Diagnosis in the genomics era

Rady Children's Institute for Genomic Medicine in San Diego, California, has a pioneering programme, headed by **Dr Stephen Kingsmore**, president and CEO, that delivers life-changing genetic diagnoses for severely ill newborn babies.

Each year, hundreds of thousands of children are born with unidentified genetic diseases, and many of them end up in neonatal or paediatric intensive care units with difficulty feeding, epileptic seizures, or other serious issues. In fact, more than 20% of infant deaths are ascribed to genetic disease, yet the gene at fault is often not obvious looking at the child.

A NEEDLE IN A HAYSTACK

There are around 20,000 genes in the human genome, so searching for a disease-causing mutation is like seeking a needle in a haystack: a painstaking process that, for many children, simply cannot be completed fast enough to deliver life-saving treatment.

But, thanks to Dr Kingsmore, Dr Dimmock, and their growing team of expert colleagues, all this is changing. The world-renowned paediatric specialists have devoted themselves to creating a super-team that develops and deploys novel techniques for ultra-rapid whole genome sequencing and analysis, to achieve rapid genetic diagnoses in acutely ill babies and infants. In fact, last year the team achieved the Guinness World Record for the fastest genetic diagnosis, taking just 26 hours. On average, a full genome sequence for most infants can be generated and analysed in around two or three days.

The impact of diagnosis by whole genome sequencing is often life-changing. The team now routinely test their critically ill patients for over 5,000 diseases, of which over 500 have highly effective treatments. Crucially, in at least 70 of these not found by routine newborn screening, the early initiation of treatment prevents serious disability or death. For instance, if genome sequencing uncovers a mutation in a gene for digestion, causing a baby to be unable to process a particular nutrient which then effectively becomes a poison, a simple change of diet can halt the disease: the sooner the condition is diagnosed, the less long-term organ damage the child will suffer. Minutes matter.

UNRAVELLING THE GENOME

In a series of clinical trials funded by the United States National Institutes of Health, the Rady Children's Institute team are analysing the clinical and social benefits of rapid genome sequencing for diagnosis in newborns. They reason that sequencing the whole genome identifies disease-causing mutations overlooked by other approaches which sequence only the protein-coding regions of the genome, known as 'exomes'. Paradoxically, sequencing the whole genome is also faster by one day than exome sequencing. Days matter.

The Rady Children's team's world-record-breaking diagnostic speed was achieved by harnessing two main factors: improved technologies for genome sequencing, and increased understanding of what matters to physicians treating acutely ill infants, which enables the genome to be interpreted in the context of disease.

The first of these – genome sequencing technology – took the form of three state-of-the-art 'next generation' DNA sequencing machines made by San Diego-based Illumina, purchased through a $120 million gift to establish the Institute from philanthropists Ernest and Evelyn Rady. Just one of these machines can sequence three genomes in a day which means the team can simultaneously obtain the genome of both a child and its parents, which may be crucial to finding the genetic cause of a disease.

The second key factor is to use artificial intelligence, combined with physician expertise, to create a highly customised disease suspects list for each patient, which is then compared with the genome sequencing results. The AI system compares the symptoms exhibited by a patient with a database of over 5000 genetic diseases, to produce a shortlist of genes that might be at the root of his or her illness, which can then be studied in detail by the team once the genome is sequenced.

2 Dr Kingsmore in front of the Acute Care Pavilion at Rady Children's Hospital where the neonatal intensive care unit is located

Another key part of the Rady Children's approach is the team of experts – not just medics but also computer scientists – that Kingsmore has assembled. These handpicked scientists fine-tuned the computer hardware and software used – known as 'DRAGEN', developed by another San Diego company, Edico Genome – to enable analyses to be conducted in minutes rather than days, and with greater sensitivity than standard methods.

The overall protocol that the Rady Children's team has deployed, incorporating sequencing, computation, analysis, and clinical interpretation, enables them to quickly 'zero in' on a child's condition, delivering targeted information of immediate, vital clinical use. The final, critical element is telementoring, where the Rady Children's team provides diagnostic results in the setting of recommendations for treatment of these individually rare disorders. It is often the case that physicians may never have had a newborn diagnosed with that disorder before, and so need help figuring out the best therapeutic approach.

