Ambry Genetics®
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ExomeNext Patient Consent Form (Optional) - Page 1 of 2

PLEASE CIRCLE ONE OF THE TEST OPTIONS BELOW.*

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

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

1. TEST PROCESS

ExomeNext involves sequencing and analysis of the ~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 underline a Mendelian condition (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 diseases-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.

2. TECHNICAL LIMITATIONS

Not all exons in the genome are targeted. Approximately, 5% 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. large 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)).

3. 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 candidate alterations with overlapping features consistent with the patient's reported phenotype. Analysis begins with characterized genetic etiologies and if no candidate 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 "candidates" 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.

4. 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-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 of candidate alterations by Sanger sequencing will be performed for all candidate alterations that fail to meet quality thresholds. De-identified co-segregation results for the family members will be included in the primary report. For candidate mitochondrial DNA alterations, only mutations in the proband with apparently >15% mutant load by NGS will be confirmed using an alternate method. If no candidate alterations 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.

5. 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.

6. 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.

7. 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. Additional findings (aka notable findings) with limited clinical overlap do not routinely undergo co-segregation analysis or confirmation via Sanger sequencing. 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.

Initials_____

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

8. 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.

9. 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.

10. SECONDARY FINDINGS

Exome sequencing of a single individual for a clinical indication may result in the identification of other incidental mutations unrelated to the indication for testing (aka "secondary findings"). Secondary findings results are available for the proband and each family member sequenced as part of the trio. The patient undergoing testing along with family members sequenced as part of the 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 member may receive secondary findings reports. Each trio family member opting-in will undergo an individual secondary findings analysis and report. Please note, pathogenic mutations that may be present in a family member but not in the proband may be detected and reported.

ACMG SECONDARY FINDINGS RECOMMENDED LIST* (OPTIONAL-NO COST)

In 2013, the American College of Medical Genetics and Genomics (ACMG) released "Recommendations on Incidental Findings in Clinical Exome and Genome Sequencing." The group recommends that laboratories performing diagnostic exome sequencing (DES) actively search and report alterations in genes from among a provided "minimum list" of genes. The list was last updated in 2016 and includes 59 genes associated with roughly 28 genetic conditions determined by ACMG to be well-recognized and known to have a strong link of causation. The conditions were chosen if preventative measures and treatments exist. Cancer predisposition risk, later-onset cardiac syndromes, connective tissue disorders (Marfan Syndrome, Loeys-Dietz Syndrome), and childhood-onset disease are among types of conditions included. Secondary findings results are available for all probands and members of the trio, regardless of age. Family members may be able to infer carrier status based on the proband's results.

The ACMG and AAP offer the following precautions when performing genetic testing in minors: 1) Parents or guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood-onset conditions. Ideally, the assent of the child should be obtained; 2) Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality; 3) For ethical and legal reasons, health care providers should be cautious about providing predictive genetic testing to minors without the involvement of their parents or guardians, even if a minor is mature. Results of such tests may have significant medical, psychological, and social implications, not only for the minor but also for other family members.

AMBRY'S EXPANDED SECONDARY FINDINGS** (OPTIONAL)

For an additional cost, patients and members of the trio may also order an expanded secondary findings report. In addition to the ACMG recommended list, each patient/family member can choose from an expanded set of reportable secondary findings including recessive carrier status, cancer predisposition, adult onset disease and childhood onset disease. Please note, DNA variants associated with drug metabolism and risk of common multifactorial diseases (i.e. coronary artery disease, obesity, asthma, etc.) are not analyzed or reported as part of the expanded secondary findings report.

Please complete and submit the Expanded Secondary Findings Request Form to request this option.

**A complete list of genes for all the Secondary Findings categories described above can be found at: ambrygen.com/exomenext-forms

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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