Ambry Genetics™

15 Argonaut,
Aliso Viejo, CA 92656

Toll Free 866 262 7943
Fax 949 900 5501
ambrygen.com

CLIA# 05D0981414
Laboratory Director: Wengi Zeng, PhD, DABMG

Exome Requisition - Proband (All Blue Highlighted Fields Required)

REQUISITION AND CONSENT

PATIENT INFORMATION

Last Name	First Name	Middle Initial	DOB (MM/DD/YY)	Date of Death (if applicable)

Street Address	City	State	Zip

Preferred Contact Phone Number	Gender	Ethnicity
	☐F ☐M ☐Unknown	☐African American/Black ☐Asian ☐Caucasian ☐Hispanic ☐Jewish (Ashkenazi) ☐Specify:_____

ORDERING PHYSICIAN AND/OR OTHER LICENSED MEDICAL PROFESSIONAL

Name (Last, First, Degree)	Facility Name	NPI#

Street Address	City	State	Zip

Phone	Fax	E-mail

ADDITIONAL RESULTS RECIPIENTS

Medical Professional Name	Phone	E-mail/Fax

Medical Professional Name	Phone	E-mail/Fax

Form Completed By	Phone	Fax	E-mail

CONFIRMATION OF INFORMED CONSENT 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.

Does this patient give consent to the use of their sample for research? ☐Yes ☐No Consent is implied if a box is not marked (For patients in NY State, research consent will NOT be implied if left blank).

Medical Professional Signature _____ Date: _____

☐ INSURANCE BILLING (INCLUDE COPY OF BOTH SIDES OF INSURANCE CARD)

A completed Advance Beneficiary Notice (ABN) of coverage is required for Medicare patients who do not meet medical criteria for testing (see website for form)

Name of Insured	Relation to Patient? ☐Self ☐Parent ☐Spouse	Insurance Company Name

Street Address	City	State	Zip

Insurance Phone	Member ID	Group #

Authorization #	Authorization Date

PAYMENT INFORMATION / PREPAYMENT

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

Card Number	Exp. Date	CVC #

Cardholder Name	Amount $

Signature	Date

☐ INSTITUTIONAL BILLING

Facility Name

Street Address

City

State	Zip Code

Contact Name

Phone Number

NOTES

Ambry may require credit card information for insurance samples prior to initiating testing (does not apply to Medicaid and Medicare). Your patient will be notified if this information is needed.

Complete and detailed clinical information on page 2 provides a clear indication for testing (i.e. medical necessity) and assists in determination of insurance coverage.

Ambry recommends a patient-specific letter of medical necessity (LMN), as most insurance carriers will require one for processing (a LMN is not required for Medicare patients that meet medical guidelines).

Ambry Genetics will contact the patient if the out-of-pocket amount for this test order is estimated to exceed $100.

For single site analyses, insurance pre-verification will not be performed unless specifically requested.

Patient Acknowledgement: I acknowledge that the information provided by me is true to the best of my knowledge. For direct insurance/3rd party billing: I hereby authorize my insurance benefits to be paid directly to Ambry Genetics Corporation and authorize them to release medical information concerning my testing to my insurer. If applicable, I authorize Ambry Genetics Corporation to be my Designated Representative for purposes of appealing any denial of benefits. I understand that I am financially responsible for any amounts not covered by my insurer for this test order.

I also fully understand that I am legally responsible for sending Ambry Genetics any money received from my health insurance company for performance of this genetic test.

Patient Signature: _____ Date: _____

Exome Requisition (minimum of a trio required)

Patient Name_____

SPECIMEN INFORMATION (HIGHLIGHTED FIELDS ARE REQUIRED)

Collection Date	Specimen ID	MRN

Specimen Type

☐ Blood ☐ Cultured fibroblasts (fetal demise samples only accepted for 8814: First-Tier Exome only) ☐ DNA

TEST SELECTION

EXOME SEQUENCING IS FOR WHOLE FAMILIES:

Exome sequencing is for whole families; please send samples from all first degree relatives. For all scenarios we request that you send samples from all first degree relatives from the beginning of testing for co-segregation analysis (exome sequencing prices include testing of family members when submitted at initial time of testing).

SELECT ONE TEST OPTION:

☐ **8814 First-Tier Exome only** ☐ **8816 First-Tier Exome reflex to CDE** ☐ **8800 Clinical Diagnostic Exome**

ACMG SECONDARY FINDINGS MINIMUM LIST: In 2013, the 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. In following these recommendations, an "*ACMG Minimum List*" secondary findings report will be issued as a default for all exome orders.

ICD-9 CODES (PLEASE SELECT ALL THAT APPLY)

☐ 277.9	Unspecified disorder of metabolism	☐ 334.9	Unspecified spinocerebellar disease	☐ 756.0	Anomalies of skull and face bones
☐ 299.00	Autism, current infantile or childhood	☐ 345.40	Focal epilepsy with complex seizures or partial epilepsy with complex seizures	☐ 759.7	Multple congenital anomalies
☐ 315.39	Other developmental speech disorder			☐ 781.3	Hypotonia, hypotonicity
☐ 315.9	Unspecified delay in development	☐ 345.60	Infantile spasms	☐ 783.41	Failure to thrive
☐ 319	Unspecified intellectual disability	☐ 345.90	Epilepsy unspecified	☐ 783.42	Delayed milestones
☐ 330.8	Other cerebral degener childhood	☐ 742.9	Uns anomaly brain or nervous system	☐ Others	_____

ORDERING CHECKLIST

THE FOLLOWING ITEMS ARE REQUIRED FOR TESTING TO COMMENCE:

___ Detailed patient clinical history/clinic notes
___ A copy of the family history (pedigree)
___ Copies of previous test results
___ Family members available for testing
(please send all 1st degree relatives from the beginning of testing)

Required documents can be emailed to **CDE@ambrygen.com**, uploaded to Ambry's secure upload page at **www.ambrygen.com/secure-upload/**or faxed to **949-900-5501**.

FAMILY MEMBERS AVAILABLE FOR TESTING

NOTE: Please identify each family member available for testing below. The "Exome Requisition – Family" form is ALSO required for each family member being tested

NAME (FIRST AND LAST)	RELATIONSHIP TO PROBAND	AFFECTED (Y/N)
	Proband	

PROBAND'S CLINICAL OVERVIEW (SELECT ALL THAT APPLY)

__ Multiple congenital anomalies
__ Cancer predisposition
__ MR/ID/DD not syndromic
__ ASD
__ Metabolic
__ Neurologic (childhood-onset)
__ Neurologic (adult-onset)
__ Musculoskeletal/Structural
__ Hematologic
__ CardioPulmonary (childhood-onset)
__ CardioPulmonary (adult-onset)
__ Psychiatric
__ Immunologic/Infectious
__ Hematologic

PLEASE PROVIDE A BRIEF SYNOPSIS OF THE PATIENT'S PHENOTYPIC SPECTRUM:

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Exome Patient Consent Form

1. DIAGNOSTIC EXOME SEQUENCING – TECHNICAL LIMITATIONS

Not all the exons in the genome are targeted: There are many regions of the genome that cannot be captured and sequenced, including many exons. This is due to many factors, including highly repetitive regions and areas of the genome that are highly GC-rich. >97% of exons are targeted.
~10% of Exons that are targeted may not be well covered: The minimum on-target base coverage of any given exome is ~ 90% at 10x, leaving approximately 10% of the exome not covered at levels to reliably call heterozygous variants. With Ambry's established run conditions, ~90% of the bases are expected to have quality scores of Q20 or higher, which translates to an expected base-calling error rate of 1:100, or an expected base-calling accuracy of 99%. Each individual may have slightly different coverage yield distributions within the exome. Given the wide application ranges, clinical sensitivities and specificities for any individual exome are not established.

Certain mutation types are not detectable: The assay is limited in the detection of certain mutation types such as large rearrangements, copy number variation (CNV) mutations, mutations involved in tri-allelic inheritance, mitochondrial genome mutations, epigenetic effects, trinucleotide repeat expansions, and X-linked recessive mutations in females who manifest disease due to skewed X-inactivation. (For rearrangements and CNV, CGH-SNP array analysis is recommended prior to exome sequencing).
Non-Mendelian Inheritance: Exome sequencing is limited in detection of alterations that are confounded by various factors such as penetrance, variable expressivity, multifactorial disease, epigenetic factors, mitochondrial mutations, phenocopies and UPD.

_____ I understand the technical limitations of exome sequencing.
(initial here)

2. TESTING & ANALYSIS PIPELINE

Several thousand variants will be identified in one person's genome through whole exome sequencing. This variant data will be filtered through a developed pipeline in order to resolve variants of interest based on the clinical presentation observed and options ordered. While the analysis tools are applied to every variant, it is important to note that most variants identified do NOT undergo interpretation by a medical director. Only those variants identified as "candidate mutations" are reviewed by a medical director and can be placed into a patient's chart.

