Center for Genetics and Precision Medicine in Clinical Trials: A UNITED PARTNERSHIP

Q&A

by Jill Johnston and Karmen Trzupek

Under a strategic partnership, WCG and InformedDNA™ launched the Center for Genetics and Precision Medicine in Clinical Trials. This partnership unites InformedDNA's substantial genetics resources and industry leading team of >80 nationally distributed genetic specialists with WCG's global network of 550 experts in clinical trial optimization and its proprietary industry Knowledge Base™ that provides deep understanding of more than 90 percent of all industry-sponsored protocols.

Together, the partners have the capability to deliver unparalleled insights and guidance for the optimal application of genetics in clinical trials. Their partnership tackles the challenges of managing genetic information in trial and protocol design as well as harnesses the power of genetics to identify, recruit and manage patients in clinical trials. Perhaps as important is the care and attention these partners render to patients, bringing patient-centricity to life.

We asked Jill Johnston of WCG and Karmen Trzupek of InformedDNA to address several questions about supporting patients for genetic testing in clinical trial settings:

Q Let's start with the first question to Jill. What is the current landscape of genetic testing and counseling in clinical trials?

A Jill Johnston: We know there is a significant push in the industry toward precision or personalized medicine – for example, we see a larger percentage of clinical trials are incorporating genetic testing into their protocols over the past 12 months than in the preceding years (see **Table 1**). And we see even more trials in planning stages in the upcoming months.

The number of studies that are incorporating personalized medicine and tailoring medical treatments to the individual characteristics and genetic variants of patients is on the rise. We are seeing a significant percent of oncology-based programs that use this approach, but we're also seeing an increased use of this strategy for both rare diseases and more common medical conditions.

A Karmen Trzupek: Yes, you're absolutely right, Jill. For nearly 10 years now the FDA has approved more new specialty drugs than traditional drugs (see, e.g., interactive graphic for Number of orphan drugs addressing rare diseases approved by quarter[1]). Drugs for orphan and rare diseases make up the largest piece of that pipeline. When you think about that, it becomes obvious that genetic testing is important because a significant proportion of rare diseases have a genetic origin or contribution. There's a shift toward the development of therapies for these rare genetic diseases. The emphasis in this area has increased dramatically since the first FDA approved gene therapy about a year and a half ago.

Q Thank you both for that discussion. How is the industry addressing the need for genetics in clinical trials?

A Jill: Over the past several years, we have been seeing pharmaceutical companies develop clinical trial programs very specifically around genetic variants, whether for a common indication or a more rare condition. As this is happening, we're also starting to see how

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hard it can be to find, engage, recruit and retain these specific patients, often depending on the incidence of that genetic variant in a particular population. If it's a relatively low percentage of the total patient population, we might have to approach a larger pool of patients than initially planned or what we've traditionally forecasted for in a study that does not include finding patients with a specific genetic variant.

Unlike traditional clinical trials where you can run a radio ad or review a database and contact patients to see if they might be interested in participating in a clinical trial, a lot of organizations have to approach patient recruitment for a personalized medicine study in a completely different way. They are starting to think about how to mitigate the risk of difficult patient identification by planning earlier for a study, upwards of a year or two in advance of starting their clinical programs. Operational teams are attempting to find these patients much earlier than traditional studies. Otherwise they risk their enrollment completion timelines and the study will be delayed.

Furthermore, organizations can't afford extra time looking for patients through a traditional screening process. Instead, we've seen customers mitigate risk by starting a natural history program in advance of their later stage clinical trials. We have an example right now that Karmen is working on where they're doing a natural history study one and a half to two years in advance of when they anticipate their interventional clinical trials to start. These companies are able to start to build their foundation of the right patient population in advance of those trials so that when they do start enrolling for their clinical trials, they have an already engaged patient population from which those patients may choose to go into a clinical trial or remain in the observational natural history program. Early planning and engagement, in these cases, may save significant time later in the program.

Q How is the WCG/InformedDNA partnership addressing the need for genetics in clinical trials?

A Jill: We're using a two-pronged approach that focuses on both the scientific needs and the operational execution. When a program includes precision medicine, the sponsor typically has an expert they are engaged with that understands genetics, but many times that consultant is academically focused on the science and not necessary a pragmatic approach to operational execution. We can instead offer an advisory perspective – helping them get their head around how to set up a genetic testing program, what is appropriate to include in the genetic test panel, how to choose an appropriate genetic testing laboratory, how to adequately support patients and providers interpret genetic test results, etc.

