COLUMBIA | PRECISION GENOMICS LABORATORY

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Informed Consent – Columbia Diagnostic Exome

1. The nature of the test and how it will be performed

What is Columbia Diagnostic Exome (CDEX)?

CDEX uses Exome Sequencing (ES) technology to search through the most important part of a person's entire genetic material, called the exome, for DNA changes that can cause disease. Instructions in the exome tell our cells how to work properly. Changes in this material can lead to disease. Because ES is more complicated than other genetic tests, the consent and ordering process must be thorough and should be done with the assistance of a healthcare provider familiar with the test. The patient/legal guardian has the option to receive genetic counseling prior to signing the consent form. Signed consent is required for testing.

How is the test performed?

A sample will be collected from you/your child/your pregnancy (i.e., the patient/symptomatic individual). Based on the family history, your healthcare provider may also recommend that samples be collected from additional family members, such as parents and siblings, to help with the interpretation of test results. Studies have shown that the likelihood of identifying a genetic cause for a patient's symptoms increases when both parents are included in the analysis, compared to when only the patient's sample is analyzed.

The first step is to extract (or "purify") the DNA from the patient and family member samples. Then the exome sequence is "read", and the information obtained is analyzed for differences between the patient's exome sequence and a reference ("normal") sequence. Everyone has places in their exome that differ from the reference, which typically do not cause medical problems. To determine whether the changes that are found are neutral, or can cause disease, the following steps are taken:

1- We compare the variations in the patient's exome to a list of variants that are known to cause medical problems in people with similar symptoms.
2- We examine variants that are disruptive in genes that are known to cause the type of condition found in the patient.
3- The variants are evaluated by an expert to indicate if they are truly likely to cause or contribute to disease.
4- Changes found will be compared to the changes seen in the patient's selected family members with/without disease (if available) to confirm that the changes are indeed the cause of the patient's condition.

2. What kinds of results may be obtained, what is their significance for health, and what should you do after receiving the results?

What kind of results may be reported?

Several types of results may be reported:

1. **<u>Variants in known disease genes thought to be causative of phenotype for which test is ordered</u>:** The patient may have one or more genetic variant(s) that are known to cause a specific genetic condition in other individuals with similar symptoms. The variant or variants would then be called a "pathogenic" or "likely pathogenic" variant and would be interpreted as the cause of the patient's symptoms. In some instances, the test will find a variant that is predicted to be important, but we do not have enough evidence to be certain about the variant being disease-associated. Such a variant may or may not be the cause of the patient's symptoms. The laboratory would report it as a "variant with uncertain clinical significance" if there is evidence strongly suggesting that it is related to the patient's condition. The laboratory may report single

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variants in genes associated with autosomal recessive conditions only when the condition could be related to the patient's symptoms.

2. **Secondary findings:** The American College of Medical Genetics (ACMG) has recommended that variants identified in a specific list of genes be reported to all individuals undergoing ES. Changes in these genes are considered to be medically actionable. These test results are not related to the symptoms for which the test was ordered, but may make a person more likely to develop cancer, heart problems or other medically important conditions that may present in childhood or adulthood. Please consult the latest version of the American College of Medical Genetics (ACMG) Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing guidelines for an up-to-date list of genes and conditions reported in this category. Please note that full secondary finding analysis will only be performed for the patient. Only secondary findings identified in the patient will be reported in family members who submit samples. Family members will not have an independent analysis for secondary findings. Check below to opt-out for receiving secondary finding results for the patient as well as all family members. If left unchecked, secondary findings will be reported.

_____ (Initial) I would NOT like to learn about ACMG secondary findings in the patient's ES. Secondary finding analysis will not be performed for any of the family members.

3. **Incidental findings:** ES may identify clinically significant variants in other genes that may impact clinical management. These genes are not part of the ACMG secondary findings gene list; and may be unrelated to the primary reason for testing. These types of variants may be reported at the discretion of the laboratory and the patient's clinical team. For example, these could be genes associated with neurodevelopmental disorders, intellectual disability, or metabolic conditions that may not present with a prenatal phenotype.

4. **Variants in genes with a limited level of evidence for disease association** (also referred to as candidate genes, genes of uncertain significance, or genes with limited evidence) can also be identified via ES. Such variants will only be reported for postnatal exomes.

5. **Risk alleles**: these are variants that have been associated with a slight or moderate increased risk for common diseases, such as blood clotting disorders. These types of variants may be reported at the discretion of the laboratory if they are considered to be related to phenotype. Such variants will only be reported for postnatal exomes.

6. **No disease-causing variants(s) found:** It is possible that the test will not find any genetic change that could explain the patient's symptoms. This type of test result does not mean the patient's condition is not genetic. The result would not change any diagnoses previously given to the patient.

Are there any types of results that will not be given to me?

Yes, there are a few types of results that will not be included in the CDEX report:

1. Some changes in genes might make a person slightly more likely to develop common adult conditions, such as diabetes or hypertension. Because these changes are not well understood, they are not looked at in detail or included in the report.

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2. Benign and likely benign variants will not be reported.

3. We might use family members' samples to help us diagnose the patient's condition. Only variants that are identified in the patient will be reported in family members, and no separate reports will be issued for these individuals. Genetic counseling and further testing might be recommended for other family members based on the results of this test.

4. Variants indicating carrier status for known recessive conditions that are unrelated to the patient's symptoms will not be reported.

5. In some cases, genetic testing can reveal that biological relationships in a family are not as they were reported to the laboratory. If relationship confirmation results do not align with what was reported to the laboratory, the patient's healthcare provider will be contacted to determine how to proceed with testing.

What should I do if there is a positive result?

This is a test to identify a genetic cause of the patient's clinical condition. If the test is positive, the patient/ legal guardian may wish to consult a healthcare provider, have further genetic counseling or undergo further independent testing.

3. What are the limitations and risks?

1. At the current time, the test does not interrogate 100% of the exome. Therefore, there is a possibility that there could be a variant that is associated with a condition that is not detected by the ES test.

2. The CDEX report is generated based on current medical knowledge. A variant that is not known to be the cause of a genetic condition today may be shown to be disease-causing in the future. The patient's healthcare provider may request re-analysis and ask for an updated report for a fee. ES is not currently validated to detect large-scale alterations in the DNA content of the patient's cells, such as microdeletions or microduplications, chromosome rearrangements (such as translocations), genetic disorders that are caused by expansion of repetitive regions of the genome, variants in the mitochondrial DNA, epigenetic changes such as changes in methylation patterns, as well as low-level mosaicism. If one of these conditions is suspected, your provider should order the appropriate test.

3. ES is not able to detect variants in the 99% of the DNA that is not part of the exome, including parts of the DNA that help regulate gene function.

4. ES may detect findings of uncertain significance, which cannot be proven with complete certainty to be disease-causing (see types of results described above).

5. Finding a disease-causing variant may not result in a treatment, cure, or a prognosis (knowledge about how a disease is expected to progress).

6. Standard laboratory limitations caused by human error, such as sample contamination or sample mix-up, may occur, but are unlikely.

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7. In the United States: The Genetic Information Non-discrimination Act (GINA) prevents insurance companies from using your genetic information to deny health insurance coverage or for employment purposes. However, the law does not cover other types of insurance, such as life insurance, disability insurance or long-term care insurance. The detection of a secondary finding may affect future ability to obtain these forms of insurance. By New York State Law, consent is required for the release of these results to insurance companies. However, the patient may be required to release this information to the insurance companies for the contract with them to be valid.

8. ES may identify genetic changes that may require additional testing to be completely evaluated. This could result in anxiety, uncertainty, and additional expenses that may or may not be covered by medical insurance and may or may not provide additional useful information.

9. ES may identify serious, untreatable genetic conditions. It can result in unexpected psychological trauma, both for the patient and his/her family. The detection of such a condition could also affect the health or health care needs of the patient's siblings, children, or other close relatives.

4. Who will have access to the results?

The results of the CDEX will become a part of the patient's medical record. Test results are stored in the laboratory's computer records and are automatically sent to computerized medical records of NewYork-Presbyterian Hospital and Columbia University.

Columbia University, NewYork-Presbyterian and Weill Cornell Medicine and their related entities participate in an Organized Health Care Arrangement (OHCA). This allows us to share health information to carry out treatment, payment and our joint health care operations, including integrated information system management, health information exchange, financial and billing services, insurance services, insurance, quality improvement, and risk management activities. Organizations that will follow this Notice include Columbia University, NewYork-Presbyterian sites, Weill Cornell Medicine and their related entities.

5. What else could happen to my genetic data?

In accordance with CLIA, CAP, and CLEP guidelines, the laboratory will keep the identified CDEX raw data in the lab for at least 7 years. The final report will be kept as long as possible, at least 7 years. I consent to the sharing of my de-identified health history and genetic variants through publications, presentations at scientific meetings, and through institutional and/or NIH-funded databases such as ClinVar or ClinGen. I understand that although I may not personally benefit from this, the sharing of data might accelerate medical research and help other families. I will email the laboratory at PGLsupport@cumc.columbia.edu if I do not consent to the sharing of my data as described above. I have the option of allowing my coded data to be used for research purposes:

_____ (Initial) I consent to the use of my/my child's coded genomic data for research purposes. Additional written consent is required for any research study that may involve return of results.

6. Sample Retention

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_____ (Initial) I consent to the use of my/my child's specimen as well as other samples submitted for analysis for genetic research studies and/or to be used for quality assurance, assay development and validation. Additional written consent is required for any research study that may involve return of results. The duration of the retention of my/my child's sample will depend on the individual research study. By not initialing here, my/my child's sample will be destroyed not more than 60 days after completion of testing.

7. Consent for CDEX

All of the above has been explained to me, to my satisfaction, and my signature below attests to the same.

Patient (person being tested):_____DOB_____

_____ _____ Date: _____

Print Name of Patient/Authorized Representative Signature of Patient/Authorized Representative

Relationship to Patient, if applicable: _____

7b. Consent of family members submitting a sample for evaluation of patient's results.

Samples obtained from family members can help evaluate the results obtained on the person being tested. The results obtained from these samples will be used solely for this purpose. Separate reports for family members will not be issued.

Family Member #1:

Name of Family Member: _____DOB_____

Signature: _____Date:_____

Relationship to Patient: _____

Family Member #2:

Name of Family Member: _____DOB_____

Signature: _____Date:_____

Relationship to Patient: _____

7c. Health care provider obtaining consent:

Print Name:_____Signature:_____ Date: _____