Dr. Aaron Carroll:

Welcome back to the Healthcare Triage podcast. Today, we have a returning guest and a new one. Returning is Erin Conboy. She's an Assistant Professor of Pediatrics and Medical and Molecular Genetics at Indiana University School of Medicine and Director of the Undiagnosed Rare Disease Clinic. Also joining us, new to the program, is Stephanie Ware. She's a Professor of Pediatrics and Medical and Molecular Genetics and also the Vice Chair for Clinical Affairs for Medical and Molecular Genetics. Stephanie and Erin, both of you, welcome.

Dr. Erin Conboy:

Thank you. Good to be here.

Dr. Aaron Carroll:

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Why don't we start with Stephanie since we've talked to Erin before. We like to start always by asking people what do you do? What is a professor of pediatrics and molecular medical genetics and a vice chair for clinical affairs? What do you do, and how did you know you wanted to do that, and how did you get there?

Dr. Stephanie Ware:

I am a physician scientist, so I see patients who have genetic disease, rare disease. And then I have a research lab, and the research lab, we have two basic areas of interest. One is really understanding how heart defects happen in babies, how the heart forms abnormally, and the other is trying to understand the genetics of that, of really what are the genes that control the way the heart forms in a baby. And then we also work on other cardiac diseases that can be inherited, heart muscle disease, rhythm problems.

Dr. Aaron Carroll:

How did you decide this is what you want to do?

Dr. Erin Conboy:

I went to medical school, and actually after my first year of medical school, I joined the MD-PhD program because I decided I wanted to also incorporate some research. During my graduate school work, I did work on gene regulation and became very interested in developmental biology as part of that and how organs form. And then I went on to do clinical training in pediatrics, and as part of taking care of kids, and learning how to take care of kids as a resident, I really became fascinated by kids who had very unusual symptoms, kids who had birth defects, and trying to better understand how to best take care of those individuals, how we could understand what it was that caused their problems, and genetics was sort of a natural part of that.

I didn't realize that genetics could be area of clinical specialty, but it happened that the area where I went to do my pediatric training was very strong in clinical genetics. I went on and did a

fellowship there, and it was a really nice way to merge my interests on a research side, in terms of developmental biology and how organs form and clinical care of taking care of kids with birth defects or risk for cardiac problems.

Dr. Aaron Carroll:

Erin, how about you? How did you get to where you are, and how would you describe what you do?

Dr. Erin Conboy:

Like Stephanie, I didn't know that you could do medical genetics clinically. I really liked genetics when I was in college, went to medical school, and decided to be a pediatrician. During my residency in pediatrics, had a fortunate ability to do a rotation in genetics and realized that of all the interesting and important diseases I've seen, the ones that interested me the most were those that were genetically based. I think part of the allure was that you could sit down and talk to a family and say, "This is why this is happening to your child," as opposed to other clinical diagnoses that are a set of symptoms and a description. You could sit down and say, "This is a genetic change. It happened randomly. It really is not anyone's fault. There's not an environmental factor here. It's a random genetic change that led to your child's problems," and really get down to why it's happening.

The other thing that I really liked about it is that medical geneticists get to spend more time with patients than any other subspecialty that I experienced. Our average time with a patient is 45 minutes to an hour or so, and that allows us to, I think, develop incredible rapport with our patients and really be there for them during this really difficult time of one, trying to learn genetics quickly during a medical appointment, then learning the diagnosis, potentially, of their child, and then moving on from there as far as next steps. It's a lot that happens in an appointment, and I liked that there was enough time given for that.

All of those things led me to then doing the medical genetics fellowship at Mayo Clinic, where I was doing my [inaudible 00:05:30] residency, and thankfully they had a fellowship there.

Dr. Aaron Carroll:

So both of you brought up that you were surprised to learn there was such a thing as medical or clinical genetics. I am sure that many listeners will feel exactly the way. Could you talk a bit about what that exactly means? How does one practice clinical or medical genetics?

Dr. Stephanie Ware:

One of the things that I love about genetics is that you really have a full scope. You have a role in making a diagnosis and trying to understand what a genetic cause of a condition is, the set of symptoms.

You sometimes play a role like a primary care physician, because for some individuals with rare disease, you need to really collaborate with their primary care doctor, who doesn't know much about that disease. You're really involved with the management plan and there are, for certain genetic diseases, there are healthcare supervision guidelines just as there are in a primary care setting, in terms of specific surveillance that gets done at a certain age or certain labs that need to be checked. You really get that long-term management with the patients.

The third thing is that there are patients that really present very acutely, that are emergent and life-threatening, and being able to make a diagnosis quickly and then recommend the appropriate therapy can be life-saving or can be brain-saving. You get to practice a full gamut. I was really attracted to that.

In terms of what kind of patients, it's a really wide variety, and that was another thing that was very attractive is that it's always something new and different. There's always something new to learn because the function of genes is still being elucidated. It's a constantly-changing practice.

But I would say some of the core things that we take care of are any child or adult who has a chromosome abnormality. Many individuals with birth defects, learning disability, and intellectual impairment would fall into those categories. And then there's sub-specialty areas. There's neurogenetics, there's cardiovascular genetics, metabolism. There's a lot of sub-subspecialty areas as well. It's a pretty vast specialty actually.

Dr. Erin Conboy:

Yeah, no, I agree. I think we see patients who are often on, what are termed, diagnostic odysseys. They've seen multiple sub-specialists and don't have an underlying cause for their disease is another group of patients that we see. Some of them have had limited genetic testing or no genetic testing and need that in order to define their underlying disease.

I think, importantly, and the thing that I tell patients often, either before or after testing, is that we have somewhere between 20 and 30,000 genes. We think that there are that many protein coding segments along our chromosomes, but we only know what 5,000 of them do. Each year there are a hundred or more new genes being associated with disease. If we see a patient in 2022, and we can't find the underlying genetic cause, we continue to look, and we bring them back for one- or two-year follow ups because in the interim, there could be a new gene discovered that explains their underlying disease.

The other, I think, important aspect of what we do is that we continue to follow patient's long-term, both for that new gene discovery aspect of things, but also because these are rare diseases that we don't know a lot about, and more is being elucidated in the literature. Management recommendations can change, and additional studies might be indicated in follow-up appointments. That's exactly how Dr. Ware was saying, we work almost as a genetics primary care physician in a sense, because we know these guidelines have been updated, and this patient needs this additional study or lab test.

Dr. Aaron Carroll:

When you get a new patient in, and you're trying to figure out what's going on, what testing do you do exactly? Is it we're just going to sequence the whole gene? Or is it you're looking for specific...? What tests do you do?

Dr. Erin Conboy:

I guess the approach to the patient would be very specific to the symptoms that they're having. But we do come up with a list, and we try to put patients into groups, I guess, based on the presenting symptoms that they have. You think about an approach from a genetic testing standpoint, an approach from a metabolic testing standpoint, and then are there other either referrals or imaging or other lab testing that could help better inform or better refine what you think the underlying diagnosis may be?

It's not always that we just go straight to a genetic test us, although genetic testing is our bread-and butter toolbox. But sometimes it could be getting us x-ray films is going to really help make a diagnosis or getting other specific lab testing. I guess the other piece is the family history. In some cases, a family history can be very informative in terms of what's going on with the patient.

In terms of genetic testing, I guess we have a couple different flavors of what we do. One is chromosome-based testing. Then the other is what we call sequence-based testing. When I talk to

patients, I usually use the analogy of, if you think of your genetic information like it's the set of library books, and then the one type of test that we do is looking and counting the number of books that are there to see if you have the right number, and then actually looking at the pages of the books to see, is every single page there. Is there any page that's extra? Is there any page that's missing? That's the chromosome-based testing. The sequence-based testing is basically reading the words on the page and seeing if there's any typographical errors, if there's any words misspelled, and interpreting that. Those are the two broad methods that we have.

Dr. Aaron Carroll:

Given that everyone has a different book, how do you know if it's misspelled, or it's just different?

Dr. Stephanie Ware:

That is the difficult thing about interpreting genetic testing is that there are tens of thousands of small differences between each of us. And if that happens to occur in a gene of interest, so if there were a disease causing misspelling in that gene, it fits with symptoms. But what these changes are called, if they haven't been categorized as disease-causing or expected variation, are variations of uncertain significance.

We as geneticists deal with variations of uncertain significance more often than we do with straightforward pathogenic or disease-causing variance. In that context, we have to look at what does that misspelling do? Is it a small misspelling, or is it a misspelling that says the gene needs to just stop in the middle? That's one thing is what type of misspelling is it?

The next thing we think about is does the inheritance pattern fit? Is it one change in one gene, dominant condition, or are there two changes on separate copies of the gene for recessive condition? Does it fit in the family? Like Dr. Ware was saying, we take a detailed family history, and if we can show that there are other affected relatives with the same genetic change, that increases our suspicion that it's a causative variant.

