The CenterWatch Monthly

January 2017 A CenterWatch Publication Volume 24, Issue 01

Personalized medicine impacting study conduct

Collecting genetic and biomarker data adding to site administrative burden

By Karyn Korieth

As the analysis of genetic data is fast becoming a significant part of clinical research programs, both to enroll study participants and understand how drugs work, investigative sites are increasingly asked to collect genetic samples and conduct genetic screenings for clinical trials.

Research sponsors want investigators to collect genetic material that either can be analyzed as part of the study or stored for future testing. Depending on the relevance of the genetic analysis to the clinical development program, the genetic sample collection may be a core requirement for study participation or an optional component of the study.

"We are seeing more industry-funded research that wants to do genetic testing to make sure that they are on the right pathway in their drug development and in targeting populations," said Megan Bailey, manager of the Office of Research Compliance, CHOC Children's Research Institute at the California-based Children's Hospital of Orange County (CHOC). "We've also seen an uptick in the number of protocols that look at genetic testing along with tissue banking because of not knowing what tests may come in the future and wanting to prepare for those."

While the increasing use of genetic biomarker data can enhance medical knowledge, lead to more efficient drug development and ultimately deliver more beneficial therapies, the approach also has implications for the efficiency of the study conduct process.

Interviews with investigators and site staff members suggest that the informed consent process takes longer for studies that include a genetic component, for example, since investigators need to ensure study participants understand what will happen with their genetic information and answer questions about how the data will be protected. Some sponsors re-

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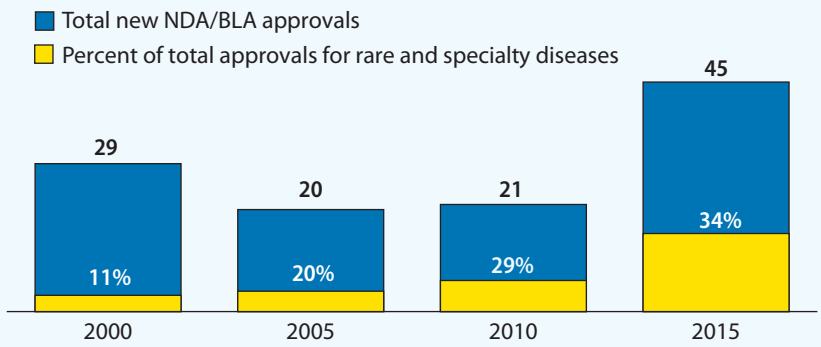
Changing pipeline composition



Source: Pharmaprojects; Evaluate Pharma

Online patient recruitment: Still nascent after all these years

Industry is ready for a revolution, but kinks still exist

By Suz Redfearn

The world of online patient recruitment has undergone an evolution since it arrived during the heady dot-com craze of the 1990s—but has that caused a revolution, one that has transformed the space?

Most say no, not yet. But it may be on its way to doing so.

It all began when the internet surged in the late 1990s: a slew of companies—largely private equity and venture-backed—formed to leverage the reach of the Internet to improve patient recruitment effectiveness.

During the dot-com craze, market entry and access to capital were easy, and numerous companies entered, including Acurian, America's Doctor, Clinicure.com, Drkoop.com, EmergingMed and Veritas Medicine to name but a few. Many of these companies did not survive when the dot-com bubble burst. Others had to modify their business models dramatically in order to survive and to remain viable.

Awareness and enrollment

What happened? What went wrong?

For one, the early business model for online recruiting companies didn't work, explained Ken Getz, director of sponsored

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quire a separate consent form for the genetic component of the study. For clinical trials that target enrollment of patients with rare genetic biomarkers, sites may also be required to screen a larger number of patients to find qualified study participants.

When genetic information isn't needed to make enrollment decisions for a clinical trial, there can be questions about whether the genetic analysis adds unnecessary procedures for investigative sites and contributes to the growing complexity of clinical trial protocols. Yet investigators interviewed by CenterWatch view genetic screening and the collection of genetic materials not as a burden, but as an essential part of clinical research going forward.

