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ExomeNext-*Select* Patient Consent Form - Page 1 of 2

1. TEST PROCESS

ExomeNext involves sequencing of the ~20,000 nuclear genes and analysis of up to 500 genes pre-selected by the ordering clinician. This process may include analysis of genes that have been previously associated with human disease (characterized) as well as those that have not been previously described to underline a Mendelian condition (novel candidate). 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. Only genes associated with the patients presentation will be analyzed and reported.

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 will be limited to the genes selected by the ordering clinician. No other genes will be analyzed or reported.

4. TESTING OF FAMILY SAMPLES

Co-segregation analysis (family studies) is performed on family members submitted at the time of testing for candidate alterations. 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. If no candidate alterations are identified, family member samples will not be tested. Testing of family members submitted after ExomeNext-*Select* 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 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 report will contain results related to the proband's primary indication for testing among the pre-selected genes. 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-*Select* results will be made by the ordering clinician and NOT Ambry Genetics.

Analysis of novel candidate 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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ExomeNext-*Select* Patient Consent Form - Page 1 of 2

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"). Therefore, secondary findings will not be analyzed or reported for ExomeNext-*Select* test orders.

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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