The answer to your question is it happens often, and it is not straightforward, as far as trying to determine if a variant is disease-causing or not in some cases. There are some cases where we've seen this change before, we know it causes disease, and that's a straightforward answer. But in others, it's much more ambiguous. Sometimes you have to wait for changes or changes like that to be added to databases so we follow patients over time to see if we can better understand their variants at follow-up appointments. But it does cause anxiety, both for the family and for the medical geneticists, sometimes, trying to figure out exactly what to do with those uncertain results.

Dr. Erin Conboy:

There are also changes that we know are important for variation, but they're not disease-causing. An example would be the word gray. You can spell gray, G-R-A-Y, or in British English, you spell it G-R-E-Y. So it's spelled differently, but everyone agrees, gray means this color that looks like this. It doesn't cause a problem. It's just something that's responsible for a difference. The more we know, the more we know. The more genetic information that's out there, the more we're able to say, "Oh, well, this is variation. That's just part of normal variation, and it's not something that is really causing disease."

Dr. Aaron Carroll:

One thing we've discussed on many episodes, that I'm still not totally clear on, so I'll admit that I sometimes am faking it here. But what is the difference between genetics and genomics?

Dr. Erin Conboy:

I think people can use those terms interchangeably and overlapping. Genomics tends to be used to apply to our entire genome, which is all of our genetic information.

Things like pharmacogenomics are where you use different parts of all of our genetic information to ask a very specific question. Does a specific change affect the way that you can metabolize a particular medication that you're going to be on?

I think genomics will increasingly be used widely in medical care, and it doesn't require a medical geneticist necessarily. I think PCPs are going to be, primary care physicians are going to be using genomics in their everyday practice, where they know what tests to order and a very clear interpretation comes back for that test. They know how to act on the patient, based on that result, just like they do if they do a blood count. It's a very specific question, a very specific answer.

I think what we do, as medical geneticists, is we use much more complex genetic testing than an individual practitioner is going to want to have to deal with in their everyday practice. To me, that's a little bit of the difference between using those terms.

Dr. Stephanie Ware:

When I think of genetics, I think of it as a term that was used for a longer period of time, maybe a little bit of an older term, referring mainly to genes and inheritance, whereas genomics, you're thinking beyond just genes, and thinking more about, potentially, the structure of the genome, interactions between genes that are being turned on and off with methylation as well as regulatory sequences.

I think, as we have learned more about genetics, we're realizing that genetics doesn't encompass everything that we do, but rather genomics does because we're not only thinking about genes anymore. We're thinking about the regulation of genes, the introns, or the space between genes that may affect the function of the gene. I think it's an attempt to understand that there's more to it than genes only perhaps.

Dr. Erin Conboy:

To go back to the previous analogy, I guess the genes are the words on the page. But you've got punctuation, you've got spacing, you've got grammar, you've got all these higher level things, besides just the words on a page, that are all important for how you understand things as well.

Dr. Aaron Carroll:

When you get a patient in rare disease clinic, and you're trying to figure it out, and you then go ahead and you perform testing. Is it that we're usually sequencing their entire gene and then just looking through the usual genes, and then the rest we put in a folder and we wait and hope somebody figures out something someday and come back to it? Or am I massively oversimplifying this?

Dr. Stephanie Ware:

No, I think you're explaining it pretty well. Sometimes, if we see a patient, and we think this patient fits very nicely into this group of disorders, we may say, "Let's send a panel," meaning a list of anywhere between a couple and thousands of genes that all seem to fit that patient's particular set of symptoms.

If the patient doesn't seem to have symptoms that would be easily put into a panel or a list of genes, then we do what's called Whole Exome Sequencing or Whole Genome Sequencing, where we sequence all 20 to 30,000 genes. But that test is only going to interpret the 5000 that we know. In that

way, like you were saying, we are able to then go back and ask for re-analysis. When patients come back to us in clinic, and we failed them the first time and weren't able to find the underlying cause, in a year or two or more, we can go back to the lab and say, "Hey, can you look at this again with today's information and see if we can find the cause now?"

I think a really cool thing about the genetic testing that we're doing now is that this can be done on a cheek swab. Often families come in and are expecting maybe some sort of intensive testing for the patient, but really we don't even have to poke them with a needle for most genetic tests. We can do many tests now on a buccal swab or a cheek swab.

Dr. Aaron Carroll:

How much does it cost, and how long does it take?

