BAYLOR GENETICS
READY WITH ANSWERS

SHIPPING Baylor Genetics
2450 Holcombe Blvd., Grand Blvd. Receiving Dock
Houston, TX 77021-2024
Phone: 713.798.6555
Fax: 713.798.2787

PROBAND WHOLE EXOME SEQUENCING REQUISITION

Patient Last Name	Patient First Name	MI	Date of Birth (MM/DD/YY)	Biological Sex
			/ /	

INFORMATION AND CONSENT FOR TESTING

Test order 1530 in addition to Proband WES analysis as detailed below will also include a separate analysis for detection of deletions and duplications plus a screen for detection of uniparental disomy (UPD) and absence of heterozygosity (AOH). To learn more about this testing please visit our website, test code 8665 Chromosomal Microarray Analysis - HR + SNP Screen (Comprehensive).

Test order 1531 in addition to Proband WES analysis as detailed below will also include a separate analysis of the mitochondrial DNA. To learn more about this testing please visit our website, test code 2055 Comprehensive mtDNA Analysis by Massively Parallel Sequencing (MitoNGSSM). This is the evaluation of the entire mitochondrial genome for point mutations and deletions. The detection threshold of massively parallel sequencing analysis for heteroplasmic mitochondrial DNA point mutations is approximately 1.5%. This will be reported separately from the Proband WES results with a turnaround time of 50 days.

Your physician has advised you (or your child) to undergo the genetic test called the Proband Whole Exome Sequencing test (abbreviated Proband WES). The purpose of this document is to provide information about the test. If an mtDNA change is identified the report will indicate recommendations for familial follow-up. Baylor Genetics will NOT automatically initiate testing on the maternal sample, if this is desired please contact client services for assistance.

◆ DESCRIPTION OF THE PROBAND WHOLE EXOME SEQUENCING TEST

The Proband Whole Exome Sequencing test is a highly complex test that is newly developed for the identification of changes in an individual's DNA that are causative or related to their medical concerns. The exome refers to the portion of the human genome that contains functionally important sequences of DNA that direct the body to make proteins essential for the body to function properly. These regions of DNA are referred to as exons. It is known that most of the errors that occur in DNA sequences that then lead to genetic disorders are located in the exons. In contrast to current sequencing tests that analyze one gene or small groups of related genes at a time, the Proband Whole Exome Sequencing test will analyze the important regions of tens of thousands of genes at the same time. Therefore, sequencing of the exome is thought to be an efficient method of analyzing a patient's DNA to discover the genetic cause of diseases or disabilities. However, it is possible that even if the Proband WES identifies the underlying genetic cause for the disorder in your family this information may not help in predicting prognosis or change medical management or treatment of disease.

◆ INDICATIONS FOR TESTING

The decision to undergo the Proband Whole Exome Sequencing test is made by you and your physician. In general, the test is used when your medical history and physical exam findings strongly suggest that there is a genetic cause for your medical issues. The test requires 5-10 cc (about 1-2 teaspoon) of whole blood. You should expect that results of the Proband WES test will be sent to your physician in 12 weeks.

◆ TESTING REPORTING

When your exome sequence is compared to a normal reference sequence, many variations or differences are expected to be found. Based on currently available information in the medical literature and in scientific databases, we will decide whether any of these variations are predicted to be causative or related to your medical condition. The Proband WES test results will be reported to your physician in two parts. Your physician will receive a copy of the focused report for your sample.

The focused report will contain results that may explain the cause of your current medical problems. In addition it may also contain information in the following categories:

Medically Actionable
The focused report may also contain information on genes and diseases that are considered medically actionable because they have clear and immediate medical significance to your health or the health of family members, whether or not they relate to your current symptoms. The American College of Medical Genetics (ACMG) have published guidelines for the reporting of these types of medically actionable or incidental findings (PMID: 23788249). These guidelines include a list of genes, which may be updated periodically, that have been determined to be considered medically actionable and therefore laboratories should seek and report pathogenic variants in these genes. In accordance with an update to this policy statement (ACMG.net), there is the option to opt out of receiving pathogenic variants information if identified in the genes listed in ACMG policy statement. It will not be reported on either the focused OR the expanded report. Additionally, the Baylor Genetics under the direction of the medical director and other faculty members may determine additional genes meet the same criteria to be considered medically actionable and therefore warrant the same reporting as the genes included in the ACMG list. However, if you do not want to receive these additional medically actionable gene results, you may also opt out of this information on the FOCUSED report. However, if the EXPANDED report is requested this information will be included, but will not be labeled as medically actionable. See the FAQ on our website for a list of examples.