"Any time there is anything extra in a clinical trial, it takes more time," said Ryan Welter, M.D., Ph.D., CEO and medical director of Massachusetts-based Regeneris Medical, which specializes in biological studies and regenerative medicine research. "But I wouldn't necessarily call it a burden. Genetic information is incredibly important in terms of screening and understanding disease processes. It is invaluable in making clinical, research and biologic decisions."

Increase in protocols that request genetic material

Recent R&D trends show the use of biomarker and genetic data accelerating in the development of drugs for many disease areas.

Analysis from the Personalized Medicine Coalition (PMC) showed that 28% of novel new drugs approved at the FDA in 2015 were classified as personalized medicines, an increase from 21% in 2014. The Tufts Center for the Study of Drug Development (CSDD) found in 2015 that 42% of all drugs in development relied on biomarker data. In addition, a recent study published in *Nature Genetics* estimated the proportion of drugs developed with direct genetic support increased significantly across the drug development pipeline, from 2% at the preclinical stage to 8% among approved drugs, and that selecting genetically supported targets could double the success rate for drugs in clinical development.

Sponsor companies use genetic biomarkers to evaluate patient response, which allows them to terminate ineffective drug candidates earlier in the development process, and to optimize clinical trial designs and outcomes by identifying which patient populations are most likely to respond to a drug therapy. Researchers also use genetic data to understand the mechanisms of both treatment response and disease process, which can help identify future targets for drug development.

"We are moving to an era where we use molecular analysis of patient samples either to enroll people in trials or understand how drugs work or don't work," said Ross Levine, M.D., a physician-scientist at the Memorial Sloan Kettering Cancer Center in New York. "Molecular profiling, whether it's based on the ideas of precision-medicine initiatives or other ideas that have come out of our national research efforts, is the future and is becoming a part of routine care."

Investigative sites interviewed for this story report that at least half of their active clinical trials request collection of genetic material, although it's not a requirement for participation in all studies.

The genetic information is typically collected from samples taken for other non-genetic study procedures. In some cases, there may be an extra tube of blood drawn during a screen-

Personalized Medicine Coalition's list of 13 personalized medicines approved in 2015

Drug name	Disease condition	Decision to treat affected by:
1. Alecensa (alectinib)	non-small cell lung cancer	ALK biomarker
2. Tagrisso (osimertinib)	non-small cell lung cancer	EGFR biomarker
3. Cotellic (cobimetinib)	advanced melanoma	BRAF biomarker
4. Nucala (mepolizumab)	asthma	eosinophil level
5. Aristada (aripiprazole lauroxil)	schizophrenia	CYP2D6 biomarker
6. Lonsurf (trifluridine and tipiracil)	advanced colorectal cancer	VEGF, RAS and EGFR biomarker
7. Repatha (evolocumab)	high cholesterol	familial hypercholesterolemia
8. Daklinza (daclatasvir)	chronic hepatitis C infection	genotype 3 biomarker
9. Praluent (alirocumab)	high cholesterol	familial hypercholesterolemia
10. Rexulti (brexpiprazole)	schizophrenia	CYP2D6 biomarker
11. Orkambi (lumacaftor and ivacaftor)	cystic fibrosis	F508del/CFTR biomarker
12. Cholbam (cholic acid)	bile acid synthesis disorders	various single enzyme defect biomarkers
13. Ibrance (palbociclib)	advanced breast cancer	ER and HER2 biomarker

Source: Personalized Medicine Coalition analysis, 2015 and 2014

ing visit or an additional frozen tissue plate prepared during a biopsy, but investigators say these procedures generally don't increase the workload for staff members.

