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The Dynamic and Multifaceted Nature of Cardiovascular Disease and Using Genetic Testing to Inform Clinical Care: An International Perspective

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Linnea M. Baudhuin, Julie De Backer, Jodie Ingles, Dianna M. Milewicz, and Anne Tybjaerg-Hansene
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Guest: Dr. Jodie Ingles from the Royal Prince Alfred Hospital and the Cardio Genomics Program at the Centenary Institute and the University of Sydney

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. The January 2021 edition of *Clinical Chemistry* is a special issue concentrating on biomarkers and cardiovascular disease examining their utility and diagnosis, risk assessment and therapy. The Q&A feature appearing in that issue provides an international perspective on using genetic testing to provide insights into the dynamic and multi-faceted nature of cardiovascular disease and clinical care. In that feature, we asked four experts with different roles in the field to discuss recent advances and ongoing challenges. We are pleased to have one of those experts as our guest in this podcast. Professor Jodie Ingles is the head of the Cardio Genomics Program at the Centenary Institute of the University of Sydney and a cardiac genetic counselor at the Royal Prince Alfred Hospital in Australia. So first of all Dr. Ingles, how did you get into the area of cardiovascular genetics?

Jodie Ingles: So, I completed my training in genetic counseling in 2003, so a really, really long time ago now. And at the time, I wasn't really sure what I wanted to do. There weren't really many genetic counseling jobs, and the first job that I got was actually with a cardiologist who just come back from overseas and was setting up a research group in the area who had inherited heart diseases and he was hiring, looking for a coordinator to help him with the patients and the research. And I had a phone call with him and I said, "Well, it sounds like actually you want a genetic counselor" and he said, "Oh, well, what's a genetic counselor?" And I explained and he said, "Yeah. Actually, it does sound like I want a genetic counselor."

So, I got that job and it was a new role. So, I basically turned it into a cardiac genetic counseling clinic coordinator, research coordinator type role and that was 17 years ago. I think the first few families I saw with inherited heart diseases was just so fascinating. I mean, what these families go through, you know, you see a family that's been through having a young family member die suddenly and the fact that we don't know a lot of things, but we do have potential to help them and

support them. But still, there's a lot we need to learn. It just really hooks you. So, I think from day one, I was hooked on cardiovascular genetics and cardiac genetic counseling and how we can use genetics to better help these families who really go through a lot.

Bob Barrett: Well, from those 17 years of experience, how do you use genetic testing to inform on the care and treatment of cardiac patients?

Jodie Ingles: Genetic testing is really useful. And I mean, we've been using it at some level basically for nearly two decades. And then, when I started, we were offering research-based genetic testing. We would look at about five genes. It would take about two years. And then, when we got a result, it was really exciting. We could feed that back to the family. The main use of genetic testing throughout those two decades and even right now is actually for the families. So, if we can be confident that we found genetic cause for an individual's cardiac disease, then we can use that as a tool in the family to test for the presence or the absence of that particular genetic variant.

And so, that role of cascade genetic testing of knowing who is at risk of developing disease and who can be released from clinical screening and doesn't have to worry about developing the condition. That's, I guess, the primary role of genetic testing and always has been and is still at the moment. I think the really exciting thing is that there's definitely an emerging role of being able to use the actual genetic result to better understand what condition the patient has, what the natural history of their disease is, even so far as thinking that we might be able to use that gene result to better decide who is at risk of sudden cardiac death, who is at risk of getting heart failure and maybe needing a transplant in the future.

And then, there's also a group of patients that we are starting to see now where genetic testing actually helps us to better understand their precise diagnosis. So, maybe we thought they had one condition, but genetic testing actually helps to see that they had another, similar but different condition and even a subset of our patients that don't actually meet any diagnostic criteria. And so, genetic testing can help give them a diagnosis. And for a family that doesn't even know the name of the condition affecting their loved one, to actually be able to say to them "Well, genetic testing has helped us work out that you have this cardiomyopathy, or this arrhythmic syndrome" is a really powerful thing. So, that's one of the really exciting -- I think potential areas where genetic testing is going in the future.

