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Q1 Your exposure to genetic research began as a teenager, including time at the Weizmann Institute of Science in Rehovot, Israel. How did this formative experience inspire your path into paediatric genomic medicine, and how does it still shape your vision today?

I was a high school senior in Northern Ireland, and I had the good fortune to win a scholarship from Marks & Spencer, London, UK, who packed me off to the Weizmann Institute of Science before starting university. I was enrolled as a medical student and believed that that's what I wanted to do with my life. While I was in Israel, I interned with the Late Professor Shraga Segal, and he got me working on a mouse model of cancer. These mice were immunodeficient and had a disorder called Chédiak–Higashi syndrome. I was fascinated. By the end of that summer, I realised that I didn't really want to be a doctor at all. I wanted to do what these scientists did at the Weizmann Institute of Science: research, and I wanted to do that for the rest of my life. So, I kept going back every summer, and I would suffer through medical school, which at the time was mainly rote learning of textbooks. Then I would get my mental escape in the summertime at the Weizmann Institute of Science, where I continued to do research.

Chédiak–Higashi syndrome is a genetic immunodeficiency, and it occurs in humans as well as mice. One of my first projects, when I had my own lab years later in the USA, was to see if we could identify the gene that caused the syndrome, and we were successful. So, yes, something that happened as a teenager, serendipitously, left an unequivocal mark on my life, which persists to this day.

Q2 At Rady Children's Institute for Genomic Medicine, San Diego, California, USA, your team has demonstrated that rapid whole-genome sequencing (rWGS) can yield actionable diagnoses in infants who are critically ill. From a clinical management perspective, what have been the most significant impacts of rWGS on outcomes, for example, time to diagnosis or treatment precision?

For this, we have to go back 15 years. Illumina, San Diego, California, USA, approached me, and at the time, I was in Kansas City, Missouri, USA (before I joined Rady Children's Institute for Genomic Medicine). They said, "Hey, we've got a new genome sequencer that can turn a result around in about a day, and we're not sure what to do with it." So, I talked to some of my colleagues at Children's Mercy Hospital, Kansas City, Missouri, USA, and they said, "Let's decode the genomes of babies in our neonatal ICU (NICU)."

Now, for those who don't know, 10–15% of babies go into the NICU when they're born, and sometimes it's because the baby was born prematurely, or the delivery didn't go smoothly. In many other cases, however, it's because of something

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that just wasn't anticipated. The baby is delivered and immediately starts to have symptoms. These are mystery babies.

The thing about babies that people don't really get is that the younger a child is, the faster a disease progresses. For old folks like me, it takes days or weeks to get sick, while in children, it takes hours, and in babies, it takes minutes. You can have a baby that's looking great, but 15 minutes later, that baby could be morbidly ill. So, in this setting, there is extreme urgency. What we have realised is that there are about 10,000 different genetic diseases, and these are some of the principal reasons why babies are admitted to NICUs. Nobody knew this 15 years ago. It was just assumed that they had common things like immature lungs or immature livers, because there was no such thing as decoding the genome. When we started to put that to work, we found, much to our amazement, that over a third of the babies whose genomes we decoded had a genetic disease. Over the last 15 years, that's been recapitulated maybe 100 times around the world, and it's now universally accepted, irrespective of where a baby's born. Many countries in the world now have policies that say that if a baby is admitted to an ICU, then the baby will get genome sequencing as part of their healthcare provision. The sequencing needs to be done as fast as is humanly possible, because it has profound implications on how the baby is managed. Until you know what's causing the illness, you're treating the baby blindly. You may get it right, but chances are that you won't with 10,000 possible genetic diseases, all of which are very rare. The likelihood that you're treating the right thing without knowing what the genome says isn't high. You have more luck playing the lottery.