The other part of the partnership's approach comes from the operational side. Through conversations between WCG, who has the expertise in clinical trial development, and InformedDNA, who has the expertise in genetics, we are able to provide direction on how these studies should be logistically executed. A lot of protocols give high-level direction as to how to execute the study, but we need to think about what's going to happen in various scenarios in the actual study. How are patients actually going to progress through the clinical trial – from initial engagement to protocol completion? How are we going to engage the treating providers in the field who manage these patients? How are these potential patients going to sign an informed consent? We often find that pharmaceutical companies and biotechs may engage the academic genetic specialist, but that person might not be accustomed to figuring out how to get that program started from an operational execution perspective.

Then we also need to figure out how to operationalize the trial so that the patient's journey is supported, and patients actually want to participate in the trial. From a site perspective, how are the sites expecting to engage with these patients? Do they have experience in managing genetic test results with patients? It is also different from other trials from a patient recruitment perspective. First of all, the genetic testing and results of that testing are much more sensitive than a typical laboratory result. What things need to be put in place so that everything has been thought through and that there's smooth sailing into and throughout the clinical trial?

What we find is that many groups are not thinking about all those operational details – how is it actually going to work in reality? That's where WCG and InformedDNA come together to help that customer think through the process and develop a pragmatic approach that is easy to understand and provides a clear work flow process of a patient's journey through the study.

Q Given that background, what challenges have you found with implementing genetic testing in clinical trials from the operational or tactical aspects of genetic testing and counseling?

A Jill: We know that smaller community hospital centers and some of the independent research sites may not have access to full-time genetic counselors or have limited, if any, experience with genetic testing in the way that we're talking about. Typically, in the past, those investigational sites may have chosen to pass on a study like this and let the larger independent health networks, academic medical centers, or institutions take on that type of work just because they didn't have the expertise in-house to support those trials. But potential patients don't necessarily sit in large urban centers or next to large institutions that may have traditionally been well-suited to do these clinical trials. We need to broaden our reach. These patients may be located anywhere across the United States or world, and new solutions to reach these patients have to be developed. We can support the pharmaceutical companies with advisory services, and the patients with appropriate genetic counseling because InformedDNA has developed a virtual telemedicine model to reach patients regardless of where they are located.

Table 1: Market for Clinical Development Phase II/III (outsourced) = $19.754B

Precision Medicine portion of the Clin. Dev (Phase IIb/III) Market = $6.9B	• In 2017, for the first time ever, personalized medicines accounted for over a third of all new medicine approvals at the FDA • FDA CDER approved 46 new molecular entities (NMEs) – new drugs, agents or therapeutic biologics – in 2017 • Of the 46, a total of 16 classified (35%) as personalized medicines, the most of any year, topping the 13 (out of 45) approvals in 2015
Precision Medicine Center of Excellence Market Size (3.5% of market) = $242M	• Citeline study found that 73% of all ongoing/planned trials using biomarkers are in oncology, and that 94% of all patient pre-selection/stratification trials are in cancer. • In a separate 2015 study, Tufts CSDD also found that oncology dominates personalized medicine R&D, followed by the neurology and cardiovascular therapeutic areas. In an industry survey, CSDD found that companies involved in personalized medicine reported that 73% of oncology compounds rely on biomarker data, while only 42% of all compounds rely on such data.

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A Karmen: What we do to address this need is what I often call the screening funnel. We start with helping community physicians recognize which patients would be good candidates for referral to genetic counseling and additional screening. We then perform a series of telephone-based genetic counseling sessions; we spend a lot of time with these patients and families. We take a detailed medical and family history for all patients and then determine the best candidates for genetic testing. Only those patients who meet more rigorous criteria undergo testing, and only a small subset of those patients test positive for the gene of interest. We also need to think about the patients who test both negatively and positively for the genetic variant. All patients, regardless of the test outcome, need to be treated with empathy and need help in interpreting their results.

We're also not relying on these community physicians to recognize ultra-rare diseases. We're partnering with them in such a way that we're helping them to recognize some of the symptoms of that disease and then making it very easy for them to refer those patients for evaluation. We can figure it out from there. Then only the patients with the genetic variants of interest get referred on to the large clinical research centers. This helps to manage both study resources and patient expectations, as patients who travel to clinical research centers often cling to the hope that they will qualify.

Q What are the tactical challenges of genetic testing in a clinical trial?

A Karmen: When pharmaceutical companies offer patients sponsored genetic testing as part of screening for their study, they often want to test for only the gene of interest for their study. But for a disease that is highly genetically heterogeneous and can be caused by over 100 genes, testing patients for only a few genes doesn't offer tremendous value to that patient community. Physicians frequently aren't motivated to order that very narrow testing if they know that only a small percentage of their patients are going to test positive.

Meanwhile, genetic testing labs have moved away from single gene testing toward panel-based testing – meaning the inclusion of many genes in one test. These tests offer the potential to identify the genetic cause of disease in a large number of patients. But there are risks associated with these large panel tests. One of the challenges is that our ability to perform this wide-scale genetic testing has far outpaced our understanding of the meaning of the results.

As a genetic counselor supporting clinical research programs, I work with clients to find the right balance between narrow-focused and very large panel testing and the interpretation of results. We work with our client partners to understand the patient community and develop a testing strategy that benefits all parties, the research program, physicians, and most importantly, the patients.

Q Can you address challenges particular to rare disease cases?

A Karmen: In a rare disease gene, we don't typically have a massive public database of patients who've been tested for that gene. Most of the pharmaceutical industry under-recognizes how much uncertainty can come out of a test report. They often picture test results yielding only positive or negative outcomes. But in reality, a test report may state, "This gene variant is of uncertain significance." You can imagine a patient or even a provider getting back a report with "variants of uncertain significance" in six different genes that are all somewhat related to the same broad clinical diagnosis. What do you do with that? That's certainly where we have a big role to play in our partnerships with clients. The very core of genetic counseling is supporting patients and families around obtaining a genetic diagnosis and understanding their genetic disease – so we are not just supporting patients and families, but really diving into the genetic testing. We look at the meaning of all those different variants and help patients and providers understand what is important (and what is likely just noise) and outline the next steps.

Genetic counseling also leads to a tremendous increase in patient engagement. I have seen so many individuals with rare diseases that are just hungry to understand their disease better. If you give them a clear positive result, even if they don't qualify for a current trial, that result still provides a lot of meaning, particularly in a disease area where there are so many genes that can cause the disease. Patients increasingly tell me they go to a conference and meet people who don't just say, "Oh, I have RP (retinitis pigmentosa)." They'll say, "Oh, I have RP from the MAK gene. What gene do you have?" They talk about the gene. That's because there's so much research that is gene-focused. Even if a patient doesn't qualify for a trial today, they understand that it's important to know "their gene" to follow the appropriate research.

Q In the course of that partnership, what lessons have you learned from your experiences either from the synergy or from being able to leverage each other to develop new capabilities?

A Jill: I'll start by noting that we're continuing to learn. One lesson we've learned so far through the partnership is that the industry as a whole, including clinical operations leaders at pharmaceutical companies and CROs, do not have a good appreciation of the challenges of running a precision medicine trial. It's a lot more upfront planning about how this study is actually going to work. We try to help them realize that they need to think more in advance and put in more planning well ahead of time than what they have traditionally done in a study that doesn't include genetic testing. We now know that we have to educate our industry a little more because this is relatively new approach for them.

Another lesson is that with all the consumer genetic testing services out there, clinical operations leaders may think that the process of obtaining and testing genetic samples is relatively simple. It's just another lab test or swab of the cheek. They may not be thinking about it in a clinical research setting – ensuring that the lab is CLIA-certified; how to properly consent patients; have a genetic counseling

Table 2: Lessons Learned

1.	Teach clients to think ahead and plan to build-in genetic testing and counseling before the trial starts – strategic, operational tactical, and a genetics' data and analysis plan
2.	Don't expect to find enough patients by traditional methods, precision medicine trials require much more upfront planning
3.	Consider setting up a natural history registry
4.	Trial constraints may require "patient funneling" – a series of patient screens to select those most suitable for a trial.
5.	Enroll enough patients to power statistics after funneling
6.	Prepare to counsel patients who are not selected for the trial as well as those who are selected for a trial
7.	Ensure that critical enabling technologies are well in hand, e.g., variant database, mobile connections, etc.
8.	Connecting with patients is the core of the function and creates highest value for the patients and the broader community
9.	The very core of genetic counseling is supporting patients and families around obtaining a genetic diagnosis and understanding their genetic disease – so we are not just supporting patients and families, but really diving into the genetic testing.

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discussion with the patients before and after that testing is done; how to return the results to patients during and after a study; and going through and challenging their internal SOPs or work instructions, which had been built for traditional studies.

