

September 2015 - David Flannery

David Flannery:

So, we're ready now?

Female Speaker:

Yes, please.

David Flannery:

Good. Okay, well I wanted to thank you for inviting me to do this. And I also wanted to point out that I'm doing this not only as the medical director of the American College of Medical Genetics and Genomics, but also on behalf of the Intersociety Coordinating Committee that Dr. Bob Wildin heads at the NIH; it actually was his idea to start this series of talks.

Today, I'm going to talk about understanding genetic tests and how they're used. And I'm doing this from the perspective of a clinical geneticist, which I was for 29 years at the Medical College of Georgia in Augusta, Georgia prior to starting this job with the American College of Medical Genetics and Genomics. I just wanted to start and sort of just remind people that genes are made of DNA and they're carried on chromosomes. In the day, people used to say that every specialty had its organ, and the genetic's organ was the chromosome. But now we've gotten into much more detail in chromosomes, and we'll talk about that.

And can I go back to that? In section three, it sort of hops; there we go. I just want to point out that genetic disorder is a result of alterations in genetic material. And as you can see in the picture, the types of changes can be break of a chromosome, or an extra piece of a chromosome, a change in a single base in a DNA code of a gene, or there could be expansions. And we'll talk about these.

And the other thing is just because something is genetic does not mean it's inherited. There certainly are many genetic diseases where the gene change has happened spontaneously, potentially in the course of -- prior to conception. Or, in the case of cancers, it's something that is acquired during a person's lifespan.

So today I'm going to talk about the types of genetic tests that are available, what the tests entail, what the different tests can detect, and then how to decide which test or tests are appropriate for a genetic given clinical situation. Okay, let's go to number five. When we talk about genetic tests we can talk about chromosome tests, which are called cytogenetic tests. We can talk DNA tests, or sometimes called molecular tests. And then there are biochemical tests from various metabolic disorders. And we're only going to talk about cytogenetic and molecular tests today.

Okay, where did it go?

Female Speaker:

It is where ours is. It says meeting password.

David Flannery:

Excuse me? The presentation has --

Male Speaker:

Yeah, what are -- what is the meeting password?

Female Speaker:

Genetics.

Female Speaker:

-- password is genetics.

David Flannery:

Okay. Should I pause here?

Female Speaker:

Please, a minute, Dr. Flannery.

David Flannery:

Okay.

Male Speaker:

Looks like somebody else took over the screen.

David Flannery:

It's not responding.

Male Speaker:

Yeah.

Female Speaker:

I'm getting the doctor; give me a minute.

David Flannery:

Okay.

Female Speaker:

Should we, maybe, let Dr. Rosenberg [spelled phonetically] know that we can see his messages?

Male Speaker:

Yeah.

Male Speaker:
Probably so.

Female Speaker:
Alan [spelled phonetically], we can see your messages.

Alan Rosenberg:
I hear you, Claudia [spelled phonetically], thank you.

[laughter]

I'm not sure how or why that's happened. I shouldn't have anything on your screen. I'm -- it's amazing.

Male Speaker:
Alan, you're sharing your screen.

Alan Rosenberg:
How did I share my screen with all of you?

[laughter]

Male Speaker:
I don't know but you did.

[laughter]

Male Speaker:
It's magic.

Male Speaker:
What is the meeting password?

Male Speaker:
I clicked at the top where it says "Exogenetic Testing," and your slide then came up. There was a tab for Alan Rosenberg and one for meeting info and quick start.

Alan Rosenberg:
I hope my message has gone away [laughs].

Female Speaker:
It has.

Alan Rosenberg:

It wasn't too scandalous. I wasn't saying [laughs]. It was -- its public information that I'm president of Accenture US Services, Inc [spelled phonetically].

Female Speaker:

I was just afraid you were going to go further.

Alan Rosenberg:

I was, I was going to make a smart remark to Beth [spelled phonetically] with some potential who wanted to know who it was; that it was okay, but I'd tell them I only charged \$10,000 an hour for consulting fees. But --

[laughter]

-- oh no, that's Accenture who charges that [laughs]. I was kidding.

