Worldwide Clinical Trials

When Genes Speak: Making the Decision to Share or Withhold Failed Screening Results

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The responsibilities of sponsors regarding additional testing and disclosure of genetic screening results to patients and their families are ambiguous, particularly when the findings do not influence medical treatment, rendering clear guidelines essential. At Worldwide, we often discuss this issue with sponsors of trials requiring patients with a rare genetic disease. As genome-wide association studies for non-rare diseases become more prevalent, these questions will arise more frequently. For instance, if a patient with known Alzheimer's disease (AD) screens negative for a specific apolipoprotein E variant that the study focuses on, should the study team inform the patient or explain why they were not eligible for the trial? The best course of action depends on various factors, such as the disease or population under study, the relationship between genotype and phenotype, the associated risks, the potential impact on care, the test itself, and specific parameters of the testing laboratory. Seeking expert advice to plan these trial design elements from the outset can save sponsors significant time and effort in the long term.

Best Practices & Considerations

Implementing genetic testing in the clinical development strategy involves many topics, including:

- The type of test used
- The country in which the clinical trial is conducted
- Decision to disclose the results
- The principal investigator's role in the choice
- Site communication regarding expectations on genetic result sharing for non-enrolled patients who lack a route for follow-up
- Genetic counseling services and providers
- Ensuring that unenrolled patients' clinical trial experience matters
- Coordinating parties responsible for result disclosure and protocol for result delivery
- Setting expectations for the level of assistance patients will receive from their clinical research organization

Rationale for Non-Disclosure of Genetic Test Results to Clinical Trial Patients

The country where researchers conduct the study most directly impacts decisions regarding results disclosure. In the U.S., the FDA and HHS regulations do not mandate or prevent the return of individual research results or results that contain incidental findings. In the E.U., there is a patchwork of regulations that support participant access to data, and although many countries may strongly prefer the return of results, none fully mandate it.

There are often valid reasons to withhold genetic test results from participants. However, these reasons do not apply to cases where a clinically significant or well-known genetic variant would necessitate changes in disease management. Instead, the disclosure discussion typically pertains to the gray area involving variants whose significance is unclear or uncertain.

From an ethical perspective, it might seem that trials should disclose any genetic results uncovered during a trial to patients. However, the decision should also weigh the ethics behind providing potentially confusing information that does not affect the patient's medical treatment. Patients and families may struggle to fully comprehend that results do not always affect treatment management processes. In such cases, shared knowledge provides no net benefit and instead can create doubts, concerns, and even confusion around the patient and family's risk level.

Beyond the patients, disclosure increases site burden, mainly because it requires a role as a point of contact responsible for addressing any complications if patients need additional support following information delivery. Proper disclosure requires support from doctors, site staff, or genetic counselors, all of whom have limited resources to begin with.

There may also be strategic reasons to omit genetic status result sharing. Patients in rare disease trials are often geographically dispersed, so logistics and regulatory expectations for result reading and patient communication vary from country to country. For example, Germany requires a physician to order genetic testing and read the results to patients — they permit no other medical professional. By comparison, the U.S. allows genetic counselors to share, but genetic counseling is not a uniformly recognized profession across the world. These inconsistencies make creating a standardized protocol for conveying genetic results challenging.

Factoring in Investigator Expertise & Experience

If the genetic test checks all requirements for disclosure, our standard recommendation is to leave the decision to individual investigators' discretion, refraining from explicitly including disclosure in the protocol. This suggestion is particularly valid in large studies, as sites have widely varying degrees of clinical research and genetic testing expertise and experience. Some sites may not have the resources or expertise to address patient concerns with the required care and detail. Some sites may not be fully informed about the lab's requested tests and the significance of the results. Sharing results with patients without adequate resources for proper dissemination would be unethical. With AD, for example, a site would only test their patients within the context of a clinical trial, rendering them without sufficient capacity or understanding to disclose genetic testing results to patients accurately. Providing genetic counselors for every screen fail (SF) patient is an ineffective and costly option — counselors are scarce, regardless of the previously mentioned global differences.

Guide Sites With an Experience-Based Strategy Factoring Location, Disease, & Population

Careful planning enables sponsors to support the delivery of genetic test results in various ways. For instance, although there is no standard regulatory requirement to return these results, working with the latest information on local standards fosters effective strategy development. A customized approach can leverage the site or physician's familiarity with local regulations. This method also allows those closest to the patient to address any specific ethical considerations on a case-by-case basis.

Other questions that require attention include the level of information included with the patient informed consent form (ICF), the protocol, and how to support investigators directly. At Worldwide, we apply our experience and understanding to help sponsors make these decisions depending on the situation. As a rule of thumb, considering ethics board preferences and patient concerns surrounding transparency, it's crucial to be prepared with a clear rationale for disclosure decisions.

Justification for Providing Genetic Test Result Disclosures

Trials should disclose a genetic variant if it impacts care management, but it becomes unclear if a drug focused on the given variant succeeds in the future. For example, if approved, AD drugs in Phase III readouts could change clinical management for patients with specific variants. Therefore, depending on the indication, preserving genetic information may be worthwhile. Even if it has no bearing on treatment now, it could in the distant future, pending drug approvals and scientific advancements.

In the rare community, patients tend to have ownership over their information — they want to know their variant at the time of SF in the trial. Disclosure directly to patients is an option, but this angle requires a sponsor to predetermine the requisite resources. Patients are increasingly interested in learning these data and more fully understanding the biological underpinnings of their conditions.

