EPISODE FOUR:

Charting a Path to Prevention

Dr. Keith Stewart, Mayo Clinic | January 7, 2018

Welcome to The Precision Medicine Podcast, where experts come to discuss the problems oncologists, reference labs, and payers face as precision medicine grows, and consider solutions for advancing the quality of patient-centered cancer care.

Jerome Madison: Welcome to the precision medicine Podcast. I'm Jerome Madison, Vice President of Provider Relations for Trapelo and one of the hosts of the Precision Medicine Podcast. Today, we have Dr. Keith Stewart, the Carlson and Nelson Endowed Chair of the Mayo Clinic Center for Individualized Medicine. Dr. Stewart, thank you for taking time to be on the show.

Keith Stewart: Well, thank you for inviting me, Jerome. Pleased to be here.

Jerome Madison: Now, for those who can read your dossier out there, you've done a lot of work in the area of precision medicine. And, when you listen to the current conversation, there's many who feel that today is the beginning of the era of precision medicine. But you were doing research on gene sequences to find drivable targets in the 90s. So, can you tell us what drew you to this work, and where we are today in the big picture of achieving precision medicine?

Keith Stewart: Well, my own experience started back in then 1990's when sequencing a single gene was a six-month-long endeavor and a triumph to sequence one gene. And it really wasn't until the sequencing of the human genome in 2003, and the subsequent drop in pricing over the subsequent years, that have made it possible to study the whole genome in real time at reasonable cost.

Keith Stewart: So, we are still really in the earliest days of precision medicine, as it will evolve over the next few decades. I like to tell people it's like being in a radiology department, when chest x-rays were first discovered 100 years ago, and we've got a long way to go. So, I would say that, yes, it's here, in certain instances already, but it's certainly still in its infancy.

Jerome Madison: Yeah. You are one of the researches that I've heard recently on a panel that talked about prevention when using precision medicine tools, and you talked about the healthy genome. What does that mean, and how is that relevant toward what we do in everyday life?

Keith Stewart: Yes, I've had people tell me there's no such thing as a healthy genome, unfortunately. But what we mean by that is the genome of people who are still healthy and haven't' yet developed significant illness. And it has become a significant focus for us at Mayo Clinic over the past few years as we move more

from diagnosing and treating existing disease to trying to use genomics to prevent and predict, not to predict and prevent.

Keith Stewart: In some areas, cancer being the mother ship here at precision medicine, it's become part of our daily routine. And there are some malignancies that point to one cancer for example, where treating a patient without genomic information would be almost unheard of today. Other diseases like Leukemia and Lymphomas fall into the same category.

Keith Stewart: We've also seen remarkable progress in diagnosing rare disease through a program we call our diagnostic odyssey program. And, in fact, many of the diseases we treat at Mayo Clinic are under the category of rare diseases and often have gone undiagnosed for decades. But the big opportunity, and I think the one that has got us most excited, is the possibility, because of the declining costs and advancements in technology, that we can sequence the genome of people while they're still well, and try to predict and intervene in a way that might reduce the burden of cancer; that might reduce the instance of inherited disease; that might one day might venture to find who's at risk for Cardiac Sudden Death and other illnesses. So, that's the power and the promise of sequencing healthy genomes.

Jerome Madison: If I'm not mistaken, you and I believe your team at the Mayo Clinic, you guys are involved in the All of Us project that is sponsored by the National Institutes of Health. What's the goal of that program?

Keith Stewart: Well, this is an ambitious program that was started during the Obama presidency, but was a bipartisan supported initiative to sequencing, or to at least study one million Americans. And part of that longitudinal study would be to do genomic sequencing for exactly the reasons we just discussed—to see if we could figure out how to use the genome in improving the health of the nation. Those one million people are now being enrolled. The Mayo Clinic's role is to store, to collect and store, retrieve and dispense the bio specimens from those one million individuals.

Keith Stewart: So, we will be collecting, we are and will be collecting 35 million samples—a split between our Rochester and our Florida campuses—for the use of researchers over time to better understand the part of the genome and human health. That's our role. It's a very ambitious plan. It follows similar initiatives in other countries. For example, in England, the company, Genomics England, on which I actually sit on their board, has just announced the completion or are about to announce the completion of sequencing 100,000 whole genomes for patients to be treated in the National Health System there.

Keith Stewart: So, there are similar initiatives underway worldwide. But achieving the U.S. effort of one million people will be a very important landmark and important resource for researchers to use for decades to come.