CLINICAL AND CULTURAL ADVANCES

Rady Children's Institute has an inclusive and outward-looking ethos that includes not only conducting cutting-edge genomic medicine research, but also working in tandem with the Rady Children's Hospital – the largest paediatric hospital in the state of California – to translate these advances into revolutionary new standards of patient care. The Institute's stated goals therefore include conducting research to enable the prevention, diagnosis, treatment and cure of childhood disease, contributing to knowledge and data-sharing among like-minded researchers, and establishing a strategy for genetically-personalised medicine in the broader community.

The impacts on paediatric healthcare are already being felt, with over 50% of babies tested getting a diagnosis and this figure set to rise. Even if a genetic diagnosis does not lead to a cure, the psychological impact upon families of having a name for their child's disorder should not be underestimated. The value of the Rady Children's approach is that it comprises a single, broad test, rather than the traditional approach of sequential testing for different syndromes, which can 'prolong the agony' for worried families seeking a diagnosis.

The Rady Children's Institute's Clinical Genome Center can currently process over a thousand genomes a year, but Dr Kingsmore would like to see the technique becoming much more prevalent, practised in neonatal and paediatric intensive care units across the world. Of course, widespread adoption requires intensive investment, and Kingmore and team are constantly pursuing philanthropic funding to extend the programme to every Children's Hospital with a neonatal intensive care unit world-wide. Although the research is at a pioneering stage, Dr Kingsmore and the Rady Children's team clearly have great ambitions. Their work and intentions can only be to the benefit of those parents desperately seeking answers for their children.

Q&A

with Drs Stephen Kingsmore and David Dimmock

Dr Kingmore, what first drew you to the area of genomic medicine? How did you first get involved?
Stephen: Well it happened by accident. All my career I've been working on applications of new technologies that may have a bearing on medicine, and over the last decade it became increasingly apparent that genome sequencing was going to transform health care dramatically. Decoding genomes of acutely ill infants seems to be the biggest opportunity today.

And what would you say have been the key advances leading to the ability to achieve a diagnosis in just 26 hours?
I think the key thing has been speed. A variety of advances have come together to allow incredibly fast genomes – and diagnoses. In order to make a diagnosis you used to test diseases one at a time. Since there are over 5,000 diseases and for any given baby there's a list of a couple of hundred that might be causing their symptoms, it was remarkably difficult to make a diagnosis before the child either died or was sent home. Next-generation sequencing is an incredible thing – it allows all diseases to be tested at once, and that's a complete paradigm shift.

And then the second thing has been that internet-based cloud computing and software improvements allow us to analyse genomes almost instantaneously. The first human genome took about 13 years to complete, and our world record was 26 hours! But on a routine basis we can do it in roughly two days if we really need to.

How many patients have you diagnosed so far using this current approach?
Seven months after starting at Rady Children's, we've diagnosed 26 of 58 babies. Before that we also diagnosed 32 of 72 babies at Children's Mercy Hospital. What's different in San Diego is that we've established a team with some of the best people in the world - guys like David Dimmock, Joe Gleeson, Narayanan Veeraraghavan, Matthew Bainbridge, Yan Ding, Shimul Chowdhury and Shareef Nahas – who have immense combined experience in doing this.

What is it about the Rady Children's Institute that makes it better placed than other institutes to conduct this kind of research and translate it into benefits for patients? Presumably the team you have built is one of the key points?
Yes. We really are a team of exceptional people and I'm just privileged to be called the boss of this revolutionary new approach to saving children's lives. How did we get them to Rady Children's? I think it's a combination of things truthfully, and sometimes it's a bit of a mystery to me how we manage it. Undoubtedly, I had a reputation and that helped a wee bit. Of course, having a total endowment of $170 million helps a big bit. It means people know that there's a strong financial footing, and that something big is going to happen. I think also that what we're trying to do is something that resonates because there's nobody else in the world currently focused on it. Of course, we live in San Diego which is starting to become recognised as the world's centre for genomic medicine, and that helps a lot.

