Ambry Genetics®

ExomeNext® Patient Consent Form (Optional) - Page 1 of 3

Please Circle One Of The Test Options Below.*

ExomeNext-*Proband* **ExomeNext-*Proband* plus Mito** **ExomeNext-*Trio*** **ExomeNext-*Trio* plus Mito**
ExomeNext-*Rapid* **ExomeNext-*Duo*** **ExomeNext-*Duo* plus Mito**

* For ExomeNext-*Select* orders please use the "ExomeNext-*Select* Consent Form".

Test Process
ExomeNext® involves sequencing and analysis of up to ~20,000 nuclear genes and may include sequencing and screening for proven mutations in the mitochondrial genome (mtDNA). This process includes genes that have been previously associated with human disease (characterized) and those that have not been previously described to cause a Mendelian condition (uncharacterized/novel). Whole exome sequencing differs from whole genome sequencing as it targets the ~1-2% of the protein coding regions (exons) of the genome. Whole exome sequencing provides a time and cost effective method of sequencing all of an individual's genes since ~85% of known disease-causing mutations are expected to occur within the exons. The goal of ExomeNext® is to identify the underlying molecular cause of an affected individual's condition.

Technical Limitations
Not all exons in the genome are targeted. Approximately 1-2% of the exons that are targeted may not be well covered. The empirical coverage data for specific genes can be found on the Ambry Genetics website. Certain mutation types may not be detectable (eg. some copy number variants, methylation abnormalities, mutations in genes with highly homologous pseudogenes, and expansions of trinucleotide repeats) and exome sequencing is also limited in the detection of alterations confounded by various non-Mendelian factors (penetrance, variable expressivity, multifactorial disease, epigenetic factors, phenocopies and uniparental disomy (UPD)).

Testing & Analysis Pipeline
Several hundred thousand variants will be identified through whole exome sequencing, and all variants will be filtered through an in-house developed pipeline, Ambry variant analyzer (AVA), based on types of alterations, minor allele frequencies, and various mutation databases. Next, a thorough clinical and medical review is performed by our medical team to identify clinically relevant alterations with overlapping features consistent with the patient's reported phenotype. Analysis begins with characterized genetic etiologies and if no clinically relevant alterations are identified among characterized genetic etiologies the case may then move to the second step for analysis of novel genetic etiologies. Analysis of novel genetic etiologies is only available for ExomeNext-Trio test options. Variants that are considered "relevant findings" thought to be involved in the syndrome being investigated will undergo further analysis and interpretation by an ABMG-certified laboratory director and will be included in the primary report.

Testing Of Family Samples
ExomeNext-*Proband*/ExomeNext-*Proband* plus Mito involves whole exome sequencing of the patient (proband) only. Additional family member (parents, siblings etc.) samples may be submitted for co-segregation analysis. Providing family member samples improves the likelihood of a more definitive diagnosis. Analysis of novel genetic etiologies is not available for ExomeNext-Proband test options. ExomeNext-*Duo*/ExomeNext-*Duo* plus Mito involves whole exome sequencing of two individuals (duo): the patient (proband) and one other family member, preferentially a parent or other first-degree relative. Additional family member (parents, siblings etc.) samples may be submitted for co-segregation analysis. Providing family member samples improves the likelihood of a more definitive diagnosis. Analysis of novel genetic etiologies is not available for ExomeNext-Duo test options.

ExomeNext-*Trio*/ExomeNext-*Trio* plus Mito is a family-centered approach to whole exome sequencing and involves the sequencing of three individuals (trio): the patient/fetus (proband) and two other family members, preferentially parents or other first-degree relatives. If an informative trio is not available, analysis of novel genetic etiologies will not be performed. Co-segregation analysis (family studies) is performed for candidate alterations on the trio, when family member specimens are submitted at the time of testing. Providing family member samples improves the likelihood of a more definitive diagnosis.

Confirmation by Sanger sequencing will be performed for all relevant finding alterations that fail to meet quality thresholds. De-identified co-segregation results for the family members will be included in the primary report. For relevant mitochondrial DNA alterations, only mutations in the proband with apparently >15% mutant load by NGS will be confirmed using an alternate method. If no relevant findings are identified, additional family member samples will not be tested. Testing of family members submitted after ExomeNext® testing is completed is available at standard Specific Site Analysis pricing.

Family Member Discrepancies
As with any family-centered genetic testing, there is a possibility that the family genetic relationships do not align with what is reported by your family. If relationship confirmation results are not as reported to Ambry, your clinicians will be contacted to determine how to proceed with testing. Options can include switching from trio to duo testing or sending in another first degree family member, as well as modifying family member information in the report.

Clinical Information And Results Interpretation
ExomeNext® test interpretation and analysis is significantly enhanced by the provision of a full and complete clinical history. For informative results and the best likelihood of a conclusive diagnosis, it is critical to provide all relevant clinical and family history information to the ordering clinician and to Ambry Genetics. Testing will not begin until the laboratory has received the required paperwork and specimens.