For some babies, there are curative therapies. For instance, there's a disease called spinal muscular atrophy where you can give them gene therapy. It's a once-in-a-lifetime dose, and they're cured. However, the clock's ticking, and if they already have irreversible neurological damage, they won't recover; it's a race against time. How quickly can we pick up a baby with spinal muscular atrophy and get them the gene therapy? In the future, we hope to have effective or curative treatments for most of these diseases, and genome sequencing will become more and more powerful. Even today, in our current era, which means there isn't a gene therapy for most diseases, the information remains very powerful, because there are conventional therapies that make the baby better, even though they might not cure the baby. Above and beyond that comes the whole psychological and social aspect of the situation, where parents know what's going on, doctors and nurses know what's going on, and there is trust in the system. The parents, empowered by that knowledge, can make decisions on behalf of their baby. Until you know what's causing the baby's illness, the doctors are essentially in charge, and you don't have the ability to make decisions. Once the doctor knows and tells you, then you can retake charge and say, "Okay, I now understand the consequences, and I can make these decisions." If the baby is going to die, that ability is very empowering. You, as the parent, can decide the circumstances. How much do you want intensive care to continue? There are all kinds of practical elements, like bonding and getting last rites, but above all, there's this knowledge for parents that their child had a disease. It's not a curse. It's not something that the parents did wrong during pregnancy, where they may have had a cigarette or a glass of wine; parents are racked with anxiety and guilt otherwise. This is one of the most revolutionary things to ever happen in neonatology.

Q3 A highlight of your work in rWGS is your 2021 world record for 'The fastest molecular diagnosis using rWGS' in 13.5 hours, beating your previous record by 6 hours. Could you detail the work that went into this achievement and describe the positive effects patients have seen/will see as a result?

When we identified this for the first time, the idea of speed relating to genome sequencing was just a foreign concept. Nobody had ever thought about that before. However, the more we dug into it, the more we realised that there was a golden set of hours related to birth delivery, admission to the NICU, and the initiation of therapy, that we really needed to optimise. We needed to turn this into an engineering project. We needed to make it scalable so we could do it repeatedly with every baby who would need it. We needed to make it cost-effective so that the system could bear this. We needed an educational piece because neonatologists didn't know genomics. They still don't, nor should they, but they needed to know how to utilise this new technology and, most importantly, how to utilise the information we were returning. For 15 years now, we've been pushing the envelope to say, What does that look like? It's an ecosystem. It's a healthcare delivery platform. People get hung up on the fact that we're decoding a genome, but honestly, that part is easy. Just in this past week, we had the publication of 491,000 British genomes from the UK Biobank, Stockport, UK. Decoding genomes at scale is commonplace now, but this ecosystem is not common, and there is still much work to be done to democratise this. Right now, in the USA, we estimate that only 3% of the babies in an NICU who would benefit from genome sequencing are receiving it. Even for those babies, it's often ordered as a last resort, rather than something you put on the admission orders. We have at least another decade of work to do to make this standard of care and to see it be democratised around the world. How do we equip neonatologists? How do we equip hospitals to be able to do this at scale for every baby who will need it?

Q4 You received the Precision Medicine World Conference (PMWC) Luminary Award in 2022, which recognised your contributions to implementing precision medicine in acute paediatric care. What does 'Rapid Precision Medicine™' (Rady Children's Institute for Genomic Medicine) look like in practice?