Jerome Madison: Wow. That's quite a bit. So what do we do with all of this data? How do we make it interconnected?

Keith Stewart: Well, I think that the organizers of this All of Us project have a number of goals. One, they want to make sure that it's truly representative of the population in the

United States: that minorities are represented in equal proportion to the presences in the country; that it covers the spectrum of age and other diversity issues. They will also, I think, tell you that it's not just about genomics, in this case, it's about other biomarkers. It's about mobile monitoring, wearable devices and not just genomics.

Keith Stewart: It's a broader effort than just purely looking at the role of the genome, but other optics, other biomarkers, other environmental influences and outcomes. But I think some of you have heard of the Framingham Project which started I think in the 1970's. There's just been a goldmine for researchers for the last 40 or 50 years. This will build on projects like that in a very extensive way, and I think will be the gift that keeps on giving to medical research in the United States and worldwide.

Jerome Madison: Sure. Your program at the Mayo Clinic has a branded GeneGuide. What are conditions that are currently contained in the Mayo Clinic GeneGuide, and how do patients leverage that information?

Keith Stewart: Well, one thing we've already explored and talked about on this podcast are efforts in cancer, rare disease and healthy genomics. Those are all services that we offer to patients who are actually able to come to me or clinic for care. And we realized that there was perhaps a gap in the direct-to-consumer or at least consumer-initiated testing market for a more serious health -elated product that introduce people to their genome, that educated them of what it could and could not tell them about their health.

Keith Stewart: And, so, we developed this as a “physician order,” but “initiated by consumers” application that runs on a website through the company Helix—a bit like your iPhone—where your genome is sequenced to Helix, and then you can purchase apps over time: Mayo Clinic GeneGuide being one of those. And, what we're trying to do there is to introduce to those people who have not yet been exposed to their genome to some of the health knowledge that you can derive from that product. So, it includes four different categories of testing, which encompass about 20 genetic tests.

Keith Stewart: It tests for, for carrier inherited conditions or conditions you would inherit from your family. Those include things like cystic fibrosis, hearing loss. It also includes in the app what we would call more environmentally sensitive predispositions; things like cardiac disease, atrial fibrillation, macular degeneration. It includes some pharmacogenomics. So, your ability to metabolize drugs such, as over-the-counter medications for peptic ulcer disease or heartburn, Ibuprofen for muscular skeletal pain, as well as your risk of anesthesia with some specific inherited conditions.

Keith Stewart: And finally we look at some medically relevant traits such as lactose intolerance and alcohol flush. We've also built into the APP the ability to document your family history and pedigree to do a breast cancer risk assessment and to get some of your medical ancestry, at least on the continental level. So, it contains a lot of information. It's a heavy and educational tool, and we hope it's something that people will use to both educate themselves and perhaps others.

Jerome Madison: The Mayo Clinic Center for Individualized Medicine—after hearing you speak on various panels and of course the information you're giving here—you guys seem to have a very broad vision of how precision medicine can benefit all patients, both healthy and sick. But how do we get the healthy patients to care more about genetic testing?

Keith Stewart: Yeah, that's a good question. And that's one of the reasons we built the APP is we feel there is an education gap, and it's not just in patients, it's also in healthcare providers and the payers. Others are broad deficit, because genomics is relatively new and most of us, including myself, I had no education in genomics when we went to medical school or trained as a nurse, or an x-ray technician. So, there is a deep need for education across a wide spectrum of the public and the health care community. I think people have paid attention to genomics, they've read about it in the media, they're aware of it, they've seen other companies with health care products in the marketplace.

Keith Stewart: I think there is an awareness, but still a large gap in translating that awareness into utilization. So, that's what things like the All of Us Program, our Mayo Clinic consumer app or some of our efforts in offering this to healthy patients who come to Mayo Clinic. A lot of those efforts already in do that. We do have plans for example, Jerome, to expand our efforts substantially in terms of the volume of patients we are testing. We would hope over the next couple of years to move from hundreds or even thousands of patients to hundreds of thousands of patients getting genomic sequencing that come to our clinic and other institutions around the country.

Keith Stewart: Others have done this, of course, like Geisinger Health Care System, very successfully has sequenced hundreds of thousands of people, and that's just something that we feel is worthy of emulating.