Dr. Stephanie Ware:

There's a real push in the genetics community to make this more and more rapid. In fact, in some intensive care units, there's increasing data out now that rapid and very aggressive exome or genome testing can give diagnosis rates for patients where there's a suspicion of a genetic problem of 30 to 40% and that that can really significantly impact management. The rapid testing, to us, is about out a 7 to 14 day turn-around, but there are studies out there, where on a more research basis, where you can get 48 to 72 hour turn-around. In terms of the actual technology, the minimum amount of time it takes, once the lab receives the sample, is about 36 hours. But it's the time to do the computing, the bioinformatics, and then the actual interpretations, the longest chunk of that time.

Dr. Aaron Carroll:

I imagine this needs a fairly large amount of computing power. Is that a rate-limiting step?

Dr. Stephanie Ware:

It's terabytes of data, and it is rate-limiting for an institution that's trying to set up genome sequencing like we are. We have to make sure that we have enough space to store these things. Other places that - I'm not sure how they do it - but they must have cloud-based data system infrastructure, but we are running into data-saving issues and have to have lots of space for this.

As far as cost, it depends on insurance. Sometimes patients can get an out-of-pocket cost of free, which is really nice. But sometimes some out-of-pocket come back in the $3000 to $4000 range, which is often prohibitive. We have some options where we try to ask labs for lower cost or free testing.

But I guess the take-home message is, no matter what that ends up being, we try to do our best to find ways of testing. There are some genetic testing companies that are offering free panels that are sponsored by drug companies. Sometimes we can get some answers that way. We try to find ways of getting testing to patients, even if the cost is high.

Dr. Aaron Carroll:

I guess part of what I was getting at is this is not the same thing as spitting into an ancestry.com vial and sending it off for $30.

Dr. Stephanie Ware:

No, it's a little bit more complicated than that.

Dr. Aaron Carroll:

Actually, asking about the computing power, this is, imagining again, not something that you're running on your desktop computer in your office. But it doesn't require massive supercomputer, or is it...? How much computing power do you actually need?

Dr. Erin Conboy:

We do use the IU supercomputers to store large amounts of data. What happens is when the raw sequence comes off the computer, that's the largest file. That's called a FASTQ. It has all the raw data, all the As, Cs, Ts, and Gs, and all of that data. That is then analyzed and put into smaller files that are Variant Call Files, or VCFs. Those are smaller, because it's just telling you, "These are the variants that we're seeing," because we've already looked at all the As, Cs, Ts, and GS and compared them to expected. Now we're saying, "These are the variants that we found." That's a lot less data. Those Variant Call Files can be actually sent to us via email and downloaded onto desktops. It takes a little while as far as saving and things like that. So that is possible. But the FASTQ files or not things that we can go back to the clinical labs and ask for. We have to ask for that already-called file that has a limited number of variants in it.

Dr. Aaron Carroll:

I'd love to just pivot a little bit and ask you a bit, how does this tie into newborn screening, because clearly we're not doing this on newborns? But many of these things are going to be identified in that way. How are you plugged into newborn screening?

Dr. Stephanie Ware:

I think the newborn screening basically every condition that's on there, from a inborn era of metabolism standpoint, is classified as a rare disease. IU School of Medicine and our department does have the contract with the Indiana Department of Health for coordinating the newborn screening for inborn errors of metabolism for most of the state. There's some counties in the northeast of the state, where there's a high Amish population, that are coordinated by the group up there, that we collaborate with fairly extensively.

But newborn screening is just the heel stick that's done on all babies throughout the state when they're born. The blood's put on a blood card. The screening is done for these metabolic conditions, and if the screen is positive, then that is referred to our group to do follow-up screening and diagnostic testing and then do the management of those patients. They're essentially all rare genetic diseases that are being screened for.

Dr. Aaron Carroll:

But I'd imagine that most of the screens that we're using are not genetic tests. The screens for newborn screen are not genetic tests, or are they genetic tests?

Dr. Erin Conboy:

In general, most of the conditions that are on the newborn screen are metabolite only. We're looking for high or low metabolites that indicate a particular metabolic disorder. In the case of a few, in particular, cystic fibrosis, there is a reflex test that goes to sequencing of CFTR. If someone screens positive for an initial screen, then sequencing happens as a reflex to try to figure out what is the cause of the screen positive for CF.