It's not really about the genome. The genome is a very powerful piece of technology, but the point here is to deliver optimal care. The idea that care needs to be tailored to the genome (genome-informed care) is what we mean by precision medicine. It's not that the genome is the only data stream; it's just that it's one that is really important in at least half of the babies in the ICU. However, there are other -omic streams that are coming online as well, and what we want to do, particularly with the possibility of 10,000 different genetic diseases, is to get people to think about individualised and genome-informed care. This is so that the moment we have a genome answer, we can turn it into a specific therapeutic regimen that is tailored to the child's specific condition. To that end, we have employed a group of experts for 5 years now. We maintain a website called GTRx™ (or Genome-To-Treatment; Rady Children's Institute for Genomic Medicine),[1] and it helps you navigate what to do next when you have a label for a child's disease but have never seen the disease before in a baby. The website details steps such as confirmatory tests, specialist consultants to get advice from, and therapies to be considered for the baby, even before harnessing those consultants' advice. The intent of the website is to take frontline neonatologists and paediatricians and equip them to practice something that they were not taught in medical school, in their residency, or in their fellowship, which is a highly tailored approach to medical care that delivers more optimal outcomes. One of the wonderful things about that is that it also delivers optimal cost efficiency. Having a baby in the NICU for 1 day in the USA costs at least 3,500 USD, and many of these babies could be in the hospital for months because the cause of their sickness is unknown. Therefore, this rapid precision medicine approach saves money, largely because the babies start on an informed management plan, and so a disposition (e.g., the threshold the baby needs to meet to be safely discharged from the NICU) is also apparent.

Q5 BeginNGS® (Rady Children's Institute for Genomic Medicine) is a groundbreaking programme that could redefine newborn screening. How does it differ from current Recommended Uniform Screening Panel-based methods, and what impact could it have if adopted at scale?

Everybody probably knows the heel prick that a baby gets on the first day of life: it creates a blood spot on a card, which gets sent to a regional laboratory and is tested biochemically for different conditions. The number

of conditions varies depending on where you're born. For instance, in California, USA, it's about 80 conditions. This has been going on since the mid-1960s, so we're 60 years into this practice. The conditions are selected carefully, and every baby gets screened, so that is around 3.7 million babies in the USA. The vast majority of them will be normal. However, for the rare few, you'll be able to give lifesaving treatment. This is for conditions that are so severe that this intervention is likely going to save their lives, and you're accepting the fact that, for most of the population, screening will give them no benefit. It's a very careful balance. You have to think about these things: how much bother am I creating, since 99.9% of those tested are healthy, and the results can often be false positives, but for those that are real positives, I actually have the potential to save a life?

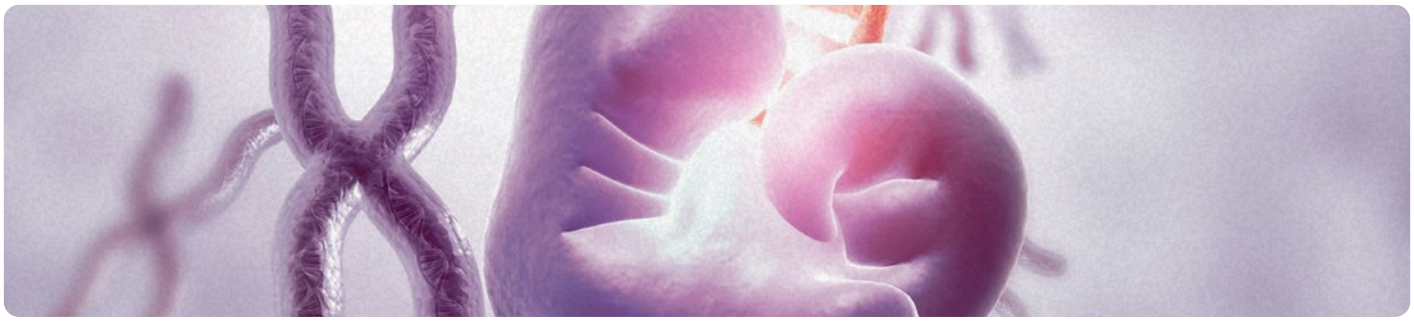
Our idea was to take everything we learned from decoding genomes in NICUs and see if we could form factor a genome for this new purpose. Why, when we're already testing for all these conditions? The screening is typically done through biochemical testing, and unfortunately, for many genetic diseases, there is no biochemical way to measure them. For example, if your baby has seizures or heart disease, there's no way to detect that through biochemical means. Thus, our goal was to do the same as we do for biochemical disorders, but with genomes, so that we could bring the benefits of newborn screening to every condition that fits the criteria. In other words, it has to be really severe, and there has to be a highly effective therapy that will change the outcome if I find out the baby has or will have this condition. We've been working on this idea now for about 5 years, and have developed a test that could screen for just >500 different diseases. However, we are still developing the platform, because it isn't perfect right now: it's not cost-effective, it's not fully scalable, and the performance metrics aren't quite there. We're also enrolling babies around the USA and will soon do so in other countries around the world, so that we can test this out. We need to build up evidence to show that this works and it's safe, with the goal for it to be implemented as a standard test. We're 15 years behind where we're at with diagnostic genome sequencing in the NICU, so we're playing catch-up. In an ideal future, we would like to have a belt-and-braces approach, with babies in the NICU getting a diagnostic genome that screens for 10,000 disorders, and all the healthy babies getting screened for 500 or even 1,000 conditions, which will catch the babies before they get sick. For many babies, we would prevent them from actually needing to go to the ICU in the first place by catching their illness before it develops. That's the vision of the future that we're pushing into. It's still early, and it's still research, but I'm excited about the potential.

