PEDIAPOD FEB 2023 TRANSCRIPT

Geoff Marsh
Hello and welcome back to Pediapod. This month, pharmacogenetic profiling in children with medical complexity.

Children with medical complexity typically require multiple medications throughout the course of their treatment. For many medications, dose requirements, efficacy and risks of adverse drug reactions are partially determined by an individual's genetic profile and many medications prescribed to children often have established gene drug interactions.
Another feature of children with medical complexity is that they increasingly undergo genome-wide testing early in life as a diagnostic test. So could this genetic data be repurposed to aid precision prescribing in this priority pediatric population?
Early Career Investigator Greg Costaine is a physician scientist at the Hospital for Sick Children in Toronto, Canada. He recently published a retrospective study in Pediatric Research which aimed to assess this potential for utilizing the data from diagnostic-focused genetic testing for genotype-guided prescribing.

Greg Costaine
I'm Greg Costaine. I'm a Canadian medical genetics doctor and physician scientist at SickKids Hospital in Toronto, Canada. My interest in genetics and in healthcare research for children is long-standing. I started off however, in mathematics during my undergraduate training and my master's training. And then I discovered through some other research experiences that I was particularly keen to be able to see my research having a day-to-day impact. I then pursued MD and PhD training in a combined program at the University of Toronto. And at the end of my medical training, I was faced with a choice between residency training in pediatrics or residency training in medical genetics. And I chose to do the latter because I had been so impressed by how genetics information was being integrated into the care of children at a big hospital like ours. During my five year residency program, I had some fantastic opportunities here to be involved in early studies of whole genome sequencing as a clinical diagnostic test for the purposes of trying to explain their major health issues and improve their care. When I finished my residency, I was fortunate to get a position as a physician scientist here at SickKids. And so I started on staff here in 2020. It was at that point that we started to appreciate that the fact that we were doing more and more genome sequencing for children at this hospital gave us opportunities, not only for explaining the health issues that they came to us with, but for trying to leverage all of the information we get from sequencing a genome to improve other aspects of their care experience.

Geoff Marsh
Tell me a bit about the patients at your place of work. You said that they often have genome wide sequencing early on in life. But then these children with medical complexity also end up going on to use more and more medications as they age. Is that right?

Greg Costaine

That's right. A specific population that we have studied and that this hospital has special expertise in are kids with medical complexity. One particular important statistic about this population is that while they account for less than 1% of the whole pediatric population, they account for more than 30% of all of the health care expenditures that we have in pediatric medicine in our Province of Canada. And we're lucky here that we have a very coordinated complex care program that tries to streamline care and coordinate care for these complicated children.

Geoff Marsh
So essentially, you're suggesting that we're missing a trick for something along the lines of precision prescribing practices in this population, by tapping into clinically relevant pharmacogenetic data from the genomic data that this population tends to get?

Greg Costaine
There does seem to be this opportunity. We showed that 'polypharmacy', or being prescribed multiple medications is common. And we show that the types of medications that these children are often prescribed often have a known pharmacogenetic association.

Geoff Marsh
So tell us a little bit about the study design and and how you got a good measure of the potential of the genomic information to better tailor medications to these patients.

Greg Costaine
The first thing that we did was that we looked back in our records over many years at over 800 children with medical complexity who had been followed in this special complex care program we have at our hospital. We reviewed all of their prior genetic testing, we reviewed their major medical needs, and we reviewed their medications at a single point in time. From that we were able to observe that it's common to be prescribed multiple medications at any one point in time when you have medical complexity, and that medications that are most commonly prescribed to these children are the same medications that we know have pharmacogenetic associations. Next, for a subgroup of those children for whom we had already organized genome sequencing on a research basis, we were able to extract their medications in more detail. And we were able to use the genetic information we already had to describe their pharmacogenetic profile with the idea that we would identify genetic differences that might tell us about their metabolism of common medications. What we found in this smaller group of 50 children is that almost half were currently prescribed a medication for which their pharmacogenetic profile suggested dosing might have been adjusted at the point of prescribing.

Geoff Marsh
What do we mean adjusted- a different dose or a different drug altogether? Or either?

Greg Costaine
Either. In some cases, a different dose to avoid therapeutic failure, and in some cases, potentially escalation to a different class of medications so that a period of prolonged treatment trial might not have been attempted because it was less likely to be successful.

