Ambry Genetics®

Patient Name: _____ DOB: _____

Aliso Viejo, CA 92656 USA | Toll Free: 866 262 7943 | Fax: 949 900 5501 | ambrygen.com

ExomeNext-*Prenatal* Test Requisition Form - Page 1 of 6

FETUS INFORMATION

Last Name	(Fetus of) First Name	Middle Initial

Street Address	City /State	Zip Code

Preferred Contact Phone Number	Biological Sex: ☐F ☐M Gender by Ultrasound: (if different from marked): _____	Ethnicity: ☐African American ☐Asian ☐Caucasian ☐Hispanic ☐Jewish (Ashkenazi) ☐Portuguese ☐Other: _____

SPECIMEN INFORMATION*

Fetal Specimen Type (s)* ☐Cultured CVS* ☐Cultured Amniocytes ☐DNA, Source: _____

Gestational Age at sample collection: _____

Note: Direct CVS or amnio is not accepted at this time. Please complete the "Genesis Laboratories Test Requisition Form" to request culturing.

*For POC /discontinued pregnancies, please complete the standard "Clinical Genomics Test Requisition Form" and order 9999 or 9999-R

Collection Date	Specimen ID	MRN

SENDING FACILITY Facility Type: ☐ Physician/Physician Group ☐ Referral Lab ☐ Hospital

Facility Name (Facility Code)	Address	City	State /Country	Zip	Phone

ORDERING PHYSICIAN AND/OR OTHER LICENSED MEDICAL PROFESSIONAL

Name (Last, First, Degree) (Clinician Code)	Phone	Fax	Email	NPI#

ADDITIONAL RESULTS RECIPIENTS

☐ Primary Contact	Medical Professional Name (Clinician Code)	Phone	E-mail or Fax
☐ Primary Contact	Genetic Counselor Name (Clinician Code)	Phone	E-mail or Fax

CONFIRMATION OF INFORMED CONSENT AND MEDICAL NECESSITY FOR GENETIC TESTING

By ordering testing, the undersigned person represents that he/she is a licensed medical professional authorized to order genetic testing OR is a representative of a licensed medical professional authorized to order genetic testing; acknowledges the patient has been supplied information regarding genetic testing and the patient has given consent for genetic testing to be performed and the signed consent form is on file. I confirm that this is medically necessary for the diagnosis or detection of a disease, illness, impairment, syndrome or disorder, and that these results will be used in the medical management and treatment decisions for this patient. Furthermore, additional results recipients information is true and correct to the best of my knowledge.

My signature here applies to the attached letter of medical necessity (if applicable). If you do not want your signature on this TRF to apply to the attached LMN, please provide an LMN and/or Clinical Notes with your order and check here. ☐

Does this patient give consent to the use of their sample for research? ☐Yes ☐No

Medical Professional Signature: **Date:**

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BILLING

☐ PATIENT PAYMENT

☐ Check (Payable to Ambry Genetics) ☐ Visa ☐ Mastercard ☐ American Express ☐ Discover

Card Number	Exp. Date	CVC #

Cardholder Name	Amount $

☐ INSTITUTIONAL BILLING

Facility Name		
Street Address		
City	State	Zip Code
Contact Name		
Phone Number	E-mail	

☐ FINANCIAL ASSISTANCE

In order to expedite consideration for eligibility for Ambry's E.P.I.C. Program, please provide the total annual gross household income: $_____ and the number of family members in the household supported by the listed income: _____ .

Patient Acknowledgement: I acknowledge that the information provided by me is true to the best of my knowledge. For patient payment by credit card: I hereby authorize Ambry Genetics Corporation to bill my credit card as indicated above.

I affirm that I have offered genetic counseling and guided the patient's family through the entire counseling process required for whole-exome sequencing.

_____	_____	_____
Clinician Name (Clinician-Geneticist/Genetic Counselor)	Clinician Signature	Date

Patient Acknowledgement: I affirm that my clinician has offered genetic counseling and has reviewed with me the whole-exome sequencing process prior to testing, and I would like to proceed with test processing

_____	_____	_____
Patient Name	Patient/Guardian Signature	Date

FAMILY HISTORY*

**Please identify each family member available for testing below. The "Clinical Genomics Family Member Test Requisition Form" is ALSO required for each family member being tested.*

Name (Last, First)	Relationship to proband	Affected
		☐ Yes ☐ No ☐ Partial ☐ Possible
		☐ Yes ☐ No ☐ Partial ☐ Possible
		☐ Yes ☐ No ☐ Partial ☐ Possible
		☐ Yes ☐ No ☐ Partial ☐ Possible