"Thus, our goal was to do the same as we do for biochemical disorders, but with genomes"

Q6 You've previously described the first two phases of BeginNGS: moving from technical feasibility to an early clinical trial. What have you learned from these stages? What excites you most about Phase III, the 100,000-infant trial, and what results are you expecting?

Phase I was about prototyping the test and seeing if it could be done. We ticked that box and showed that it was feasible. Phase II involved running a small trial in the NICU with a further developed test, and that went off without a hitch. That was really a safety trial. Could we do this? Would we have some major issues related to implementing this in the real world for the first time? We had no adverse events, and we had 100% specificity without a single false positive, which was really encouraging. There were, I think, four or five true positives in 120 babies.

Then we moved on to the current phase, where we're enrolling babies in various locations across the USA, such as San Diego County, California; Memphis, Tennessee;



and Denver, Colorado. Soon we'll be doing the same in other areas of the USA, like Salt Lake City, Utah; Rochester, Minnesota, at the Mayo Clinic; and Rutgers University, Newark, New Jersey. That will allow us to enrol 10,000 babies by the end of next year. We're also close to extending this to the Gulf region and the Middle East, specifically in Ar-Rayyan, Qatar, at Sidra Medicine, and in Riyadh, Saudi Arabia, at the King Faisal Specialist Hospital and Research Centre. One of the exciting things coming up now is the opportunity to go international, because the incidence of genetic disease varies around the world, and some of the diseases that we are targeting are much more common in other countries. It's going to be really interesting, and we can't wait to see what those results look like.

Q7 AI and machine learning are commonly used in sequencing pipelines. How has your team leveraged AI over the past decade, and what role do you see for automation in improving the scalability and accessibility of genome sequencing?

AI has come to the public's knowledge in the last 5 years, and people think of it as something new. But AI, as in machine learning, and earlier versions of AI have been around for many, many years. In fact, decoding a genome wouldn't be possible without it. The genome is the equivalent of a book that is 400 feet tall, and we decode it on average 40 times; the amount of information we generate from a single human genome is staggering, and it is way more than a human being could ever process. So, from the get-go, we have been reliant on computing and pushing the envelope on biological computing, using whatever automation or AI tools were available. That's been true since 2005, when our ability to decode human genomes became a reality.

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Over time, however, the relevance of AI has changed. In the early days, it was all about how we could train the machines to decode the genome, and then how we could use that information to interpret the genome. As of 5–7 years ago, that was really all that we were using AI for. They were sophisticated tools for turning signals into DNA bases and then allowing humans to be able to inspect the genome, pick things out, and make a diagnosis. More recently, AI is allowing us to automate genome interpretation, so we are able to increasingly arrive at a diagnosis without a human being having to look. Now, that doesn't mean that we won't need humans anymore. Even when you have autopilot on an aeroplane, you still need two pilots in the cockpit, despite the fact that the plane could technically fly itself. That's one thing to make really clear: you still need people in charge who are evaluating performance, even though you're using AI tools.

