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DECENTRALIZING PRECISION ONCOLOGY TRIALS:

OPPORTUNITIES AND CHALLENGES FOR IMPLEMENTING A PATIENT-CENTRIC MODEL

A GENOMEWEB/ PRECISION ONCOLOGY NEWS VIRTUAL ROUNDTABLE

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A cancer patient's best chance to receive biomarker-informed personalized treatment is often within a clinical trial. Traditionally, interventional trials require patients to travel to a designated trial site to receive treatment and for data collection. However, the costs, travel, and time required for this approach create barriers to participation for many of the patients who could benefit from these trials.

According to an estimate from the American Cancer Society, only about eight percent of cancer patients partake in clinical trials, and only about 27 percent have the option of joining a trial in their own community. Studies have also shown that a large number of late-stage oncology drug trials fail to enroll the necessary number of patients and close because they don't meet the target recruitment goal after three years or more.

But decentralized clinical trials – those that employ telemedicine, mobile apps, wearable monitoring devices, and local labs and imaging centers – may facilitate greater patient participation in research.

This GenomeWeb report is a summary of a Virtual Roundtable discussion, sponsored by PGDx, titled, "Decentralizing Precision Oncology Trials: Opportunities and Challenges for Implementing a Patient-Centric Model." In this discussion, panelists discussed how pharmaceutical companies and researchers are rolling out decentralized strategies, and how those strategies are improving enrollment and better serving underserved patients.

The discussion was led by Turna Ray, managing editor of Precision Oncology News. The panel included Jonathan Cotliar, chief medical officer at Science 37; Kristen Deak, associate director of clinical study genetics and molecular diagnostics at Duke University; Sameek Roychowdhury, medical oncologist and member of the Translational Therapeutics Program at Ohio State University Comprehensive Cancer Center; and Lee Schwartzberg, chief medical officer at OneOncology. Their discussion was followed by a question-and-answer session with the audience.

Challenges of Traditional Clinical Trial Design

Among the chief barriers to enrolling patients for site-based precision oncology clinical trials is that therapy targets like gene alterations or immune markers can appear very rarely across cancer patients, said Roychowdhury. If the small number of eligible patients do not live near the testing site, or if the logistics of joining the trial are too burdensome, the trial will not be able to recruit in the numbers required, and the patients will not be able to benefit from the experimental agent. "You've got to make an appointment, see a physician you don't know, travel to a big clinical research center, meet team members you don't know, navigate this giant campus versus the small office you're used to. There's a 25-page consent form, a long visit, screening appointments you have to travel for, extra exams," he said. "You may have to come back for a biopsy as part of this study, and you may have six- or ten-hour days."

Centralized clinical trials can also require biomarker testing at the trial site instead of accepting test results from elsewhere, Roychowdhury said. He gave an example of a patient who had tested positive for a KRAS mutation in a CLIA-certified laboratory.

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Roychowdhury referred the patient to a clinical trial across state lines that required multiple hours of travel. The trial required that the patient undergo additional testing for the mutation, which took three and a half additional weeks before the patient could begin treatment. "And people can't wait with metastatic or advanced cancer," he said.

Cotliar's company, Science 37, recently announced a trial called the ALpha-T trial in collaboration with Roche and Foundation Medicine. The study is investigating the ALK inhibitor alectinib – already approved to treat ALK-positive non-small cell lung cancer – as a treatment for other ALK-positive solid tumors. According to Roche, recruiting 50 eligible patients for this study with a site-based approach would require screening 25,000 patients and would take between seven to 10 years, said Ray.

Cotliar said that Science 37, along with Foundation Medicine, is helping Roche to employ a hybrid site-based/decentralized approach to the trial to improve enrollment. "This is not about whether a decentralized approach or a traditional approach is better or is worse. The way I look at them is they're not mutually exclusive, and they're both important aspects of drug development," he said. "If we can supplement what might happen at the site with a virtual cohort or a decentralized aspect to a trial, we get the best of both worlds, and we're able to find patients who are maybe willing and able and who live in relative proximity to where those clinical trial sites are active."

In-House Versus Send-Out Biomarker Testing

Biomarker testing for the ALplha-T trial is being performed centrally by Foundation Medicine, which provides send-out biomarker testing for hospitals, after which Science 37 steps in to complete the enrollment process. But Ray noted that many institutions are now considering whether to implement local biomarker testing in-house.

