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Crowdsourcing Clinical Trial Protocols

BY ROBERT H. CARLSON

The design of a clinical trial protocol typically has input from a small research team—rarely more than 10 reviewers and usually far fewer.

And the number of patients who review a protocol in detail and offer input is typically… zero.

Now, though, a different kind of clinical trial is about to begin enrolling patients, a trial that used crowdsourcing to develop the protocol. The trial will evaluate the use of metformin in men with rising prostate-specific antigen after localized treatment for prostate cancer.

Faster trial development and increased patient accrual are among the goals.

Crowdsourcing is a phenomenon of the Internet age, a collaboration of many people in an online community who are asked to contribute services, ideas, or content to an enterprise for little or no financial cost.

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Best Gastrointestinal Cancer Papers, 2013

BY GAURI VARADHACHARY, MD

What have we learned about advances in GI cancers from the 2013 publications? The literature in the past year suggests a continued emphasis on evaluating the role of predictive markers and understanding cancer biology/heterogeneity.

A brief review cannot do justice to the vast number of important publications, so I highlight here five significant papers from 2013—I have chosen one (or more with a similar theme) for each gastrointestinal disease site that signifies the advances, drawbacks, and additional work planned ahead.

RAS Mutations and Management of Colorectal Cancer—Looking beyond *KRAS* Exon 2 Mutation; Updated PRIME Study (*Douillard et al: Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. NEJM 2013;369:1023-1034*)

The original report from the PRIME study (*JCO 2010;28:4697-4705*) concluded that panitumumab-FOLFOX4 was well tolerated and significantly improved progression-free survival (PFS) in patients with wild-type (WT) *KRAS* tumors. Consistent with the results from other studies, patients with *KRAS* mutations in exon 2 (codons 12, 13) did not benefit from the addition of anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) therapy in the PRIME study.

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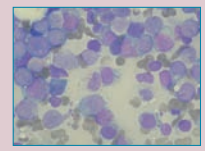
New AML Score Improves Risk Evaluation

BY HEATHER LINDSEY

A new prognostic score for acute myeloid leukemia (AML) based on information about seven mutated genes and associated epigenetic changes may one day help guide treatment for a subset of patients, according to new research now available online ahead of print in the *Journal of Clinical Oncology* (***doi: 10.1200/JCO.2013.50.6337***).



The researchers evaluated gene mutations and expression, as well as epigenetic changes, in which the chemical modification methylation impacts DNA expression without altering the DNA sequence.

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CROWDSOURCING CLINICAL TRIAL PROTOCOLS

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The protocol for this trial has input from 43 physicians and 33 patients.

"We want to use the collective, creative, and intellectual capacity of the crowd—researchers, patients, survivors, and advocates—to shape this clinical trial into something that has the highest likelihood of attracting patients and the interest of other researchers," said the principal investigator, **Matthew Galsky, MD,** Director of Genitourinary Medical Oncology and Associate Medical Director of the Cancer Clinical Trials Office at Tisch Cancer Institute at Mount Sinai School of Medicine in New York.

The platform for crowdsourcing the trial was the "Protocol Builder" from Transparency Life Sciences (transparencels.com) (TLS), a company that is also using the process to develop trials in irritable bowel disease, Parkinson's disease, and multiple sclerosis.

The metformin trial is funded in part by a $225,000 unrestricted grant from the Prostate Cancer Foundation.

'Knowledge Media/ Network'

Although crowdsourced projects often use social media to contact participants, Transparency CEO **Tomasz Sablinski, MD, PhD**, said he doesn't see social media as the best way to connect with patients or researchers for input on a clinical trial.

"If you put the questions on Facebook or Twitter, 99 percent of people who respond will have no connection with the question," he said. "We are talking about targeted distribution tools from the Internet, which are patient advocacy groups, physician associations, and professional groups."

Sablinski said he prefers to call this platform "knowledge media" or a "knowledge network."

"Increasingly we use knowledge networks in health care but not in clinical trials." He explained that he founded Transparency Life Sciences in 2010 to introduce this new model of drug development made possible by modern computer sciences, technology, and new communication and knowledge-generation patterns.

In December 2012, TLS received Food and Drug Administration clearance to initiate a Phase II study assessing the utility of the antihypertensive drug lisinopril as adjunctive therapy in multiple sclerosis. Both lisinopril and metformin have the advantage of FDA approval and extensive safety data.