The really exciting thing now, with large language models and generative AI and agentic AI, is that we can actually start to interface the brains of physicians and parents with this complex space. The major problem now is not decoding genomes at scale. It's upskilling the medical workforce so that they can cope with this information torrent and the fact that there are 10,000 diseases, about which they know almost nothing, that they now have to deal with. This goes for parents, too: how do they cope with all of this information? In the future, these newer tools will essentially provide physicians with an accessory brain that is a specialist in the information needed to perform medicine at a very different level (rapid precision medicine). It will be the same for parents, so that they'll be able to fill in the gaps in their knowledge regarding these diseases. The issue with one of these rare or ultra-rare diseases is that parents need to become specialists in that disease. If they go into a regular

doctor's office, where the doctor isn't familiar with their child, they will need to educate that doctor or nurse about their child's condition; they will be the expert. They won't be able to prescribe drugs or diagnostic tests, but they will know more about that condition than the healthcare provider does.

Ultimately, we want to provide these tools to parents and frontline paediatricians. What's super exciting right now is thinking: how do we build this? How do we ensure that it's safe? How do we roll it out? How do we overcome all of the concerns that people have about the fact that it is AI? There's a lot of work to do to go from a concept to reality.

Q8 Ethical concerns remain prominent in the context of newborn genome sequencing. How should clinicians counsel families on these issues, and what safeguards are essential to maintain public trust while enabling clinical innovation?

This is a very difficult question. We live in an era where there is a lot of public distrust. It's unparalleled, and this arose, really, during the COVID-19 pandemic. Subsequent to the pandemic, distrust seems to be increasing rather than decreasing. Whether you're involved in something new, like genomes, or in standard care provision as a physician, it's a new phenomenon, and the rule book doesn't apply. I think the first thing to realise is that people no longer have a broad trust in expert advice of any type. They want to consider alternative truths, and that requires tolerance, patience, and a new set of tools (thinking about engaging and educating as opposed to care delivery). That's all new, and do we have answers for it yet? No, I think we're really struggling. When I was being trained in medicine, this was not top of mind. The doctor was right. You came to the doctor, they gave you what you needed, you did what you were told, and bingo, but that's not the world we live in anymore. Now it's a discussion. I don't think that that's necessarily bad, but it is more complicated, so we have to be aware of it. On top of that, we're doing new things that were not part of care practice previously, so those concerns are heightened.

When genomes arrived on the scene 15 years ago, there were immense concerns about genome information, and that was largely because people didn't understand it. They thought, and many people still do think, that your genome is like the 10 Commandments, that it's a definitive set of rules written by God, and that's not the case. The genome is like any other type of information. It confers risk or benefit for whatever it is you're dealing with, whether it's the likelihood of developing diabetes or living to be 87 years old. It's not a declarative text. People constructed a whole new set of rules and ethical concerns because they thought, 'Oh, my word, we're uncovering something; we're opening Pandora's box'.

Fifteen years later, many people are now realising that that's just not the case. The genome was massively overblown; sometimes it gets things right, but it often doesn't. Even if you have, let's say, variants in the cystic fibrosis gene, that doesn't mean you're going to have cystic fibrosis. If you do have cystic fibrosis, it doesn't necessarily mean you're going to develop severe lung disease either. But we didn't know any of that, and people still get very confused about it. Even really well-educated people still tend to think of the genome as some special type of information. As a result of that, we have several laws related to genome information, because they think it's exceptional. Frankly, those laws are a little immature. We need to get over that, though it's going to take time. It was good to put those laws in place, but now we need to get rid of the hype and understand that this is just another type of data. It doesn't have the implications that people feared it did.

