Ambry’s test offerings are designed to provide flexible, comprehensive options tailored to your patients’ personal and family histories.

New Solutions for Identifying a Genetic Diagnosis

Identifying and understanding a genetic diagnosis – especially when many prior evaluations have not done so – allows for accurate disease identification and management. It also offers accurate genetic counseling for a family. Our ExomeNext testing has successfully been used to identify both inherited and de novo causative gene mutations in a diverse variety of single-gene and mitochondrial disorders.

Ambry’s ExomeNext detection rate is 30% for characterized genes, and an additional 7% for novel genetic etiologies (Farwell K, et al., Genet Med., 2014).

We offer you two options for clinical diagnostic exome sequencing. ExomeNext and ExomeNext-Rapid use the same process, analysis, and reporting; the only difference is turnaround time and price.

ExomeNext and ExomeNext-Rapid Test Descriptions

<table>
<thead>
<tr>
<th></th>
<th>EXOMENEXT</th>
<th>EXOMENEXT-RAPID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turnaround Time (TAT)</td>
<td>8-12 weeks</td>
<td>2-5 weeks*</td>
</tr>
<tr>
<td>Price</td>
<td>$5,800</td>
<td>$15,129**</td>
</tr>
<tr>
<td>Number of Genes Analyzed***</td>
<td>Up to ~20,000</td>
<td>Up to ~20,000</td>
</tr>
<tr>
<td>Mitochondrial Genome</td>
<td>Included</td>
<td>Included</td>
</tr>
<tr>
<td>Number of Individuals Sequenced</td>
<td>Trio</td>
<td>Trio</td>
</tr>
<tr>
<td>Family Studies</td>
<td>Included</td>
<td>Included</td>
</tr>
<tr>
<td>Secondary Findings</td>
<td>Included</td>
<td>Included</td>
</tr>
<tr>
<td>(see p.7 for details)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Trio samples required to guarantee ExomeNext-Rapid TAT
** Only institutional and cash billing are accepted for ExomeNext-Rapid
*** Analysis begins with characterized genetic etiologies. If no relevant alterations are identified, analysis continues for novel genetic etiologies. Trio samples are required for analysis of novel genetic etiologies.
Inherited Disorders are Collectively Not Rare

Individually, some genetic disorders may be limited to a handful of families across the world. Collectively, conditions with an underlying inherited cause are not rare.

Historically, genetic disorders have been diagnosed by clinical symptom evaluation. Causative gene identification is challenging if the number of affected individuals is low. As such, there are many inherited conditions that have unidentified causative genes. Many people remain “medical mysteries” after a diagnostic odyssey, may be receiving ineffective treatment, or carry incorrect diagnoses. Exome sequencing can change that.

Most mutations causing Mendelian disorders are located within the exons (Pussegoda KA, Clin Genet., 2010). Exons represent functionally important parts of the gene they are translated into proteins. The human exome (exons for the entire human genome) is only 1-2% percent of the entire genome.

Efficient and Effective at Finding a Genetic Diagnosis

ExomeNext uses next generation sequencing methods targeted to the nuclear genome. Mitochondrial DNA sequencing is also performed. This, coupled with powerful bioinformatics, identifies a clinical answer efficiently and effectively – genetic changes in the exome are expected to cause about 85% of known diseases (Choi M, et al., Proc Natl Acad Sci U S A, 2009.) There is significant potential to identify an informative medically actionable answer with clinical exome sequencing.

Clinical Indications for ExomeNext

- The suspected genetic condition and has become a “diagnostic odyssey,” with no genetic explanation identified from prior testing
- Limited or no comprehensive tests are available for the suspected condition
- Clinical presentation does not correspond with a known genetic disorder, but a novel genetic etiology is suspected
- Clinical presentation is unclear/atypical and may involve multiple gene, making ExomeNext a more practical approach
- Available targeted genetic testing for a fetus with a likely genetic condition has failed to arrive at a diagnosis
### Diagnostic Yield with Exome Sequencing

