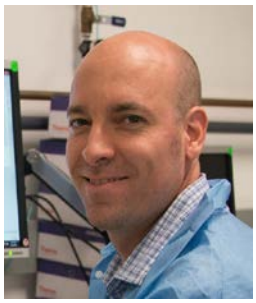
Clinical Chemistry

Advanced Whole-Genome Sequencing and Analysis of Fetal Genomes from Amniotic Fluid



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Guest: Dr. Brock Peters is the Senior Director of Research at Complete Genomics in San Jose, California and of BGI Shenzhen in Shenzhen, China.

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.

Amniocentesis is a common procedure usually performed to collect cells from the fetus to allow testing for abnormal chromosomes. Cells from the amniotic fluid are collected through centrifugation, cultured, and after about two weeks, analyzed by fluorescent *in situ* hybridization, or FISH, or with a microarray to detect abnormal chromosome copy number changes or large chromosomal structural rearrangements. These tests have become the gold standard for detecting Down Syndrome and several other serious birth defects because they have a low false positive rate. However, they are unable to detect the majority of birth defects.

In the April 2018 issue of *Clinical Chemistry*, a paper demonstrated the feasibility of generating an accurate whole genome sequence of a fetus from either the cellular or cell-free DNA of an amniotic sample. The senior author of that paper is Dr. Brock Peters. He's the Senior Director of Research at Complete Genomics in San Jose, California, and of BGI Shenzhen in Shenzhen, China. He's our guest in today's *Clinical Chemistry* podcast. Dr. Peters, what was the overall goal of this study?

Dr. Brock Peters: It's pretty straightforward. We just wanted to see if we could enable highly accurate whole genome sequencing from DNA isolated from an amniocentesis procedure. There really hasn't been a lot of work done on this. We found that both the DNA that you get from cells that are collected in the amniotic fluid or the DNA that's freely floating in the amniotic fluid are both good sources of material for whole genome sequencing and we were able to get highly accurate and reproducible results from both. We actually were able to get DNA of a sufficient quality that we would be able to enable some of our next-generation technologies which we think in the future could enable almost error-free genome sequencing.

Bob Barrett: Doctor, what are the practical implications of this study?

Dr. Brock Peters: The study demonstrated for the first time the sequencing of the whole genome of fetuses from amniotic fluid. This method could be added to current amniocentesis procedures to detect serious birth defects that are missed with current technologies. Most current tests only detect gains or losses of whole or large pieces of chromosomes; single-based changes are completely missed. But since amniocentesis procedures are commonly performed with older parents and older parents are more likely to have kids with serious birth defects, it could lower the rate of children being born with serious birth defects significantly.

Also, it would give doctors a heads-up on potential curable health issues before the child is born. There are some good examples of children who have rare unsolved diseases at birth and it leaves doctors scrambling to find an answer in a race to save the child's life. With amniocentesis sequencing, this would be a much less stressful event with faster results. And finally, it's a genome for life. So it would become part of the child's medical record and be useful for the rest of their lives.

Dr. Brock Peters: Did you find anything interesting in the samples that you studied?

Bob Barrett: We did. I would say the most interesting mutation, and this was something that wasn't present in either of the parents, was in a gene called CHD8. Mutations in this gene have been associated with Autism Spectrum Disorder. And while we can't be sure that the child would eventually develop such a disease, it might alert the child's doctor to look more closely for early signs of autism so that treatment can be started immediately. Not surprisingly, we also found that many of the fetuses are carriers for severe disease but would be expected to be healthy. Finally, we found a few examples where certain drugs might be dangerous in a few children, and if alternatives to these drugs exist, they might be a better choice.

Dr. Brock Peters: Were there significant advances in next-generation sequencing that made this study possible?

Bob Barrett: The biggest advance was that, using our current technology, we were able to lower the amount of input DNA required for sequencing. Some of the early sequencing protocols started from millions of cells of DNA. And in our study, there were times where we only had a few thousand cells worth of DNA so we needed to adjust our methods to enable starting from that few number of cells.

Dr. Brock Peters: Do you see the techniques described in your paper replacing FISH or other currently used procedures?

Bob Barrett: I think it's a good question. I think that at least for now I don't see that happening. FISH is a really good technique for detecting large chromosomal changes and it's been validated and used for many, many years. And so, we don't really have that kind of experience yet, I would say, with whole genome sequencing.

Down the road, I believe that we will and eventually we can replace things like FISH. But currently, I view this more as this is an add-on to FISH or other such commonly used procedures.

Dr. Brock Peters: Well, finally, doctor, let's look ahead. What are your future plans for this technology?

Bob Barrett: I think it really depends on if there's market for this kind of information yet. Currently, we envision developing a smaller test that might only look at a few thousand genes with well-characterized severe diseases associated with them as opposed to looking at the entire genome. The other thing is using amniotic fluid as a great source of fetal material but it's obviously limited in that not every pregnancy undergoes an amniocentesis. Starting from maternal blood would be much more useful since all pregnancies essentially are subjected to some form of a blood test.

BGI as well as other companies currently provide blood tests to detect Trisomy 21, which is the cause of Down Syndrome, as well as some other large chromosomal changes. We can perform a similar test to what we described in this paper on that sample type, and that would be a test that would be helpful to a much larger population of patients.

Another thing to consider is that, as more testing of maternal blood is performed, more patients will get amniocentesis procedures to confirm the results from blood tests, not just those mothers that are 35 years of age or older. We view this as an excellent opportunity for our test because people will want to get the most accurate and comprehensive results to ensure that their unborn child is healthy.

Bob Barrett: Dr. Brock Peters is a Senior Director of Research at Complete Genomics in San Jose, California, and of BGI Shenzhen in Shenzhen, China. He has been our guest in this podcast from *Clinical Chemistry* on whole genome sequencing of fetal genomes from amniotic fluid. I'm Bob Barrett, thanks for listening.