Duke University recently installed in-house NGS testing, said Deak. Her team weighed considerations such as test turnaround time, ownership of the test material and resulting data for biomarker research, and the ability to integrate the data with Duke's internal databases for trial matching. They decided to use assays from PGDx, validating the tests to ensure clinicians had the same experience they had with send-out test results. "The PGDx assay was also FDA cleared, so that provided us with a reimbursement path due to the announcement of some local coverage determinations," she said. "We hope that the assay being in-house will not only increase the number of patients that get the testing but also will increase our ability to match them with the right trial at the right time."

Schwartzberg said that OneOncology, which supports 11 community oncology practices throughout the country varying in size from under 10 oncologists to over 100, entered a non-exclusive partnership with Foundation Medicine for biomarker testing. This allows OneOncology to have many tests from many health systems performed by a single test provider. OneOncology's philosophy, Schwartzberg said, is to order biomarker testing at the first sign of advanced disease, meaning many patients with many cancer types are being tested. "We do have one practice that has begun to internalize testing. But, just like the experience at Duke, I would imagine, you have to have a certain volume to make that worthwhile, and it has to be a critical mass," he said. Additionally, in-house testing can require access to resources such as laboratory equipment and bioinformaticians that only the largest community hospitals have. Schwartzberg added that commercial testing labs have enhanced their testing processes to reduce turnaround time to return test results more quickly, as patients are often anxious for results and providers are anxious to begin therapy.

Challenges and Uncertainties in Decentralized Trials

The biggest challenges to decentralized trials, Schwartzberg said, are FDA regulations requiring a principal investigator to have direct oversight of the trial. "In fact," he said, "if there's ever an FDA audit, the first question they ask is, 'How many studies are you overseeing? And how do you ensure that you're seeing those patients?' That's almost antithetical to the concept of a decentralized trial." Schwartzberg said that FDA regulations for clinical trials will need to be fundamentally changed to improve decentralized trials.

Cotliar said that, while FDA and other regulatory body regulations can be improved, all the regulations and guidelines required to ensure high-quality trials can currently be fulfilled in decentralized trials. "In our earlier days at Science 37, I think there were a lot of questions about oversight from a [principal investigator] perspective, and we've been fortunate enough to have a number of direct policy-level meetings with both the FDA and a number of ex-US regulatory bodies ... to the point now where they've been satisfied with what oversight and quality look like in the model, especially from a PI's perspective, and where we're running fully virtual, pivotal, registrational trials in this model."

Cotliar said that there are still many unanswered questions about decentralized trials that need to be answered before pharmaceutical companies embrace them more completely, including if trial safety, survival, adverse events, patient satisfaction, provider satisfaction, and data quality are concordant with trials following the traditional model.

Very small changes to trial processes can improve decentralization, said Schwartzberg, a lesson he and others learned during the COVID-19 pandemic. Signing informed consent forms digitally, for example, was not common practice before the pandemic. Additionally, the transfer of data from health records to clinical trial data capture systems is becoming more streamlined. "Something that intrigued me over the years was the reluctance of sponsors to import data into the [electronic data capture system] directly from the [electronic health records], which is such a logical and simple principle," he said. "Why would you want to have it in a paper case report form or electronic case report form where errors can creep in, as opposed to getting it from the native source?"

Roychowdhury agreed that small steps can be taken to improve decentralized trials before increasing their complexity, noting that trials for oral drugs that can be easily shipped and self-administered by patients can be decentralized first, then lessons from those trials can be applied to higher-complexity trials of parenteral therapies in the future.

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Involving Community Oncologists in Clinical Trials

Decentralized trials likely require including oncologists at community health centers where many patients are treated, Ray said, and she asked the panel what the challenges and opportunities are in involving community oncologists. Community oncologists often want to participate in clinical trials, Schwarzberg said, but their care design is optimized to care for many patients, meaning they typically do not have much protected time to work on trials. Likewise, clinical research is not often a primary goal of community care institutions. This makes opening a community institution as a trial site for an agent targeting a rare biomarker especially difficult to justify. "One of the hardest parts of doing clinical trials in the community is opening a trial where either no patient or, even worse, one patient goes on a trial, as you would expect in a very rare-biomarker-driven trial," he said. Opening a hospital as a trial site requires regulatory processes, IRB approval, and long-term follow-up, whether for one patient or many. "If you take capacity away for a trial like that, then you can't replace it easily," Schwartzberg said.

To include community oncologists in decentralized trials, Science 37 has developed a practice called "bring your own investigator," by which the company can provide trial support and training to community oncologists whose patients wish to participate in a trial off-site. "It's really a way of maintaining a relationship that patients have with their docs so that they both feel supported," he said. "The patient obviously feels supported because the person that they've entrusted their standard of care to is now their investigator on a trial. The investigator can be supported by technology tools and remote coordinators, and – if there are in-home visits – our own fleet of nurses."

Can Trial Decentralization Lead to Greater Diversity in Trial Populations?

Removing geography as a barrier to clinical trial participation could, in theory, improve trial participation among groups that often participate at lower rates, said Ray, including those whose travel and spare time is limited by their economic situation, as well as members of minority races who may be distrustful of medical research due to a history of racist research practices in the US. She asked the panel how successful decentralized trials have been in overcoming these challenges and what opportunities there are to further improve diversity in trial populations.

Cotliar said that while "the jury's still out" on the impact of decentralized precision oncology trials on trial diversity, Science 37 has seen high rates of diversity in trials in other fields as compared to site-based trials, largely due to the relaxed travel requirements. "I don't think that there's anything miraculous about that," he said, "because if you're telling somebody that they can stay on their couch for a trial as opposed to having to take time off from work and drive into a site, you're going to have some incremental benefit. But the numbers we've seen have been impressive." However, he said, it's not as obvious that decentralized precision oncology trials will see the same improvements in diversity due to the rarity of some of the biomarkers in question.

Roychowdhury agreed that, while helpful, decentralizing trials will not solve all the barriers to trial diversity, especially distrust in clinical research. However, issues as simple as needing to travel to and navigate large medical campuses can be alleviated by decentralizing trials. "I think it can solve some issues," he said. "But I'm not sure that it's going to overcome some of our socioeconomic, ethnic diversity issues in clinical trials."

Schwartzberg said that building trust with patients during long-term care is critical to addressing disparities caused by distrust of medical research. "If you have a well-functioning practice that's high quality and is perceived as high-touch as well, you can get those patients on a trial," he said, "But it's quite a bit of work to do that."

Deak said that Duke is seeking to address inequities in biomarker testing to improve clinical trial access by using their reimbursable in-house testing solution to ensure all patients are tested regardless of insurance status. She said that only about a quarter of late-stage cancer patients are receiving genomic testing, and a fraction of those patients are receiving comprehensive genomic profiling, which includes tumor mutational burden and microsatellite instability metrics. She said that simply increasing the number of medical centers that are performing tests can increase the diversity and number of patients being tested. The PGDx assays that Duke is implementing include FDA-cleared bioinformatics analysis and reporting, allowing labs without bioinformaticians to employ them as well.

Schwartzberg added that solutions to disparities in testing and care need not always be highly sophisticated. "For example, we designed a trial that has an app for patients, and they can order a rideshare paid for by the trial directly from the app," he said. "So, they don't even have to call the community oncology practice, which is busy, to coordinate that. They can actually be empowered to do that on their own at no cost to them. So, I think those kinds of creative solutions are important."

Are Decentralized Oncology Trials a Pandemic Fad or Here to Stay?

To turn decentralized trials from a pandemic phenomenon into a more permanent feature of the drug trial landscape, new practices and technologies will need to be brought to bear, said Schwartzberg. He noted the Hospital at Home model of care has begun to deliver hospital-level care in patient homes and could be implemented to deliver parenteral therapies in decentralized trials. The development and adoption of remote or wearable monitoring devices will also allow for the collection of decentralized trial data without doctors or nurses needing to visit patients. Schwartzberg said that continued remote trials will require the liberalization of certain regulatory issues. "During the pandemic, we were allowed to, in some cases, do consults by telemedicine across state lines, which isn't necessarily allowed and may or may not stay," he said. "But those kinds of things – easing those regulatory barriers and allowing more remote monitoring and interactions between providers or research coordinators and patients – will be very useful." Cotliar agreed, noting that employing a model used in other

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countries by which national medical licenses allow doctors to consult with patients across states or regions would be a major help to decentralized trials.

