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Predictive and Precision Medicine with Genomic Data

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Guest: Dr. Linnea Baudhuin is a board certified Clinical Molecular Geneticist and Laboratory Director in the Department of Laboratory Medicine and Pathology with a joint appointment in the Department of Clinical Genomics at the Mayo Clinic in Rochester, Minnesota.

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.

Molecular diagnostics is now firmly rooted in laboratory medicine and the January 2020 issue of *Clinical Chemistry* is devoted to this topic. In that issue, Dr. Linnea Baudhuin reviews genome and exome sequencing as they're used in clinical practice. She is a board certified Clinical Molecular Geneticist and Laboratory Director in the Department of Laboratory Medicine and Pathology, with a joint appointment in the Department of Clinical Genomics at the Mayo Clinic in Rochester, Minnesota. Her clinical and research interests lie in the areas of cardiovascular genomics, genetic testing technology, genetic variant interpretation, and consumer genomics, and she joins us in this podcast. So, Dr. Baudhuin, how are genome and exome sequencing used clinically today and how does this contrast to how they're used in the research setting?

Dr. Linnea Baudhuin: Yes, well clinically, genome or exome sequencing is most often used to help diagnose patients who have complex medical conditions and who are suspected of having an underlying genetic component, and this is commonly referred to as diagnostic odyssey. Clinical exome or genome sequencing may also be the diagnostic test of choice for number of other clinical scenarios including such things as autism or moderate to severe intellectual disability. And in contrast to much of the research testing that is out there, clinical exome and genome sequencing is performed in a laboratory under tight regulatory and quality control conditions.

In addition to the diagnostic odyssey, another exciting clinical application for this type of testing is known as rapid genome sequencing, and this can be used for critically ill newborns in the Neonatal Intensive Care Unit, and in both the diagnostic odyssey and NICU settings, it's really been surprising to see the benefit of this type of sequencing and it's provided a diagnosis in about 25% to 30% of cases and this number remains consistent throughout the years.

Now, you asked about the research setting for this type of testing. So, in contrast to the clinical setting, there are numerous national/international research projects that are investigating the use of genome and exome sequencing in apparently healthy individuals. So, this is in contrast to the clinical setting where it's used really for a medical purpose.

And some examples of these large research projects include Geisinger's MyCode initiative, the NHGRI's ClinSeq, and the various Genomes2People research projects through Harvard Medical School. So, again, these projects are investigating the use of genome sequencing for apparently healthy individuals and they have been touted to offer a new opportunity to provide predictive and precision medicine to individuals and their families, from the standpoint of diagnosis of current and potentially future genetic conditions, clinical management guided by genetics, and gene based pharmaceutical management which is also known as pharmacogenetics. However, while the promise of genomic medicine and precision therapies based on new genetic and genomic knowledge is great, I think many would agree that we are still a long way away from providing very many concrete applications in this area. And furthermore, there are a lot of scientific and ethical questions about the benefits, the harms, and the cost of genomic testing of apparently healthy individuals. So, this type of testing does have a lot of controversy around it.

Bob Barrett: Well, that's interesting. Could you give us some insights as to some of the potential risks or harms to presumably healthy individuals getting their exomes and genomes sequenced?

Dr. Linnea Baudhuin: Yes, there are potential risks and harms in this scenario and it's really important for healthy individuals and actually any individuals who want to get their exome or genome sequenced to receive proper pretest counseling so that they are aware of the potential pros of the testing as well as the potential cons or risks of the testing. And I would say that many individuals just are not aware of the limitations of testing and how results might affect them and their family.

On the flip side, after the testing is done, post-test counseling is also very important so that individuals being tested really understand the implications of the result, whether positive, negative, or somewhere in between. And ethicists have repeatedly drawn attention to concerns that patients and research participants could experience great distress; they could misunderstand the results; they could suffer mistreatment by uninformed physicians and healthcare providers; and, they could use excessive

amounts of medical resources in attempts to follow up on their testing.

In the Q&A, Dr. Wylie Burke has pointed out that much of this type of testing of healthy individuals can produce results of uncertain significance, and it really has the potential to provide misleading information about multifactorial conditions.

She further points out that there are really many inconsistencies in how laboratories interpret genetic variants. And, when you're talking about sequencing healthy individuals, this is an unselected population and genetic variant interpretation in unselected populations is much more difficult compared to genetic variant interpretation when the individual has a clinical reason for testing.

So, this also creates another type of risk that the variant might be interpreted incorrectly and also, with the chance of having a negative result from this type of testing, it could lead to false reassurance in a healthy individual because they might not understand the limitations of the testing. On the other hand, as pointed out in the Q&A, some might argue that current evidence including experimental trials and historical observation has suggested that these risks have really been overestimated, but since we're still in the fairly early stages of these research projects, it's probably too soon to say how much these potential risks will hold water and it's probably advisable to proceed with caution.