David Flannery:

Okay, so now I have control again? Yes.

Male Speaker:

What is the meeting password?

Female Speaker:

Genetics.

Male Speaker:

Genetics.

David Flannery:

All right. So chromosome testing is looking at chromosomes and other A4 karyotype. And as you can see here, this is the result of a karyotype. And normally, chromosomes come in pairs. And typically, people have 23 pairs of chromosomes. Chromosomes are typically shown this way, from largest to smallest, with the sex chromosomes over separately.

Chromosome abnormalities can include having an extra chromosome, like this extra chromosome 21 here, which produces a genetic imbalance of the genes on that chromosome and produces Down syndrome. What you're probably unfamiliar with is how chromosome tests are done. And what happens is blood is drawn; it is typically in an anticoagulant, usually heparin. And then, the blood is cultured with fithemaglutinina. And they are stimulated and cultured, typically for three days, although they can be done for a little bit shorter than that. They then add colchicine in a hypotonic saline, and this then enables them to spread out the cells on a slide. They then digest the chromosome, actually remove a lot of proteins, and then, they stain it. And they look at it under the microscope, and then take the visual image

and sort out the chromosomes to make that neat karyotype. So, this is labor intensive; it takes time.

And typically, we use karyotypes to diagnose a condition such as Down Syndrome. And even though you may feel confident a child has Down Syndrome looking at them as a geneticist, you still would do a karyotype first to confirm, indeed, the child has Down Syndrome. But secondly, to determine if it's due to what we call trisomy, where there's three separate chromosomes, or whether it's due to what's called a translocation producing trisomy, in which case there's up to 50 percent risk that it's inherited from a parent who has rearrangement of their chromosomes in what's called a balance translocation. This would impact the recurrence risk.

So, karyotype can detect whether there are too many or too few chromosomes; whether there's a missing part of a chromosome, which means they then have only one copy of the genes for that region of the chromosome. So, we have duplication, in which case you would have extra copies of genes; and then translocations, which I just mentioned, where you have pieces of chromosomes that are broken and reattached to each other.

Now --

Female Speaker:

Excuse me, Dr. Flannery, can people remember to set their phone on mute, please? We're getting some background noise. Thank you very much.

David Flannery:

[affirmative] Now, karyotyping has its limits because many deletions or duplications that are clinically significant are not visible, even under the microscope, and we commonly call those microdeletions or microduplications. And we can detect these by using what's called a FISH test, which stands for fluorescence in situ hybridization. And what a FISH test involves is taking a probe, which is single stranded DNA, that has fluorescent molecules attached to it, and depending on what chromosome and what region of a chromosome you're trying to look at with the FISH probe, it would match up with the particular code of genes in that region. And as you can see here, it's applied to the chromosome, and it attaches where the complimentary region is.

Now, what can happen is, as we see in the next slide, if we can get there, there are some conditions, such as one called DiGeorge syndrome, in which what happens is you have, using this probe specific to the DiGeorge critical region, you see that in one chromosome, 22, that region is present because the probe could attach. In this other 22, it could not attach because that region is missing. So, there is a invisible to the naked eye and into the microscope microdeletion in that region of that chromosome, but the FISH test demonstrates that that region is missing.

And there are other microdeletion syndromes; one of more common one is Prader-Willi in -- or Angelman syndrome. We'll talk about that subsequently. And then there are duplications that can be detected. In one form a Charcot-Marie-Tooth disease, they actually can use these DNA probe here for this region of this gene. And they look for duplications or extra copies of genetic material there, which confirms that form of Charcot-Marie-Tooth. A very rare disease that you probably never heard of, and I'm probably mispronouncing because I've never seen a case, called Pelizaeus-Merzbacherr --there is a duplication of a particular region.