Carrier Status and Pharmacogenetic Information

Carrier status for autosomal recessive conditions will include disorders recommended for reproductive screening by professional societies such as ACMG or ACOG, which includes: Cystic fibrosis (CFTR), Sickle cell anemia (S allele, HBB), Familial dysautonomia (IKBKAP), Tay-Sachs disease (HEXA), Canavan disease (ASPA), Fanconi anemia group C (FANCC), Niemann-Pick type A, B (SMPD1), Bloom syndrome (BLM), Mucolipidosis IV (MCOLN1), Gaucher disease Type I (GBA), Hemolytic anemia due to G6PD deficiency (G6PD* X-linked inheritance).

See below for options regarding receipt of certain categories of results in the focused report. In addition to the focused report, an expanded report will be available if you and our physician decide to request it.

Consent continued on next page

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INFORMATION AND CONSENT FOR TESTING

The patient's sample will have certain findings confirmed by a second methodology (Sanger sequencing) based on the following guidelines.

- Pathogenic or likely pathogenic variants related to patient phenotype will have Sanger confirmation.
- Variants of unclear clinical significance (VUS) related to phenotype with established autosomal dominant inheritance pattern will have Sanger confirmation when at least one parental sample has been received.
- VUS related to phenotype with established autosomal recessive inheritance will have Sanger sequencing when there are two variant alleles when at least one parental sample has been received.
- VUS related to phenotype with established X-linked inheritance will have Sanger confirmation when at least one appropriate parental sample has been received.
- Medically actionable pathogenic variants and carrier status mutations for autosomal recessive conditions recommended for reproductive screening will have Sanger confirmation.
- As determined by the laboratory, additional confirmation beyond these categories may also be performed.

Once the focused report is received the expanded report can be ordered (no additional charge). The expanded report may contain information on diseases and genes that do not relate to your current condition, or may develop many years from now, or do not have any known link to disease, according to current knowledge. Information included in the expanded report is not Sanger confirmed (unless determined necessary by the laboratory). In discussion with your physician, the expanded report can be ordered for up to 6 months after the focused report is received, for no additional charge. A requisition for ordering the expanded report is available on our website. Please allow 4 weeks for the expanded report. Because medical information continues to advance, it is important to know that the interpretation of the variants is based on information available at the time of testing and may change in the future.

◆ REPORT EXCLUSIONS

The report will not include findings in genes causing adult onset dementia syndromes for which there is presently no prevention or cure. If the proband has a phenotype that clearly indicates such a disorder we recommend pursuing targeted testing based on phenotype and not WES testing. However, please note that if the patients has a clinical presentation that could indicate such a disorder or a mixed neurological phenotype then results may be returned for genes that have an allelic association with dementia or dementia is a component of the phenotype will then be reported in the proband and the parents.

We expect to find hundreds of variations when comparing the DNA to the reference sequence, most of these do not relate to disease and therefore will not be reported. The raw sequence data generated by the WES is available for request once a WES report has been issued. Please see our website for further information regarding this.

◆ REQUEST FOR BIOLOGICAL PARENTAL SAMPLES

Biological parental samples are requested to facilitate interpretation of Proband WES results. Proband WES will NOT be performed on the parental samples. The parental samples will be tested by other targeted methods for changes in genes that are highly likely to be causative of disease (related to patient indication for testing) to confirm mode of inheritance, de novo status, etc. These studies will be performed at no additional charge. Additionally, carrier status for reproductive screening will also be reported. A separate parental report will not be issued. The laboratory will decide which changes will need parental studies based on the following criteria.

