welcome to enroll in the International PPB/*DICER1* Registry. To learn more about the Registry and inquire about enrollment, please click the button below or call 612-813-7121.

Inquire about PPB/*DICER1* Enrollment