Now, another use of FISH is for rapid diagnosis of trisomies. And, for example, if we have a newborn in the neonatal intensive care unit who has severe congenital heart disease and physical abnormalities, one might be concerned that the child may have what condition is called trisomy 18. Now, trisomy 18 is very severe. The chance of survival to age one is very small, despite aggressive medical care. And cardiac surgery in this setting would be, potentially very risky for that child. A karyotype takes 72 hours, but using interface FISH, where they take the cells and they deposit onto them these FISH probes, they can sit there and look and detect, in this case here, that there are three signals for chromosome 18 in these white blood cells, confirming that the child, indeed, does have trisomy 18. This test takes a few hours to get results, rather than days, so it can be extremely useful in this setting and help parents and physicians have informed discussions and make decisions.

So, now we're going to move on and talk about a patient who needs genetic testing. We'll talk about how we make decisions about testing, and then, what tests would be indicated. So, we have a hypothetical patient, a boy who has microcephaly hyperactivity, seizures, developmental delay, verbal apraxia, which typically is manifested that they have a very limited vocabulary -- say five, six, seven, eight words total -- and a very happy affect in this patient. So, the doctor is concerned the child may have Angelman Syndrome. Now, we know that 68 percent or so of cases have a microdeletion of a region of chromosome 15. So, the first logical step in evaluating this child for Angelman Syndrome would be to order a FISH test, with a specific DNA probe that detects this region of chromosome 15.

And so here, the test has been done, and the result is that no deletion was detected in the Angelman Syndrome critical region. And the next step is, well, we're still concerned it's Angelman Syndrome; we don't know how to manage this patient. So, we go and we just look. And 11 percent of cases are caused by mutation in the UBE3A gene; 7 percent have uniparental dysomy, three have what's called an imprinting center defect; and then a smaller number have other abnormalities. So, logically the next step would be to do the UBE3A gene sequencing.

This is probably a little schematic for you because it's explaining the process of how they do gene sequencing. And it's become automated in machines now, where they can put in the DNA after amplifying the region of the genome that is targeted for the testing. And then, the machine basically goes through and is breaking up the gene in looking at what the pieces of the gene are. And it then generates a diagram like this, which is showing you what the code is going along a segment of the gene.

And here, we have results of sequencing the UBE3A gene in a patient who has a abnormality in the UBE3 gene. It's showing that the patient has a change at this point in the gene, which is not the normal base which should be in that region. So, therefore, it's a mutation that is causing the problem.

Now, sequencing results can be complicated because there can be changes in the gene, and you have to determine whether they cause a problem or not. American College of Medical Genetics and Genomics and the Association for Molecular Pathology put out a joint policy statement this year, establishing standards and guidelines for the interpretation of what we call sequence variance, because a change in the code could simply be a variant, or it could be causing a problem. It's we establish standards for how you would interpret whether a change is what we call pathogenic, which means we feel confident that it causes the gene to malfunction; likely pathogenic, which means it's most likely does cause malfunction; benign, which means a change in the gene produces no effect on how the gene functions, or likely benign. And then of course, unfortunately, at times it's of uncertain significance. And for the, for the physician and the family, and I'm sure for the payor, getting to that point and the result comes back of uncertain significance can be a bit of a challenge.

Now, sometimes, we'll have a false negative test result. So, you do the test. You don't find a change in the gene. Well, the patient may have a change in the gene you tested, but there's another gene that's also responsible for producing what we call the same phenotype, which is the abnormalities in the body or behavior, or combination of those two. They could have a sequence change that cannot be detected by sequence analysis, which includes what we call a large deletion. And frequently, if you know a gene is prone to have deletions when you do a sequencing test, you may then, if it's negative, reflex to doing a FISH probe for -- looking for deletion.

And then, sometimes, the test would be negative. The patient has a sequence change in a region of the gene that's not covered by the test, because not all regions of all genes are adequately sequenced and covered. And this especially applies to whole genome and whole exome sequencing, which will be a, I think, a topic of two more -- two talks later.

So, now another useful test are what we call our chromosome microarray tests. And I know you all have heard about this. Typically, it's called a gene chip that uses comparative genomic hybridization to look missing regions or extra segments of regions or chromosomes. And the easy way to think about it is that it's performing thousands of FISH tests simultaneously. And I'll show you.