- Using Sanger sequencing parental samples will be tested to determine inheritance in the proband for genes related to patient phenotype.
- Parental samples will not be run for genes with autosomal recessive inheritance pattern that only have one VUS sequence change identified related to patient phenotype.
- We will not report parental data for medically actionable pathological variants identified in the proband (child). If such testing is desired it can likely be completed at a later date, for no additional charge, once consent is given to your provider. Once a test order is received it will take several weeks to complete the additional testing.
- We will report parental data for carrier status recommended for reproductive screening.
- Parental inheritance information will not be included for any of the genes reported in the Expanded report.
- For other biological relatives submitted, Sanger sequencing will be performed only for changes related to the patient phenotype, as described above (Items 1 and 2).

Potential Risks and Discomforts

(1) It is possible that you could have a mutation in a gene included in the Proband WES test, but the Proband WES test was unable to detect the mutation. Therefore, it is possible that you may be affected with one of the conditions tested by Proband WES, but that the test did not detect the condition.
(2) The Proband WES test does not analyze 100% of the genes in the human genome. There are some genes that cannot be included in the test due to technical reasons.
(3) Results may be unclear or indicate the need for further testing on other family members, usually parents. It is possible, that additional information may come to light during these studies regarding family relationships. For example, data may suggest that family relationships are not as reported, such as non-paternity (the father of the individual is not the biological father).
(4) If you sign the consent form, but you no longer wish to have your sample tested by Proband WES, you can contact your doctor to cancel the test. If testing is complete, but you have not received your results yet, you can inform your doctor that you no longer wish to receive the results. However, if you withdraw consent for testing after 5 p.m. the next business from the day of sample receipt by the laboratory, you will be charged for the full cost of the test.
(5) The cumulative results of Proband WES testing on many samples may be published in the medical literature. These publications will not include any information that will identify you personally.
(6) Due to the fact that many different genes and conditions are being analyzed, there is a risk that you will learn genetic information about yourself or your family that is not directly related to the reason for ordering the Proband WES. This information might relate to diseases with symptoms that may develop in the future in yourself or other family members as well as conditions that have no current treatment. If you have concerns about learning about other diseases unrelated to your current medical problems, please tell you doctor so that the results will not include this information.

Consent continued on next page

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INFORMATION AND CONSENT FOR TESTING

Please read the below statements carefully and check the appropriate box and initial.

For Options 1 & 2: If neither box is checked, or if form is not signed, the lab will default to the NO/ do not report option.

Initial

1. Carrier Status for Autosomal Recessive Conditions Recommended for Reproductive Carrier Screening

_____ ☐ YES: Please report carrier status. By checking this box, I choose to receive information regarding carrier status.

_____ ☐ NO: Please do NOT report carrier status. By checking this box, I choose to NOT receive information regarding carrier status.

2. Pharmacogenetic Variants

_____ ☐ YES: Please report genes involved in drug metabolism. By checking this box, I choose to receive information regarding drug metabolism. Currently, this is limited to the reporting of pharmacogenetic variants to VKORC1/CYP2C9 (altered warfarin metabolism) and CYP2C19 (altered Plavix metabolism).

_____ ☐ NO: Please do NOT report genes involved in drug metabolism. By checking this box, I choose to NOT receive information regarding drug metabolism.

For Option 3: If no choice is selected, or if the form is not signed, the lab will default to 'do NOT report' option.

Initial

3. Medically Actionable (3 choices)

_____ ☐ YES/ALL: please ONLY report pathogenic variants in genes included in the ACMG policy statement AND pathogenic variants in genes that Baylor Genetics has determined are medically actionable (defined as having clear and immediate medical significance to your health or the health of family members).

_____ ☐ YES/ACMG ONLY: please ONLY report pathogenic variants in genes included in the ACMG policy statement (defined as having clear and immediate medical significance to your health or the health of family members).

_____ ☐ NO: please do NOT report pathogenic variants in genes included in the ACMG policy statement AND do NOT report pathogenic variants in genes that the Baylor Genetics has determined are medically actionable. Pathogenic variants in genes in the ACMG policy statement will not be reported in either the focused or the expanded report. I also chose not to receive information regarding Baylor Genetics determined medically actionable findings, but if the expanded report is requested this information WILL BE INCLUDED in that report, but will not be labeled as medically actionable.

For Option 4: If neither box is checked the lab will default to the YES/release option.

4. Option to allow release of updated results

We may periodically review old cases when new information is learned regarding the significance of changes in a particular gene. If a possible diagnosis can be made with this information we would like to issue an updated report to the physician who ordered your Proband WES test. The current schedule for this review is every year, but is subject to change and does NOT include a complete review of all of your data.

_____ ☐ YES: if new information is known regarding clinical significance of information that may not have previously been included in my Proband WES report I would like for you to issue an updated report to my physician who ordered this Proband WES testing.

_____ ☐ NO: please do NOT issue an updated report if there is new information regarding the clinical significance of my Proband WES data that may not have been previously reported.

◆ **FOR SAMPLES SUBMITTED FROM NEW YORK STATE**

_____ Initial

Specimen Retention: My sample shall be destroyed at the end of the testing process or not more than 60 days after completion of testing. However, I hereby authorize the lab to retain my sample(s) for a longer retention in accordance to the laboratory retention policy for internal laboratory quality assurance studies and possible research testing.

Consent authorization on next page

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INFORMATION AND CONSENT FOR TESTING

Due to the complex nature of the Proband WES testing it is recommended that families seek genetic counseling in conjunction with testing.

I hereby authorize Baylor Genetics to conduct genetic testing for myself (or my child) for the Proband Whole Exome Sequencing test (Proband WES) as recommended by my physician.

Signature _____ Date (MM/DD/YY) / /

Printed Name _____

Relationship to Proband _____

Proband Name _____ Proband DOB (MM/DD/YY) / /

Physician's/Counselor's Signature _____ Date (MM/DD/YY) / /

Parental/Other Relative Testing Authorization

I hereby authorize Baylor Genetics to conduct genetic testing for myself for the purposes of clarifying results for the Proband Whole Exome Sequencing test (Proband WES) that is being performed on my child's blood sample as recommended by my child's physician. I understand that my sample will not be subjected to Proband WES, but will be subjected to targeted testing methodologies (Sanger sequencing). A separate report of these data will not be issued.

Mother's Signature _____ Date (MM/DD/YY) / /

Printed Name _____ Maternal Date of Birth (MM/DD/YY) / /

Father's Signature _____ Date (MM/DD/YY) / /

Printed Name _____ Paternal Date of Birth (MM/DD/YY) / /

Other Relative's Signature (Or Parent/Legal Guardian) for Sample Submitted _____ Date (MM/DD/YY) / /

Printed Name _____ Other Relative's DOB (MM/DD/YY) / /

Relationship to Proband _____

SEE NEXT PAGE FOR POTENTIAL RESEARCH OPPORTUNITY

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ADDITIONAL STUDIES - RESEARCH

There may be research studies that you may be eligible for and may be of interest to you. Please read the following statements carefully and check the appropriate box. If the "YES"/contact option is chosen please complete the additional information requested. Please note that if neither box is checked the lab will default to the "NO"/ no contact option.

Initial ☐ YES, Baylor Genetics may share my contact information with researchers who have a Baylor College of Medicine Institutional Review Board (IRB) approved research study for which I may be eligible for participation. There is no obligation to participate if contacted. No information, other than the contact information below, will be provided to the researcher.

Authorization and contact information MUST be completed, or we will not be able to reach you regarding these opportunities.

◆ AUTHORIZATION

Signature | Date (MM/DD/YY)

Printed Name

Relationship to Proband

Proband Name | Proband Date of Birth (MM/DD/YY)

◆ CONTACT INFORMATION

Phone # | Alternative Phone # | Email

Address | City | State | Zip

Preferred Method of Contact ☐ Email ☐ Mail ☐ Phone

Initial ☐ NO, I DO NOT wish to be contacted regarding participation in research studies.

Initial ☐ YES, Baylor Genetics may contact my/my child's doctor who ordered the Proband WES test to discuss research studies that I/my child may be eligible for. There is no obligation to participate if contacted. If choosing YES, please make sure that the "Authorization" section above is completed.

◆ ORDERING PHYSICIAN CONTACT INFORMATION

Physician Last Name | Physician First Name

Phone # | Phone #

Address | City | State | Zip

Initial ☐ NO, I DO NOT want my/my child's doctor contacted regarding research studies.