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Predicting the Cost and Pace of Pharmacogenomic Advances: An Evidence-Based Study

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Guest:
Dr. Ramy Arnaout is an Assistant Professor of Pathology at Harvard Medical School.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett. Genomic research had been widely expected to transform medicine, but progress has been slower than some have expected. To critics delays represent broken promises and/or a sign that at least some of the money spent on genomic research might have been better spent elsewhere.

In the April 2013 issue of *Clinical Chemistry*, Dr. Ramy Arnaout and his colleagues of the Harvard Medical School published a paper regarding the cost and pace of pharmacogenomic advances. Dr. Arnaout is Assistant Professor of Pathology at Harvard and he is our guest in this podcast.

Dr. Arnaout, it's been 10-years since the human genome was first sequenced. Some people have wondered why there hasn't been more progress while other researchers say we have learned a lot. Did that debate have anything to do with your work?

Dr. Ramy Arnaout: Yeah it had everything to do with it. So my research group works on genomics, I teach genomics. I really believe in genomics, so do many of my colleagues. But when I think back, ever since I was a medical student, I've heard people express skepticism about genomics.

I hear people say, sure, it's led to a lot of cool science, but how many people has it really cured for all the money that's gone into it? And by the 10th anniversary of the draft sequencing of the genome which was a year two ago now, you are starting to see this skepticism in the press. You read articles with titles like Revolution Postponed or Bursting the Genome Bubble, things like that.

So with some people it had gotten to where you are either for genomics or you are against it. It was almost like a theological or philosophical divide and that just didn't seem like the best way to be thinking about the field.

So a couple of us, couple of my co-authors and I got to talking, and we thought well it wouldn't be better if genomic research were more like a store and you could just walk in and say well, how much for curing this disease or that disease or when we have that done by, then we could all sit down together and compare numbers instead of philosophies.

So that seemed like a better way of getting somewhere and that's really where the study came from.

Bob Barrett: Why pharmacogenomics?

Dr. Ramy Arnaout: It's a good question. When you look across genomic medicine, I guess I'd have to say there are a lot of exciting things going on. There is non-invasive prenatal testing. There is whole genome sequencing to diagnose medical mysteries. There is sequencing cancer. There is sequencing outbreaks of super bugs, sequencing the immune system which is something we are working on in my lab.

So ten years after the draft human genome, all these things are actually happening, and it's very exciting for me and my colleagues, not just because our research is in genomics, but because we practice pathology and so many of these things fall under the umbrella of clinical chemistry, clinical microbiology and molecular pathology, and the other subspecialties in our field.

But of all of them, the one that's probably furthest along is pharmacogenomics, which is choosing or dosing a drug according to the variants in your genome that help make you who you are. It really is personalized medicine. And since it's furthest along, we thought pharmacogenomics would be most likely to have the data that we could use in order of forecast where things are going.

Bob Barrett: Give us an example of where pharmacogenomics is poised to make a difference for patients, as an example of genomic medicine?

Dr. Ramy Arnaout: Well there are several which we discuss in our study, but the one people are probably most familiar with if they have heard about any of them, really the poster child, is drug called is Warfarin. And Warfarin is a blood thinner that millions of people, especially older people with heart disease, use to prevent getting blood clots, which can lead to strokes and death, and as you can imagine if your dose is too high, you bleed which can also be life threatening.

So the problem is different people need different doses and without looking at the genome you can't predict who will

need how much, but if you do look at the genome, researchers working in genomics have found that a set of just a few known genetic variants do a pretty amazing job of predicting what dose you will need.

So that's an example of where pharmacogenomics, choosing a dose according to which of those variants you have, is poised to make a real difference. And there are hospitals out there right now that are in fact doing this.

Bob Barrett: So in this case you are talking about drug related adverse outcomes. This is a big problem?

Dr. Ramy Arnaout: Yes so things like bleeding or clotting in response to Warfarin -- in fact by any measure. You can think of two kinds of adverse outcomes. They are the dramatic ones like bleeding or having a bad reaction to a drug and those are called adverse events.