So, this is from a now defunct laboratory called Signature Genomics. But it was in their educational material that they had. And so, basically, what they do is using the same kind of micro processing technology that they use to make a silicon, you know, computer chip, they can actually put tiny pieces of gene sequences onto one of these silicon chips, or glass chips. And you can then know which one are there. And so what they do is they put probes that are

attached to this chip that are unique segments of every chromosome. And so, depending on the number of probes it can represent every genetic region of the entire genome. And that's pretty much what chromosome microarrays are like currently.

So, here is the chip; here is the probes attached to the chip. You then take the patient's DNA and you take it so that you -- heat it so that the DNA separates from being double stranded and to be single stranded. And then, these pieces are put into the machine, in the chip, and they all sort up and pair up with their various -- that they match up to.

And so here though you have a case where the patient's DNA doesn't attach to this probe, and so, there's not a match for that area. And they have -- now computer processing analyzes the entire chip. And it comes up and it gives you a report that tells you if you've got duplicated genomic material from a particular region, or multiple regions, or a deleted genomic region. And sometimes, you'll find multiple deletions or duplications simultaneously, although that's not as common.

Now, the microarray can tell you if there's a duplication or deletion, but it can't tell you if it's been caused by a rearrangement of a chromosome. So, sometimes having another chromosome microarray then leads to the need to do the old fashioned chromosome test, which is sort of counter intuitive, I'm sure, to many people. But it can be a necessary next step in evaluation. Microarray results make 10 to 15 percent more diagnoses than karyotyping in the evaluation of patients with idiopathic learning disabilities. Some microarrays have been reported as having as high as 28 percent rate of diagnosis. And ACMG put out a practice guideline in 2010, affirming the use of chromosome microarray as a first tier genetic test in evaluating patients with an intellectual disability and/or multiple congenital anomalies.

And just recently the European Internal Hemogenetics published a report talking about the clinical utility of genomic testing and, particularly, looking at what subsequent medical recommendations came about in patients after they had a microarray test done that showed an abnormality. And in some instances, this would have to do with management of the patient, such as doing further testing, knowing there's a high incidence, say, of seizures and having the patient evaluated for that, or the child may have an increased risk of developing cancer down the line. They'll send surveillance for whatever type of tumor that might be would be indicated; and other sorts of investigations that would be indicated.

Now, just like with doing sequencing of genes, a microarray test may tell -- come with a result that they say is normal, or say it's, you know, pathogenic, likely pathogenic, likely benign, a variant of unknown significance. And when you have a variant of unknown significance, the lab frequently recommends testing the parents to see if either of them has the same change in the gene. Because if either parent has the same change in the gene and that parent is healthy and normal, then that change is not pathogenic. Conversely, if the parents were tested and neither has that same change, it's not possible to say for sure whether the change in the child is causing the child's problems, although you would be suspicious of that.

Now, someone had asked about SNPS, and so I tried to talk about its called SNP arrays. And they are microarrays that have what we call single nucleotide polymorphisms in them. And what a single nucleotide polymorphism is a variation of a single based pair of the DNA sequence from the typical. And so here's a picture diagram of what a SNP is. So here, at this one location in this gene sequence, this individual has this sequence at that point, and this individual has this base. SNPs do not necessarily change the function of a gene, and typically, they don't. That's why they're called single nucleotide polymorphisms, because a polymorphism doesn't have functional effects.

As of the last time I checked, SNP arrays have 1.8 million probes for SNPs, and they have different ones they use. And if the test in the individuals tested has a specific SNP in the specific gene, that's called a positive result. It can also detect small deletions and duplications. But what's really interesting is doing the SNP arrays can yield surprising information beyond that, and it's called loss of what we call heterozygosity.

And so, it was first called to a geneticist's attention in an article in Lancet in 2011, which called attention to the fact that they could identify incestuous paternal relationship by SNP array. And what they found in this article was that these green regions of these various chromosomes had two copies of the same rare SNPs. And the -- this degree of what we call homozygosity is best explained by the parent's being related to each other and passing down SNPs that they carried by being related to each other. And this actually does come up. We had an internationally adopted girl who had mental retardation, non-specific abnormal facial appearance. And since she'd been adopted internationally, there's no family or prenatal history available. And her parents had been trying to find what was the cause for her problem, to figure out what could be done for her more specifically. And she had had all these tests done before she came to see us.