Bob Barrett: Well, what do you think are some of the biggest challenges and how genetic testing is used currently right here at the start of 2021?

Jodie Ingles: You know, this is a really good question. And this is from my perspective, I see patients in the clinic, but I also lead a research group and I spent a lot of my time with a research hat on. And one of the things I'm really interested in is how we can use genetics to better manage and treat the patients that we're seeing. I think one of the biggest challenges that we face at the moment is genetic testing is being used for so long in the clinic. I think that can sometimes be a little bit of complacency that this is a routine clinical test. And in some instances, it is. But in a lot, it's really not. And I think what we really need to understand is that research needs to be embedded into this setting as much as possible. And we really don't understand a lot about the underlying genetic architecture of many of these conditions. We don't understand the full phenotype spectrum of some of these conditions, the role of polygenic and non-genetic factors like, what high blood pressure does to a patient with hypertrophic cardiomyopathy.

And so, there's this huge range of uncertainty and I think that we need to be really careful that we see that there's a lot of uncertainty and that there's a lot we still need to actively do to try to understand that. We had an experience in the last couple of years where we had a few patients that we were seeing: two of them had had a sudden cardiac death and were deceased (and so, this was postmortem investigation and genetic testing), and two who'd had a cardiac arrest and survived. All four patients had no evidence of any cardiomyopathy on any of their investigations. And yet, the genetic testing that we performed picked up truncating variants in a gene called PKP2 and that basically suggests an arrhythmogenic cardiomyopathy. So, the fact that these four individuals who had really significant sudden cardiac arrest without any obvious cardiomyopathy was something that we really hadn't ever seen.

And so, I guess things like that for me always remind me that there's still so much that we don't understand. If we think for one minute that we understand what we're doing in this particular field, something will happen that makes you realize knowing the fact we really don't understand things. And so, we have to be really careful, always checking that what we think is correct actually is correct and keeping an open mind that potentially we might be wrong. I think it's really important.

I think one of the other big challenges is, you know, we spend a lot of time focusing on how we can better understand and what we can do with the gene results. But also, we need to

focus a lot of energy on showing the value of genetic counseling in the setting, but also the value and the support needs of the families as well because we can do all this fancy genetic testing, but if the patients don't understand what we're telling them, what's the point in any of it? So, I think that there needs to be equal energy in helping how we actually implement this type of information into families and into health care settings in ways that actually can be informative and used. And so, that's also one the research area. As a genetic counselor, I think obviously it's important to show the value of what we do. Yeah. So, I think that they are probably some of the big challenges that we face right now.

Bob Barrett: As a genetic counselor, you're giving patient some sensitive possibly emotional information. What is your perspective of how patients cope with the results of genetic information for cardiac conditions?

Jodie Ingles: I think from my experience and seeing these families -- and I mean, I sometimes seeing them when they're really at an awful point. I see families where they've had a 13-year-old drop dead suddenly out of the blue completely, no previous diagnosis, and then they get told that potentially it is a genetic condition. And we have to provide genetic counseling and go through the need to access postmortem tissue and then providing results back of. Then, there can be a lot of uncertainty in those results. The thing that I'm always reminded is that people actually are very resilient. I think we have to be as honest with them as we can about what we do and don't understand that we're actively trying to work to support them as much as possible and to do the best by them. And so, I generally find that as long I am honest with patients and really paying attention to their questions and checking in with them that they understand as much as possible what I'm saying to them.

I generally find the people to cope with this information. Some of the more challenging things are, you know, I've talked about a sudden death a lot, but we know that families that have had a young sudden cardiac death can have really significant ongoing psychological difficulties because of that. We know that they can end up with post-traumatic stress and prolonged grief. And so, how you provide genetic counseling and genetic testing on top of that can be something that can take a bit of skill and you have to understand that sometimes to some families, genetic testing is really not in a top priority for them right then and there and, actually, we need to work to find a psychologist that the family can see and help sort some of those things out. So, I think that's -- it really demonstrates the need for genetic counselors in cardiology clinics. Because I think that we're trained to deal with those psychosocial support needs as well as have the skills to

understand the genetics and how it relates to the patients as well. I think that's really important.

Bob Barrett: Equitable health care access is a particular concern in many countries. How can we ensure that genetic testing is equitable?

Jodie Ingles: So, I'm sure that this is a concern in every single country. Even the wealthiest country still have a social gradient at some level. So, understanding disparities in access to genetic testing is really, really big focus of mine. I think that this is something that we really don't spend enough time on. And the issues are: there are disparities in the way that people access genetic testing. So, that's one issue. But then, when people get genetic testing, there's disparities in how what the risk use of misclassifying a variant for person who is from an ethnic group that's not well represented in our big population databases. The risk that their genetic result is wrong, a variant that's called being a causative when it's actually not. It's actually much higher because we don't understand the population variants in those particular ethnic groups.

So, there's kind of difficulties at every level. We've done some research recently in Australia showing that there's clear disparities in who can actually access genetic testing in a specialized clinic. And so, patients don't even need to pay to come to our clinics. They don't need to pay for genetic testing. We offer everything free and yet we still see very clear health disparities and so understanding why that's the case. I think that's something that we all need to be thinking about and trying to address. And I think the biggest issue is that we focus a lot and the field is moving so quickly into a space where we can use genetics and an individual genetic result to guide management, to give highly advice to families to improve outcomes and all this really great things where we hope genetic medicine is going to take us.

But, at the moment, that's actually are going to be something that it will be realized for white people -- and we shouldn't be doing all of this work just to benefit one small part of our population. It's something that we need to address now. We need to work out ways that we can creatively use technology to address health literacy to be able to get information to people who don't necessarily speak English. Now, we need to do research to understand why some cultural and why some ethnic groups have culture reasons why they wouldn't want genetic testing because, if we can understand those things, we can understand how we can address any potential barriers and ensuring that some groups can get the benefit of all this work that we're doing. So, for me, this is a really, really big issue on something that all of us need to be thinking about and trying to address.

Bob Barrett: Well, finally, Dr. Ingles, let's look ahead what do we need to do to ensure that we can provide genetic testing to meet the demands in the future?

Jodie Ingles: So, some of the key things: I think that we need to embed and fund research at all levels of how we use genetics in cardiology clinics because we don't know enough yet, but this is the main stream clinical test. There's still a huge amount we need to do. I think that we need to ensure that genetic counseling is a really critical component of genetic testing. Genetic counselors are important in all aspects of how we manage families with inherited conditions and in the process of genetic counseling even more so, the role of genetic counseling is even more important, but we need -- as we scale up genetic testing and as genetic testing becomes used in more areas of clinical medicine, I think we need more genetic counselors.

We need them to be better supported. We need technology that can help support some of the roles that we do. And then, finally, as I was saying before about the health disparities, we really need to address and consider health disparities and we really don't want to do all this clever research and end up with this really great precision medicine approach to caring for families with inherited heart diseases and have it only benefit one small part of that population. It needs to benefit everyone and we need to be clever and think about how we do that and address it now because it's only going to become a bigger gap. So, I think those three things are really key.

Bob Barrett: That was Dr. Jodie Ingles from the Royal Prince Alfred Hospital and the Cardio Genomics Program at the Centenary Institute at the University of Sydney in Australia. She is one of the four experts participating in the Clinical Chemistry Q&A feature on the role of genetic testing to provide insights into the nature of cardiovascular disease and clinical care. It appears in the January 2021 issue of *Clinical Chemistry*, a special issue on biomarkers and cardiovascular disease examining their utility and diagnosis, risk assessment and therapy. I'm Bob Barrett.