Jerome Madison: Dr. Stewart, for those who will Google you in particular, they come across the groundbreaking research that you and your team did on an older drug, thalidomide, which was used to treat insomnia for pregnant women back in the fifties and sixties. But, unfortunately it resulted then in thousands of birth defects and ultimately pulled from the market. However, your team discovered that this drug was particularly effective in treating multiple Myeloma, which is fascinating in itself, but what did you learn from that research that we can apply today in finding new uses for existing or even older drugs, and what led you to even examining that drug for better uses?

Keith Stewart: Well, this is a fascinating story, and it is really a testament to the power of genomics and precision medicine. The story, as you just illustrated, is that thalidomide was marketed initially for morning sickness as a very safe drug because in testing in animals, particularly mice had shown no side effects, including in pregnant mice. It turned out to be profoundly noxious in humans with significant birth defects, and it eventually almost disappeared from the market, but it lingered around to treat this very small population of patients with leprosy.

Keith Stewart: It was discovered accidentally to be effective in the cancer I treat as a physician, which is called multiple myeloma. But we never really understood how it worked,

and I was engaged along with many other people in trying to understand how this morning sickness pill could possibly treat the cancer. And then we had a breakthrough when a group in Japan did studies on the genetics of this drug in its ability to cause birth defects, and they found that it actually binds very specifically to a single gene, a single protein, which is made by a single gene.

Keith Stewart: And when we saw that, we immediately went to work to determine if this was the same target that was important in multiple myeloma treatment. And it turned out it was. And, so, now we have very precise understanding of how this old drug binds to specific genetic target and turns on a genetic machinery within the cell that results in the destruction of this particular cancer. These drugs are widely used now in this cancer and other cancers. There are ways you can test ahead of time to see if the gene is functional. If it's mutated, then the drug won't work.

Keith Stewart: And it's actually led to a whole new field in drug discovery where you can take half of the molecule and modify it to degrade multiple proteins. So, diseases like Parkinson's and breast cancers and other targets have become much more amenable to treatment as a result of this discovery—originally in Japan—and then work that we engaged in ourselves. So, it's really a beautiful example of how genomics and precision medicine can come together to explain old mysteries but also lead to new therapies moving forward.

Jerome Madison: Yeah. Fantastic. Fascinating work. When we look at areas in which you guys, I mean, very broad application of precision medicine tools. When we talk about specifically disease prevention, what data is needed before we can really routinely use genetic testing for disease prevention?

Keith Stewart: Yeah, so with respect to the payment for genetic testing, in cancer it's fairly routine to get paid, at least for some basic genetic testing and newly diagnosed patients is becoming increasingly common. That one, we'll get paid for doing a workup of a rare disease patient, particularly if they're younger in the neonatal intensive care unit. But the area where we're not really seeing a lot of payment yet is in this healthy individual sector, and it's not just sequencing the genome, it's also something we call pharmacogenomics, which is the ability to look at the genes and metabolize drugs and try and predict adverse events or side effects or the tolerance of specific prescription medications.

Keith Stewart: The problem there is that the promise of the testing takes many years or even decades perhaps to come to fruition. And, so, I think probably correctly insurance companies and a lot of peers have held off in reimbursing these tests until there's better evidence, that by doing such testing, you're not just adding to health care expenses, but you are showing enough benefit that it is worth paying for, even if the benefit is deferred. It's going to take some time to accumulate that evidence.

Keith Stewart: The All of Us Program we talked about will be one of those ways in which that's done. We have conducted pharmacogenomic tests in over 10,000 patients and we've run the world's biggest randomized phase-three trial of the drug, Plavix, and it's pharmacogenomic in over 5,000 patients. When all these bits of evidence start to fall in place, we do suspect that this will become over time reimbursable through other means. Right now, for most individuals, it's an out-of-pocket expense,

although some of them who were farsighted, large employers are beginning to adopt this as a benefit for their employees.

Keith Stewart: One of the reasons I think it will become reimbursable is that the cost is now pretty low. We can certainly do pharmacogenomic testing for just a few hundred dollars. We can do whole genome testing for around a $1000, or just slightly over that for healthy individuals. And I think for tests that you're born with and never changes in the 95 years you're alive, I think this is going to turn out to be a real bargain. But we do need to accumulate the evidence in support of that. I think, as you know, there are some screening tests I'll give you, prostate-specific antigen to detect prostate cancer.