Results and Interpretation
The primary report will contain results related to the proband's primary indication for testing. Overall result categories will be dependent on the pathogenicity of the alteration along with the phenotypic overlap of the gene with the proband's symptoms. Results will be released to the ordering clinician, and the final clinical interpretation of ExomeNext® results will be made by the ordering clinician and not Ambry Genetics.

When applicable, analysis of novel genetic etiologies may allow for the discovery of genes not currently reported in association with a known genetic condition, and this may be a pathway toward diagnosing a previously undescribed genetic defect. However, under certain circumstances a diagnosis will not be readily available. Since new scientific information becomes available on a regular basis, this could alter the interpretation of previously reported results. In the event of a change in interpretation, an unsolicited re-classification/amended report may be issued to the ordering clinician. Re-analysis may also be performed by request. Please contact the laboratory for re-analysis options.

Secondary findings, pathogenic and likely pathogenic mutations unrelated to the current clinical presentation, will be reported in a separate Secondary Findings Report (See "Secondary Findings" below).

Clinical Course/Prognosis Of Disease
Identification of a specific genetic variant does not predict the onset, severity, or spectrum of human disease with any degree of certainty. Similarly, the absence of a sequence variant may reduce, but will not eliminate the possibility of being affected with a specific condition.

Standard Laboratory Limitations
Standard laboratory limitations apply to each specimen drawn for testing, including but not limited to: sample mix-up, samples unavailable from critical family members, inaccurate reporting of family relationships, mosaicism, low-level heteroplasmy or technical limitations. Under these potential, yet rare circumstances, exome sequencing may not be capable of generating an accurate result.

Secondary Findings
Exome sequencing of a single individual for a clinical indication may result in the identification of other incidental variants unrelated to the indication for testing (aka "secondary findings"). When requested, pathogenic and likely pathogenic alterations from within the list of genes recommended by the American College of Medical Genetics and Genomics (ACMG) are reported (Green, 2013; Kalia, 2016; Miller 2021; Miller, 2022). For ongoing pregnancies, the Childhood Onset Diseases Secondary Findings are also included at no additional charge. Secondary findings results are available for the proband and each family member sequenced as part of the duo or trio. The patient undergoing testing along with family members sequenced as part of the duo or trio may or may not want to be informed of these potential secondary findings (see "Technical Limitations"). The family members chosen as the ExomeNext® trio are at the discretion of the laboratory. Thus, not all consented members may receive secondary findings reports. Each duo or trio family member opting-in will receive their own secondary findings analysis and report. Please note, pathogenic or likely pathogenic mutations that may be present in a family member but not in the proband may be detected and reported.

Ambry Genetics' Results Disclosure Policy
Due to the complexity of genetic testing and the important implications of the test results, these results will be reported through the ordering provider. Your results report may be available to you after it has been released to you by your healthcare provider, upon your request, or as required to comply with local, state and/or federal regulations and laws. You should contact your provider to obtain and discuss the results of the test and potential medical management recommendations for clinically significant test results. Additionally, the test results could be released to all who, by law, may have access to such data. See Ambry's Privacy Policy for more details: https://www.ambrygen.com/legal/notice-of-privacy-practices

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Terms and Conditions

Patient Acknowledgement: I acknowledge that the information provided by me is true and correct. For direct insurance billing: I authorize my insurance benefits to be paid directly to Ambry Genetics Corporation (Ambry), authorize Ambry to release medical information concerning my testing to my insurer, to be my designated representative for purposes of appealing any denial of benefits as needed and to request additional medical records for this purpose. I understand that I am financially responsible for any amounts not covered by my insurer and responsible for sending Ambry money received from my health insurance company.

For patient payment by credit card: I hereby authorize Ambry Genetics Corporation to bill my credit card as indicated above. In order to expedite consideration for eligibility for Ambry's Patient Assistance Program, please provide the total annual gross household income: $ and the number of family members in the household supported by the listed income: . I authorize Ambry Genetics Corporation to verify the above information for the sole purpose of assessing financial need, including the right to seek supporting documentation.

For NY Residents: I understand that under New York State law, Ambry Genetics must discard my sample after the longer of (a) testing completion and (b) 60 days after the Date of Collection above.

☐ I agree that Ambry Genetics may retain my sample for 6 months after the completion of all testing, including the testing above, any additional testing of my sample that I authorize within the initial 6-month retention period, and any extended or additional testing of the sample necessary and required to demonstrate the integrity of the sample tested or to resolve the analysis of a test with a previously indeterminate result.

☐ I do not agree that Ambry Genetics may retain my sample for 6 months after the testing above has been completed.

I have read or have had read to me all of the above statements and understand the information regarding molecular genetics testing and have had the opportunity to ask questions I might have about the testing, the procedure, the risks, and the alternatives prior to my informed consent. I agree to have the molecular genetic testing described within or above.

Patient Signature *(or Parent/Guardian if patient is a minor)*	Date
Patient Name *(Print)*	Name and Relationship *(Parent/Guardian if patient is a minor)*

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