A Karmen: We've also learned that some groups have an outdated notion that you don't have to return any data to participants from research-based genetic testing. Fifteen years ago, when I was involved in clinical and molecular research studies, we in fact could not return research results to participants. We have done a full 180° on that, where now the guidelines that came out last year from the National Academy state that you must have a plan in place for returning research results to participants, that research participants deserve that information, and they deserve it in a way that they understand it. We've learned that education needs to take place because many small pharma companies, but sometimes larger ones as well, often still maintain that outdated mindset. They think they can do any kind of research genetic testing they want on the back-end without results disclosure.

A Jill: Patient engagement and patient centricity are such hot discussion topics right now. The process and workflow for people who are engaged with including the patient voice in the clinical trial are often at odds with the clinical operations people who are just trying to get the study done in a simpler and more streamlined way. I always see that challenge between the two.

Others may not always be able to include the patient voice into their discussions, but Karmen and the people she works with bring a different perspective. They are speaking with patients in a much different way than a physician or study coordinator would in the confines of a clinical trial. They're getting to know those patients and the patients feel a very strong connection with them. Having the patient's view from the genetic counselor perspective helps bring another dimension of patient centricity or patient engagement to the conversation that may not have been there before.

Our role, to convey a result from a genetic test that may have long-lasting ramifications, requires that we need to think about that result from a patient engagement perspective. It's a totally different type of discussion that we need to think about how to deliver.

A Karmen: What often happens when pharmaceutical companies engage patients to include their perspective in their programming is that they only hear the perspective of the patients who are willing to be engaged. That's a small subset of the total patient population. It's important to think about how we can engage and support patients who aren't currently participating in the clinical trials and natural history studies.

We need to understand why these patients are not participating, the barriers to clinical trial participation, the concerns patients have, and what we can do to support the broader population. Especially in a rare disease, we need to understand these factors to address challenges and increase enrollment rates.

It's also important because sometimes a sponsor might think, "Well, we're getting pretty close to enrollment of our phase two trial, and we've gotten great feedback from a couple of the patients who've been really engaged with us." But, if that's successful, now the sponsor needs to prepare for a phase three study, that's going to be larger, and what if they have already engaged all of the really excited patients? The challenge then is to reach a broader patient population; they may still have a long way to go.

Q I'm also curious about patient advocacy. How do you see that relevant to the discussion on patient engagement and education we're having?

A Karmen: My absolute favorite part of my job is getting to work at this interface between the patient, the patient advocacy organizations, and the pharmaceutical companies developing therapies. I think the patient advocacy organizations are extremely important. We're doing a program right now in collaboration with the Foundation Fighting Blindness for patients with inherited retinal diseases. We're currently working with them on innovative ways to support genetic testing and genetic counseling and then help patients input clinical and genetic data into the patient registry. The purpose and the primary goal of that program is to accelerate the pace of clinical trial development and enrollment. We need to understand which patients have which genetic subtypes of diseases, so we can enroll patients broadly in trials.

We are also expanding efforts to look at more innovative ways to develop programs where we engage multiple different pharma partners, who are all working together in the same, or similar disease areas. How can we all work together, toward that common goal? That's quite different than the way the traditionally competitive pharma market functions. We are asking them to consider, "How can we all work together, with the patient advocacy organization, to support the whole community?"

Summary

The partnership between WCG and InformedDNA is working to create a system that incorporates both the patient voice and the operational voice; we summarize our lessons learned experience in **Table 2**. Our novel approach to genetic counseling supports not only our clients, but also our patients and their families by helping them obtain a genetic diagnosis and understand their genetic disease, the implications, and their options. We have learned that this requires us to think about clinical trials from both a patient engagement and operational perspective. Our high-touch and novel approach allows us to connect two different voices that are often at odds with each other to create a trial that is successful for all parties involved. JoPM

Jill Johnston is the President of Site Support and Management at WCG Clinical Services, which has partnered with a genetic expert services provider to support biopharmaceutical companies, CROs, institutions and investigator sites in designing and conducting clinical trials that use genetics. Here, she is responsible for creating transformational site activation solutions that stimulate growth, accelerate study starts, and maximize efficiency for those who perform clinical trials. She has more than 25 years of clinical research experience.

Karmen Trzupek is the Director of Clinical Trial Services at InformedDNA, which recently partnered with WCG Clinical Services to provide genetic services and expertise within clinical trials. She is a certified genetic counselor who specializes in supporting patients with rare genetic diseases. She works with biotech and pharma companies to develop precision medicine strategies, and to create and implement programs to identify and engage patients with genetic diseases and rare genetic variants in clinical trials. Karmen has worked in clinical genetics for 18 years.

Reference

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