If opting not to share the information, sponsors must prepare a rationale for why sharing is not advisable. If the test is still undergoing research, providing a commercial genetic test as a follow-up could be beneficial. Additionally, if a genetic finding is diagnostic and needs a follow-up, even though the patient will not enroll in the trial, sponsors should consider who is responsible. This scenario includes investigating whether there are any legal mandates on reporting. For example, in Spain, researchers are legally obligated to return results in serious, actionable findings, even against participant preferences. If the site is responsible, the sponsor must establish whether they need to provide any assistance.

All these instances represent various case-dependent scenarios. At Worldwide, we apply our experience working with such cases to help our partners sort through the contingencies and plan operational logistics for these aspects.

CLIA Compliant Laboratories for Genetic Testing

Laboratory selection is an essential piece of every genetic testing strategy. From the whole trial standpoint, it is crucial to vet laboratories appropriately. Questions to ascertain whether a lab can fulfill the protocol's screening and reporting requirements include:

- Certification
- Diagnostic report sign-off procedures
- Test validation protocols
- Test methods and standard operating procedures for lab qualification
- Laboratory-obtained complete list of reported disease-causing mutations in the gene
- Coverage and read depth of the gene in question

Selecting the wrong lab is unfavorable and can contribute to genetic test results and complications with proper sharing. Labs often lack uniformity in reporting their results and may differ in interpreting a given mutation as pathogenic or a variant of uncertain significance. Sites need this information for screening; if the reporting does not match the protocol's intentions, investigators may enroll or deny trial patients incorrectly. Perhaps more troubling is that if the site informs patients about their results from these inaccurate interpretations, some sites may be inconsistent with their enrollment, especially if using more than one laboratory. If a trial reports results to participants, the laboratory needs to be CLIA-certified in the U.S. Similar requirements are also required in the E.U. (ISO 15189).

Managing Public Perception: The Importance of Every Patient's Clinical Trial Experience

In some cases of genetic testing, even if deciding to withhold results, simply "dropping" the patient after SF is an unacceptable response. For example, genetic test results contradicted previous testing information reported to a patient in one of our studies. The patient was confused about their condition and armed with many questions. In this case, protocols must consider the level of the sponsor and the PI's responsibility toward that patient, especially if the PI is not involved in the patient's usual care. Whether a patient ultimately enrolls in a trial or not, how they feel when they separate from the clinical trial has a ripple effect on enrollments for all trials. Patients often talk and, especially with rare diseases, have a tight-knit community; patients can share one bad experience widely, which can negatively impact clinical trial enrollment in the future.

"Helicopter research" should be avoided at all costs. Patients who feel that the study team came in, collected their data, and left without providing any benefit or explanation will likely feel exploited. In alignment with the FDA's goal to better incorporate the patient voice in drug development and decision-making, trials must address the needs of patients and their families. The expectation of learning the results and the possibility of free testing for potentially affected members may have influenced the patient's decision to participate in the trial. Sponsors must consider these expectations and evaluate the benefits of providing follow-up that will meet them, even for patients who do not pass the screening period.

Ultimately, sponsors need to develop a plan around genetic disclosure or non-disclosure in context with the disease and respective population. As an experienced CRO, we can help partners consider how given scenarios will play out with patients and sites. We can formulate a strategy to address these questions and develop a plan before engaging patients.

The Who & How of Genetic Screening Disclosure

While we generally recommend non-disclosure, there may be instances where it is appropriate. However, a customized approach that allows for site discretion is necessary. There is no regulatory guidance on the responsibility or methodology for delivering genetic testing results. However, disease-specific recommendations have been established, such as the excellent process developed by the Alzheimer's Prevention Initiative Generation Program.

Sites are not always familiar with genetic testing, meaning that sponsors and CROs must communicate a clear policy on genetic counseling and disclosure procedures. For a large study, multiple visits with a genetics expert are impractical.

Provisions for the policy should include the following:

- **Guidelines for selecting genetic counseling and disclosure providers:** local and centralized remote genetics professionals with qualifications conforming to local laws.
- **Pre-disclosure education materials:** remotely accessible materials for self-directed learning, such as videos and brochures.
- **Genetic counseling and disclosure materials:** study-specific handouts and talking points that ensure a uniform experience for patients, regardless of provider expertise.
- **Outline of genetic counseling session:** an ordered list of covered content.
- **Follow-up call:** communication to ensure patients feel alright after disclosure.

This process requires one visit, reducing the burden on participants and the site. It ensures that patients receive the necessary information, regardless of the experience level of site personnel, and includes follow-up. We can assist in adapting a suitable framework to the specific needs of a given clinical trial. Although preparation is required, having a framework in place ensures consistency in genetic counseling and disclosure.

Big Picture

Sponsors should consider their genetic testing strategy long before the clinical trial starts. This strategy should include a plan for if and how to divulge genetic information to patient volunteers if it has no immediate bearing on medical management.

The strategy should include:

- The rationale for decision on divulging
- The related protocol language
- The ICF language
- Items discussed with the investigator
- Items the investigator should discuss with prospective patients
- Criteria for lab selection
- Navigating international laws regarding which healthcare professionals can divulge genetic information

Each genetic testing situation is complex and unique, requiring a customized approach. Worldwide has broad experience with genetic testing and can help you craft a strategy that seamlessly fits into your overall development plans. Reach out to our experts today to discuss your genetic screening needs for your next clinical trial.

References

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