People also thought that genome information could do profound harm (e.g., it would lead to anxiety, depression, etc). Now, that's not to say that it's not a valid fear, but once again, it was overdone. In fact, we've found that people, when confronted with genome information, don't have catastrophic reactions in the way that we had anticipated. The pendulum swung over to one side, and now it's swinging back, and it still has a ways to go before we reach what we might regard as an equilibrium state. I don't want to disregard this at all, but I just want to say that over the last two decades, I've watched us go from complete paranoia to realising that many of our worst fears did not happen.

Having said that, we are facing cyber threats like we have never seen before. We just talked about AI, and one of the biggest uses of AI is for cyber threats. This isn't necessarily tied to genomes, but it's tied into the confidentiality of any healthcare or financial information that you might have. We need to be very concerned about our confidentiality and privacy in an era when the internet knows an awful lot about every one of us, and these AI tools can grab this information with a couple of keystrokes or a sentence spoken. The genome absolutely needs all of the same security safeguards that healthcare information gets, and we need rules that protect

confidentiality and privacy, as well as rules related to who owns that information. The best way to think about this is that the genome is healthcare information that ought to be treated like anything else in your medical record. If you've had an ECG, a chest X-ray or a blood test, the genome is similar in that you have a right to a copy of the results, and you are giving your doctor and a healthcare organisation permission to hold that for you because they are providing services to you.

Now, in the USA, we've got the Genetic Information Nondiscrimination Act of 2008 (GINA). It's a great law that largely protects citizens from discrimination because of their genome. There are certainly loopholes in GINA, and one of the things that we spend a lot of time doing is alerting parents to the implications for them and their child when we generate this data, that GINA is not perfect, and that there may be consequences for them. We have to do that in a way that enables them to make a decision while weighing the risks and benefits. Many countries don't have a genotype law, but they need one. Meanwhile, in the USA, we will need to revise the GINA law and reduce the loopholes as we learn more.

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Q9 Finally, looking towards the next generation: what advice would you give to young healthcare professionals who want to be a part of this ongoing genomic revolution?

First of all, there continues to be a huge need for physicians who are going to do research. Right now, we have challenges related to, for example, substantial cuts in federal funding for medical research, but that need is not diminished. We still need the brightest young minds to be thinking about a research career. They won't be as well paid, and they'll probably have to work harder than their peers with less job security, but we need them, and we'll continue to need them. That is the fulcrum around which things improve.

How you acquire skills has changed quite a bit. It used to be that you needed to get into a laboratory, get your hands wet, and learn how to mix chemicals. That's how I started. These days, many of the new discoveries are electronic, so being skilful in terms of programming and knowing how to use AI is increasingly important and will continue to be important. The types of experiments that we can contemplate would have been completely unimaginable years ago. Just this morning, I was on a call, and we are currently collating 491,000 genomes into a database to perform analyses. The scale of what's possible is completely unparalleled, and what I think of today as unbelievable will seem mundane tomorrow. It's going to be a very exciting era.

Another thing that has changed dramatically is the emphasis on rare diseases. When I was young, medical research was focused almost exclusively on common diseases, as was drug development. However, we have now realised that rare diseases collectively are as common as common diseases, and that we have neglected them for decades. As a result, we have few effective therapies. We also still massively underutilise diagnostic tools. So, this is a whole new avenue. There are thousands of diseases for which there are no therapies. We don't understand how hundreds of diseases work. There are still probably 10,000 new genetic diseases to be discovered. We now have a playbook, the likes of which we've never seen before, which is amazing. But we also have a huge set of tasks ahead of us to fill in all the gaps in our knowledge, and then to do all the hard work to turn those into improvements in healthcare.

At the same time, however, you have to understand that the maths doesn't work out anymore; we live in societies that have tapped out the ability to pay for healthcare, and so the old way, which was new benefits at any cost, can't survive. We now need to be aware of the maths at all times: how will we be able to do this and afford to do this, and how will we be able to do this equitably for the population? Tragically, one of the lessons we've learned is that healthcare advances don't often make it across the population. They make it to the top 1%, 5%, or maybe even 20%. So, armed with that knowledge, how do we fix this?

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