Is anyone in the family affected with a similar phenotype as the proband? ☐ NO ☐ YES, please list exact relationship to proband, symptoms and age of onset of symptoms:

_____

Any stillbirths or SABs? ☐ NO ☐ YES, please describe:_____

Is there any consanguinity (conception between blood relatives) in the family? ☐ NO ☐ YES If yes please describe: _____

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PREVIOUS STUDIES

LMP: _____ EDD/EDC:_____

Egg donor used: ☐ yes ☐ no

Sperm donor used: ☐ yes ☐ no

Previous affected child/pregnancy: ☐ yes ☐ no

Imaging studies:

☐ Fetal echocardiogram ☐ MRI

Please describe any abnormalities: _____

_____

Prenatal Screening/Testing Performed:

Maternal Serum Screening: ☐ Normal ☐ Abnormal

Genetic Testing:

NonInvasive Prenatal Screening:

☐ Normal

☐ Abnormal (describe):_____

Chromosomes/Karyotype:

☐ Chromsome Microarray Analysis (CMA)

Results:_____

☐ Karyptype

Results:_____

☐ Other:_____

Lagging growth/IUGR: ☐ yes ☐ no

Suspected overgrowth: ☐ yes ☐ no

Ultrasound Measurements: BPD: _____ NT: _____ CRL: _____

TEST

Exome Sequencing Test options:

☐ 9999P ExomeNext-*Prenatal**

(Maternal sample required for MCC studies and included in testing)

☐ Opt-out of analysis and reporting of Novel Genetic Etiologies

(See "Exome Patient Guide" for details)

**Institutional billing or patient payment only*

Secondary Findings Report*:

Check below to order the Secondary Findings, disease causing alterations unrelated to the reason for testing. Two categories of Secondary Findings are included with the ExomeNext-*Prenatal* Test: Childhood Onset Diseases and The ACMG Recommended List. Please choose from the secondary findings reporting options for these categories below. If no boxes are checked, secondary findings will not be reported for the fetus.

Childhood Onset Disease:

These include findings associated with childhood onset diseases.

☐ Yes: I choose to receive Childhood onset secondary findings

☐ No: I choose to decline Childhood onset secondary findings

ACMG Reocmmended List:

The ACMG Recommended List of secondary findings includes disease causing variants identified among a list of genes. Please select your preference or this category of Secondary Findings.

☐ Yes: I choose to receive the ACMG Recommended List of secondary findings

☐ No: I choose to decline the ACMG Recommended List of secondary findings

**For a complete report of expanded secondary findings options and pricing please complete the "ExomeNext Expanded Secondary Findings Request Form" and submit with the sample.*

PRENATAL CLINICAL DETAILS (PRENATAL TESTING ONLY)

Prenatal Clinical Details (Prenatal Testing Only): *Please describe any clinical details in the box provided below*

☐ Abdominal Abnormalities ☐ Dysmorphic Features ☐ Head/Skull Abnormalities ☐ Skeletal/Limb Abnormalities

☐ Cardiovascular Abnormalities ☐ Facial Abnormalities ☐ Kidney/Bladder/Ureter Abnormalities ☐ Other Ultrasound Findings

☐ Chest/Thorax Abnormalities ☐ Genital Abnormalities ☐ Lung Abnormalities

PLEASE PROVIDE A BRIEF SYNOPSIS OF THE ULTRASOUND FINDINGS

ORDERING CHECKLIST (Required*)

☐ Proband/fetal specimen

☐ ExomeNext-*Prenatal* TRF with patient & clinician signatures

☐ Clinical history (attach clinic notes)

**Orders with missing requirements will be placed on hold until all requirements are received.*

ORDERING CHECKLIST (Highly Recommended)

☐ Family member specimens** (1 family member TRF required per individual)

☐ Family history or pedigree

☐ Previous test results

***Please complete a "Clinical Genomics Family Member TRF" for each family member submitted for testing. Please send all 1st degree relatives and informative relatives at the beginning of testing.*

CONTACT INFORMATION

All documents can be secure uploaded at ambrygen.com/secure-upload, or faxed to 949-900-5501.

AmbryPort 2.0 is a new secure client portal that allows order submission, test status updates, insurance authorization status and report downloads.
All required documents can be completed and directly uploaded through AmbryPort2.0 during the ordering process or after order submission.
Please visit portal.ambrygen.com/signup to sign up.

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EXOMENEXT PATIENT GUIDE

Proband Initials _____

1. TEST PROCESS

ExomeNext involves sequencing and analysis of the ~20,000 nuclear genes in addition to 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. 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 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, and additional family members 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. 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 beyond the trio will not be tested. Testing of family members after testing is completed and starts at $400 per sample.

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 Primary Report will contain results related to the proband's primary indication for testing. All candidate alterations will undergo Sanger confirmation and co-segregation analysis. 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.

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 mutations unrelated to the current clinical presentation, will be reported in a separate Secondary Findings Report (See "Secondary Findings" below). This report will be separate from the Primary Report.

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Proband Initials _____

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"). 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"). Secondary findings results are also available for each family member chosen to be sequenced as part of the trio. 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 will undergo an individual secondary findings analysis. Please note, pathogenic mutations that may be present in a family member but not in the proband may be detected and reported. Secondary findings reports are issued in a separate report and available for the proband and each family member sequenced as part of the trio.

At this time, there are no standard recommendations regarding the return of secondary findings results for an ongoing pregnancy, therefore the option of secondary findings is available to all patients at this time. It is recommended that referring clinicians discuss the benefits and limitations of secondary findings with their patients.

CHILDHOOD ONSET DISORDERS (NO CHARGE)

During analysis of the fetal exome, alterations that are expected to lead to childhood onset disorders but unrelated to the ultrasound findings and indication for Prenatal Exome Testing may be revealed. All prenatal exome tests offer the option for secondary finding results related to childhood onset diseases at no additional cost.

ACMG SECONDARY FINDINGS RECOMMENDED LIST* (NO CHARGE)

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 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. Among the condition types are cancer predisposition risk, later-onset cardiac syndromes, connective tissue syndromes (Marfan Syndrome, Loeys-Dietz Syndrome), and one childhood-onset disease (familial hypercholesterolemia). Secondary findings results are available for all probands and members of the trio, regardless of age. These results may include the conditions listed above. 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.

*A list of the ACMG recommended genes and diseases can be found at: ambrygen.com/exomenext-forms

AMBRY'S EXPANDED SECONDARY FINDINGS** (OPTIONAL)

For an additional cost, patients and family members chosen as 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, and adult 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 and reported as part of the expanded secondary findings report.

Please complete and submit the Expanded Secondary Findings Request Form to request this option.
ambrygen.com/exomenext-forms

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

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FILTERED VARIANT CONSENT FORM

PROBAND NAME : _____

PROBAND DOB : _____

Ambry Genetics provides the list of raw filtered variants when requested, with the understanding that the data will be used strictly on a research basis, and not for clinical purposes. Other than those described in the final report, the variants have not undergone thorough interpretation and/or may represent sequencing artifacts as most have not been confirmed by a second laboratory method. In the case that additional important findings related to the phenotype in question are identified, clinicians should immediately contact the laboratory for verification, and possibly, generation of an amended report. This list of variants may include secondary findings. All patients undergoing diagnostic exome sequencing (DES) have completed a consent form which includes the opportunity to opt-out of secondary findings disclosure.

Filtered variant list *(provided in excel format at no charge)*

PHYSICIAN CONSENT:

I understand that the receipt of the raw filtered variant list may include secondary findings, potential sequencing artifacts, and variants which have not undergone interpretation and the patients/family members listed below are aware that I am requesting this data. I also understand that any information gleaned from review of this data, outside that which is described in the patient's final report, is strictly for research purposes and shall not be used for clinical decision-making purposes. I understand that Ambry Genetics recommends against the delivery of these data to patients.

Signature : _____ Date : _____

Printed Name : _____ Phone : _____

Institution : _____ Email Address : _____

PATIENT/GUARDIAN CONSENT:

I understand that my doctor has requested receipt of the raw filtered variant list resulting from the diagnostic exome sequencing (DES) performed for me/the person for whom I am the caregiver. I acknowledge that the information included in the data files may include secondary findings, potential sequencing artifacts, and variants which have not undergone interpretation. I also understand that these data are for research purposes only and shall not be used for clinical decision-making purposes. I understand that Ambry Genetics recommends against the delivery of these data to patients.

NAME AND DOB OF EACH PATIENT/FAMILY MEMBER FROM WHOM YOU ARE REQUESTING THE RAW FILTERED VARIANT LIST: (ONE LIST WILL BE PROVIDED PER FAMILY)

NAME	DOB	PATIENT/FAMILY MEMBER SIGNATURE	DATE