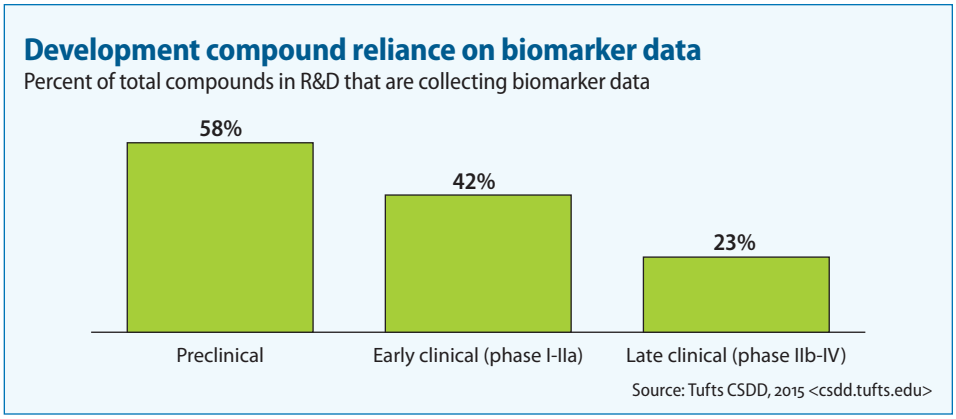
"We are typically sent one lab kit and all of the collection tubes needed for the specific visit are contained in the kit. If there is a genetic marker that we are drawing for, it's in the kit. There are no extra steps for us," said Gabrielle Lewis, director of Clinical Research at Regeneris Medical.

Most blood samples for genetic analysis can be sent to the lab for processing the same day and don't prescribe specific handling requirements. Yet some sponsors ask investigative sites to hold on to samples until they reach a certain volume before shipping if there are price benefits in batching the samples. In those cases, a freezer may be needed and the site must ensure the sample is still viable when shipped. Studies looking for specific enzyme levels associated with a disease state may also require that sites have capabilities to store and process genetic samples. In addition, study protocols increasingly require sites to provide and regularly maintain ultra-low temperature freezers, which have the capability to safely store DNA and other genetic material, as a prerequisite for study participation.

"We have to be savvy at the site on how to store samples properly and have the needed equipment," said Lesia D. McBride, director of the Community Clinical Research Center (CCRC) at the Indiana-based Community Hospital of Anderson and Madison County. "We've always had the -70°C freezers, but now there is a discussion about -85°C freezers coming into play. Sites should make sure they have the right equipment for storage and that they have the right personnel trained to ship those samples so they are not destroyed or compromised during shipping. Sites are more challenged because of the equipment we need to purchase and maintain. They are not cheap pieces of equipment."

Although investigators report that study requirements for the collection of genetic material have had minimal impact on staff workloads so far, as sponsor demand for genetic data collection continues to grow, investigative sites may need to evaluate whether additional resources will be needed in the future.

"We see genetic data collection as very much an extension of our mission, vision and values at CHOC Children's. We do not consider it a burden," said Brent Dethlefs, executive director of CHOC Children's Research Institute, which conducts both basic science and clinical research. The hospital's Hyundai Cancer Genomics Program also began a molecular profiling study in 2011 that has compiled genomic data from some 400 cancer patients. "But there is no doubt that this presents a resource challenge. It's important to pay attention to our infrastructure and look forward, as the field continues to progress, to ensure we are ahead of the curve. We don't want to catch our chief executives by surprise when suddenly we need more space or more human resources to bring to bear on this."



Additional time required for informed consent

When a clinical trial includes a genetic component, the investigator or site staff members typically need to spend more time with potential participants during the informed consent process to answer questions and ensure study participants understand what will happen with their genetic information, the scope of any intended future research use and the intended duration of sample storage.

"There are time constraints on making sure that we have explained everything to the subject well enough," said CCRC's McBride.

Informed consent for the collection of genetic samples may be obtained either in the main informed consent form or a separate document, depending on the approach required by the research sponsor.

Investigative research sites at academic medical centers or hospitals that develop their own clinical trial protocols and informed consent forms have needed to revise their processes and documents to incorporate new national medical society and industry recommendations about disclosing genetic results to participants and to ensure the consent process addresses ethical review board concerns. The Industry Pharmacogenomics Working Group (I-PWG), an informal association of 20 companies involved in pharmacogenomics research, for example, has developed guidelines that recommend consent for future use of samples should patients withdraw their consent and request destruction of their samples.

"Participants should be given control over their material, deciding for what it will be used and how broadly it will be distributed," said Sharon Terry, president and CEO of the Genetic Alliance, a nonprofit health advocacy organization that includes a network of more than 1,200 disease-specific advocacy groups. "There is usually pushback on this because researchers are not using network-age technologies to recruit and stay engaged with people. Instead of recruitment and consent, this should be thought of as ongoing engagement."

