COMMENTARY: The right way to use genetic information in clinical trials

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WHEN A PATIENT receives a drug or therapy, the outcomes can vary widely from good to poor, or even result in an adverse event. These outcomes may appear to occur randomly, but most variability in treatment response can be attributed to personal underlying differences. For many diseases, genetic susceptibility factors account for much of this variability.

Take the case of PARP inhibitors for breast cancer, for example. Early studies of PARP inhibitors for late-stage, triple-negative breast cancer failed to show a clear benefit. These were large, well-designed randomized studies. Later clinical trials of PARP inhibitors, in patients with BRCA-positive breast cancer, were highly successful. The difference? The early studies failed to stratify trial patients by their underlying genetic cause of disease.

As this example shows, when differences in genetic variants are accounted for in clinical trial design, interventional trials can become much more successful for particular patient groups. To the extent possible, patients can receive therapy tailored to their own individual biology. This is known as personalized medicine, and it is taking hold for many diseases with strong genetic predispositions, such as breast cancer and heart disease.

In reality, almost every disease can be better treated through some degree of personalized medicine. Today, genetic risk factors are known for most common diseases. With personalized medicine, drugs and therapies can be targeted toward the genetic makeup of an individual rather than the disease as a whole. With targeted treatments, each of the groups may benefit.

Personalized medicine is proving to be extremely effective, but the clinical trial protocol for incorporating and utilizing this genetic data is complex. Traditional clinical trial models do not factor in the complications that arise with the incorporation of genetic testing, processes or handling of the data itself.

It's complicated

For many physicians in clinical practice, genetic testing can feel daunting or even confusing. Because they may not feel comfortable ordering genetic testing or have access to genetic counselors, physicians often avoid participating in the referral process for these types of clinical trials. They may not be aware of the variety of resources available to them as they consider genetic testing for their patients. There can also be misconceptions with trial design or the anticipated process associated with the clinical trial. When investigators decide they want to participate in a study utilizing genetic testing, many assume that all they need to do is add a genetic test to the initial screening period.

It can be much more complex than that.

The first challenge is identifying qualified patients. For trials aiming to target patients with rare diseases or rare variants associated with more common diseases, the right patients may be hard to reach. By definition, these patients are rare, and located throughout the country. They won't be clustered near major medical centers or clinical trial sites in major areas. In addition, a huge number of patients may need to be screened during the patient identification process. For a variant that is only found in 1 to 2 percent of the population, more than 15,000 patients will need to be screened to identify 300 qualified patients.

Genetic testing for a clinical trial or natural history program is frequently completed as a pre-screening procedure, which may actually extend the screening period compared to a more traditional clinical trial. The genetic testing often takes longer to return results than a common laboratory panel. Once the results are returned, a genetic counseling session needs to be set up and if the patient tests positive for the specific variant, then additional screening procedures can be completed to see if the patient actually qualifies for the specific study being investigated. Since genetic data can be unfamiliar and confusing, patients and families often have questions and need someone to explain their results. Furthermore, the patients who test negative for one trial may still qualify for another clinical trial, focusing on other genetic variants. High-touch patient engagement greatly increases the likelihood of patients remaining interested in future clinical trials.

Genetic counselors are a crucial part of the equation to help patients understand their genetic test reports, and to avoid misinterpreting their genetic data. As genetic testing becomes more common in clinical trials, the need for genetic counselors will increase. It seems unfeasible that genetic counselors can be placed at every clinical trial site, and the shortage in personnel suggests this won't be remedied anytime soon.

Implementing genetics effectively

To successfully develop personalized therapies, operationalizing these trials may need to follow a different path than the traditional clinical trial model. The following considerations will help trials do so successfully.

Genetic testing choice: When planning a clinical trial, sponsors need to consider the right genetic test not only for that specific trial, but for the patient population. A small test for a specific gene will require fewer resources and may provide researchers exactly what they need. However, for a disease with multiple possible underlying causative genes, a small and specific test isn't likely to get a lot of buy-in from patients and providers. In addition, patients who test negative multiple times across a series of different small panels, using very small targeted tests, frequently report pessimism and give up on ever being able to qualify for a clinical trial. Patients and providers are more likely to want to participate in a program that offers more comprehensive genetic testing, but larger tests can return uncertain and confusing results. Choosing the right size and scope in genetic testing is a balancing act. Utilizing genetic experts in the design and implementation of clinical trial screening programs can ensure that these issues are thoughtfully considered and optimized.

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Genetic counselors: Genetic counselors are the key ingredient to a successful use of genetic testing and stratification in clinical trials. Genetic counselors can be beneficial in many areas such as patient and provider education, engagement and retention. They can set appropriate expectations regarding the kind of information the test will provide, and they can also provide personalized education on test results. Telephone-based genetic counseling can enable sponsors to provide this level of support for patients and physicians all over the country, regardless of where a specific patient is actually sitting.

Education: Recently, the National Academies of Science, Engineering and Medicine recommended that clinical studies return trial results to research participants in a thoughtful and supportive manner. But providing genetic information to participants who may not know how to understand or interpret their results isn't empowering if they aren't also provided with the tools to use that information to make decisions about their health and their family's health. It's essential that genetic counseling is accessible to empower participants to make informed decisions about the results of genetic testing. This is one of the major benefits genetic counselors can provide. Genetic information can be confusing, and it can have a lot of implications. Even negative test results can be confusing for patients. For example, if someone tests negative for mutations in BRCA1 and BRCA2, they need to know they may still be at increased risk for breast cancer, and use that information to make informed decisions about future care.

Continuous engagement: When genetic counselors spend time discussing the results with the patient, the patient fully understands the implications of their results for not only them, but also their family. This can open a pathway to finding more subjects for the trial through family members. In addition, educating patients about negative results in addition to positive results allows them to feel more engaged and think of clinical trials in a positive way. This will keep the patients who test negative engaged in case they qualify for a future clinical trial.

Site selection: With rare diseases, patients will be geographically distributed. When a sponsor is limited to a small number of sites, they should focus their sites on areas where there are specialists already referring patients to genetic testing for that disease. The site should be close to those referring providers. In addition, telephone-based genetic counseling allows patients to be tested regardless of geographic location, so screening is not limited to select areas.

The future of personalized research

This is only the beginning of the era of personalized medicine. But it is already clear that when diseases are treated as a single entity, regardless of the underlying genetic causes, any one single therapeutic approach is highly likely to fail. The treatment of almost every disease can be improved by some sort of personalization if patients are stratified by their genetic cause of disease. Clinical trial protocols need to reflect that. As a result, treatments that will be developed in trials will be more efficient and targeted in the future, and benefit all patients. ■

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