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## Cardiovascular Genetics: Case Studies

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## CARDIOVASCULAR GENETICS: CASE STUDIES

KENNETH G. ZAHKA<sup>1</sup>

It's really a pleasure to be here. I want to thank Kathleen [Engel] and Dena [Davis] for inviting me. As I was thinking about how I was going to start this off, I absolutely promised myself I wasn't going to say anything about lawyers. I'm actually quite anxious, because this is, in fact, the first time I've spoken to a group of lawyers. It is, however, of course, not the first time I've spoken in front of lawyers, and I wasn't going to say anything until the court stenographer was here, and it does send chills up and down my spine.

So I promised myself I wasn't going to say anything, I was going to be really good, but I had to.

Now, the question is, why am I on the panel, and my sense of why I'm on this panel is to give you some grounding about how this all gets found out, why is this a problem, and keep in mind that I am here as a clinician, somebody who takes care of patients, and somebody who is either one step removed from your primary care provider or sometimes I get direct referrals from a family or so forth directly asking me to evaluate their cardiovascular problem, usually in their children or if they have concerns about an inherited cardiovascular problem they'll come and see me, and then very frequently I will see a problem that I will then seek the help of a geneticist. And when Dr. Wiesner speaks a little bit later today, you'll hear from somebody who is a geneticist who only very occasionally gets direct referrals but is always in a position of trying to understand the genetic basis of disease's based on the observations of other health professionals that tend to funnel patients to her.

So I'm going to try to give you how I think of genetic disease as a clinician and what you might expect your physicians to think about or what you might expect the health professionals and companies to be thinking about as they look at patients.

The next thing I want to say before we start off with the slides is that it's very important to realize that there is an enormous variety of humanity and that variety is also based on our environment.

I think it is fair to say that as much as I will try, I can never play professional basketball. I could try every day to exercise and practice and practice and there's no way that I would be in the NBA, and perhaps one in contrast could say that there would be nobody in the NBA or there would be few people in the NBA who could do pediatric cardiology and there are some people who are very gifted in language and others who are not.

So there's a huge variety of humanity, some of which is genetically based, some of which is environmentally based, and our understanding about how they interplay is really now only at a very basic level.

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And, for example, the complexity of all of us is extraordinary. How our genes carry out instructions is very complicated, and so it's not like having a Pentium or one gigahertz memory chip. We're not all exactly the same and we can't all be expected to be the same.

And that leads to another important thing to think about during today from a clinician standpoint, and that is something that Commissioner Miller brought up yesterday: What is asymptomatic? And what is 'sick'? These are not black and white questions, and it's very important to realize that what are symptoms to one person are normal to another, and what represents illness to one person is just the normal everyday facts of life for another person, and it's not anything that is black and white.

Also remember that everyone has risk, and that risk may be through behavioral things. I enjoy riding my bike and I enjoy riding my bike very fast, and about four years ago I hit a rut in the road and flew over the handlebars at 25 miles an hour and broke my arm and broke six ribs and had a concussion. I could have broken my neck and in that instant would have been forever changed. But the fact of the matter is, that the behavior of riding my bike at very fast speeds, in fact, put me at some risk, perhaps at greater risk than all of my genes put together.

Lifestyle. I don't know if any of you smoke. Smoking is a choice that clearly puts us at risk for health problems, significant cardiovascular health problems, and then, yes, we all have our genes. We can't change our genes usually, but maybe sometime in the future we can.

And then the other things we would like you to think about, at least from a clinician's standpoint is that we make choices in our society, and, in fact, I would think we already sanctioned some forms of genetic testing, and Georgia [Weisner, M.D.] may disagree with me, but, for example, when I had my life insurance physical, they drew my blood for cholesterol. Now, God knows what else they drew it for because I signed the form without actually reading it. Maybe I signed off that they could run my whole human genome. I actually don't know. I just trusted them that they did my cholesterol.

Well, clearly my cholesterol is related to my diet and my activities, but it has a very strong genetic component to it. So they did, in fact, do a component of genetic testing on me, not at a terribly sophisticated level, but at a level that would allow them to make some decisions about where to rank me, and we allow the life insurance companies to make decisions based on that form of genetic testing, at least in the very simplistic way I see as a clinician that would have allowed them to disadvantage me with regard to how much I paid for life insurance or maybe whether I had life insurance at all.

What I'd like to do in the next 10 or 15 minutes is use a case approach which we all use in medicine as you use in law to give you a flavor for how we as clinicians think about things that are oftentimes obviously genetic. But I want to stress to you that probably a day does not go by or a patient does not go by where I don't think in terms of genetic issues for their cardiovascular health.

Well, how does a doctor, how does a clinician, think about genetic problems? Well, one thing may be just in terms of history. You don't need extensive sophisticated genetic testing. It may be that somebody has some particular symptom or there's an enormous richness in your family history. What kind of heart defects were in your family? What kind of blood vessel problems were in your family? That can give us a real clue as to what kinds of problems might be present from a

cardiovascular standpoint, and that's just one small area. It happens to be my particular interest.

Well, there may be things that are obvious when your physician examines you. There may be some very distinctive features that you never realized that tip them off that, yes, you have a genetic problem. I'm not talking about obvious things that you might be aware of, such as Downs syndrome. I'm talking about various subtle things.

There may be routine laboratory tests, and I'll go back to the cholesterol test as an example. If you have a cholesterol of 5 or 600, that means you have a genetic abnormality in how cholesterol is taken care of in your body, and it's a clear sign of that.

Increasingly the patients and/or their parents bring things up. There are very frequent media stories, some of them accurate, some of them not so accurate, some of them overstating, some of them, in fact, understating important health issues, and never, ever underestimate as a clinician the power of the Internet to raise questions and occasionally answer questions for families. It is not unusual for me to have a family say, "I saw on the Internet X, Y or Z, what do you think?"

Let me go through few cases. Now, some of this will be doctor speak, and I can assure you the doctor speak is not the important part and these are true cases, and I do believe that many of the people who I'm talking about today would be proud to have you learn about their problems. "Tommy" is a 28-year-old who I took care of when I was in Baltimore and he had a repaired congenital heart defect, a defect in his heart that he was born with. It happens to be called "tetralogy of Fallot," and as frequently is the case, he brings his fiancé to his yearly checkup. This is actually always an interesting sign when our adult patients who are born with a congenital heart disease instead of bringing their mom and dad bring their fiancé, and you always know that you're in for a, we have to have some serious talk here, and she's very eager to learn about his heart problem and discuss the risk of their having a baby with a similar problem.

"Tommy" really had no other medical problems. He's a great guy, he graduated from college, but he really struggled in college. He does have some learning problems, and he's currently working for a sports marketing firm, which I think a couple of months ago actually went out of business.

Now, he does have a genetic problem, however, most heart defects are not strictly genetic. As I said, some are obviously genetic. There are many children with Downs syndrome who are born with heart defects, but we are increasingly able to identify a number of chromosome problems that we've never known before where there is a predisposition for heart disease, and Tommy has 'partial deletion of Chromosome 22.'

Now, it's not important that you know what 'partial deletion of Chromosome 22' is, but it is important as people interested in health discrimination and the law that you know what this may cause.

First of all, there's a 50 percent risk of offspring having congenital heart defect, having this particular chromosome problem and having learning problems. Well, you say as an employer, "That's no big deal. That doesn't affect Tommy, right?" But it does affect your health insurance and whether he's going to be around.

There's clearly a risk that "Tommy" may miss work or have healthcare expenses, some of those may be related to fertility and pregnancy issues, and the possibility that he might need heart surgery in the future.

The next case is "JS," he is a 22-year-old who passed out twice in his early teens. Each time he had a brief seizure. Sometimes people seize when they pass out. Everybody said, "Oh, this is just simply fainting." He, however, had a cousin who died instantly while swimming. This is a clue that might come from a history. His physical examination is entirely normal. This particular guy had something called "long QT syndrome," in which the repolarization of the heart -- this is an electrocardiogram -- takes too long. It's a genetic disease that has a huge number of variations. Sometimes people are totally asymptomatic from it, never pass out, never have heart rhythm problems, but sometimes the first indication that they have it is that they die suddenly, and clearly their offspring are at risk for having this as well.

There is a risk of sudden death, there's a need for chronic medication, need for implantable defibrillator, some risk to the offspring, and this all represents healthcare costs and potential other costs for you as employers.

This happens to be my cousin, a 51-year-old who had exercise intolerance and dizziness since he was 18. It turns out that he has a genetic problem called "hypertrophic cardiomyopathy," which is something where the heart muscle is far too thick. So you think, "Why does he have too much heart muscle?" Well, the instruction manual for how to build the right amount of heart muscle wasn't laid out right, but it took 18 years to manifest itself. It turns out his mother has the same thing. He is from Kansas City and had an unthinkable episode in Boston.

He was admitted to Mass General, and his cardiologist wanted to try some number of new heart cath tracing procedure to help his heart, and I got in the loop because my mother called and said, "His insurance company doesn't want to pay for it, what should he say?" It turns out this guy was a very valuable employee for this company and because of that, the company went to bat for him.

And there are clear long-term risks even for this, and for this company, all those medical problems clearly were outweighed by the fact that my cousin was a great employee, but, you know, there's lots of stuff for him in the future.

The last case is a 25-year-old who has been employed for three years by a local manufacturer to install shelving units to display its product in retail stores. His brother at age 38 had emergency surgery last month to replace his aorta when it tore while he was doing some weight lifting, and his brother was diagnosed with Marfan syndrome. "JR" has it as well. Marfan syndrome is an autosomal dominant disorder of connective tissue.

That's doctor speak, but it just means something that comes from our genes. It can be passed on to our children. It has major abnormalities in a lot of other parts of our bodies, and we can oftentimes, but not all the time, diagnose it precisely.

But the interesting thing with Marfan syndrome is with advances in medical and surgical treatment, people can live to in their 60's and 70's and have a very normal lifestyle.

But there is a need for chronic medication. There may well be a need for interventional surgical procedures. There's clearly a risk of having offspring with the same medical problems, and for those of you who are thinking, "How am I going to pay for all of this with my self-insured health plan.?" You have to think about these issues.

So in conclusion, I tried to set out some of the issues that we think of as clinicians. How do people get to us? How do we diagnose people? Some of the issues are never black and white in medicine through some case presentations, which gives you a sense of just one tiny, tiny area of cardiovascular genetics.

Remember, cardiology is not the center of the world. There are huge numbers of different problems in medicine that are genetically oriented. We have probably about 40,000 genes. We don't know what most of them do. We don't know how most of them are carried out. We don't know how the instructions are carried out very well.

Some of these abnormal genes, which I presume someday we'll be able to test for, are never clinically expressed, and so we still rely on clinical medicine in order to identify people who need genetic testing, who would benefit from genetic testing, and who need treatment based on that genetic testing.

Now, I'm presuming that someday all of our advances in molecular biology are going to facilitate how we do these things and what they mean, and just think back 40, 50 years ago. No one ever thought, "Why should we measure cholesterol, what can we do about it?"

Now, who would ever not think of measuring cholesterol? Because either you can do dietary modifications, you can do Lipitor, and there are huge studies which document the benefit of cholesterol reduction, either by diet or by medication, and it took 10, 20, 30 years to figure that out, but we need to be able to proceed with that kind of evidence-based approach to medicine in order to be able to make this information valuable. We can't be afraid of it, but we have to know how to use it and we have to know how to use it in order to bring better health to our patients.