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Confidentiality and proper data protection are among the chief concerns expressed by potential participants. Some patients worry that individual genetic data could be used against them by an insurance company or employer. Investigators interviewed for this story, however, stated that genetic data doesn't inherently present greater privacy risks than any other data collected in a clinical trial.

"Your DNA is highly confidential and you want to preserve that information. But all healthcare data is incredibly confidential. Our informed consent process should be the same for all privileged healthcare information, no matter what. Our systems are already set up to safeguard this information, whether you are giving a sexual history, a psychological history or just a basic medication history. All protected health information pieces require the same amount of vigilance," said Regeneris Medical's Welter.

Site staff also must answer patient questions about whether they will have access to the results of genetic tests and, when appropriate, provide genetic counseling for patients or have study participants follow up with a medical geneticist to discuss research findings.

"While some studies do share the results of the study-specific genetic tests with subjects, not all do. Also, some studies collect samples for future testing, which typically are not shared with the patient since any identifying information about the patient is removed from the sample once it is sent to a genetic repository," said Marshall L. Nash, M.D., a principal investigator at the Georgia-based NeuroStudies.net, a clinical research site that focuses primarily on finding treatments for Alzheimer's disease.

Investigators report that study participants generally don't object to collection of their genetic material, even when it's an optional component of a research study, once their questions about privacy protections have been answered. A study published earlier this year by the Royal Marsden NHS Foundation Trust in the U.K. found that 78% of cancer patients surveyed said they would donate their tissue for genetic research. Other studies published in medical journals also report generally favorable public attitudes about participation in genetic testing.

"We underestimate patients' willingness and their incredible motivation to be part of something bigger than themselves," said Sloan Kettering's Levine. "Particularly in cancers where people feel their disease is rare and not studied enough, I am always impressed and humbled by patients' excitement to be part of trials. When people come to Sloan Kettering, they don't say, 'I don't want you to poke and prod the DNA of my tumor.' They say, 'Are you going to do everything you can to figure out what's in it?'"

Increased patient recruitment challenges

When genetic studies are added to a clinical research program as an optional sub-study for participants, investigators find they don't affect patient recruitment since the efforts focus on finding volunteers for the overall study, not the genetic component. Yet investigative sites often find it more difficult to recruit for clinical trials that target patients with a specific genetic variant, and site staff might be required to screen a larger number of people to find study participants that could qualify. Some companies offer free genetic testing kits to help investigators identify potential study participants with the specific genetic biomarker criteria required. Other sponsors pay for the additional screenings that are needed, but sometimes screening costs are shared between sites, CROs and sponsors.

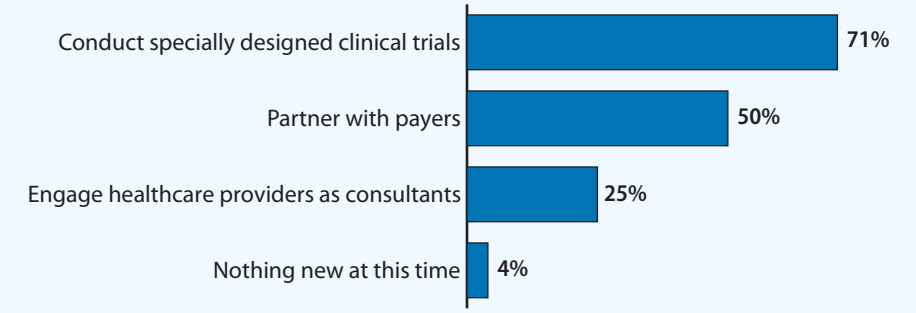
For rare disease protocols that require enrollment of patients with specific genomic alterations, which are notoriously difficult to recruit given the small patient populations, investigators typically work with patient advocacy groups or use social media to advertise the research study and find the right participants.

