

NOTE: Please obtain patient signature on consent form below. If a signed consent is not submitted, the Children's National Medical Center Anatomic Pathology Resequencing Laboratory assumes that the ordering clinician has reviewed and obtained the patient's informed consent.

INFORMED CONSENT FOR *DICER1* MOLECULAR GENETIC TESTING

I, (name) _____, voluntarily request of Children's National Medical Center Anatomic Pathology Resequencing Laboratory to perform DNA-based testing of *DICER1* in myself/my child (child's name _____), in an attempt to determine whether I/my child have a gene mutation and are at increased risk of developing pleuropulmonary blastoma (PPB) and/or associated disorders. These tests will be performed by laboratory technologists using clinical guidelines for best practices. Patient confidentiality will be maintained at all times in accordance with HIPAA.

The following points were explained and I understand that:

TEST PURPOSE

- The purpose of DNA testing is to determine if myself/my child have a mutation in the *DICER1* DNA sequence that may indicate a susceptibility to PPB and related conditions of the PPB Family Tumor Predisposition Syndrome.

TEST METHOD

- DNA is extracted from whole blood samples. Polymerase chain reaction is performed using primers for all 26 coding exons of *DICER1* including intron-exon junctions. DNA is sequenced using conventional dideoxy sequencing on an Applied Biosystems analyzer. The DNA sequence is assembled and compared to the published genomic reference sequences (RefSeqNM_030621). Sequence variants are assessed for predicted effect on protein product. When possible, correlation with other affected family member's sequence is performed.
- If no sequence variants consistent with disease causation are identified, the sample can be referred for deletion/duplication testing. A quantitative PCR assay is used for analyzing for deletions of all or part of individual coding exons 2-26. Each amplicon signal is compared to known, validated two-copy internal control exons. This test will be performed by special request if desired.

TEST SENSITIVITY

- Based on our preliminary research findings of 85 children with pleuropulmonary blastoma, approximately 70% of individuals with a clinical diagnosis of PPB are expected to harbor a mutation in the coding region of *DICER1*. Based on the performance of our assay we anticipate >95% rate of detection of coding region mutations. Our assay will not identify promoter mutations, deep intronic mutations and/or methylation changes that may affect *DICER1* expression. In addition, there may be other gene changes that contribute to risk of tumor development that are currently unknown. A negative test may only be informative in certain families.

TEST LIMITATIONS

- DNA testing requires a blood sample, buccal swab, or skin biopsy, all of which have risks associated with obtaining the sample. Additional samples may be needed if the sample is damaged in shipment or inaccurately submitted.
- DNA-based studies performed are specific to *DICER1*. The accuracy of genetic testing is limited by the methods employed, the clinical diagnosis, and the nature of the specific condition for which testing is requested. In some cases, the test will detect an alteration in the gene, called a mutation. In other cases the test is unable to identify an abnormality although an abnormality may still exist either in the gene tested or in another, as yet unidentified gene, associated with PPB. This event may be due to the current lack of knowledge of all genes that may predispose to PPB or an inability of the current technology to identify certain types of changes (mutations) in a gene.

- These tests represent the newest service currently available for clinical laboratory testing; however, improvements will be made as scientific knowledge advances. As with any complex genetic test, there is always a small possibility of a failure or error in sample analysis. Extensive measures are taken to avoid these errors. The methods are not 100% accurate due to the possibility of rare genetic variations in the DNA of an individual or due to the complexity of the testing itself. A low error rate, estimated to be approximately 1 in 1000 samples, is thought to exist in any laboratory.
- It is the responsibility of the referring physician or health care provider to understand the specific utility and limitations of the testing ordered, and to educate the patient regarding these limitations. Specific information describing indications, methodology and detection can be found on the *DICER1* Mutation Testing Information Sheet which is posted on the websites of the International PPB Registry (<http://www.ppbregistry.org>) or the PPB Genetic Study website (<http://ppbgeneticstudy.cnmcresearch.org>).
- It is recommended that myself/my child be offered genetic counseling prior to obtaining this test and for assistance in interpretation of the results. I have been provided with the *DICER1* Information Sheet which lists genetics counselors familiar with pleuropulmonary blastoma genetic testing should I wish to seek counseling and do not have a local genetics counselor or medical geneticist who can perform this for myself/my child.

TEST RESULTS REPORTING AND INTERPRETATION

There are several categories of test results that may be reported including:

- A significant sequence abnormality IS detected, and is predicted to be associated with a genetic disease.
- A sequence abnormality IS detected, but its significance is UNKNOWN. Additional testing of the patient and/or other family members may be recommended to help determine the significance of the result.
- A deleterious sequence abnormality IS NOT detected, however my clinical diagnosis may still be correct. This event may be due to medical science's current lack of knowledge of all the gene(s) involved with the disease or the inability of the current technology to identify certain types of mutations in the gene(s) which cause the disease.
- Accurate interpretation of test results is dependent upon the patient's clinical diagnosis or family medical history and that the reported family relationships are true biological relationships. An erroneous clinical diagnosis in the patient or family member can lead to an incorrect interpretation in the laboratory result.
- I understand that I may wish to obtain professional genetic counseling prior to signing this consent form. Results may have clinical or reproductive implications for my family members. In rare cases, persons with genetic diagnoses have experienced problems with insurance coverage, employment and other entities. Participation in genetic testing is completely voluntary.
- I understand that a positive test result is an indication that myself/my child being tested may be predisposed to or have the specific disease or condition tested for and may wish to consider further independent testing, consult my or his/her/their physician or pursue genetic counseling.
- Due to the complexity of DNA testing and potential implications of test results, results will be reported directly to the ordering provider. Patient results and information will remain confidential and may only be released to other parties with my expressed written consent.

SPECIMEN RETENTION AND ADDITIONAL TESTING

- The Children's National Medical Center Anatomic Pathology Resequencing Laboratory does not return the remaining sample to individuals or physicians; however, in some cases, it may be possible to perform additional studies on the remaining sample. The request for additional studies must be made by my referring physician or other authorized healthcare professional. Samples will be retained in the laboratory in accordance with the laboratory retention policy. I do understand that I have the right to withdraw this consent at any time by notifying the Director of the laboratory in writing. Upon receipt of withdrawal of consent notification, the laboratory will promptly destroy the sample or portions thereof that have not already been used.

It is possible that advances in testing technology and increased knowledge of disease processes could change the interpretation of the original test results, enable improved interpretation of test results or permit future retesting with greater sensitivity and accuracy. We request your permission to use leftover samples for PPB research once all patient identifiers have been removed. If you do not wish to have leftover samples be used for PPB research, please initial below.

I can request that remaining DNA **NOT** be used for research purposes by initialing here: _____

The risks, benefits and limitations of DNA testing have been explained to me. I have read and will receive a copy of this consent form. My signature acknowledges voluntary participation in testing but in no way releases lab and staff of Children’s National Medical Center Anatomic Pathology Resequencing Laboratory from their professional and ethical responsibility to me.

Patient Signature

Date

Patient Name (print)

Date of Birth

Parent / Guardian Signature Date (if child is a minor)

Date

Parent Name (print)

Date of Birth

Second Parent / Guardian Signature Date (if child is a minor)

Date

Second Parent Name (print)

Date of Birth

Physician/Counselor/Clinician Statement:

I have explained DNA testing to the patient/parent/guardian. The consent form and limitations of genetic testing were reviewed with the patient/guardian. I accept responsibility for pre- and post- test genetic counseling.

Clinician Signature Date

Clinician Name (print) Date