

**Article:**

J. Park, L. Kricka, P. Clark, E. Londin, and P. Fortina
Clinical Genomics: When Whole Genome Sequencing is like a Whole-body CT Scan.

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Guest:

Dr. Jason Park is Director of the Advanced Diagnostics Laboratory of the Children's Medical Center, Dallas, and Assistant Professor at the University of Texas, Southwestern Medical Center.

Bob Barrett:

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

Over the past decade genomic testing has emerged as a clinical tool available in multiple hospital and independent laboratories across the United States. In the November 2014 issue of *Clinical Chemistry*, an opinion article titled "Clinical Genomics: When Whole Genome Sequencing Is like a Whole-body CT Scan" framed the clinical utility of genomic testing in the context of another recently transformative test, whole-body computed tomography scanning, more commonly known as a CT scan.

One of the authors of this *Clinical Chemistry* opinion article is Dr. Jason Park, Director of the Advanced Diagnostics Laboratory at the Children's Medical Center, Dallas, and Assistant Professor at the University of Texas, Southwestern Medical Center in the Department of Pathology, and the Eugene McDermott Center for Human Growth and Development. Dr. Park is our guest in this podcast.

Doctor, first tell us what is clinical genomics?

Dr. Jason Park:

Clinical genomics is the medical practice of using genomic tests to diagnose and manage patients. Genomic tests may broadly include microarray tests which look for deletions or duplications of regenerative DNA in a patient's genome.

In addition to a microarray test there are genomic sequencing tests that examine the regions of DNA which are the blueprint for proteins. This is known as exome testing. Genome sequencing tests may examine both the regions which are the blueprint for protein as well as many other regions. This is usually known as whole genome sequencing.

Bob Barrett:

Can you give us some examples of when genomic testing has been used clinically?

Dr. Jason Park: Microarray genomic tests have been used clinically for almost ten years now in the United States. Importantly, in early 2014 the Food and Drug Administration cleared the first microarray test system to be used for the diagnosis of chromosomal abnormalities.

Another type of test, genomic sequencing, is being used to test for multiple genes. Some clinical laboratories are providing exome tests which theoretically include all genes. Other clinical laboratories focus on target panels of genes which are associated with a specific clinical syndrome. The syndromes being evaluated by this approach are numerous and include, for example, epilepsy, immune dysfunction, and inherited cancer syndromes.

In the case of inherited cancer syndromes, the National Comprehensive Cancer Network (the NCCN) now recommends using genomic sequencing testing for patients that have tested negative by more common and highly penetrant familial cancer gene test. So patients that are negative by the usual cancer gene test are now being recommended to be sequenced by these larger genomic sequencing panel tests.

Bob Barrett: Let's talk about CT scans and genomics, what do they have in common?

Dr. Jason Park: Bob, as I have watched genomic testing enter into clinical use in my hospital and other hospitals across the country, I was struck by how this is a truly transformative technology which is however still in its infancy. We are now testing hundreds of genes at a cost similar to testing only one or two genes by the traditional DNA sequencing methods.

However, along with my enthusiasm for genomic testing, I am acutely aware of how as a medical community we are generally not prepared on the appropriate use of this technology. I think genomics is finding its clinical role in a similar manner to CT scanning. The clinical application and maturity of CT scanning is probably at least a decade ahead of genomic testing, however.

Bob Barrett: So genomic testing parallels CT scanning because they are both transformative technologies?

Dr. Jason Park: Right, they are both transformative technologies which have utility in certain clinical scenarios. For example, CT scan imaging technology is an invaluable tool in clinical medicine that uses x-rays to produce cross-sectional images of the human body. The CT scan is a relatively noninvasive procedure that allows us to basically see into the body.

However, not all clinical scenarios need a CT scan. A patient with a traumatic injury to only say their foot doesn't need a CT scan of their entire body. Just as all clinical scenarios do not require a whole body CT scan, not all clinical scenarios require whole genome sequencing.

Bob Barrett: But while I understand the inappropriate use of CT scans may risk unnecessary radiation to the patient, what risk is there in doing genomic testing?

Dr. Jason Park: In addition to the risk of exposure to radiation, whole body CT scans do have an additional risk of incidentally detecting things of unknown significance. These findings are referred to as incidental, and incidental findings are typically unrelated to the original clinical indication for doing the CT scan, and they may or may not represent true disease. However, although they may be biologically benign, incidental findings can lead to harm in the form of patient stress, anxiety, and potentially the harm from unnecessary follow-up diagnostic tests or procedures.

Although genomic tests do not pose an immediate physical risk such as radiation; genomic testing does pose an analogous risk to whole body CT scan in terms of revealing unexpected findings or findings of unknown significance.

Depending on the type of information revealed by the test, there may be significant consequences for the patient as well as their related family members.

Bob Barrett: So what kind of consequences can genomic testing information give to patients or family members?

Dr. Jason Park: Well, there are many types of risk from genomic testing information, but a couple that come immediately to mind are, first, there is the potential harm to a patient in knowing their risk of future disease. Second, there can be an unexpected discovery of consanguinity in the family history. Third, these tests may detect a finding of unknown significance which also can have harm.

Bob Barrett: I want to go back to that first reason you talked about, what type of harm can be caused just knowing your risk of future disease?

Dr. Jason Park: Huntington's disease is an example of harm from knowing about future risk of disease. Huntington's disease is a devastating adult onset neurodegenerative disease. For over 30 years we've known that there is an increased risk of suicidal ideation and suicide amongst patients that are asymptomatic, but at risk for Huntington's disease.

We can imagine that an asymptomatic person without any family history of Huntington's disease may have exome or whole genome testing done for preventative health or health screening.

If their genomic test discovers a pathogenic DNA change associated with Huntington's disease, that patient will need both short-term and long-term counseling not only for their future disease, but to help the patient cope with their new and unexpected diagnosis.

Bob Barrett: Interesting! So knowledge of future risk of disease may result in current disease in the form of suicide. What about the discovery of consanguinity? What do you mean by that and how can that be harmful?

Dr. Jason Park: Microarray genomic test performed on a child can not only diagnose disease in the child, it can also inform whether the parents are closely related. Indeed, the test performed on a child can reveal whether the patient's parents are consanguineous or first-degree relatives.

If for example the child's mother is not legally an adult by age, certain legal jurisdictions may require reporting the family to local authorities as a potential sexual abuse case. Thus in the case of an incidental identification of consanguinity, the test result of the child may have significant consequences for the family.

Bob Barrett: So in the case of consanguinity found on microarray genomic testing, there potentially serious legal implications for the entire family. Regarding the final example you previously gave, what is the risk of finding something of unknown significance?

Dr. Jason Park: Whenever we look at the results of any exome or whole genome test from an asymptomatic person, we see that there are thousands of DNA variants that are predicted to change the proteins that are made; some or none of these protein changes will lead to disease.

The genomic research and medical community do not yet have the knowledge to predict the disease causing potential of every single DNA variant. For example, there are about 23,000 genes in the human genome; less than 7,000 of these genes are described in the most comprehensive of databases, and only a fraction of these genes are actively studied by research programs.

So you can imagine when we test for 23,000 genes in a single patient we are guaranteed to identify DNA variations of unknown significance.

However, although these variants are of unknown biological significance, they may be a source of anxiety for the patient as well as the patient's family.

Bob Barrett: So in other words an exome or a whole genome test takes a look at all of the genes and gives us a whole bunch of information that we don't know what to do with?

Dr. Jason Park: That's right, we have a lot of information, but we have insufficient knowledge to interpret all of that information. I am sure that with the completion of each new genomic study we will be better at understanding and predicting which DNA variants are truly abnormal, but regardless of the number of genomic studies, we are likely going to need to head back to the research wet labs to characterize each of these changes and see what they actually mean.

Bob Barrett: So are the potential risks you've mentioned a barrier to broader clinical use of genomic testing?

Dr. Jason Park: Bob, these potential risks are possible barriers to implementation, but they aren't new ones. We recognized these problems from the earliest days of testing single genes. They already exist numerous professional guidelines for managing these risks.

The novel aspect for clinical genomics is that previously existing risks are now magnified in proportion to the larger number of genes tested. Although this raises challenges, I believe that by recognizing these risks we can counsel patients and mitigate the potential for harm.

Bob Barrett: Given these risks, when do you think genomic testing should be performed?

Dr. Jason Park: Well, I go back to the analogy of CT scanning. The CT scan is a powerful diagnostic tool, but sometimes a CT scan is not necessary. Instead, depending on the clinical situation, other imaging technologies that are cheaper and faster may be more appropriate. The use of chest x-rays and ultrasounds are still very useful and relevant in modern medicine. Not every clinical case requires a CT scan; some physicians would say, not every case requires any imaging study whatsoever.

Similarly, clinical genomics is exciting and will become a common diagnostic test at some point in the future. But I predict, there will be clinical scenarios decades into the future where targeted DNA testing, enzyme testing, or no genetic testing at all will remain the standard of care.

Bob Barrett: So it's your view that not everybody will need a genomic test?

Dr. Jason Park: Exactly! If a patient has a specific clinical syndrome which is known to be comprised of defects in a single gene, then we only need to test that single gene. To do a genomic test of all the genes when only a single gene is needed, well, to me that's the same as doing a whole body CT scan for a patient with a suspected broken arm.

In other words, don't order a whole body CT scan when a targeted x-ray is sufficient. Similarly, don't order a whole genome sequencing test when a targeted gene sequencing test is sufficient.

Bob Barrett: So you think there will continue to be a role for single gene testing?

Dr. Jason Park: Absolutely! Not only will there be a continued role for single gene testing, but for certain clinical indications there will continue to be a role for testing a single DNA variant within a single gene.

In addition there are certain genetic diseases that we currently routinely test for protein function rather than the DNA change. This will continue for the foreseeable future.

Bob Barrett: Can you give us an example of a genetic disease caused by a DNA change, but tested by a non-DNA method?

Dr. Jason Park: Sure! There are many examples, but the one I see every day in my pediatric hospital, is the diagnosis of cystic fibrosis. Cystic fibrosis is caused by harmful DNA variants that lead to a defect in a protein channel. The protein channel loses its ability to regulate the flow of chloride ions.

A defect in regulating the flow of chloride ions results in abnormal secretions in the lungs and digestive track, and over many years this causes a very devastating disease. In cystic fibrosis, thousands of DNA variants are known to cause the defects in the protein chloride channel, and there are clinical DNA tests that can identify many of these variants.

However, the gold standard diagnostic test for cystic fibrosis is not a DNA test, but a traditional chemical test known as the sweat test. The diagnostic yield, simplicity, and low cost of the sweat test all are factors that ensure that the sweat test will continue to be done for many years to come.

Bob Barrett: So cystic fibrosis, that's an example where the best diagnostic test is an old-fashioned measurement of salt concentration rather than sophisticated DNA testing. Nice to know everything is not going to be changing, let's look

ahead though. As you look into the next ten years or so, what do you see as the future role of genomic testing?

Dr. Jason Park: I think clinical genomics will be in a role to the future of medicine, and will have a particularly marked impact on the diagnosis and management of rare diseases and in the field of oncology.

However, we are still in the first decade of clinical genomic testing and we are still learning about both the potential utility as well as the limitations of this technology.

The practice of clinical genomics is still in its infancy. In addition to further technological advances and a better understanding of genetic mechanisms of disease, we need a better understanding of the utility, quality, cost-effectiveness, and societal implications of clinical genomics.

Bob Barrett: Dr. Jason Park is Director of the Advanced Diagnostics Laboratory of the Children's Medical Center, Dallas, and Assistant Professor at the University of Texas, Southwestern Medical Center in the Department of Pathology, and the Eugene McDermott Center for Human Growth and Development. He has been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening!