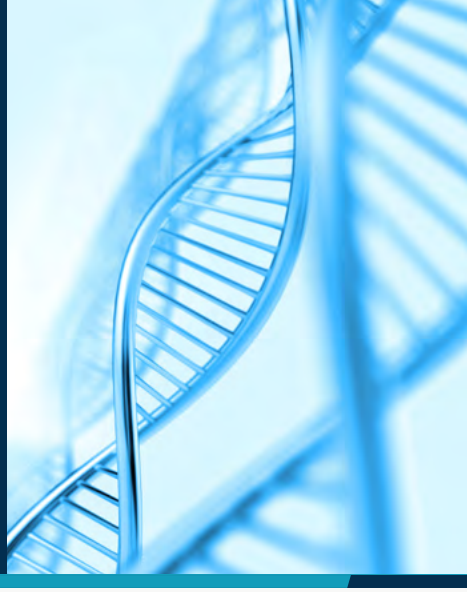
Worldwide Clinical Trials

# 8 Frequently Asked Questions About Genetic Testing in Clinical Trials



Genetic testing provides patients with a diagnosis for their illness, helps patients and family members to understand risks of developing diseases, and is often used as an entry criterion clinical trial participation.

As a leader in the use of genetic testing in clinical trials, particularly in rare disease trials, we have engaged in many conversations with sponsors about how to utilize genetic testing and the concerns associated with them. Our Derek Ansel, MS, CGC, Vice President, Therapeutic Strategy Lead, Rare Disease, provides answers to a few of our most commonly received questions around genetic testing.

## 1 What are the benefits and limitations to using genetic testing?

Genetic testing may help confirm a clinical diagnosis, help predict disease prognosis and progression, facilitate early detection of symptoms, allow for family planning and genetic counseling, inform optimal treatments and therapies, and/or promote enrollment in clinical trials. However, genetic tests can be expensive and may not be covered by insurance.

In some cases, the gene associated with a patient's condition may not yet be discovered or included on the test ordered and the interpretation of genetic variants may change over time as new information is uncovered. A positive molecular diagnosis does not always mean the individual will develop a disease, and it may be difficult to predict how severe symptoms may be. While the Genetic Information Nondiscrimination Act (GINA) prohibits discrimination by health insurance companies and employers based on a genetic test result, GINA does not apply to life, long-term care, or disability insurance.

## 2 Can prior genetic testing results be utilized in a trial, or should a new genetic sample be taken before participating?

Using existing genetic tests in a trial depends on the program, protocol (including eligibility criteria), and the scope, performance, and outcome of the genetic test. It is important to consider the type of testing performed (e.g., single gene testing vs comprehensive panel), the reportable range (e.g., genotyping for known variants vs sequencing only vs sequencing and concurrent deletion/duplication analysis), and whether the interpretation of the genetic testing results may have changed over time.

To ensure genetic testing results were obtained using the latest sequencing technologies and interpretation framework, it may be prudent to have all participants undergo a centralized genetic testing service prior to enrollment. If this is not feasible, review of historical test results by a genetics professional can be performed, however it can take a considerable amount of time to properly review genetic test results and interpret them in the context of the participant's clinical findings.

## 3 What is the difference between a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory vs a research laboratory?

The Centers for Medicare & Medicaid Services (CMS) regulates all clinical laboratory testing performed on human samples in the US through CLIA. CLIA was developed to ensure quality laboratory testing and accurate, reliable, and timely test results via quality systems, proficiency testing, personnel requirements, and laboratory inspections. Research laboratories are typically exempt from CLIA standards and may not have the same quality systems or laboratory and personnel requirements in place. Non-CLIA research laboratories are unable to return results that could be used "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.

## 4 Why is the turnaround time for whole-genome sequencing and whole-exome sequencing (WES/WGS) longer than a single-gene or panel test?

Single gene and panel tests are typically performed via high-throughput assays that target a specified number of genes. Identified variants are interpreted and reported according to the laboratory's policy. In contrast, WES/WGS performs sequencing on the entire exome (>18,000 genes) or genome, which requires more time for sequencing, interpretation, and reporting because all identified variants must be considered in the context of the patient's indication for testing.

## 5 What's the process for variant classification and reclassification?

Most clinical genetics laboratories follow the guidelines set forth by the American College of Medical Genetics and Genomics and Association for Molecular Pathology (ACMG–AMP). Population frequency data, variant type, clinical observations, experimental studies, and indirect and computational evidence are all utilized to classify variants into one of five categories (benign, likely benign, uncertain significance (VUS), likely pathogenic, and pathogenic). When new information is available, a variant may be reclassified (e.g., from VUS to pathogenic) and if the new classification is clinically significant, an updated report is provided to the ordering clinician.

## 6 Why should you use a centralized genetic testing provider for a clinical trial?

By using a centralized provider, each sample is processed and analyzed at a single laboratory using the same assay methods and interpretation and reporting guidelines. Further, using an experienced centralized genetic testing vendor avoids classification discrepancies between laboratories, and it reduces the logistical burden at the site level as all samples go to the same laboratory.

## 7 What should a sponsor consider when looking to leverage a centralized genetic testing provider for a clinical trial?

There are many laboratories that offer similar services, so selecting a single provider can be a daunting task. Some things to consider when selecting a laboratory include:

- Testing turn-around time
- Reflex strategy, as appropriate
- Certification, pending the final country strategy
- Diagnostic report sign-off procedures and if the report has all protocol-required elements
- Appropriate test validation protocols, including test methods & SOPs for lab qualification
- Appropriate technology (methylation analysis, FISH, NGS, etc.)
- Laboratory-obtained complete list of reported disease-causing mutations in the gene
- Coverage and read depth of the gene in question
- Variant reporting

Lastly, the decision to return test results to patients may impact the laboratory used in a clinical trial setting.

## 8 What happens once a sample is received?

Once a sample is received, DNA is extracted and the requisitioned test is performed via next generation sequencing. Each variant identified within the reportable range of the panel is reviewed and interpreted by an expert team of scientists, genetic counselors, and laboratory directors, and a final clinical report is returned to the ordering clinician approximately 10-21 calendar days after sample receipt.

While we've answered a few of the common questions received about genetic testing, there are many misconceptions around the use of genetic testing in the clinical trial setting. To discuss your specific questions or how you could leverage genetic testing in your trial, please contact us.