And so SNP arrays were available. And we said, "Well, you know, let's take a look at this." Well, this girl had a very high degree of homozygosity of regions of her chromosomes. And it corresponded to the biologic parents being very closely related; like, closer than first cousins. And so, it led us to be concerned that she might have some sort of autosomal recessive disorder, because she could have received two identical copies of an abnormal gene from her related parents. But we didn't have a clue as to what that might have been; and that was back in 2012.

Here we have another patient we saw back in Georgia. And this girl had a very complex phenotype with mental retardation, non-specific dysmorphism, so she was, you know, unusual looking, but not characteristic of any particular appearance. She had multiple congenital anomalies and she had endocrine dysfunction. And so we did a SNP array on her, and one of the regions with homozygosity was the -- had contained the gene for Bardet-Biedl Syndrome type seven. And she had features compatible with this condition, but she lacked most -- many of the characteristic features. And so, what we decided to do was go and try to get the sequencing for that specific gene done on her. Unfortunately, she had [unintelligible]

Medicaid, and it did not get approved. And I'm not sure what's happened with her since that time.

All right. Now, we're going to talk about another patient's situation: A three-year-old boy who's not walking and has only a few word vocabulary. His growth is normal. He has a long facial profile. Family history is not significant. And so, what would be the first test to evaluate him? Well, as I mentioned, you know, the ACMG practice guideline had recommended chromosome microarray in this setting as the first tier test. So, of course, that was done and is normal. So, you go, "What's next? I mean, what test do you order? There has to be some logic to this." Well, the most common cause of intellectual disability in males is something called Fragile X Syndrome. So, the physician sends blood for Fragile X testing. And this comes back and showed -- oh gosh, I must have something out of sequence. Anyway, it shows expansion of the Fragile X gene. This is showing that it's what we call a CGG repeat.

And Dr. Jack Carlson [spelled phonetically] gave me these slides, and it shows you that normally, people have 29 or 30 of these three base pair repeats in that gene. When you have significantly increased number of repeats, you end up with dysfunction of the gene, which produces then what we call the Fragile X Syndrome. And this is showing another way that they do it, which -- what they used to call Southern Blot testing. And it actually was a more tedious process than the previous one they're showing, what we call PCR testing. And it actually used radioactive labeling to be able to show where the region that you're concerned about is. And the size of this corresponds to the number of repeats. So, our patient had 330 repeats, and so, had Fragile X.

The mom needed to be tested because of risk of having other affected male increases depending on how many repeats she has. So, depending on the number of repeats that the mom is found to have affects whether or not there's a greater than 50 percent risk of another male having this condition, or a lower risk of it happening. In addition, women who have expansions of the gene are at increased risk of developing premature ovarian failure and should be monitored for that.

And then, what's most interesting about this, and something that we only learned over time, is that her father should be offered testing. I put "should be tested," but he should be offered testing because he could have it. We call it premutation expansion of that gene, which places him at risk for developing what's called Fragile X Associated Tremor Ataxia Syndrome as he gets older. And knowing that he has that would certainly make it much easier for neurologists to diagnose why he's developing a tremor, rather than start worrying about doing all kinds of tests for all kinds of other potential neurologic disorders that produce tremors.

There are many other trinucleotide repeat disorders. You've all heard of Huntington Disease. There are a whole host of spinocerebellar ataxias that have trinucleotide repeats. And then, there's a condition called myotonic dystrophy, which is produced by trinucleotide repeats.

And we've reached the end there. I think we've given people enough time for questions as well.

Female Speaker:

Great. Dr. Flannery, thank you very much. We really appreciate you taking the time to speak with us today. At this time, I'd like to see if there are any questions from anyone on the line for Dr. Flannery. Well, Dr. Flannery, I have a question for you while we're waiting to see if anyone else from the audience has a question.

David Flannery:

[affirmative]

Female Speaker:

I'm wondering if you could address that if the types of mutations that are detected by FISH can also be detected by CMA, why would you choose one type of testing over the other?

David Flannery:

Right. Well, in the case, say, for Angelman Syndrome, if, you know, the patient's phenotype is such that you feel very concerned that it's Angelman's Syndrome, doing a FISH test would be, you know, probably, you know, less expensive than doing a chromosome microarray test. You're correct. A microarray would be able to detect that region; at least, most microarrays would have probes for that region. But, you know, that's -- you know, it depends on how confident the physician is. You know, a pediatrician who's concerned about the child might very well do the chromosome microarray, whereas an experienced medical geneticist would see the patient and, you know, be concerned specifically about Angelman Syndrome and then be, you know, doing that test. You know, it has to do with the people seeing the patient and their experience.

Female Speaker:

Great. Thank you.

David Flannery:

[affirmative]

Female Speaker:

So, I have another question, but I'm going to see if [laughs] there are others out there with a question first.

David Flannery:

And so like our -- with our webinars, people type in questions, but I don't see where you have that here.

John Goldenring:

Yeah, this is Dr. John Goldenring, Pediatric Medical Director out in California. Can you hear me?

David Flannery:
Yes [affirmative].

John Goldenring:
I wonder if you'd review a little more for us about the utility of the microarray testing, and particularly, if you'd address the issue of kids who have Autism.

David Flannery:
All right.

John Goldenring:
What is the clinical utility --

David Flannery:
[affirmative]

John Goldenring:
-- of finding microdeletions in kids who have Autism?

David Flannery:
[affirmative] Right. When we're talking about the clinical utility --

John Goldenring:
Well, I mean you showed that article, which I'll go get her, from Europe --

David Flannery:
Sure, right.

John Goldenring:
-- which goes into a lot of stuff. But I want to focus particularly on the Autism thing. I think we see the largest number of microarrays made -- requests maybe coming from all these kids -
-

David Flannery:
Right.

John Goldenring:
-- who have Autism. And I, as a pediatrician, haven't found any good literature that says this is clinically useful at this time. And I will qualify my statement because there may be something that we discover over time. But at this time, we don't know what that means.

David Flannery:

Right.

John Goldenring:
Why would you do this?

David Flannery:
Right. There are other articles besides that one from Europe about changes in management of patients after chromosome microarray testing, including after doing them for children with Autism. And it has to do with what region is found to be abnormal, and then, what other medical issues could result from that. And most often it would be, you know, there's, like, an increased risk for having some other medical problem, such as renal abnormalities or, you know, some other problem in terms of neurologic function, or risk of congenital heart disease that was not, you know, necessarily going to be obvious. And I can, I can try to track those down for you and, you know, send them to --

John Goldenring:
Oh no, I think that's actually fascinating if, indeed, we got back reports as pediatricians and said, "You know, because this particular area is involved here, we think there's a higher risk of X." And that's not something I've seen a lot of, and I --

David Flannery:
Right.

John Goldenring:
-- find that fascinating; and it would be interesting to see if that could be quantified. And, yes, I think many of us would appreciate --

David Flannery:
Sure, okay, I'll try to find --

John Goldenring:
-- seeing that.

David Flannery:
-- some of the other articles, as well. And, you know, just my personal experience, I've had the experience of, you know, having a child who, you know, we did the testing and it came back with a microdeletion in a particular region. And among the genes in that region were one that was associated with -- I forget what type of cancer. And so, it was like, "What do we do with this?" Send him to the pediatric hematologist/oncologist, you know, and they have to then figure out how you would evaluate the child and monitor them for development of that particular tumor. And that was when I -- that's one I specifically remember.

And then, I do remember a patient where, in that region that was involved in the child, that there was, you know, increased risk of having either -- I think it was a renal malformation or

it was renal agenesis. And so, you know, that led to doing ultrasound of the kid's kidneys, which were fine, but I suppose we found out he only had one kidney; that could have some significant implications for his life.

But I'll be happy to try to find those other articles for you, as well. I just -- it was just fortuitous that that one from Europe happened to just pop up in my email [laughs] when I was working on putting this talk together. And it was like hot off the press, so I figured that was a good one.