<table>
<thead>
<tr>
<th>DISEASE CATEGORY COHORT</th>
<th>TOTAL # OF PATIENTS</th>
<th>DIAGNOSTIC RATE</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal abnormalities</td>
<td>30</td>
<td>10%</td>
<td>Carss et al. 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hum Mol Genet*</td>
</tr>
<tr>
<td>Severe intellectual disability</td>
<td>100</td>
<td>16%</td>
<td>de Ligt et al. 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N Engl J Med*</td>
</tr>
<tr>
<td>Sporadic severe early-onset epilepsy</td>
<td>264</td>
<td>17%</td>
<td>Epi4K Consortium 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nature*</td>
</tr>
<tr>
<td>Suspected mitochondrial disorders</td>
<td>102</td>
<td>22%</td>
<td>Lieber et al. 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neurology*</td>
</tr>
<tr>
<td>Childhood neurodevelopmental disease</td>
<td>118</td>
<td>27%</td>
<td>Dixon-Salazar et al. 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sci Transl Med</td>
</tr>
<tr>
<td>Pediatric-onset ataxia</td>
<td>28</td>
<td>46%</td>
<td>Sawyer et al. 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hum Mutat*</td>
</tr>
<tr>
<td>Hereditary spastic paraplegias</td>
<td>55</td>
<td>75%</td>
<td>Gaia et al. 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Science*</td>
</tr>
<tr>
<td>Retinal dystrophy</td>
<td>33</td>
<td>76%</td>
<td>Abu-Safieh et al. 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Genome Res*</td>
</tr>
<tr>
<td>Genetics laboratory cohort</td>
<td>250</td>
<td>25%</td>
<td>Yang et al. 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N Engl J Med</td>
</tr>
<tr>
<td>Genetics laboratory cohort</td>
<td>500</td>
<td>37%*</td>
<td>Ambry Cohort Data</td>
</tr>
</tbody>
</table>

*Includes novel gene findings

ExomeNext-Rapid is available when you need an expedited result to immediately impact medical management (like the NICU). Almost half of the neonatal samples we have tested to date have identified a diagnosis.

**When to Consider ExomeNext**

- **CLINICAL EVALUATION**
  - Medical history
  - Family history
  - Symptom evaluation

- **TARGETED TESTING**
  - Chromosome analysis (microarray, karyotype)
  - Single gene tests
  - Specialized gene panels

**EXOMENEXT**

In the absence of other clinical indicators, this testing strategy could be considered. Clinical evaluation(s) may also suggest that ExomeNext is a more appropriate initial step.
The First 500 Exome Tests at Ambry

**POSITIVE FINDINGS**
- 84% pediatric patients, 16% adult patients
- 23% were within newly characterized genes (2012-current)
- 6% had “dual” diagnoses found by exome sequencing testing
- 2% of causative mutations identified were deletions/indels > 40 nucleotides

**NOVEL GENETIC ETIOLOGIES IDENTIFIED**
- Found in 7-8% of patients; extensively evaluated before reported
- Clinical significance of many corroborated by subsequent scientific publications

**Data Sharing**
In 2016 we launched AmbryShare, our data-sharing program that includes one of the largest public exome sequencing databases of human genome (exome) sequencing data. It contains 10,000+ anonymized aggregated genomes (exomes) of consenting patients with disease. This dataset is intended to be utilized for the medical research community in an effort to better understand disease. As well, we have always shared de-identified data with research collaborators and public databases, such as ClinVar. More details can be found at ambrygen.com/exomenext-data-sharing.

**Family Centered Analysis**
ExomeNext is a family centered analysis process. Optimize your diagnostic rates and turnaround time by submitting trio samples and samples from additional first degree relatives. Testing additional relatives (beyond the trio) is often very helpful, and something we offer.

For specific guidance from the medical literature (Biesecker LG and Green RC, N Eng J Med., 2014) about which family members to select for exome sequencing, please visit ambrygen.com/exomenext-faq.
Gene Coverage

We know you are interested in gene coverage as it applies to your clinical scenario. To help, we have created an Interactive Gene Coverage Tool that displays the consensus coding sequences (CDS) covered by ExomeNext’s platform. This helps you know if ExomeNext or ExomeNext-Rapid is a good fit for your patient before you order the test. The Tool can be found at ambrygen.com/resources/exome/search_coverage.php.

Exome Sequencing with Raw Data Only

We offer two options to order exome sequencing without clinical reporting. These test are run through our standard exome workflow and raw data are provided. Please contact us regarding pricing and logistics.

<table>
<thead>
<tr>
<th>OPTION</th>
<th>SAMPLE TYPE</th>
<th>TAT**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Exome sequencing and raw data</td>
<td>DNA or whole blood</td>
<td>10 -15 weeks</td>
</tr>
<tr>
<td>2. Exome sequencing, filtered variant list, and raw data*</td>
<td>DNA or whole blood</td>
<td>10 -15 weeks</td>
</tr>
</tbody>
</table>

* Filtered variant list provided in Microsoft Excel file format
** 10-15 week TAT is for projects with 10 samples or fewer

Three Steps - From Samples to Report

SAMPLE SUBMISSION

ExomeNext sequences an informative trio of first-degree relatives, (usually the proband and his/her biological parents) to achieve estimated turnaround times.

ANALYSIS AND REVIEW

Variants are filtered through our in-house bioinformatics pipeline and analyzed. Each genetic alteration is reviewed to determine its pathogenicity and gene overlap with your patient’s clinical symptoms. Candidate alterations are chosen for co-segregation analysis. The mitochondrial genome is also analyzed for characterized mutations.