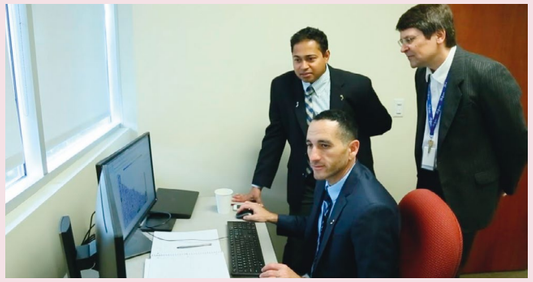
So has San Diego being a centre for genomics helped you collaborate, for example with Illumina or other industry bodies, to bring the work on faster?
Absolutely. Quite a few of our team have been working alongside Illumina for as much as a decade. As we thought about moving here there was a lot of dialogue with guys like Dr Eric Topol at the Scripps Research Institute and with Illumina. There are 800 biotech companies in San Diego, many of them focused on genomics, and it really makes a huge difference to be surrounded by these companies. If you think about it, most of them have virtually no access to real-life patients and so they are very excited about their ability to test their new diagnostics and treatments with us. So, that truly has been a big benefit.

It also has an interesting side effect – genomics in general is a huge employer in our region, and that means that our populous are somewhat unique in terms of their genomic literacy: they know what a genome is. That means that when we approach parents of a critically ill baby in an intensive care unit who are having the worst day of their life, they have a basic understanding of why somebody is approaching them and saying, "I think we can potentially help your kid if you'd like to enrol in this study". That's made a big difference in terms of our rate of enrolment of children.

The impact of diagnosis by whole genome-sequencing can be life-changing

Why is this method so helpful for babies in particular?
Babies are unique for several reasons. When a baby is born, it's independent for the first time. It's the first time its lungs have ever been used, at least to breathe, and the same with much of its metabolic status. Genetic diseases have been lingering there ever since the baby was formed, but it's only at birth that many of them come to light because those organ systems have never been used before. So, there's a very high incidence of genetic diseases at birth. They're the leading cause of death in infants (children up to one year of age). They're also the leading cause of death in neonatal intensive care units (NICUs) and in paediatric intensive care units (PICUs).

When you're able to give a diagnosis using this method, how does that help the infant and their family?
Let's imagine that a baby is born and it has a disease. The baby winds up being transferred to a special unit, like a NICU, to receive treatment and a race is on to make a diagnosis. Now until you have a diagnosis, doctors use what is called a clinical diagnosis. For example, this baby has a seizure disorder, or this baby has hypoglycaemia. That's a clinical diagnosis and based on that you'll follow the best treatment for that clinical diagnosis. Given that there are 5,000 genetic diseases, that treatment is rather empiric, rather generic and not specifically targeted to the underpinning cause of the disease. So, when we get a molecular diagnosis by decoding the genome, we're able to give specific targeted treatment for that child's precise genetic changes.



Above: Lab technician Luca Van Der Kraan prepares samples for testing

Right: Shareef Nahas, Clinical Lab Director, Sergey Batalov, Senior Bioinformaticist, and Narayanan "Ray" Veeraraghavan, Director of Information Technology collaborate to complete the crucial final step of interpreting the sequenced data

So, let's take seizure disorders. That's something we see not every week, but nearly every week; babies are born and they have seizures. There are literally hundreds and hundreds of genetic disorders which can cause babies to start seizing at birth and to continue to seize. The treatments for infantile encephalopathy, this seizure phenomenon, are incredibly different. Some infants need special diets, some of them need anti-epileptics. With anti-epileptics, these range enormously in terms of which ones you use.

For example, we had a child just a couple of weeks ago. The baby was born seizing, continued to seize and within two days we were able to diagnose the child as having Otahara syndrome, and to find the specific genetic mutation. That particular disorder has a highly specific anti-epileptic treatment protocol. We started that and the baby stopped seizing and is now at home. We had a baby with the same gene defect in our NICU a year ago, prior to rapid genome sequencing. That baby waited eight weeks to get a diagnosis and seized continually for eight weeks. That's an example of what we're dealing with and that's why this is so revolutionary. Seizing is not good for a baby's brain so a quick diagnosis can protect the brain from further damage.

