Clinical Chemistry

Clinical Trials in Precision Oncology

Article: Susan Mockus, et al.
Clinical Trials in Precision Oncology.
Clin Chem 2016;62:442-448.
http://www.clinchem.org/content/62/3/442.abstract

Guest: Dr. Susan Mockus is the manager of Clinical Curation and Analytics at The Jackson Laboratory for Genomic Medicine in Farmington, Connecticut.

Bob Barrett: This is a podcast from a *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

Precision medicine, employing genome-guided biomarkers and therapeutic strategies, has changed clinical trial recruitment and reporting. An increasing number of clinical trials have an eligibility component requiring the absence or presence of a specific molecular variant to validate predictive biomarkers that inform or recommend therapeutic action. Systematic implementation of reporting standards is needed to ensure consistency and specificity of biomarker data, which will in turn enable better comparison and assessment of clinical trial outcomes across multiple studies.

The March 2016 issue of *Clinical Chemistry* published a mini review titled "Clinical Trials in Precision Oncology." The first author of that paper is Dr. Susan Mockus. She is the manager of Clinical Curation and Analytics at The Jackson Laboratory for Genomic Medicine in Farmington, Connecticut, and she's our guest in this podcast. Dr. Mockus, how is next generation sequencing of tumors helping oncology patients today?

Dr. Susan Mockus: Well, it's been known for a long time that changes in our DNA can give rise to mutation that will drive to our formation and the metastasis in cancer progression. Really, the idea is if we can identify these mutations, could we then intervene therapeutically to prevent cancer progression. Historically, and even today, we have laboratory tests that will look for either one actionable mutation in one gene at a time, or maybe even a couple of mutations in several genes at a time. With the next generation sequencing, we're actually able to simultaneously look for thousands of mutations and hundreds of genes all in the same test. What this means to the oncology patient is that we increase the likelihood of detecting actionable mutations and therefore, can identify potential therapies that the patient will respond to or even have a lack of response to.

Bob Barrett: How do you use the data generated through the next generation sequencing to produce clinical reports?

Dr. Susan Mockus: Well, here at The Jackson Laboratory for Genomic Medicine, we have a 358 targeted gene panel that goes through our full test system, starting with a wet lab, bioinformatics and then finally, the generation of the clinical report. Now, with the clinical report generation, one of the tools that we built from the ground up is a clinical knowledge base, and that clinical knowledge base stores information on mutations, those that connect to targeted therapies in clinical trials. So when a patient sample comes in, we rapidly identify the actual mutations and look for the connecting therapeutic data in our clinical knowledge base. That knowledge base is all built on a systematic control vocabulary that allows for reproducable capture of data related to those mutations and therefore, consistent and reproducible retrievable of that data so we can synthesize all the information together to go up on to the actual clinical report.

Bob Barrett: How are these clinical reports used by physicians?

Dr. Susan Mockus: So for the physician, the clinical report generated from these types of next generation sequencing tests, is one tool in the management of patient care. In this particular tool, what we do is we take thousands of genetic variants that may have been identified and distill them down to just the ones that are actionable for the oncologist. Not only do we include on the clinical report the list of actionable mutations, but we also include -- well, are there any FDA approved therapies for that mutation? FDA approved therapies in an indication other than what the patient has? Or, are there any available clinical trials that the patient would be eligible for based on this test?

So by doing that, we take a very complex assay with very complex data and distill it down into something that's easy to read and can rapidly identify, synthesize, interpreted information around those actionable mutations. That, along with all the other patients data is meant to help the oncologist determine what sort of treatment strategy should be used for that patient.

Bob Barrett: Dr. Mockus, tell us how researchers are incorporating assessment of somatic mutations into clinical trials.

Dr. Susan Mockus: We're beginning to see more and more biomarkers for somatic mutations, different vocabulary words, with similar connotations, more and more of those clinical trials are recruiting on patients with particular biomarkers.

The trials are meant to not only look at the efficacy, or how well the drug works, but is there also a correspondent biomarker in the patient that will help us rapidly predict those patients that will respond to that therapy or even not

respond to that therapy. So most of the trials we're seeing that are newly recruiting on patients do have that biomarker data component.

Bob Barrett: What are the barriers to effective use of biomarker data in those clinical trials?

Dr. Susan Mockus: So we see two major barriers right now at biomarkers and clinical trials, it's not only in clinical trial registries but also in scientific publications in general. The first major barrier, it's really a language problem. The way we name genes and we name variants is not consistent across the field and in the community. This make it very difficult to know if, in a clinical trials recruiting on particular mutation, is that the same mutation in a different trial? It's a matter of semantics. You maybe drink out of a coffee mug and I may drink out of a coffee cup. Mug and cup are the same thing, we have to have the ability to know that, and so that's one of the biggest barriers with clinical trial. There's no consistent way that we capture mutational data in these trials, and that prohibits us from doing cross analysis, comparative analysis across different results from clinical trials. So that data analysis blind spot of nomenclature and how we name things is one of the largest barriers.

The other barrier that we have, as well, is this lack of disclosure. So we know that many trials -- there're federated requirements to include in clinical trials that are happening. However, there's no regulation that they have to include what biomarkers are being looked at, and so there should be more open disclosure of those particular biomarkers. That will enable better patient recruitment and better analysis across studies.

Bob Barrett: Well, finally doctor, tell us about the solutions you propose in your article to address these barriers.

Dr. Susan Mockus: In the article, what we've done is outline the problem, these barriers that we see, and the potential solutions for them. The first solution is to get our semantics on sync in the community. One of the ways to do that is to have specific ways we name genes, and there are societies out there like HUGO, the Human Gene Nomenclature Committee, that has a recommended way we call a particular gene, and in addition, what we call a "genetic variant," there's also societies that have rules and regulations of how we should call those genetic variants. The one that we use most often is called "HGVS", it's the Human Genome Variation Society.

So the first, that we have to have an acceptance of how we name genes and how we name variants, then we need to build systems to be able to input the data in the same way. For example, in our clinical knowledge based, we use a

regular expression system, and that system means that even though you have multiple ways to call a genetic variant, it could only be entered into the system, it forces you to enter it into one particular vocabulary. The reason that's important is because it also guarantees retrieval of that data in the same manner. If you have multiple people working on the system, like we do here at The Jackson Lab, then you know the system has been built so all of those different people are putting information in the same way, so we can rapidly retrieve it. Those are the main proposals that we've outlined in the paper. How do you name a gene? How do you name a variant? How do you try to build a system that enforces that so you can have consistent and reproducible retrieval?

Then the last barrier that we focused on in the review article was in regards to programmatic access. And it's particularly related to clinical trial registries, in which clinical trials will change on a daily basis, new trials will be added, deleted, et cetera. So one of things that we think is really important is that we have a way to programmatically check and see what biomarkers those trials are recruiting on, and then in addition have, by doing that, we'll be able to update our systems internally. It's not something that any human being could do. We definitely need the aid and so it requires that the registries have a way to input that. Right now, biomarker data and the eligibility component of the trial -- it doesn't necessarily have to be there, it's all over the place, there's no definite spot where a computer could even go in to pull it out.

So those three things, gene naming, genetic variant, and programmatic access are pivotal to our steps in precision medicine.

Bob Barrett: That was Dr. Susan Mockus, the manager of Clinical Curation and Analytics at The Jackson Laboratory for genomic medicine in Farmington, Connecticut. She has been our guest in this podcast from *Clinical Chemistry* on Clinical Trials in Precision Oncology.

I'm Bob Barrett. Thanks for listening!