REPORTING

Each case goes through several levels of medical review, and a report is issued. Each of our reports is tailored to the proband, and involves a comprehensive literature review and analysis. Raw data are also available on request.
Primary Report

Any genetic alteration that may be contributing to your patient’s described clinical phenotype is reported on the Primary Report. Below are result types that may be found on a Primary Report:

<table>
<thead>
<tr>
<th>CHARACTERIZED GENETIC ETIOLOGIES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Clinically relevant alteration(s) detected</td>
</tr>
<tr>
<td>Likely Positive</td>
<td>Alteration(s) with likely clinical relevance detected</td>
</tr>
<tr>
<td>Uncertain</td>
<td>Alteration(s) of uncertain clinical relevance detected</td>
</tr>
<tr>
<td>Negative</td>
<td>No clinically relevant alteration(s) detected</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NOVEL GENETIC ETIOLOGIES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertain, Strong Evidence</td>
<td>Alteration(s) of potential clinical relevance detected</td>
</tr>
<tr>
<td>Uncertain, Moderate Evidence</td>
<td>Alteration(s) of potential clinical relevance detected</td>
</tr>
<tr>
<td>Negative</td>
<td>No alteration(s) with potential clinical relevance detected</td>
</tr>
</tbody>
</table>

Notable findings: these are alterations of potential interest in characterized genes that do not currently meet criteria for reporting as a primary result but cannot be ruled out entirely. If identified, notable findings will be included in the supplemental pages of the Primary Report.

Secondary Findings Report

Secondary findings analysis and reporting are an option included with ExomeNext and ExomeNext-Rapid and reported separately (Secondary Findings Report). Secondary findings include mutations in genes unrelated to your patient’s indication for testing. Secondary findings are available for the proband and, if applicable, family members included in the ExomeNext trio.

1. The American College of Medical Genetics and Genomics’ (ACMG) recommended reporting secondary findings among 56 genes. This option is included in the price of testing. Each proband/trio family member can opt in/out of this analysis on the “ExomeNext Proband” and “ExomeNext Family Member” test requisition forms. A complete list of the ACMG recommended 56 genes can be found at ambrygen.com/exomenext-forms.

2. At an additional cost, there is an option to receive an expanded analysis of secondary findings, beyond the ACMG minimum list. To order the expanded option please complete the “Expanded Secondary Findings Request Form.” This and a complete list of the expanded secondary findings genes can be found at ambrygen.com/exomenext-forms.

3. Only pathogenic or likely pathogenic mutations as defined by ACMG or previously characterized pathogenic mutations are reported on the Secondary Findings Report. Variants of unknown significance and benign alterations are not reported.
Specimen Requirements

BLOOD
- Specimen: 6-10 cc blood in purple top EDTA tube (preferred) or yellow top citric acetate tube
- Storage: 2-8°C; do not freeze
- Shipment: Room temperature for two-day delivery

SALIVA
For ExomeNext, saliva will only be accepted for family members
- Specimen: Two Oragene saliva tubes
- Storage: At room temperature in sterile bag
- Shipment: Ship room temperature for two-day delivery

DNA
- Specimen: 20μg (10μg minimum) of DNA in TE or Qiagen EB buffer, 50-100ng/μl by pico green, OD 260/280 of 1.8-2.0 and 260/230 of >1.5. Send picture of agarose gel of DNA run with high mw genomic DNA standards, if available
- Storage: -20°C
- Shipment: Ship on ice or dry ice for next day delivery

CULTURED FIBROBLAST CELLS
- We accept cultured fibroblast cells only, in sterile plastic tube
- Amount: Three T25 cell flasks or suitable alternative at 80% confluence
- Storage: 2-8°C up to 72 hours; do not freeze
- Shipment: Ship overnight at ambient temperature, to arrive Monday-Saturday

Please visit ambrygen.com/exomenext for complete specimen requirements.

Required Forms and Documents
Please include the following when ordering ExomeNext to ensure turnaround times. These begin upon receipt of all samples, documents and insurance approval. All forms are at ambrygen.com/exomenext-forms.

1. ExomeNext proband Test Requisition and Consent Form
2. ExomeNext family member Test Requisition Form
3. Clinical history (clinical notes, summaries)
4. Family pedigree
5. Previous test results (including genetic tests, labs or imaging studies)
6. Letter of Medical Necessity (LMN) or Insurance approval (not applicable for institutional billing or gratis cases)

Note: Preauthorization is highly recommended and can greatly reduce insurance approval times. We can help you with this.
Ordering Testing Is Easy With Ambry

STEP ONE: ORDER TEST KITS
You can order our test kits three ways:

• Online at ambrygen.com/specimen-submission-kits
• By email at KitRequest@ambrygen.com
• By phone at +1-949-900-5798

STEP TWO: COMPLETE TEST FORMS (ONLINE OR HARD COPY)
Our General Test Requisition Form (TRF) is included in test kits. This and specialty-specific TRFs are online at ambrygen.com/forms. For a quick and seamless way to order testing from your computer or mobile device, our secure online client portal (AmbryPort2.0) is available (more details later in this brochure).

STEP THREE: WE CONFIRM INSURANCE BENEFITS FOR YOU
Ambry’s billing policy is to preverify insurance coverage (with or without patient sample) for genetic testing. We will contact the patient after their sample is received, if their out-of-pocket cost is estimated to exceed $100. You can also complete an Insurance Preverification Request Form and fax it to the Insurance Verification department at +1-949-900-5501 with a copy of the patient’s insurance card, if available.

We are contracted with many large U.S. health insurance plans. A list by region can be found online at ambrygen.com/insurance-lists-region. For any questions, please call the Insurance Verification department +1-949-900-5794 or email Preverification@ambrygen.com.

STEP FOUR: SHIP SAMPLE TO AMBRY GENETICS
Package sample(s) in the pre-paid shipping envelope according to our test kit instructions. All specimen requirements are found at ambrygen.com.

STEP FIVE: SECURELY TRACK SAMPLE AND RESULTS ONLINE
AmbryPort2.0 is a secure, HIPAA-compliant online client portal, and details about it can be found later in this brochure.
Ambry Expertise

SUPPORT
Board-certified genetic counselors, laboratory directors, and medical directors are readily available to assist with test selection, case reviews, and result interpretation.

INSURANCE
We are contracted with the majority of U.S. commercial insurances and Medicare. All out-of-network patients are treated as in-network to minimize out-of-pocket costs. Insurance, Medicare, and Medicaid coverage varies. Preverification is recommended.

PATIENT PROTECTION PLAN
Ambry’s billing policy is to preverify insurance coverage (with or without patient sample) for genetic testing. We will contact the patient after their sample is received, if their out-of-pocket cost is estimated to exceed $100. We are committed to working with you and your patients to make the genetic testing process as simple and cost-effective as possible, and our Billing Department is available to answer any questions your patient may have. Our Billing Department can be reached by phone at +1-949-900-5795 or billing@ambrygen.com.

PROGENY’S FAMILY HISTORY QUESTIONNAIRE (FHQ)
With Progeny’s FHQ, patients can complete their family health history at their own pace. Pedigrees are automatically generated and managed along with all submitted data. With no re-entry of data, referral and clinical decisions can be made immediately. Template FHQs are available for use in your clinic at no cost, or custom questionnaires can be designed for you. Visit progenygenetics.com/clinical/trial for more.

ABOUT AMBRY GENETICS
Ambry Genetics is a privately-held healthcare company with the most comprehensive suite of genetic testing solutions for inherited and non-inherited diseases. Since 1999, Ambry has tested approximately half a million patient samples benefiting 90% of all U.S. patients covered by public and private insurers. Ambry is dedicated to scientific collaboration by offering its rapidly growing database of anonymized genomic data (variant frequencies) free to the global medical research community to fulfill the promise of the human genome to cure or manage all human disease. Ambry is dedicated to the belief that human health should not be patented or owned, and genomic data should be freely shared so we can try to understand all human disease.

To order your complimentary sample submission kits, please contact:
Ambry Genetics
15 Argonaut
Aliso Viejo, CA 92656 USA
+1-866-262-7943
info@ambrygen.com

For more details about these tests, visit ambrygen.com

Complete references used to develop clinical content are available at ambrygen.com
AmbryPort2.0

AmbryPort2.0 is an online customer interface, which includes features such as:

- Insurance preverification and order submission
- Ability to get status updates and track samples
- Ability to print and/or download patient reports
- Patient-specific auto-generation of letters of medical necessity
- Patient signature form to easily obtain patient signature during clinic
- Ability to upload insurance paperwork, medical records and other patient-specific documents

CURRENT AMBRY CUSTOMERS

If you currently use Ambry Genetics and have an email on file with us, please attempt to login to your account by going to ambrygen.com and clicking the AmbryPort 2.0 login link on the upper right corner of any screen. Click reset password and insert your email address. If successful, a password reset will be sent to your email account. You can then change your password.

If you have any questions or concerns, please contact our Client Services department at +1-949-900-5500.

USER GUIDE

A user guide is available and can be found here at ambrygen.com/ap2

SYSTEM REQUIREMENTS

- Compatible with: desktop, tablet and mobile devices
- AmbryPort 2.0 works with: Safari, Chrome, Firefox, and Internet Explorer Version 8 or higher
- We recommend using the most current browser version to insure full functionality of the AmbryPort 2.0 interface

Now available: new enhancements to Patient List Screen and secure document downloading through AP2 -- visit ambrygen.com/ap2 for more details