One other risk that I wanted to bring up that is often not talked about has to do with potential privacy concerns regarding the genomic data. Specially, with direct-to-consumer genetic testing and research genomic testing where databases may ,be targeted. And finally, although we do have the Genetic Information Nondiscrimination Act or GINA, which protects patients against health insurance discrimination, it does not protect against long term disability or life insurance discrimination based on genetic information. So, it's really important for individuals who are interested in getting their genome sequenced, that they are aware of all these risks.

Bob Barrett: Well, what about benefits, are there times when it might benefit healthy individuals to get their exome or genome sequenced?

Dr. Linnea Baudhuin: Well, there probably are some benefits in some subsets of individuals. Although, it is currently not standard of care to have proactive or predispositional sequencing of apparently healthy individuals, and it should be pointed out too that there is really limited reimbursement for most preventive

screening practices, especially when it may take years or decades to derive benefits from the testing.

That being said, there are some benefits to sequencing healthy individuals related to what's known as medically actionable results. For example, finding genetic variants related to monogenic risks for rare heritable conditions, including those that may impact the individuals personally or may potentially impact their current and/or future children. There is also some benefit to finding out relevant pharmacogenetic results with the identification of genetic variants, important for drug metabolism and response. And a lot of emphasis has been placed on medically actionable results.

And I thought it was really interesting in the Q&A where Drs. Leslie Biesecker and Eric Green took a little bit of issue with how much has been made about the actionability of genetic risk. And they say that their research suggests that this concept of medical actionability is a false flag that really artificially simplifies the complexity of how humans utilize information. They point out that there are varying definitions of medical actionability which can incorporate things like prophylactic surgery, enhanced surveillance, and lifestyle changes, but there is also non-medical actionability which can incorporate personal, familial, commercial, and even societal activities. And then, some others say that there is a very high probably that almost everyone will benefit substantially, both medically and non-medically, from genomic information and the overall risks are very low.

And then Dr. Robert Green in the Q&A also points out that from a standpoint of which healthy individuals should get tested right now, he points out that there are substantial numbers of technologically and medically sophisticated individuals who are responsibly curious about their genomes and for these healthy individuals, as long as they truly understand the risks and benefits, genome sequencing could be a perfectly reasonable option.

Bob Barrett: You touched on the benefits of sequencing critically ill newborns with rapid genome sequencing, but what about sequencing presumably healthy newborns, are there benefits or potential harms to sequencing all newborns at birth?

Dr. Linnea Baudhuin: Well, this is really a great question and it's a highly controversial area and most of the opinions against sequencing presumably healthy newborns really revolve around what is known as a child's right to an open future. So, in other words, sequencing a baby's genome at birth could reveal genetic variants that increase risk for conditions that occur in childhood or maybe not until adulthood. And

there's really a large consensus within pediatric, genetics, and ethics communities in the United States and globally that children should not be tested for adult onset-only conditions. And there are opinions that if we do research on children, we need to consider what rights they have to privacy, particularly about information that will not be relevant until they are adults, and what harms as well as what benefits may accrue from seeking out this information years or decades before it's necessary. On the other side of the coin are active studies and projects involving genomic analysis of presumably healthy newborns.

So, for example, there's a research study underway in the U.S. and it's called the BabySeq Project, and it's a randomized clinical trial aimed at investigating how to best use genomics in clinical pediatric medicine, and it involves sequencing of newborns and delivery of results related to childhood-onset genetic conditions. But interestingly, BabySeq has had a relatively low participation rate, only around 7%. And this is for numerous reasons, but in part, due to lack of interest and/or discomfort with genetic testing.

The most commonly cited reasons for declining participation in the study were concerns over privacy and implications of results. So, there does seemed to be some hesitation in the general community as well about having newborns sequenced. Despite all this, there are still ambitious plans out there for sequencing newborns and, in fact, there's one plan out there in the United Kingdom for all children to receive whole genome sequencing at birth. And the hope for these types of activities are that all newborns could be sequenced thereby setting the stage for a lifetime of medical care and self-directed preventive actions tailored to each child's genome. And indeed, many commentators often suggest that universal genome sequencing at birth is inevitable, although many disagree with this notion.

Bob Barrett: Well, is all exome and genome sequencing created equal? Is it the same or is there any variability that the consumer or patient should be aware of?

Dr. Linnea Baudhuin: All exome and genome sequencing is not the same, and I think that many individuals in the health care and general public communities are really not aware that there are many differences with exome and genome sequencing, and that each laboratory that performs this type of testing has a similar yet different product. Actually, in this issue of *Clinical Chemistry*, there is an article and accompanying editorial that describes interlaboratory differences in exome sequencing and the same principles can be applied to differences in genome sequencing.

So, each lab has some variability in the regions of the exome and genome that they interrogate in a high-quality manner. So, one test from one lab maybe missing certain relevant regions compared to another test from a different lab and vice versa. Additionally, there is really a great deal of variability in how extensively and how accurately the sequence data is interpreted, and this is a really key point.

High quality variant interpretation, so when a genetic variant is found and it's determined to be pathogenic or benign, this high-quality interpretation really requires a lot of effort. It requires in-depth curation of materials and data related to individual variants and genes and proper application of interpretative criteria. There have been multiple publications out there that have reported on discordant variant classification between laboratories due to the differences in how they approach variant interpretation as well as gene-based knowledge. And as you can expect, misclassified variants can have serious clinical consequences that can impact individual patients as well as their family members.