Keith Stewart: It's a very sensitive test, but it turns out perhaps that it's become controversial in that you find a lot of cancers, perhaps you end up doing surgery and procedures that may not have been necessary. So, I think there's going to be quite a long time until we have enough evidence to see this routinely applied.

Jerome Madison: Our goal here at Trapelo is to lead the conversation with payers, providers, and, of course, genomic testing companies, to bring them together on this conversation of access and scale of precision medicine. And you've just been talking about it, because where the rubber meets the road is reimbursement. But, what are your ideas of how and why insurance companies should pay for precision medicine tools?

Keith Stewart: Well, again for cancer rare disease, I think the benefits are much more immediately obvious in cancer. Getting the right drug to the patient at the right time is going to actually save money and produce better outcomes. I believe, and again, I think some would argue that the proof of that still also needs to be firmed up. Rare disease. I think for, particularly for children, who may have lifelong disabilities, finding the right diagnosis and preventing future unnecessary testing, perhaps leading to specific therapies. Also, I think eminently reimbursable in the short term/near term.

Keith Stewart: Again, when we come to healthy genomes, my own belief is that we will first see advantage in pharmacogenomics. I had my own pharmacogenomics done, too. I recommend it for everybody. And the test I had done, which only cost a few hundred dollars, looked at 450 prescription medications. And, I often tell people that I don't think I'll ever take a new medication without consulting that list, to make sure that it's on the "safe to take" list before I actually swallow. And we hope that that will demonstrate itself as a reduction in the millions of drugs, side effects that are experienced every year in the United States or this estimated over a hundred thousand deaths due to drug adverse events.

Keith Stewart: I think we can really impact that. So, I do think that even the cost, relatively inexpensive tests and given the potential benefits that this is likely to be something that people will be paying for soon. As I already stated, I think the sequencing everybody's genome, which is ultimately our goal.

Keith Stewart: And I should have said this earlier, At Mayo Clinic, we have a vision that anybody that comes to our institution in the not -too-distant future, will be able to avail

themselves for genome sequencing as part of their healthcare. But I think that vision is still some ways off, and we need to build a base of solid evidence to support that, I think, before it will be routinely reimbursed.

Jerome Madison: For those out there who do want to find more about what you guys are doing at the Mayo Clinic Center for Individualized Medicine, what's your website? Where can they connect with you via social media? Where should we send them?

Keith Stewart: Well, if you just Google Mayo Clinic Center for Individualized Medicine, it would take you to our website. We also have a Facebook page. We have presence on twitter and, like you, we do a regular blog that people can avail themselves of. All of it should be fairly easy to find through one of those outlets.

Jerome Madison: Absolutely.

Keith Stewart: Of course, if you're a patient, and you want to come and see us or visit with us under a specific genetic issue, then please feel free to call me or clinic, and we can help you out.

Jerome Madison: Outstanding. Well, we want to thank Dr. Keith Stewart, the Chair of the Mayo Clinic Center for Individualized Medicine, and of course, all of our listeners for joining us today. We hope you'll tune in for the next episode of the precision medicine podcast, and, don't forget, you can download full transcripts of today's episode at precisionmedicinepodcast.com. If you enjoy this episode, you probably know someone else who would, too. So, please tell them. They'll thank you, and so will we.

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About Our Guest: A. Keith Stewart, MB.ChB., MBA

Keith Stewart is a consultant in the Division of Hematology and Oncology, Department of Internal Medicine at Mayo Clinic. He currently serves as the Carlson and Nelson Endowed Director of the Mayo Clinic Center for Individualized Medicine and is recognized as the Vasek and Anna Maria Polak Professor of Cancer Research. Dr. Stewart's current responsibilities at Mayo Clinic relate to the application of genomics to human health across the spectrum of discovery, translation, and application to clinical practice.

Dr. Stewart has served in several leadership roles across both research and clinical practice at Mayo Clinic, including as Dean for Research in Arizona, and as a member of the Arizona Executive Operations Team and Clinical Practice Committees. He has served on multiple boards for both non-profit and commercial organizations, including currently as a Non-Executive Board member with Genomics England and the Scientific Advisory Boards of Helix Inc. and Veritas Genetics, Inc.

His own research interest is in the genomics and biology of myeloma, and he has led numerous clinical trials of new drugs for this blood cancer. Dr. Stewart has over 25 years of sustained national funding for a laboratory research program and has authored over 300 journal articles and other written publications. He has served as an Associate Editor of Blood and ASH Clinical News.