Cotliar reiterated that trial decentralization will not apply to every clinical trial, but decentralizing individual elements of trials can be helpful to patients, "whether that's a remote e-consent, whether that's having a safety visit once a month where they don't have to drive to the site, whether that's having local imaging instead of getting a PET CT scan done four hours away," he said. "I think about gene and cell therapy trials where there's a primary intervention and then 10 to 15 years of follow-up. If you live across the country, why do you have to fly to New York if you live in Los Angeles? There's got to be a way of doing those activities remotely."

AUDIENCE Q&A

The following question-and-answer session has been lightly edited for clarity and length.

Turna Ray:
Do you think community-based oncologists are sufficiently aware of new biomarker-driven trials?

Lee Schwartzberg:
There definitely is an awareness issue because new biomarkers are being identified literally on a daily basis. And it's a wonderful application of understanding the biology of human cancer so much better now, and yet there's an information overload issue. So, our approach to that has been, "Well, we're going to centralize some of that decision-making for you." But even there, it's very difficult. Community oncologists are generalists for the most part, and it's hard to keep up with everything. So yes, we welcome all kinds of creative solutions for community oncologists. If they get a genomic report on a patient with a potentially actionable marker, they need to know about that. And of course, we're approaching it in one way, but there are many solutions to that issue.

Turna Ray:
Is Foundation Medicine doing the tissue testing and liquid testing to identify patients for the ALpha-T trial?

Dr. Cotliar:
Yeah, they are, but the protocol does allow for anybody who gets tumor sequencing done outside of Foundation Medicine to also be eligible. So we need to make that door as broad as possible, whether that's done at an academic institution with their own in-house capabilities, whether that's done by another commercial organization. We don't want to make this eligibility for the trial be dependent upon who you may or may not have been lucky enough to be sequenced by.

Turna Ray:
Are there any sample types for biomarker testing that are more amenable or decentralization-friendly?

Dr. Cotliar:
I know that saliva and blood are both easier than doing lung biopsies in somebody's home. So yeah, I think that if it's saliva or blood, we've done that historically in the home.

Turna Ray:
Can the enormous interest in liquid biopsy and the fact that there's also interest in decentralized trials work hand in hand to increase precision oncology access?

Dr. Roychowdhury:
Yeah. The study that we're working on now and enrolling patients in is to help us rapidly accrue patients who are positive for FGFR genes in cholangiocarcinoma. Only maybe 8,000 patients a year have cholangiocarcinoma, and maybe 15 percent of them have FGFR genes that know to be activating and actionable. And so we want to develop liquid biopsy approaches to study these patients, both to diagnose them and to monitor their response to therapy with serial blood samples. And then, we know that as patients become resistant, we have now second-generation FGFR drugs – kinase inhibitors that are the next generation and that are mostly in phase one clinical trials. So this is our way of learning how to use liquid biopsy and then bring new drugs to those patients when they need them as they eventually, unfortunately, develop drug resistance.

So it's answering a couple of questions at the same time, but really accelerating how quickly we can study this population by offering them consent remotely anywhere in the country to do this for serial blood monitoring of FGFR positive cancer. There was a neat study in Japan where they compared real-time tissue testing and liquid biopsy for diagnosis. And so we've been talking about what's the right sample type. Many of these patients we're talking about have probably been already diagnosed, but when you're talking about an initial diagnosis of metastatic disease, liquid biopsy has a lot of potential, and we're still learning how to implement it, what the true sensitivity is for certain genetic changes.

But in this study in Japan – they call it GI-SCREEN and GI-GOZILA [and it was published] in *Nature Medicine* last year – the turnaround time was 20 days faster. And doctors were willing to wait. It turns out that patients who had the liquid biopsy-matched therapy are, on average, going on studies more than twice as often. So four percent went on to a study for clinical trial therapy when they got tissue-based testing. Those that had the liquid biopsy and a qualifying alteration went on more than nine and a half percent of the time. So that's a big difference, and I think it reflects both the doctor and the patient. So you come to me and you have a test, and 11 days later, we've got your liquid biopsy, well, you and I could stand to wait to decide, "Oh, now, let's put you on an MSI trial."

But think about the patient who's waiting 31 days. I have patients call me three days later after I see them wondering about their test results. And 31 days is just too long for a doctor or patient to wait, and they went on chemo and missed the opportunity for the trial.