Laboratory of Personalized Genomic Medicine
Department of Pathology and Cell Biology

COLUMBIA UNIVERSITY MEDICAL CENTER

630 West 168th Street
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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 PGMINQUIRY@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 sample collection.

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: _____

Current List of genes for reporting of Secondary Variants (v 3.2, Miller et al., 2023 https://doi.org/10.1016/j.gim.2023.100866)

Gene	Gene MIM	Disease/Phentyope	Disorder MIM	Phenotype Category	Inheritance	SF List Version	Variants to report
ACTA2	102620	Familial thoracic aortic aneurysm	611788	Cardiovascular	AD	1.0	All P and LP
ACTC1	102540	Hypertrophic cardiomyopathy	612098	Cardiovascular	AD	1.0	All P and LP
ACVRL1	601284	Hereditary hemorrhagic telangiectasia	600376	Miscellaneous	AD	3.0	All P and LP
APC	611731	Familial adenomatous polyposis	175100	Cancer	AD	1.0	All P and LP
APOB	107730	Familial hypercholesterolemia	144010	Cardiovascular	AD	1.0	All P and LP
ATP7B	606882	Wilson disease	277900	Miscellaneous	AR	2.0	P and LP (2 variants)
BAG3	603883	Dilated cardiomyopathy	613881	Cardiovascular	AD	3.1	All P and LP
		Myofibrillar myopathy	612954	Cardiovascular	AD	3.1	All P and LP
BMPR1A	601299	Juvenile polyposis syndrome	174900	Cancer	AD	1.0	All P and LP
BRCA1	113705	Hereditary breast and ovarian cancer	604370	Cancer	AD	1.0	All P and LP
BRCA2	600185	Hereditary breast and ovarian cancer	612555	Cancer	AD	1.0	All P and LP
BTD	609019	Biotinidase deficiency	253260	Metabolic	AR	3.0	P and LP (2 variants)
CACNA1S	114208	Malignant hyperthermia	601887	Miscellaneous	AD	1.0	All P and LP
CALM1	114180	Long-QT syndrome type 14	616247	Cardiovascular	AD	3.2	All P and LP
		Catecholaminergic polymorphic ventricular tachycardia	614916	Cardiovascular	AD	3.2	All P and LP
CALM2	114182	Long-QT syndrome type 15	616249	Cardiovascular	AD	3.2	All P and LP
		Catecholaminergic polymorphic ventricular tachycardia	616249	Cardiovascular	AD	3.2	All P and LP
CALM3	114183	Long-QT syndrome type 16	618782	Cardiovascular	AD	3.2	All P and LP
		Catecholaminergic polymorphic ventricular tachycardia	618782	Cardiovascular	AD	3.2	All P and LP
CASQ2	114251	Catecholaminergic polymorphic ventricular tachycardia	611938	Cardiovascular	AR	3.0	P and LP (2 variants)
COL3A1	120180	Ehlers-Danlos syndrome, vascular type	130050	Cardiovascular	AD	1.0	All P and LP
DES	125660	Dilated cardiomyopathy	604765	Cardiovascular	AD	3.1	All P and LP
		Myofibrillar myopathy	601419	Cardiovascular	AD	3.1	All P and LP
DSC2	125645	Arrhythmogenic right ventricular cardiomyopathy	610476	Cardiovascular	AD	1.0	All P and LP
DSG2	125671	Arrhythmogenic right ventricular cardiomyopathy	610193	Cardiovascular	AD	1.0	All P and LP
DSP	125647	Arrhythmogenic right ventricular cardiomyopathy	607450	Cardiovascular	AD	1.0	All P and LP
		Dilated cardiomyopathy	615821	Cardiovascular	AD	1.0	All P and LP