He said he believes that the lisinopril trial was the first time crowdsourcing was used to design a clinical trial, and also one of the first to make intensive use of telemonitoring and other remote methods of collecting patient data (*see page 32).*

The metformin trial, TLS's first foray into oncology, is expected to start accrual sometime this spring. "Dr. Galsky came to us [with the proposal], and was pivotal in writing questions to put in our template," Sablinski said.

He emphasizes that the Protocol Builder "is not a system for people to cast a vote and put a stamp of approval on what we or an investigator think is a good idea.

"Too often researchers are so caught up with their hypothesis that they only want to hear from people who agree with them, and that ends up as a poorly designed trial if not enough skeptics see it. We like skepticism—clinical research is not black or white—it's relative."

Input from Physicians and Patients

For physician input into the protocol-building process, Galsky wrote a 36-question questionnaire asking for opinions on topics that ranged from the study's scientific rationale, to recommendations for inclusion and exclusion criteria, to suggestions for alternative endpoints.

The 43 physicians who responded included not only oncologists but also other specialists.

"We wanted to pilot that approach to determine whether or not collecting input not just from the very small study teams that usually design clinical trials but from a large number of physicians who are experts in prostate cancer and also experts in other areas such as endocrinologists—since this is a diabetes drug—and from patients" would improve the protocol, he explained.

Galsky says patients must also be involved in the clinical trial design process, "because if we are not asking questions that are important to patients, and in a way that is important to patients, then it is not entirely surprising that people do not want to sign up."

One problem with enrollment is that the questions asked are likely not the most important questions to the patients, he said. "Part of overcoming that barrier is just asking for input from the people who are participating in the trials—the patients—and one way to do that is crowdsourcing."

Matthew Katz, MD

One physician who is very active in social media and writes about it in his blog advocates crowdsourcing to help design clinical trials. **Matthew S. Katz, MD** (**@subatomicdoc**), Director of Radiation Oncology at Lowell General Hospital in Massachusetts, has written often about enlisting help "not only from physicians who are experts in a particular disease or indication, but also from patients, asking what they would like to see from clinical trial results and data." (He also spoke about his approach in *OT*'s Profile in Oncology Social Media about him in the ***10/25/13 issue***).

The effort would improve accrual, he said he believes. "In many situations, endpoints for regulatory approval are meaningless or mean little to patients, and they want something else to be measured," Katz said in a telephone interview.

And research shows that better understanding of clinical trials can improve participation rates, Katz notes, so why not aggregate online resources that educate patients well?

Crowdsourced patient-education materials would also be a great asset, he said, as would crowdsourced educational tools for doctors.

"Innovations, in the end, are tools that may help with accrual, but they must be in the best interest of the long-term health of patients," Katz said. "To me that means they should also help with the patient-physician relationship, so that the patient has a meaningful relationship with the person responsible for their care."

'Network of Microexperts'

Another company that uses feedback from patients to help design clinical trials is Smart Patients, launched last year by **Roni Zeiger, MD**, an internist and the former Chief Health Strategist at Google, and Gilles Frydman, who founded ACOR, the Association of Cancer Online Resources (***OT 9/25/13 issue***).

Smart Patients differs in that it seeks to gain insight from patients

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Using Telemedicine to Increase Trial Accrual

BY ROBERT H. CARLSON

Monitoring of safety, side effects, and quality of life will be done through a secure video monitoring platform on computer tablets given to patients, with the doctor and patient seeing and talking to each other in a setup similar to that of Skype.

One reason many patients do not volunteer for clinical cancer trials is simple: They cannot or do not want to commute to the cancer center for the extra visits a trial would require.

If traveling more than 30 miles for a clinic visit is considered a burden, then a new study shows that enrolling in a clinical trial would be a burden for more than 30 percent of men with advanced prostate cancer in the U.S.

The data are from a study presented at the Genitourinary Cancers Symposium, which showed that clinical trial sites are "poorly accessible geographically to a large subset of U.S. prostate cancer patients, a finding that likely contributes to dismal accrual," the researchers reported (*page 30*).

The same researchers, from Mount Sinai School of Medicine in New York City, reported in a separate study that 10 percent of clinical cancer trials are not completed because of failure to accrue a sufficient number of patients (*page 30*).

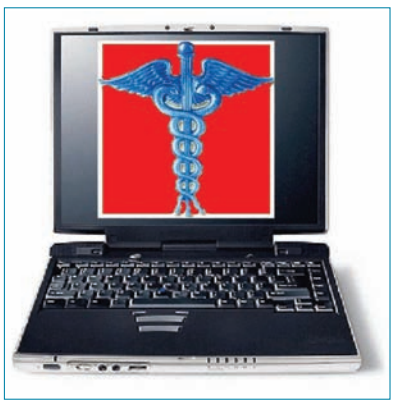
"Innovative solutions are required to address geographic barriers to access," the researchers, led by Matthew Galsky, MD, Director of Genitourinary Medical Oncology and Associate Medical Director of the Cancer Clinical Trials Office at Icahn School of Medicine at Mount Sinai, concluded, and indeed they are trying an innovative solution of integrating new information technology approaches to increase accrual and break down geographic barriers to participation.