At last check they cost about 80 billion dollars a year across the healthcare system just for inpatients. And then there is when a drug simple doesn't work for you and who knows what the true cost is of that. So yes this is a huge problem which is one reason we were interested in addressing it.

Bob Barrett: And you have used predictive methods like what they use for presidential elections and to predict the weather to figure out how much it will cost and how long it will take to cut drug related adverse outcomes in half?

Dr. Ramy Arnaout: That's right. So in modeling there is a broad class of methods called Monte Carlo algorithms, where the key is to sample from data you already have in order to make extrapolations and predictions about the future. It's named after Monte Carlo of the place for reasons that we don't have to go into, but you heard right in Monte Carlo, so methods like these are used wherever you have a lot of complicated data, whether that be predicting elections, to stock markets, to the weather, and so we thought that provided a useful approach given the data that we have for forecasting in genomics.

Bob Barrett: So how much and how long?

Dr. Ramy Arnaout: Well, according to our model, we think we are looking at something under 10 billion dollars over the course of 20 years, which boils down to less than half a billion dollars a year. And now to put that in context, that's under 10% of the annual budget of the National Institutes of Health which funds a lot of this research.

It's under 5% of the total annual research budget of the pharmaceutical industry and under half of 1% of the cost of

annual payments made by US health insurers. And our total, which would cover learning how to better choose and dose something like 40 or 50 existing drugs, is about the same as what it costs to develop just four or five new drugs from scratch.

Also, 20 years isn't that much longer than the time that currently takes to develop a new drug from scratch which is 12 to 15 years.

Bob Barrett: Doctor, what else have you learned?

Dr. Ramy Arnaout: All kind of things, let's see. First that we are going to have to be patient, that's probably be most interesting thing to come out of this work. We all know research is an investment. The way it works is you have to pay money up front but might not see the payoff for few years, and that just what our model showed.

It showed that even if we were to invest the close to half a billion dollars a year, it would be still be five or seven years before we could hope to see a meaningful improvement in clinical outcomes. Thereafter, improvement would come fast and furious, but we would have to be patient for that five to seven years.

Second, we learned that we might be able to go faster with a more coordinated approach, what we called in our study a kind of "50,000 Pharmacogenomes Project," kind of like the Million Veterans project put on by the Veterans Administration for sequencing veterans, or the Thousand Genomes Project which is a follow up to the human genome project that we talked about earlier. And that's very hopeful to be able to go faster and for less.

And the third thing that we learned is just how useful it is and how interesting it is to have numbers. And I say that according to the reactions of people who have read our study and who we have discussed our findings with.

Some people look at the numbers and think wow this is a bargain. Others look at it and think it's a waste. It's really been a Rorschach test, but at least it's getting people talking about numbers that people can agree on and value for money, instead of just talking philosophy or genomics good or genomics bad, and in that sense we have been very harden by that.

Bob Barrett: So is this the last word in prediction for genomic medicine?

Dr. Ramy Arnaout: Oh, I'd say far from it. I think part of the reason we thought it was important to do this study is because we hadn't seen anything else like it. Basically we didn't have a very good

idea about what it would take, not even to an order of magnitude in terms of dollars or years. And so we thought it would be best to just start a conversation, to do our best to pour over the data, put numbers on paper.

And what we hope is that the academic community will read it, will build on it, and test the assumptions that go in as the model, all of which are in paper, extend this approach to other areas of genomics, like prenatal testing, cancer, infections, and the other things we talked about before.

And we also hope that the public and policy makers will read and discuss these findings, and use it to help set their expectations about when and how the genomics revolution will arrive, and how much it can be expected to cost us taxpayers.

And I suppose finally we hope big thinkers will read it and be able to use it to bend the curve so to speak to make better clinical care happen faster and for less, which is after all why in work in genomics in the first place.

Bob Barrett: Dr. Ramy Arnaout is an Assistant Professor of Pathology at Harvard Medical School. He is been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening.