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Simultaneous Prenatal cfDNA Screening of Aneuploidy, Recessive Single-Gene Conditions, and Fetomaternal Blood Compatibility

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Guest: Dr. Dale Muzzey is the chief scientific officer of Myriad Genetics in Salt Lake City, UT.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Professional societies recommend preconception screening for certain inherited recessive conditions, as well as prenatal screening for common aneuploidies and fetal maternal blood compatibility. There are very good reasons for these recommendations, but testing for all three condition categories is cumbersome. It requires multiple different tests and repeated sample collection from both reproductive partners, particularly when the female partner is identified as a carrier of a severe recessive condition.

In these cases, male partner screening can eliminate the need for invasive diagnostic testing, but this is impossible when the male partner is unavailable or a sperm donor is used. What to do? Should we just accept that adherence to professional society guidelines is difficult and recognize that most pregnancies won't undergo complete screening, or can technological innovation overcome the current challenges?

A research article in the June 2026 issue of *Clinical Chemistry* describes a promising solution, a three-in-one test that does not require a paternal sample. Today, we'll speak with the article's senior author. Dr. Dale Muzzey is the chief scientific officer at Myriad Genetics in Salt Lake City, Utah.

So, Dr. Muzzey, the study describes prenatal screening across three core areas, aneuploidy, recessive single-gene conditions, and fetal-maternal blood compatibility. What makes this different from traditional screenings, and what problem does the FIRSTGENE screen solve by bringing these into one simultaneous cell-free DNA test?

Dale Muzzey: It's a good question, Bob, and the question almost answers itself. It's by bringing them together. That's really what FIRSTGENE solves. So, the main issue is that aneuploidy screening, recessive single-gene screening, and fetal-maternal blood compatibility are typically administered separately today in prenatal care. For instance, the patient

will go in and get an aneuploidy test. They may or may not get carrier screening, and they may or may not have RhD testing as well. If they get carrier testing, frequently they will be found to be a carrier, and then you would need the reproductive partner to be tested, but that often doesn't happen. In fact, when a pregnant individual is a carrier for a gene, about 59% of the time, the reproductive partner who really should get tested does not get tested at all, and so you really get an incomplete result, and that's just very challenging to the efficacy of prenatal screening.

So, what FIRSTGENE does is bring all of those together so that from just one patient, so there is no need for testing the reproductive partner, from just that one patient with one blood draw at one time. The clinician and their patient can get all of those insights together at once, and that's just extremely powerful and particularly important for the clinical workflow where a lot of clinicians need to see a pregnant individual for only about 30 minutes. They have a ton of things to cover in that visit, and genetics just may not be top of their mind, and they may not have the whole half hour to talk about it, so FIRSTGENE lets them administer that comprehensive care much more quickly and easily.

Bob Barrett: As this is a simultaneous assay, what benefits are associated with this type of screening?

Dale Muzzey: Yeah, the benefit is that there's really no sacrifice to any one part of it while doing all of them together and getting that result quickly and early in pregnancy. So, the test is available and now validated as early as eight weeks of gestational age.

The current paper in *Clinical Chemistry* shows the validation for 10 weeks or more. We've subsequently validated it down to eight weeks. What's really powerful, again, by getting all of these different modalities of screening together in one test, is that the results come quickly, too.

So, a patient tested as early as eight weeks can have a complete result typically within 10 days of that. So, in the ninth week, someone tested with FIRSTGENE has aneuploidy information, recessive information, fetal maternal blood compatibility information all at once, and that's very distinct from other clinical pathways where, again, that testing may be disjoined or may be based on a series of reflex tests where it could take up to four weeks or more to get that sort of complete answer of testing multiple people over multiple tests. FIRSTGENE can kind of compress that all into one and typically, again, give people information before that 10th week.

And if you have information before the 10th week, that really positions the pregnant individual very well to pursue

diagnostic confirmation, for instance, of the screening results. And so, they can schedule and make sure they're available for a CVS [chorionic villus sampling] or an amniocentesis and have the time to get that plan in place.

Bob Barrett: So, how do you distinguish between fetal and maternal variant detection?

Dale Muzzey: So, it's hard, Bob, I'll tell you that. It's actually really not obvious because what you have in a prenatal cell-free DNA sample is a mixture of maternal fragments and fetal fragments, and they're not labeled as such. You know, they're just DNA. They look like each other. There are some differences in terms of maybe the alleles that they harbor and some qualities like their length, but the truth is it's all mixed together, and it is a deep challenge. That's why this is an advance.

So, the way that we do it is via some custom and sophisticated bioinformatics models where we analyze the data, looking at all of the fragments that have been sequenced, and look at all of the genotypes at every single site, each allele that we observe at each site. And based on the fetal fraction of the sample, so that describes the relative proportion of fetal and maternal cell-free DNA, so, knowing that fetal fraction and knowing our observed data, we use a Bayesian model where we enumerate the different genotypic combinations that could occur. So, you could have, for instance, a homozygous reference pregnant person and a heterozygous fetus. That's one combination. You could have a heterozygous pregnant person and a homozygous reference fetus.

So, we enumerate all of the different combinations and then score the likelihood of each of those different possibilities based on the data observed and select the most likely combination. So, it is a challenging process. We invested a lot in terms of just development time, getting that right, and training the appropriate models, but that's how we disambiguate the two.

Bob Barrett: One of the study's notable advances is fetal recessive genotyping from maternal blood. How does the FIRSTGENE screen identify whether a fetus is at risk for a recessive single gene condition without a paternal sample?

Dale Muzzey: Yeah, that's, again, one of the harder parts of the test, but the main thing is to see if a fetus is actually at risk for a recessive condition. That fetus needs to have inherited two alleles, one from the mother, one from the father, that are both compromised with a pathogenic allele. Those two can either be the same allele, in which case the fetus is homozygous for that variant, or they can be different, in

which case the fetus is a compound heterozygote for that allele. The detection of each of those is subtly different. They do both rely on that likelihood statistical analysis that I mentioned a minute ago, but just focusing for a minute on the compound heterozygote state, where the fetus has inherited a paternal allele that the pregnant person does not have.

In that case, the pregnant person is homozygous for the reference allele. They have effectively zero fragments that are showing that pathogenic allele. But if you then see a slightly elevated level of pathogenic allele present, that, again, after the statistical processing and knowing what the fetal fraction is, can tell you that the fetus has inherited that allele from the father.

The baseline of the mother is negative, sort of non-carrier at that site, but then you see a signal that is consistent with the data coming from the father, so you know that the fetus has gotten that from the father. You then have to do a parallel analysis at the maternal allele, for which the pregnant person is a carrier, again, to see not just that the pregnant person is a carrier, but what did the fetus get at that site? Did they inherit the pregnant person's allele or not?

So again, we did a statistical analysis there, and if both sites include that there is a maternally inherited allele and a maternally inherited allele that are both pathogenic, then we would report that the fetus is at an increased risk. So it is challenging, and that's where a lot of the work is in this particular test.

One of the things to stress as well is that fetal recessive testing in cell-free DNA is very hard. There are other single-gene, non-invasive prenatal tests that have been developed for dominant conditions before. Those are relatively easier. The recessive part is particularly hard because of the disambiguation that you need to do at sites where the pregnant person is a carrier.

Bob Barrett: The FIRSTGENE screen is designed for use as early as eight weeks. Why is fetal fraction such an important challenge at this point in pregnancy, and how did the technology address it?

Dale Muzzey: Fetal fraction increases throughout pregnancy. It's non-linear, but in general, monotonically increasing. Typically, at eight weeks, the fetal fraction will be a little bit less than it was at 9 and 10 and so on. But there is still enough fetal fraction there in order to confidently run the test.

What we leverage are really two technologies that we execute in serial on every sample getting FIRSTGENE to take the fetal

fraction that exists in the tube, if you will, when we receive it, and actually increase it. Let me just describe those briefly. So one is a molecular amplification. We leverage the fact that fetal-derived cell-free DNA is typically shorter than maternal-derived cell-free DNA.

What you can do is size select the DNA prior to sequencing, where you effectively drop out the longer fragments and keep the shorter ones. You tune this so that it retains as many fetal fragments as you can. But by removing some of the maternal fragments, you have enriched the fetal fraction of that sample, sometimes to the tune of 50% or even twice as high, just by doing that molecular size selection before sequencing. That's the first step of amplification in FIRSTGENE.

We also do a second step we call amplified DT or for amplified depth trajectory analysis. This is all done in silico. When we sequence the fragments, we can align the ends and where they appear in the genome and identify the length of each individual molecule that gets sequenced. We can then kind of recreate computationally what we did at the molecular level by doing a size selection. We can do that size selection in multiple different windows of size in the computer, in the pipeline, so that we, for instance, do one interpretation of the data, considering fragments from 0 up to 190 bases long. We then do another analysis where it's 0 to 180, 0 to 170, and so on. By progressively making that window smaller, we are increasing the fetal fraction in each of those windows. We can actually take a sample and look at it actually in kind of multiple instantiations, like one where it's at a fetal fraction of 10%, but then another where you take that exact sample and convert it from 10 up to 12, from 12 up to 14, from 14 up to 18, for instance.

By looking at the data across that trajectory of fetal fraction levels, there are really strong insights you can gain and much greater confidence in the fetal genotype that you can identify as a result. So those two levels of amplification, which are really unique to FIRSTGENE, are what led us to operate at an earlier gestational age.

Bob Barrett: Well, finally, Dr. Muzzey, the study showed strong analytical performance across each component of the assay. What should clinicians take away from the sensitivity and specificity results?

Dale Muzzey: I hope that clinicians really take away that there's no sacrifice they're making by getting all of these results in a single, simultaneous screen. The performance of the test really was excellent. The aneuploidy results are comparable to aneuploidy-focused tests. The recessive screening results on the pregnant individual are just as good as a dedicated carrier

screen. The performance of the RhD compatibility are just as good as a dedicated RhD test. Finally, I would say that the fetal recessive inheritance, which is really a kind of emerging technology in the space of prenatal screening, the results there are also fantastic, with a sensitivity above 98% and a specificity above 99%. So

So yeah, I think there's really no sacrifice in putting them together, but actually a real large benefit in terms of the ease of use, the insights gained, and the kind of opportunity for informed follow-up that patients and their clinicians receive.

Bob Barrett: That was Dr. Dale Muzzey from Myriad Genetics in Salt Lake City, Utah. He wrote a research article in the June 2026 issue of *Clinical Chemistry* describing a new assay that combines three types of cell-free DNA screening into a single test, and he's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.