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Genetics in Precision Medicine: A Data Management Issue

By Bill Myers

The devil, as the old saying goes, is in the details.

The growing influence of genetic testing in clinical trials has offered patients seemingly miraculous results. But it also has the potential to bedevil researchers who don't carefully manage the enormous amounts of information that genetic testing can bring.

About half of all drug trials — and nearly 80 percent of oncology trials — are already collecting biomarker and genetic data from patients to offer targeted therapy, says Ken Getz, chairman of the Center for Information & Study on Clinical Research Participation and an associate professor at Tufts University.

The intricate information can be invaluable but also daunting, Getz says. He notes that a traditional Phase II study collects about a million data points; add genetic testing to the mix and you're dealing with as much as five times that amount. And the challenge is likely to grow, says Getz, pointing out that sponsors expect to increase investments in genetic testing by up to 50 percent over the next three to five years. "Our pipelines have really changed and we all sense it," he says.

The Consumer Effect

Another potential hitch is that many trial participants – and even researchers — may have skewed perceptions of genetic testing, thanks to the soaring popularity of private consumer companies like Ancestry.com and 23andMe, says Jill Johnston, president of Site Activation Solutions at WCG Clinical.

"In genetics, the more information you look at the more noise you're going to hear."

—Tricia See, genetic counselor, InformedDNA

"A lot of people think about 23andMe and think, 'Hey, I'll just take a spit test, send it back to a lab and I'll get the results,'" Johnston says. And "a lot of these organizations think they're simply adding another laboratory test. [But] ... there are a lot of requirements that have to be thought out."

For instance, Johnston says she recently worked with a sponsor who wanted to offer direct-to-patient genetic test kits, unaware that local lab results won't pass regulatory muster. "You and I can't just walk into LabCorp and ask for a chemistry panel, even if you're willing to pay for it," she says.

Plus, even a successful set of tests can raise ethical questions.

Take dementia, for example. The search for drugs to prevent or slow cognitive decline often focuses on early-onset cases, which many researchers believe have a strong genetic component. That means when screening for potential recruits, "you're basically telling that patient, 'Okay, now we know this is something your family is at very high risk for,'" says Tricia See, a genetic counselor with InformedDNA.

There's also the matter of what sponsors should do if they stumble onto other findings during their studies. That is, if they test for one genetic variant and discover a subject may have an unrelated risk for another disease.

"That raises some huge ethical implications," See says. "Are you obligated to disclose that information?"

Operational, Not Academic

Johnston suggests one issue may be that sponsors view genetic screening "academically" rather than "operationally." For example, she says she recently worked with a sponsor that wanted to conduct a clinical trial on patients with a rare variant of an otherwise fairly common disease. The sponsor wanted to use genetic screening to locate potential recruits. But only 3 percent of the population has that variant, so they would have had to screen more than 15,000 people to find at least 300 for their trial.

As the sponsor mulled the effort, it realized that ballooning logistical problems were too great to overcome, including how to handle people identified with the variant but unwilling to take part in the trial. "What do you do with all the 'Nos'? You still want to have them engaged. And you still want to educate them about their condition," Johnston says.

To avoid potential pitfalls, See says that sponsors need to focus early and hard on exactly what goals they're hoping to achieve with genetic testing – and how to obtain them. That means figuring out how wide to cast their net. If searches are too narrow, participants' patience may wear thin. "How many times are they going to come back to

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a clinical trial for a single gene test," See asks. Make studies too broad and you risk ramping up costs and bogging down findings with piles of irrelevant data. "In genetics, the more information you look at the more noise you're going to hear,"
See cautions.

Getz says that he expects mounting questions as genetic testing becomes more prevalent. "The need to find specific genetic profiles for specific treatments creates a kind of long-tail effect on the research that's "pushing our trials away from the traditional community-based investigative side and into some of the larger clinical care settings, where you have a higher volume of patients as well," he says.

Johnson argues that part of the problem is that genetic technology is so new the industry hasn't fully grasped how to incorporate it into trials.

But that doesn't mean sponsors and sites have to give the devil more than his due. Johnston offers these tips to help introduce genetic testing to clinical trials successfully:

- **Plan ahead.** Considering using genetic testing? Start planning at least nine months or a year in advance. Among things to consider: Which kind of tests (SNPs? Panels? Whole genome?), costs (and whether tests are covered by patients' insurance) and how to process and disclose results.
- **Consider natural history.** Ask potential patients what they know about their family medical history – and think about this information "holistically." That is, store it for later use even if they're not eligible for a particular trial, keeping in mind they may be perfect for focus groups or in helping to design patient-centric protocols –and may become part of a registry for future trials. An added plus: This exercise can help educate those new to trials about their research value and, potentially, as a care option.
- **Team with genetic counselors.** It's critical to make sure patients feel supported during trials. Genetic counselors can address any concerns that arise and gently explain the process and manage expectations. They can also serve as recruiting vehicles. Patients with a genetic variant tend to be more engaged in their treatment and have relatives or know other patients with the same genetic glitch. "If you find a patient who's willing to come in, they can become the best advocates for your trial. That's one thing we don't get in traditional clinical trials," Johnston says, noting that this can dramatically reduce required screening.
- **Network.** Build relationships with local doctors. Sponsors haven't traditionally tapped this source for potential study subjects. But networking can be especially helpful with rare diseases and the demands required in precision medicine trials. "Patients are very, very comfortable with their own physicians," Johnston says. "We're going to have rely on a lot more physicians to be advocates for clinical trials."