ENG	131195	Hereditary hemorrhagic telangiectasia	187300	Miscellaneous	AD	3.0	All P and LP
FBN1	134797	Marfan syndrome	154700	Cardiovascular	AD	1.0	All P and LP
FLNC	*102565*	Dilated cardiomyopathy	n/a	Cardiovascular	AD	3.0	All P and LP
		Hypertrophic cardiomyopathy	617047	Cardiovascular	AD	3.0	All P and LP
		Myofibrillar myopathy	609524	Cardiovascular	AD	3.0	All P and LP
GAA	606800	Pompe disease	232300	Metabolic	AR	3.0	P and LP (2 variants)
GLA	300644	Fabry disease	301500	Cardiovascular Metabolic	XL	1.0	All hemi, het, homozygous P and LP
HFE	613609	Hereditary hemochromatosis (c.845G>A; p.C282Y homozygotes only)	235200	Miscellaneous	AR	3.0	p.C282Y homozygotes only
HNF1A	142410	Maturity-Onset of Diabetes of the Young	600496	Miscellaneous	AD	3.0	All P and LP
KCNH2	152427	Long-QT syndrome type 2	613688	Cardiovascular	AD	1.0	All P and LP
KCNQ1	607542	Long-QT syndrome type 1	192500	Cardiovascular	AD	1.0	All P and LP
LDLR	606945	Familial hypercholesterolemia	143890	Cardiovascular	AD	1.0	All P and LP
LMNA	150330	Dilated cardiomyopathy	115200	Cardiovascular	AD	1.0	All P and LP
MAX	154950	Hereditary paraganglioma-pheochromocytoma syndrome	171300	Cancer	AD	3.0	All P and LP
MEN1	613733	Multiple endocrine neoplasia type 1	131100	Cancer	AD	1.0	All P and LP
MLH1	120436	Lynch syndrome	609310	Cancer	AD	1.0	All P and LP
MSH2	609309	Lynch syndrome	120435	Cancer	AD	1.0	All P and LP
MSH6	600678	Lynch syndrome	614350	Cancer	AD	1.0	All P and LP
MUTYH	604933	*MUTYH* -associated polyposis	608456	Cancer	AR	1.0	P and LP (2 variants)
MYBPC3	600958	Hypertrophic cardiomyopathy	115197	Cardiovascular	AD	1.0	All P and LP
MYH11	160745	Familial thoracic aortic aneurysm	132900	Cardiovascular	AD	1.0	All P and LP
MYH7	*160760*	Hypertrophic cardiomyopathy	192600	Cardiovascular	AD	1.0	All P and LP
		Dilated cardiomyopathy	613426	Cardiovascular	AD	1.0	All P and LP
MYL2	160781	Hypertrophic cardiomyopathy	608758	Cardiovascular	AD	1.0	All P and LP
MYL3	160790	Hypertrophic cardiomyopathy	608751	Cardiovascular	AD	1.0	All P and LP
NF2	607379	*NF2* -related schwannomatosis	101000	Cancer	AD	1.0	All P and LP
OTC	300461	Ornithine transcarbamylase deficiency	311250	Metabolic	XL	2.0	All hemi, het, homozygous P and LP
PALB2	610355	Hereditary breast cancer	114480	Cancer	AD	3.0	All P and LP
PCSK9	607786	Familial hypercholesterolemia	603776	Cardiovascular	AD	1.0	All P and LP
PKP2	602861	Arrhythmogenic right ventricular cardiomyopathy	609040	Cardiovascular	AD	1.0	All P and LP
PMS2	600259	Lynch syndrome	614337	Cancer	AD	1.0	All P and LP
PRKAG2	602743	Hypertrophic cardiomyopathy	600858	Cardiovascular Metabolic	AD	1.0	All P and LP
PTEN	601728	*PTEN* hamartoma tumor syndrome	158350	Cancer	AD	1.0	All P and LP
RB1	614041	Retinoblastoma	180200	Cancer	AD	1.0	All P and LP
RBM20	613171	Dilated cardiomyopathy	613172	Cardiovascular	AD	3.1	All P and LP
RET	*164761*	Familial medullary thyroid cancer	155240	Cancer	AD	1.0	All P and LP