"If you have a rare disease for which you have a genetic test, those patients usually find you. If you have a rare disease that may not have a genetic marker, they may still find you," said Douglas Lee, M.D., a pulmonologist who practices at Wilmington Health and serves as a principal investigator with PMG Research of Wilmington in North Carolina. "I have people fly from Ohio, South Carolina or Georgia to be in a study because there may only be a few places around that are involved in a research study."

The use of electronic medical records and patient databases have also become increasingly important tools for recruiting patients for protocols with a genetic component. At the Research Institute of Deaconess Clinic in Evansville, Indiana, for example, researchers used a two-prong approach for identifying a subpopulation of myocardial infarction (MI) patients with a specific genetic biomarker, which the sponsor estimated that one-in-five MI patients would have. Staff first monitored the daily hospital census for patients with a

Methods sponsors are using to prove clinical utility

Percent of total



Source: Tufts CSDD, 2015; n=24 sponsor companies <csdd.tufts.edu>

recent MI event and identified potentially eligible patients before they were discharged. At the same time, electronic medical records were used to create a post-MI patient pool based on the inclusion/exclusion criteria of the protocol.

"Patients were contacted and phone-screened for eligibility and interest. Targeted patients were then scheduled for screening appointments and genetic testing was done at the screening visit to determine eligibility," said Gregory A. Folz, administrative director of the Research Institute of Deaconess Clinic.

New partnerships emerging

New collaborations have begun to emerge that address the unique challenges associated with conducting clinical trials that include genetic screening and analysis. Consortiums are being developed around various rare disease types to facilitate study enrollment and data sharing. Partnerships between industry and research communities have also been formed to advance targeted therapies.

In one instance, the Leukemia & Lymphoma Society (LLS) recently launched a precision-medicine clinical trial for acute myeloid leukemia (AML) patients with an unprecedented collaboration between researchers, academic medical centers, biopharmaceutical companies, the FDA and multiple support groups. While a typical clinical trial only studies one drug or one combination of drugs, the Beat AML Master Trial, which will be managed by INC Research, began with four different treatments that will each be tested in one of several arms of the trial based on a particular genetic mutation.

Newly diagnosed AML patients will have their genomic data analyzed within seven days and be assigned a specific treatment arm of the trial based on the screening results. Since the study involves genetic analysis in an acute disease and most AML patients are rushed into standard treatment immediately upon diagnosis, the trial design needed to ensure that both the bone marrow biopsy and the screening analysis could be completed within a week.

"That created aspects that are unique to this trial," said Levine, one of the lead investigators who worked closely with LLS to plan and design the master protocol for the trial. "We are screening AML patients over 60 years old who have a relatively small number of standard criteria. But because we are breaking those AML patients into different subsets, we wanted to have enough patients for each subset to test the specific question. No single center can do that alone. We are hopeful that this will pave the way for other trials like this where we do genetic analysis and use that to decide about therapeutic questions and test therapeutic ideas."

"Genetic information is incredibly important in terms of screening and understanding disease processes. It is invaluable in making clinical, research and biologic decisions."

—Ryan Welter, CEO and medical director, Regeneris Medical

Through the collaboration, participants hope to show that the various stakeholders have the desire to work together and the ability to get targeted treatments to newly diagnosed patients in a narrow time frame, which could open other opportunities moving forward.

"When you look at an acute disease like acute myeloid leukemia and a newly diagnosed patient walks in the door, you need a more or less instant decision to get going with an appropriate therapy," said Nicholas Kenny, Ph.D., executive vice president and general manager for oncology at INC Research. "That puts pressure on the logistics to get the NGS [next generation sequencing] testing across this panel done very quickly so we can make an informed decision about which therapy is appropriate for the patient. If this will work for Beat AML, it becomes precedent-setting for what is achievable in other tumor types."

Looking ahead

The rapid move toward personalized medicine and an increase in clinical research programs that include genetic analysis has the potential to accelerate changes already under way in the global investigative site market. The site landscape will continue to consolidate and clinical research will move increasingly toward larger hospitals, healthcare systems and site networks as sponsors and CROs want to place clinical trials in settings that have access to large patient populations and electronic health records that can help identify specific subpopulations for genetic research.