The other one that is genetic in a sense is the screen for SCID. But that's just using, essentially, a count so that there are T regulatory cells or TREG, and they all have their own set of DNA. It's just doing a count, how many of these TREGs are present, and if they're too low, then the T-cell count is likely low, and that would flag positive for severe combined immunodeficiency. And then we see, we as in the immunogenetics group, immunology in combination with geneticists, which is often me, we complete screening genetic testing on babies that come back with positive testing for SCID. The test itself, newborn screen, is not often genetic. But the reflex testing, if patients are positive, we often go to genetic testing for that.

Dr. Aaron Carroll:

Is that coordinated throughout the state, I imagine? How do they get to you?

Dr. Stephanie Ware:

It is coordinated throughout the state. Every hospital and every county throughout the state, their blood cards are sent to the testing laboratory that's designated by the Department of Health. Then that testing laboratory coordinates with us. When they have a positive screening result, they let us know. And then we take it from there, in terms of connecting with the family and with the hospital and taking the next steps of what needs to be done in order to follow up on that positive screen.

Dr. Aaron Carroll:

I know your center just was recently recognized as a Rare Disease Center of Excellence. Can you tell us what that means?

Dr. Erin Conboy:

Sure. Yeah. It was exciting. There is a national organization that's called NORD, N-O-R-D, the National Organization of Rare Disorders. They, for a long time, have served as an advocacy and educational warehouse, if you will, for all various types of rare disorders. They decided that they were going to have an inaugural request for proposals or request for grants to form a network of centers that specialize in rare disease. We applied for that, and we were designated as one of what is now 31 centers nationally as Centers of Excellence in Rare Disease. For that, you needed to have services in both pediatric and adult. I know we've talked a lot about pediatrics today, but there are a lot of adults with rare disease as well. You had to have facilities for both. You had to have genetics, genetic counseling, social work, and then a range of the diagnostic testing, the metabolic testing, and genetic testing, imaging modalities, and specific expertise in areas related to rare disease.

I think it was a really nice designation for IU Health and for the School of Medicine. While our department drove that application, we are not the only ones that follow patients with rare disease. We really tried to assemble all of the expertise of providers throughout IU Health and IU School of Medicine that are either researching or providing clinical care for patients with rare disease. I think that helped us have a really strong application.

Dr. Aaron Carroll:

Where do you see everything going? Ff everything continues to go and zip along as it has, what's going to be different? What's the future look like in five years or 10 even?

Dr. Stephanie Ware:

The goal of genetics is really to improve patient care. And I always say I'll be happy if I'm put out of a job at some point in time because we can cure rare disease, or it can be diagnosed very early, and some therapy can be brought in that really changes the trajectory and the prognosis of those patients.

I think the idea that genetics can be used for diagnosis, but it also can be used for, what we call, risk stratification. Within patients that have any given disease, you always have some that, for whatever reason, do worse than others. Genetics is increasingly going to be able to be used to identify those within a group that are at highest risk of some complication related to their disease course. Being able to apply genetics predictively is what we really want to be able to do. Let's predict the ones that are at highest risk for something and then be able to take better care of those individuals and also be able to be better stewards of hospital resources and the cost effectiveness and so forth, by really tailoring therapy and identifying those that are going to benefit most from it.

Dr. Erin Conboy:

Yeah, my hope is that our Medical Genetics and Genomics Department is going to be able to collaborate with every specialty and subspecialty at IU, IU Health, because in the short time that I've been here, I've been impressed by the willingness to incorporate genetic testing into other disciplines' practices.

As an example, I think it was soon after I got here about three years ago, I had a conversation in with Dr. Katie Haider on the phone about a patient, because I didn't know what their eye disease was, and she's a pediatric ophthalmologist. I needed to better understand their eye disease. She had referred them to me to figure out the underlying cause of their eye disease. Because of that conversation, we now have ocular genetics clinic where we, Katie Anderson, genetic counselor in our department, Dr Haider, and I, work together and see patients who have a high possibility of having a genetically-based eye disease. That's led to management changes in their care with ophthalmology and qualification for a handful of cases for clinical trials.

Prior to us becoming part of ophthalmology clinic, for a time, there were only 10 or 11 genetic tests ever sent on patients. Now we have over a hundred patients who have testing back, and we're looking at around a little under 50% hit rate on our diagnostic rate. I think, if we can do that with more subspecialties, patients will have improved care over time. I guess that's my hope for our future.

Dr. Aaron Carroll:

Well, of course we'll have to see which of those things come true, and we'd love to have you back and talk about advances in the field. Thanks so much for joining us.

Dr. Stephanie Ware:

Thank you.

Dr. Aaron Carroll:

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