Podcast Interview: Elaine Mardis

I’m your host Prashant Nair and welcome again to Science Sessions. Eight years ago, the National Cancer Institute and National Human Genome Research Institute together launched a colossal effort called The Cancer Genome Atlas to catalog the genetic mutations that afflict cancer cells, helping to vault cancer diagnosis and treatment into the era of genomics and molecularly-targeted drugs. Last fall, a large consortium of researchers, including National Academy of Sciences member Elaine Mardis, reported the results of an analysis called the Pan-Cancer Initiative, which compared the molecular profiles of 12 types of cancers to glean similarities, differences, and recurring themes in the pattern of DNA, RNA, protein, and epigenetic changes that mark various cancers. By comparing the data across the 12 cancer types as well as the different technological platforms used to collect the data, researchers hope to obtain a manual for the molecular profiling of cancer. The manual would help answer fundamental questions such as whether the large alterations in genome structure seen in some cancers have any association with the type of tissues in which such changes occur and whether the kinds of changes amenable to treatment in one type of cancer can be similarly targeted in another type. Mardis, a professor of genetics at The Genome Institute at Washington University, St. Louis, is well-known for her leading role in developing next-generation sequencing technologies for the management of human disease. I caught up with Mardis about her involvement in the Pan-Cancer Initiative at a genomic medicine meeting in La Jolla, California.

Mardis: Pan-Cancer was really just a way of saying if we just sort of take an unbiased look at what are the similarities and differences across cancer types, I think mainly focusing on the similarities as opposed to the differences, that from the standpoint of mutations, there are a very large number of shared genes that share high mutational burden across tumor types, and moreover, we are also reinforcing the long-held notion that cancer is not just a disease of genes but a disease of pathways, and so really reinforcing the fact that there are major biological pathways in the cell that are significantly impacted by mutation.

PNAS: I asked Mardis to give a few examples of the kinds of analyses carried out as part of the Pan-Cancer Initiative.

Mardis: So a lot of the work that’s being done now from a functional standpoint is primarily involving, for example, the cancer cell line encyclopedia that was exome sequenced so we can correlate the mutations found in human cancers to mutations that have already been characterized for those cell lines, and begin to look at functional aspects such as large-scale short hairpin RNA knockdowns, for example. Or perhaps even, moving into the future, these genome editing technologies like CRISPR, for example. So I think much of those efforts are just on the upswing now as we’re completing the census of cancer genes, if you will, from the larger discovery effort in TCGA.
PNAS: So what are some of the challenges tied to converting the data from such discovery efforts into meaningful treatments for patients?

Mardis: The most challenging aspects right now certainly are still the analytical aspects, but I do think that the translation is going to be a rate-limiting step. And what I mean by that is that the way I view TCGA and the data that have been generated through TCGA is it's really foundational knowledge. So it sets the baseline of our understanding about cancer and how the genome is altered in cancer. Turning that into an interpretational tool for translation I think remains to be done. Part of what’s missing, as I’ve said, is the functional piece, because that’s a really critically important interface between foundational knowledge and application of foundational knowledge, which is really what translation is. From the analyses that we’ve done, for example, of potentially actionable genes that do or don’t have therapies already identified at some level of the pharmaceutical pipeline, there are still a lot of drugs that remain to be developed. The wealth of data coming out of the TCGA has indicated a lot more potential drug targets than maybe pharmaceutical companies were aware of already. So it potentiates a lot of new drug development, and that’s good for lots of reasons, ultimately, hopefully good for patients.

PNAS: I wondered whether cancer as a disease posed particular challenges to genetic sequencing.

Mardis: I will say that cancer in particular in the clinical setting from our experience is never presenting the perfect sample to you that you’d like to be sequencing. So there are numerous challenges that are essentially a function of the reality of the disease – small numbers of tumor cells that are available to provide DNA or RNA for assays is probably one of the biggest challenges. And the fact that when we are sampling tumors, you know, the amount that’s available for genomics as opposed to conventional pathology, there’s always going to be a tension there. And so, as we transition between what we used to do and what we’re now doing i.e., genomic analysis, we’ll work through that tension and we’ll do the best that we can, and many people, including pathologists among them, are predicting that ultimately much of next-gen type assays will essentially supplant conventional pathology.

PNAS: With the advent and increasing use of next generation sequencing technology to decode entire genomes, I asked Mardis whether whole genome sequencing might eventually obviate the need for disease-specific gene panels now in use.

Mardis: You know, you’re sort of preaching to the converted here, asking someone who already has a preexisting bias. I just want to be clear about that. The challenge in whole genome sequencing is the data analysis, so from a clinical standpoint and from a reimbursement standpoint, we’re always wanting to do whole-genome analysis but not always being able to fit that into the cost and timeframe that’s relevant for the patient. So I think there’s still a huge
opportunity and a lot of work to be done not only to reduce the cost of the sequencing, to reduce the cost and time of the analysis so that it fits, if you will, into a clinical timeframe that’s going to be relevant for patients.

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