Geoff Marsh
Presumably if you did use that information you would not only hopefully avoid things like adverse drug reactions but you would presumably also save money?

Greg Costaine
Those would be our hypotheses too and that's what we're most hoping for. That this process could potentially streamline care for children and their families, help us to avoid situations where medications are prescribed initially at an improper dose, and our hope is also as you alluded to Geoff, that there's a potential here for this process to be cheaper than the current system that we have in place. What we haven't shown yet in a prospective manner, is that this could be done at a hospital level or to scale. And we haven't shown yet that it will impact care decisions to a point that's meaningful and that it would not create an additional burden on the system that we're not expecting. The other important caveat with pharmacogenetics, particularly in children, is that our genetic profiles that we can assess and make sense of currently do not explain everything about how drugs will work for us. Even when we have at our fingertips, access to essentially someone's entire genetic sequence, we're still not able with a high degree of certainty to predict exactly how someone is going to respond to a medication, nor are we able to guarantee that there will or will not be a serious side effect.

Geoff Marsh
Do you think that tapping into this information is only really going to be worthwhile in the sort of patient population that you work with, that typically involves polypharmacy and where it's worth that extra workflow and cost. It sounds like any patient would benefit from knowing whether they're going to have adverse drug reactions or get the right dose or the right type of drug.

Greg Costaine
I think there are two schools of thought about where we think pharmacogenetics is going in clinical practice, including in pediatrics. At the one extreme, people can imagine that there would be a benefit to all children of having more information about how they might react to medications. Almost all of us, if not all of us, will have information from a pharmacogenetic profile that could be relevant. A pharmacogenetic result is not necessarily positive or negative, it's descriptive. A finding that someone might metabolize or break down a drug faster than we expect or slower than we expect could be informative. However, a finding of a normal result or a typical result, where we expect someone to metabolize drugs in the usual manner, is also a piece of information that could theoretically be useful- whether it's providing additional reassurance upfront, or if it's in explaining why or why not to continue on a certain medication over time. At our hospital, I'm aware of other efforts by my colleagues to explore the role of pharmacogenetic profiling in other pediatric populations, for example, children who might be undergoing major surgeries or organ transplants. I'm looking forward to their results being shared in the years to come because I think those study designs are going to, by virtue of their prospective nature, generate the evidence that we would need to help us make decisions about day-to-day clinical care.

Geoff Marsh
Do you think there would be a sort of snowball effect if pharmacogenetics was adopted more broadly because then we would have more and more data about adverse drug reactions, and so on?

Greg Costaine
Our experience in other areas of genetics has been exactly that. And so there can be a positive feedback loop. For now most of the data that we have about pharmacogenetics in clinical practice comes from research studies. In terms of the information that we used to decide which of the many putative pharmacogenetic associations seem to have enough clinical evidence to potentially be relevant to our patients, we used an incredible open access resource called CPIC- the Clinical Pharmacogenetics Implementation Consortium. And this is an effort that I am keen to praise because it is not self-serving, I have no other connection to CPIC. This recognition that data sharing and rigorous critiques of methodology are very important in deciding which pharmacogenetic associations might truly be clinically relevant makes this international coordinated effort so impressive and important.

Geoff Marsh
So what are you going to do next? You alluded to a prospective study. Is that on the cards in the near future?

Greg Costaine
That's one of the things that we're hoping we'll be able to move forward with over time. My interest in pharmacogenetics stems not from being a researcher who is specifically building a program related to pharmacogenetics, nor from being a pharmacist. Instead, it comes from being a medical geneticist involved in different aspects of the care of children with suspected genetic conditions, or children with medical complexity. And so I'm keen to see us using the data that we get from genome sequencing for a variety of additional purposes if we think it can help our patient population, including but not limited to pharmacogenetics. Going forward, we have other ideas about how we might be able to leverage information from pharmacogenetics to give us other information about unrelated health risks to our patients or their family members, information that might be relevant in family planning, that is, again, unrelated to the primary reason we were doing the genetic testing for our patients. And the idea that we might be able to ultimately get information from the rest of our genome sequence or from our genetic background that will help us better prognosticate about outcomes in children who have rare genetic conditions. Pharmacogenetics is not going to be a panacea that tells us exactly how to prescribe medications or when to prescribe medications or how much medication to give. We think it could be one piece of the puzzle and information that would be better to have on hand than to not have.