John Goldenring:

Thank you; that would be helpful. And, by the way, a superb summary talk. Thank you.

David Flannery:

Thank you.

Male Speaker:

Dr. Flannery, a follow up, I think, to the last question. In that -- your -- the article from Europe that you referenced about --

David Flannery:

[affirmative]

Male Speaker:

-- I think, the percentage of patients tested who had a positive finding. I -- the question I have is who exactly is -- was being tested in that study? I mean it, I mean it -- is it -- is it anyone with any sort of intellectual delay, or is it particular types of intellectual delays coupled with, perhaps, other phenotypes, or other findings?

David Flannery:

Now, this is being recorded, of course, and here I am scrolling back through the slides. I'm probably going to cause somebody to have a seizure going this fast [laughs]; that's fine [laughs]. I can't read this; 752 children with congenital anomalies and/or developmental delay who underwent chromosome microarray testing. That was the --

Male Speaker:

Yeah.

David Flannery:

-- target group there.

Male Speaker:

Right.

David Flannery:

That was -- it doesn't mention Autism in that group there, but --

Male Speaker:

Right.

David Flannery:

-- children who had congenital anomalies and/or developmental delay. And typically, you know, my recommendation, you know, if that the child just has Autism and doesn't have developmental delay, you know, I think it's unlikely that a microarray is going to identify much of anything, to be honest with you. That's just my personal opinion. That's not the opinion of the American College of Medical Genetics, nor, you know, necessarily everybody's opinion.

Megan McCarville:

Dr. Flannery, this is Megan McCarville [spelled phonetically] with the association. I -- and it was a very nice presentation. I wish I had had this, like, two years ago when I'd started trying to write policies about microarrays. But I'm curious about how much --

David Flannery:

[affirmative]

Megan McCarville:

-- you know, practitioners need to consider differences in the composition of the microarrays. Like, my understanding is that, you know, what you --

David Flannery:

Yeah.

Megan McCarville:

-- test for is dependent on what it's looking for. But I don't have a good sense for how you know or how, you know, how the year how a practitioner would know what --

David Flannery:

Right, right, yeah.

Megan McCarville:

-- you need to be looking for.

David Flannery:

Yeah, I mean what you're bringing up is that some labs, you know, have their own particular microarray, and they have their own particular probes that they use in their microarray. And, you know, it can differ from, you know, lab to lab. I know that ACMG has technical guidelines for laboratories; it has, like, standards for this. And that, hopefully, is becoming more adopted or cross-linked. But in many instances, you know, these are something that's

not -- it's sort of more like what we call an LDT sort of test --you know, laboratory developed test -- as opposed to a standard thing that's purchased. So that all, I think, is probably going towards becoming more standardized as things go along. But certainly there -- I know there are labs that have their own particular, you know, microarray that they have adopted and used. And in some instances that, you know, I guess they consider it to be a proprietary, unique product that they've chosen certain genetic regions and the depth of coverage of certain genetic regions as being, you know, more important.

At one point in time, I think there was, like, sharing of data among labs. And I'm not sure what the status of that is, you know, for them to help interpret, you know, what becomes useful and what isn't, and then also, to help people learn, you know, what might not be a variant of unknown significance anymore. You know, they help them determine that it's, you know, not pathogenic or it is pathogenic. And I'm not sure what's happened to that. I think it was Dr. David Ledbetter [spelled phonetically] that was involved with that; was driving that sort of process. But I'm not sure what's happened since he moved to another institution.

But you're correct. And it would be, you know, by now, I think, is getting more standardized. But I know there still are proprietary microarrays out there. I'm not going to say who I think has the best microarray.

[laughter]

But I would, you know, think that if they're, you know, at least adopting the technical standards that ACMG's, you know, expert review and evidence-based review process, they are recommending, sort of, what the critical elements for a microarray should include. And that should be, you know, you know, pretty reliable and appropriate to use.

Megan McCarville:
Great, thank you.

Alan Rosenberg:
This is Alan Rosenberg, and Dr. Flannery, thanks a lot for the presentation, as the others have said. I am -- leave medical policy for Anthem and its plans, including Blue Cross Blue Shield of Georgia.