_____ I understand that only a small subset of these mutations which are thought to be part of the syndrome being investigated will undergo interpretation by a laboratory director.
(initial here)

3. FAMILIAL DEGREE OF RELATIONSHIP CONFIRMATION

The analysis pipeline depends on the use of family members in order to reduce the number of variants and for providing the most informative results. Because of this, the degree of relationship among family members may be confirmed if indicated. As with any genetic testing, there is the possibility that the family relationship results do not align with the expectations of the family. If relationship confirmation results are not as reported to Ambry, your clinicians will be contacted to determine how to proceed with testing.

_____ I understand DNA testing to confirm familial degrees of relationship may be performed and that my clinicians will be contacted to determine how to proceed with testing if relationship confirmation results are not as reported to Ambry.
(initial here)

4. WHAT IS REPORTED

A report will only be generated for proband(s), regardless of number of family members submitted. However, it may be possible to infer information about family members results based on the proband's report.

Common diseases genetic risks associations are not reported: Over the last ten years, increasingly large studies have identified common variants in human DNA sequences which are associated with modest changes in the risk of common diseases such as: diabetes, coronary artery disease, obesity, asthma, etc. These variants typically increase or decrease disease risk by less than 2-fold, with a few exceptions. Many of these studies have conflicting findings. These risk variants are not analyzed by diagnostic exome sequencing.

_____ I understand that only the results from the affected individual (proband) will be reported and that genetic risk association variants for common diseases are not reported.
(initial here)

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5. ACMG SECONDARY FINDINGS MINIMUM LIST

In 2013, the 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 includes 57 genes associated with roughly 25 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, 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-onsent 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.

_____ I understand that a minimum list of secondary findings will be reported and that I have the option to not receive this information.
(initial here)

☐ **Check here and sign below to opt-out of the default ACMG secondary findings minimum list.**

Patient or guardian signature _ _____ Date:_____

AMBRY'S PATIENT-DRIVEN SECONDARY FINDINGS OPTION

(Available for CDE orders only, not available for first-tier or reflex orders) For patients ordering the Clinical Diagnostic Exome test (CDE), additional expanded options for secondary findings reporting are available. If interested, please complete "Ambry's Secondary Findings Patient Consent Form" and supply it to the laboratory along with the other required documents before testing commences.

(Please complete the "Ambry's Secondary Findings Patient Consent Form")

_____ I understand that I have the option to recieve expanded secondary findings results if I order the "Clinical Diagnostic Exome" test option
(initial here)

6. CLINICAL INFORMATION AND RESULTS INTERPRETATION

Ambry's ability to provide meaningful results will be enhanced significantly by the provision of a full and complete clinical history. Additional clinical information can only improve the interpretation of results. Withholding any available clinical or family data can significantly impact testing results. For testing to commense, Ambry must be provided with your clinic notes, family pedigree and past test results

_____ I provided all relevant clinical and family history information to my physician/provider and to Ambry Genetics. I also understand that testing will not start until the laboratory has copies of my clinic notes, family pedigree and past test results.
(initial here)

7. TESTING OF FAMILY SAMPLES

Regardless of the specific exome sequencing test being ordered, for all exome orders Ambry includes testing for co-segregation analysis (aka: family testing) if samples are sent before testing begins. We ask that you send samples from the entire family including all first degree relatives of the affected patient as well as distant relatives with the same diagnosis. The fewer the number of family samples supplied, the greater the likelihood that clinical interpretation may be impacted and the greater the likelihood of receiving an inconclusive result. Co-segregation analysis (aka: family testing) can be performed post-testing, however the service is no longer included once testing has begun for a family. The cost for post-testing analysis ranges from ~$200 and up to ~$1,500 per sample.

_____ I understand that sending family member samples decreases the likelihood of receiving an inconclusive result. I also understand that family analysis is only included at the beginning of testing and that post-testing analysis ranges from ~$200 and up to ~$1,500 per sample.
(initial here)

8. RESULTS AND INTERPRETATION

Ambry Genetics will use your exome sequence, genetic information of other related individuals, your family pedigree, and all clinical history information provided to provide the most accurate data and clinical interpretation possible at this time. This is significantly limited by our current understanding of the human DNA sequence. We currently know the function and disease contribution of approximately 20% of the ~20,000 genes within our entire genome.

When ordering Clinical Diagnostic Exome (CDE), whole-exome sequencing may allow us to discover previously undescribed genes not currently known to underlie a genetic condition, especially when these conditions are very rare. This may be a pathway toward diagnosing a previously undescribed genetic condition. However, under certain conditions a diagnosis will not be readily available.

New scientific information becomes available every day. At any time, this could significantly alter the interpretation or significance of any sequence variant. It is strongly recommended that you contact your physician/provider for regular updates on available sequence information and interpretation.

_____ I understand the risk for potential identification of a variant in a poorly described gene and wish to proceed with testing (when ordering CDE). I also understand that it is my responsibility to recontact my healthcare provider for updated information regarding DNA variants.
(initial here)

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9. CLINICAL COURSE /PROGNOSIS OF DISEASE

Finding a specific genetic variant does not predict the onset, severity, or spectrum of human disease with any degree of certainty. Predictive ability varies widely depending on the specific condition, gene, and variant identified. Similarly, the absence of a sequence variant may reduce the likelihood of being affected with a specific condition, but in NO way guarantees this.

_____ *(initial here)* I understand that the identification or genetic variant may not assist in predicting the prognosis of the condition in my family and wish to proceed with testing.

10. POST-TEST COUNSELING AND RESULTS DISCLOSURE

Only your physician/ provider can interpret testing results for your specific case and make recommendations regarding prevention, treatment, or other clinical action. All results and interpretation will be provided ONLY to the ordering physician/provider.

_____ *(initial here)* I understand that results will be released to my physician/provider and NOT to me directly and that the final clinical interpretation of my exome sequence will be made by my physician/provider and NOT Ambry Genetics. I understand the importance of seeking genetic counseling post-testing.

11. STANDARD LABORATORY LIMITATIONS

I understand that the exome sequencing may not generate accurate results for the following reasons: sample mix-up, samples unavailable from critical family members, inaccurate reporting of family relationships, or technical problems, but not limited to these.

_____ *(initial here)* I understand the standard laboratory limitations and wish to proceed with testing.

WHOLE-EXOME SEQUENCING CONSENT AFFIRMATION

Clinician (Geneticist/Genetic Counselor)

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

_____	_____	_____
Name	**Signature**	**Date**

☐ 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.

_____	_____	_____
Name (Parent or Guardian)	**Signature**	**Date**

CONTACT US

Insurance Verification or Benefit Questions: call (949) 900-5794 or email preverification@ambrygen.com

Billing Questions: call (949) 900-5795 or email billing@ambrygen.com

General Questions: call (949) 900-5500 or toll free number (866) 262-7943 or email info@ambrygen.com

General Fax Line: call (949) 900-5501

INSURANCE BILLING

Ambry recommends submitting a patient-specific letter of medical necessity (LMN), as most insurance carriers will require one for processing (a LMN is not required for Medicare patients that meet medical guidelines). Please visit our website for a full library of customizable forms.

PRENATAL TESTING

Prenatal testing is available on a case-by-case basis for most of the conditions listed on the general test menu.

Please contact a genetic counselor at (949) 900-5500 to discuss the case prior to sending a fetal sample.

PREVERIFICATIONS

To process a preverification, please complete this requisition form (TRF), make a copy of the insurance cards (front and back) and fax to the insurance verification department at 949-900-5501

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Release of Raw Data Consent Form

PROBAND NAME & DOB:_____

Ambry Genetics provides the raw sequence data and/or candidate alteration lists 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 interpretation and/or may represent sequencing artifacts as many 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. All patients undergoing diagnostic exome sequencing (DES) have completed a consent form which includes the opportunity to opt-out of secondary findings disclosure.

NOTE: RAW DATA ARE NOT RELEASED UNTIL CLINICAL TESTING IS COMPLETED & A FINAL REPORT HAS BEEN ISSUED.

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

___Raw data:

Downloadable from ftp server **($75):**

___ fastq files

___ BAM files

Shipped on hard drive **($150):**

___ fastq files

___ BAM files

___ Shipping costs (ground shipping) **($50)** or provide courier account number:_____

TOTAL: $_____

Credit card #: _____ **Name on card: _____**

Exp. Date: _____ **Signature: _____**

PHYSICIAN CONSENT:

I understand that the receipt of raw data and/or candidate alteration lists may include secondary findings, potential sequencing artifacts, and variants which have not undergone interpretation. 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 data and/or candidate alteration lists 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 & DOB of each patient from whom you are requesting raw data and/or candidate alterations list:

NAME	DOB	PATIENT/ GUARDIAN SIGNATURE	DATE

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