Disruptive Innovation Fills New Needs

Telemedicine is not new to medical care, of course, but its use in clinical trials to overcome the geographic barrier would be a "disruptive innovation—i.e., technology that may not immediately displace the current way of doing things but opens new processes that eventually will replace the old ones, he said.

"Telemedicine won't be applicable to every clinical trial from day one, but in 10 years could there be a new way of thinking about doing clinical trials? We think maybe so."

Galsky acknowledged that it will be easy for some to say chemotherapy can't be given remotely, or that Phase I first-in-human studies can't be done remotely. "We certainly appreciate those potential criticisms, but this is really creating a new model for an activity that was carried out in different ways historically."



Patients who volunteer for the trial will come to Mount Sinai for a single visit, and the rest of the study will be done via telemedicine visits once a month for the six months of the study. Patients will be given the supply of medicine at that first visit, but the drug could also be mailed if necessary.

Monitoring of safety, side effects, and quality of life will be done through a secure video monitoring platform on computer tablets given to patients. In a setup similar to that of Skype, the doctor and patient will see and talk to each other. Galsky said the system is HIPAA and HITECH (Health Information Technology for Economic and Clinical Health) compliant.

He is also exploring a system of monitoring compliance by telemedicine. He described a medication adherence monitor that will register a Bluetooth signal to the data base each time patients open the drawer to take out their medicine. "It doesn't tell us that they have actually taken the medicine, but it will tell us that they have accessed the medicine," he said.

The next level of the concept will be using telemedicine to integrate local physicians with study physicians, and he is also in discussions with a company that has a process that allows blood to be drawn in very small quantities so that the sample could be mailed to a central lab.

30 Miles a Travel Burden

For the trial reported at the GU Symposium, Galsky and colleagues searched ClinicalTrials.gov to identify all active U.S. clinical trials exploring first-line therapies for metastatic prostate cancer on Sept. 16, 2012. The researchers evaluated the geographic distribution of trial sites and estimated the minimum driving distance from each ZIP code in the contiguous U.S.

A distance of more than 30 miles was defined as a high travel burden. There were 958 sites associated with 42 metastatic prostate cancer clinical trials. Among 3,185 counties, 2,669 (about 84%) had no clinical trials available for first-line treatment of metastatic prostate cancer, although counties with larger populations of patients with advanced prostate cancer did have significantly higher numbers of clinical trial sites.

The team determined the relationship between the number of sites and the number of patients with advanced prostate cancer per county, and found a high degree of inaccessibility, since approximately 31 percent of the U.S. population resided more

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CROWDSOURCING

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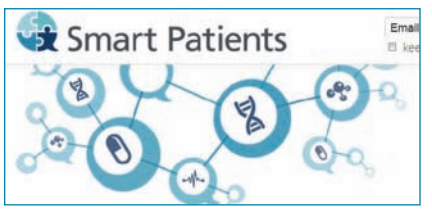
The protocol for the trial has input from 43 physicians and 33 patients.

and caregivers so that pharmaceutical companies and academics can design more patient-friendly clinical trials. But partner organizations cannot advertise on the site or contact patients who use it.

"We want to make sure Pharma and academics are designing trials addressing issues that are most important to patients," Zeiger said in a telephone interview for this article.

He offers the example of patient-reported outcomes in trials, which are usually defined by scientists: "It's ironic that we don't ask the patients what the patient-reported outcomes should be," Zeiger said, noting that



he believes researchers can do a better job with clinical trials if they think of patients as collaborators instead of passive participants.

Smart Patients finds participants through social media, patient organizations, and people searching for a community on the Internet. Zeiger said he hesitates to use the term "crowdsourcing" for what Smart Patient does and prefers instead to call his participants a "network of microexperts."

"We would not want to take the average of everyone's answer, but would prefer to take the answers from microexperts, where the input includes a dynamic discussion among the microexperts," he said.

In the metformin trial, Galsky said he will not be averaging the input but will work with a clinical trial design committee to choose which ideas to incorporate into the protocol. The regulatory approval process is the same as with any other trial.

Once the trial is completed, he said, there are also plans to inform trial participants, patients, and physicians of the results.