David Flannery:
[affirmative]

Alan Rosenberg:
So, my question is an extension of the clinical utility --

David Flannery:
[affirmative]

Alan Rosenberg:

-- question that was asked earlier. But it's to the asymptomatic individual, just one of the cases you cited, is an individual where you recommended it might prevent the future work-up if the -- if, as the father, or grandfather rather --

David Flannery:

Right [affirmative].

Alan Rosenberg:

-- aged, they developed an ataxia syndrome.

David Flannery:

[affirmative]

Alan Rosenberg:

My question is why in the asymptomatic individual would you do that, rather than simply share that possibility, and wait to see if they develop an ataxia syndrome and do the testing at that time, in terms of clinical utility?

David Flannery:

[affirmative] Well, as I, as I phrased it, the slide I did put in with how will you do it as a practitioner or clinical geneticist, you would, you know, discuss it with the grandfather and say, "You know -- you know, we know that your daughter we -- has been tested and she has an expansion of this gene. It's very likely that she inherited that from you. And, you know, there is a -- there are problems that can result from you having expansion of this gene;" and explain what the Fragile X associated Tremor Ataxia Syndrome is and the typical, you know, signs and symptoms of onset. And, you know, we never just tell people they should have testing done. We explain to them what the benefits might be, what the, you know, pros and cons might be, and let people make decisions. And so, in that setting, the grandfather might say, "Right, I certainly want to know," you know. You know, who knows, you know? But he might say, "No, I don't want to know." Well that's --you know. And, you know, they make their decision.

Now, the benefit to him of knowing that he has an expansion that places him at risk for developing Fragile X associated Tremor Ataxia Syndrome is not going to come today, tomorrow, you know, next year [laughs]. But as I pointed out, yeah, it potentially can, you know, prevent the so-called diagnostic odyssey that we talk about of people being tested for things and, you know, trying to find the underlying cause of symptoms that are not very specific. But certainly, I mean they -- the gentleman in question might say, "Well, thank you. So, if I ever develop any symptoms, you know, I'll tell the neurologist, 'I have this risk' and then, they can do the test then." And we'd say, "Fine. Sounds like you understood everything we told you very well, you know. Yeah, excellent. Just, you know, you're in charge [laughs], you know."

Alan Rosenberg:
I appreciate it. I just am wondering if --

David Flannery:
Yeah, right.

Alan Rosenberg:
-- 50 percent of people will be tested with a negative or average result, and 50 percent with a positive, why you would waste the resources today rather than waiting until that time.

David Flannery:
Yeah.

Alan Rosenberg:
And even then I wonder. But I -- it's just fine I just was curious of that so, I appreciate that.

David Flannery:
Sure, sure, sure.

Alan Rosenberg:
Using my Humanities and Contemporary Civilization in Columbia.

[laughter]

David Flannery:
Okay. All right. Well good. And then -- I -- maybe I'll send you, also, a copy of ACMG's recently published policies or -- I said policy -- it's position statement regarding looking at clinical utility of genetic testing beyond simply, you know, the benefit directly to the patient. I sort of -- which I sort of touched on here. But you may find that to be -- to be a useful report to look at as well. So, I'll send that along with some other papers about clinical utility of chromosome microarray testing.

Alan Rosenberg:
Thank you.

Female Speaker:
Dr. Flannery, we certainly would appreciate that and we'll ensure that all of the participants on today's webinar are able to get access to those materials.

David Flannery:
Great.

Female Speaker:

Are there any other questions before we say a final thank you to Dr. Flannery today? Great, well, David --

David Flannery:
Thank you very much.

Female Speaker:
-- we really do appreciate it. I thank you very much. To everyone on the phone, our next webinar is scheduled for Tuesday, October 13th. And on that webinar, we will focus on understanding CPT coding of genetic tests. So, we all hope that you can join us then. Thank you very much and have a nice rest of your day. Bye-bye.

Male Speaker:
Thank you.

David Flannery:
Bye.

[end of transcript]