"If you have a big network, you can find more of those rare diseases than you can if you are a small practice," said PMG Research of Wilmington's Lee. "If you are a small family doctor, you may have many patients that meet the eligibility requirements, but you don't know because you don't have the ability to find them, whereas I have a bigger patient database and can find them by searching my electronic medical record."

Yet INC Research's Kenny said the clinical research enterprise must find ways to keep smaller sites involved in clinical trials that include genetic analysis. Approaches could include simplifying testing requirements, for example, and reducing the administrative burden of conducting a

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clinical trial. In addition, a "portfolio approach" that offered sites multiple study opportunities within a tumor type or molecular-defined marker also could encourage wider investigator participation.

"If we let precision medicine drive trials just into bigger centers, then we've failed. That helps nobody. The physicians are not getting the experience with the drug and the patients aren't benefiting," he said. "If we can't get that right, then we have failed in our mission to broaden out what I would consider to be patient-centric trials."

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research programs at Tufts Center for the Study of Drug Development (CSDD), chairman of the Center for Information and Study on Clinical Research Participation (CISCRP). Getz is also the founder of CenterWatch, which was, in the mid-1990s, the first website to publish active industry-funded clinical trials categorized by disease for patients to identify opportunities to participate.

"The first generation Internet recruitment companies weren't positioned properly," said Getz. "They only promoted clinical trials paying for patients and the payment model was predicated on an enrolled patient—with no upfront fee required," he explained. "A lot of sponsor companies liked the low-risk approach, but the Internet companies could not deliver sufficient enrollment performance to cover shareholder and investor requirements."

That's because looking for patients on the Internet—either by intercepting them in diseased-based communities or running ads in the places they visit—resulted in "filling the top of the funnel with interested parties, but then not many of them sifted down to the bottom of the funnel to actual recruitment," said Hugo Stephenson, executive chairman of DrugDev, founder of iGuard, later named MediGuard, an online recruitment tool that was bought by Quintiles. Stephenson has now also returned to being a principal investigator in Australia.

"Years ago, the perception was that the true answer lay in simply getting the message to patients that trials were out there, and the belief was that most people would consider being in a clinical trial if they'd only heard of them," said Stephenson. "The Holy Grail was thought to be awareness, but that didn't turn out to be the case."

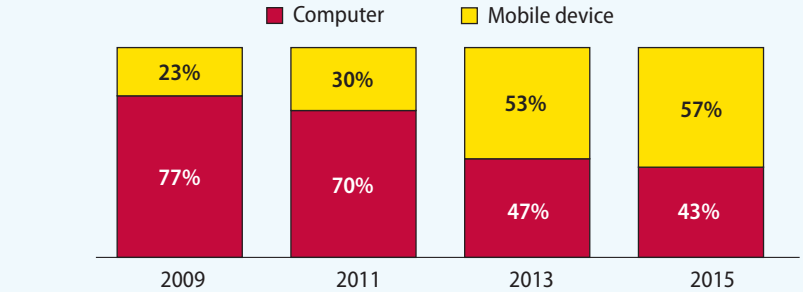
Instead, it was much more complicated than that. If a patient or their caregiver is highly motivated—envision a cancer patient with no other options or the parent of an autistic child where there is unmet need—yes, they will move mountains to enter a trial once they learn about it. But the rest of the population? Not so much, said Stephenson. And even less so if the trial is inconvenient or not particularly patient-friendly, which is even more common these days as trials have gotten more complicated. Also, the patients who are willing to be in a trial may not be the ones a study is actually looking for.

And the early online companies may have been good at aggregating useful information on trials in one or two therapeutic areas and matching potential patients against inclusion/exclusion criteria, but were unable to come up with algorithms for doing that across all trials in all areas.

All of this, said Getz, squashed the early dream of easy online recruiting.

Internet access by adults as a proportion of time spent online per day

Percent of total time



	2009	2011	2013	2015
Total hours/ day online	3	3.7	4.9	5.6

Source: KPCB

Better data crunching

The dream, however, is still alive; it just looks a bit different in an online world defined by social media and sophisticated assessment of individual behavior.

Enter Antidote. Launched in 2010 as TrialReach, Antidote is in the process of building a meta search engine for clinical trials with a free side for patients and a pay side