		Multiple endocrine neoplasia type 2A	171400	Cancer	AD	1.0	All P and LP
		Multiple endocrine neoplasia type 2B	162300	Cancer	AD	1.0	All P and LP
RPE65	180069	*RPE65* -related retinopathy	204100, 613794	Miscellaneous	AR	3.0	P and LP (2 variants)
RYR1	180901	Malignant hyperthermia	145600	Miscellaneous	AD	1.0	All P and LP
RYR2	180902	Catecholaminergic polymorphic ventricular tachycardia	604772	Cardiovascular	AD	1.0	All P and LP
SCN5A	*600163*	Long QT syndrome type 3	603830	Cardiovascular	AD	1.0	All P and LP
		Brugada syndrome	601144	Cardiovascular	AD	1.0	All P and LP
		Dilated cardiomyopathy	601154	Cardiovascular	AD	1.0	All P and LP
SDHAF2	613019	Hereditary paraganglioma-pheochromocytoma syndrome	601650	Cancer	AD	1.0	All P and LP
SDHB	185470	Hereditary paraganglioma-pheochromocytoma syndrome	115310, 171300	Cancer	AD	1.0	All P and LP
SDHC	602413	Hereditary paraganglioma-pheochromocytoma syndrome	605373	Cancer	AD	1.0	All P and LP
SDHD	602690	Hereditary paraganglioma-pheochromocytoma syndrome	168000, 171300	Cancer	AD	1.0	All P and LP
SMAD3	603109	Loeys-Dietz syndrome	613795	Cardiovascular	AD	1.0	All P and LP
SMAD4	*600993*	Juvenile polyposis syndrome	174900	Cancer	AD	1.0	All P and LP
		Hereditary hemorrhagic telangiectasia	175050	Miscellaneous	AD	1.0	All P and LP
STK11	602216	Peutz-Jeghers syndrome	175200	Cancer	AD	1.0	All P and LP
TGFBR1	190181	Loeys-Dietz syndrome	609192	Cardiovascular	AD	1.0	All P and LP
TGFBR2	190182	Loeys-Dietz syndrome	610168	Cardiovascular	AD	1.0	All P and LP
TMEM127	613403	Hereditary paraganglioma-pheochromocytoma syndrome	171300	Cancer	AD	3.0	All P and LP
TMEM43	612048	Arrhythmogenic right ventricular cardiomyopathy	604400	Cardiovascular	AD	1.0	All P and LP
TNNC1	191040	Dilated cardiomyopathy	611879	Cardiovascular	AD	3.1	All P and LP
TNNI3	191044	Hypertrophic cardiomyopathy	613690	Cardiovascular	AD	1.0	All P and LP
TNNT2	*191045*	Dilated cardiomyopathy	601494	Cardiovascular	AD	1.0	All P and LP
		Hypertrophic cardiomyopathy	115195	Cardiovascular	AD	1.0	All P and LP

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TP53	191170	Li-Fraumeni syndrome	151623	Cancer	AD	1.0	All P and LP
TPM1	191010	Hypertrophic cardiomyopathy	115196	Cardiovascular	AD	1.0	All P and LP
TRDN	*603283*	Catecholaminergic polymorphic ventricular tachycardia	615441	Cardiovascular	AR	3.0	All P and LP
		Long QT syndrome	n/a	Cardiovascular	AR	3.0	All P and LP
TSC1	605284	Tuberous sclerosis complex	191100	Cancer	AD	1.0	All P and LP
TSC2	191092	Tuberous sclerosis complex	613254	Cancer	AD	1.0	All P and LP
TTN	188840	Dilated cardiomyopathy (truncating variants only)	604145	Cardiovascular	AD	3.0	P and LP (truncating variants only)
TTR	176300	Hereditary transthyretin-related amyloidosis	105210	Miscellaneous	AD	3.1	All P and LP
VHL	608537	Von Hippel-Lindau syndrome	193300	Cancer	AD	1.0	All P and LP
WT1	607102	*WT1* -related Wilms tumor	194070	Cancer	AD	1.0	All P and LP