It's really important to note that, you know, we talked a lot about how much the cost of exome and genome sequencing has gone down and how, you know, it's becoming cheaper and cheaper, but what many fail to recognize is that high quality variant interpretation, which you really want, is still very expensive. And in fact, in the Q&A, Dr. Robert Green pointed out that with the MedSeq and BabySeq projects that he's involved in, generating high quality variant interpretations to the highest possible standards was very labor intensive, translating into thousands of dollars of interpretative effort per genome, and he further states that as the technical costs of generating the sequences become increasingly commodified, it will actually be the breadth and skill of interpretation that will distinguish the quality of leading laboratories and clinical teams of the future.

So, high quality variants interpretation is really key to delivering a high-quality test, but it does come with a price tag.

Bob Barrett: As with everything else in life, you get what you pay for.

Dr. Linnea Baudhuin: Right.

Bob Barrett: So, have any results from genome sequencing projects been surprising to you?

Dr. Linnea Baudhuin: Well, I am still surprised at how successful genome and exome sequencing have been, from the standpoint of diagnosis and providing answers for families in the diagnostic odyssey and the NICU settings. I have also been

really surprised about the higher than expected frequency of both pharmacogenetic and monogenic findings in the preemptive sequencing of healthy individuals. And, in fact, Drs. Leslie Biesecker and Eric Green point to an example of this, where they demonstrated in some of their studies that nearly half of patients with some form of early onset cancer but who lack a family history of cancer actually have a familial cancer syndrome.

Furthermore, some analysis suggests that 11% to 20% of healthy individuals may carry monogenic risk variants for dominant (or biallelic) recessive conditions. And targeted phenotyping of these individuals has further suggested that a substantial portion of this, perhaps as much as 25%, may already be manifesting clinical features of previously unnoticed or unrecognized genetic conditions.

So, it's really interesting because what was previously thought to be a very rare group of disorders, is actually more common than we thought. And, that kind of brings us around to how the technology has really helped us with that and how we probably need to start changing our mindset. So, you know, not too long ago, we've had the experience that single gene testing of even a medium-sized gene was really inefficient and expensive. So, the general approach in the clinic was to take a family history, and it had to include multiple individuals with, for example, cancer, to justify genetic testing in search of a familial cancer syndrome.

But now in today's world, we can perform exome and genome sequencing much earlier and, hopefully diagnose the first person in the family with familial cancer rather than the fifth or sixth. And I think another surprising thing which is pointed out by Dr. Robert Green is that from a big picture perspective, he and his group has been surprised by how many people want genetic information including genetic risk information. And he said that even though there are so many concerns about genetic risk information leading to anxiety, their early study shows that there is really very little distress that occurs when healthy individuals or the parents of healthy infants request and receive genetic risk information.

So, although, this is a highly controversial area, it is interesting and surprising that so many people want their genetic information and I think that we've also seen this with the popularity of consumer genomic test with things like ancestry and health risks.

Bob Barrett: Well, finally doctor, what progress has been made and what obstacles need to be overcome to fully utilize exome and genome sequencing data for precision and predictive medicine?

Dr. Linnea Baudhuin: Yes. Well, you know while exome and genome sequencing has now matured to the point of being an appropriate and effective clinical diagnostic tool, all of the experts in the Q&A that were interviewed seemed to agree that additional improvements are still needed for its widespread use with healthy individuals. And, to fully take advantage of the genetic risk information in the genome of an apparently healthy person, it's going to be necessary to sequence and interpret a large number of disease-associated genes and use the genetic information to specifically search for previously unrecognized mild and intermediate phenotypes across the longest time window possible.

So, Dr. Robert Green has pointed this out, and he has also stated that perhaps the largest deficit in the evidence base needed for the full application of genomic medicine in apparently healthy people are well-controlled long-term outcome studies in which the phenotyping after genomic testing can be performed and medical benefits and harms are tracked.

Also, we still have some deficits in how much of the genome we can interrogate and how much of it we can understand. So, there are many difficult-to-sequence genomic regions that we're currently really unable to derive data from. We also don't understand non-coding variants very well. So, deep intronic regions or regions surrounding genes or regions, you know, far upstream or downstream of genes. We still don't really know what to do with those, and we still need to have a better ability to infer the clinical relevance of genomic variants in general. So, while the promise of precision and predictive medicine is appealing, and we have made much progress--it's really just fascinating to me how much progress we've made--I think we're really still at the tip of the iceberg with what we have left to discover and implement in terms of individualized care.

Bob Barrett: That was Dr. Linnea Baudhuin from the Department of Laboratory Medicine and Pathology at the Mayo Clinic. She has been our guest in this podcast on Genome and Exome Sequencing as they are used in clinical practice. Her article is one that appears in the January 2020 issue of *Clinical Chemistry* which focuses on molecular diagnostics. I'm Bob Barrett, thanks for listening!