Another time, we were able to confirm that surgeons should go ahead with a liver transplant – a costly and risky procedure in a newborn. And on a separate occasion we stopped a surgical procedure taking place based on a clinical diagnosis – the procedure was very risky and in that case wouldn't have benefitted the infant. So, there are three examples just from the last month or so that help you understand why this is going to transform the medicine practised for newborns all over the world.

Is the Rady Children's Institute the only institute in the US offering this approach?
Almost, but not quite. We started this work at Mercy Children's Hospital in Kansas City, and so my old team are still there and still doing this. In addition, there are other groups who are now emulating our approach.

What I really struggle with is the fact that in aggregate the world experience of this is probably only 150 babies, yet there are probably 80,000 babies a year in the US alone who could benefit from this, and really this is something that ought to be available to babies globally. We're working with large children's hospitals – such as Children's Hospital Colorado, Children's Hospital of Orange County, and Children's Hospitals and Clinics of Minnesota – to grow to availability in five regional centres, and then 50, and then 500, and ultimately in about 5,000.

What do you think are the main barriers to rolling it out, across the US to begin with and then globally?
First, we need education and mentorship, so that neonatologists all over the world get up to speed on this. Second, we need hard evidence of clinical usefulness. Medicine always progresses based on hard evidence – clinical studies, ideally randomised controlled clinical trials – and typically you need several of these, and they need to be multicentre, so it takes quite a while. Third, implementing this approach is beyond the range of the vast majority of NICUs. It would be like saying, "Let's do heart transplants at every children's hospital in the world." That's not feasible, and so we need to figure out a regionalisation method whereby specialised centres can offer this to all local children's hospitals world-wide.

You have won the Guinness World Record for the fastest whole genome sequencing. Do you think that has been helpful for raising awareness of your research, whether that's within the public or among neonatologists?
The Guinness World Record's a funny thing. They pinned my name on it, but honestly, it's a team sport: Illumina were involved in that along with Edico Genome. Illumina built the sequencer and then Edico Genome built the computer chip (both the Ferrari of their class), and then it was a team of folks including me who actually set the world record. It has been really helpful – if

we publish a paper in a scientific or a medical journal, that helps with a particular audience, but Guinness World Records are something that the public can latch onto. And that really does help, because at the end of the day, we can only do these types of things to the extent that parents say yes.

Obviously, the team effort is very important to your research. Who are some of the key players in the team?
We recruited David Dimmock from Medical College of Wisconsin. He was one of the first people to get started in paediatric genomic medicine, and we were very fortunate to recruit him. He's a practising physician and many of us are technologists – it's so important to have somebody like him to give us balance. He also helps give us credibility in the medical profession.

Another example is Todd Laird, our Chief Operating Officer. Todd has run huge commercial businesses in the biotech sector and then he decided to reinvent his career and help start a research institute. If you think about our ability to go from doing this in one children's hospital to doing this globally, you need somebody who's had global commercialisation experience.

Our Sequencing Operations Director, Yan Ding, ran the biggest medical genome centre in the US, Baylor College of Medicine Genome Sequencing Center, for 20 years, and she now manages our sequencing. We have a team where every member is an expert in their field.

David, it would be great to hear more about your experience working on this project.
David: One of the things that was very obviously apparent in the beginning of the century was how difficult it was to figure out a child's diagnosis. For quite a few genetic disorders, if you make the diagnosis early enough you can treat the disorder and save the kid's life, or save their brain. But you need a reliable test. Right now, of the 5,000 plus genetic diseases we know of, we have about 30 conditions that are coupled with newborn screening in the US and I think about 12 in the UK – we're barely scratching the surface in terms of newborn screening.

Lab Technologists Laura Puckett and Luca Van Der Kraan, operating sequencing machines while Dr Yan Ding, Director of Sequencing Operations observes

The overall research protocol enables the team to quickly 'zero in' on a child's condition, delivering targeted information that can be of immediate, vital clinical use

Before I came to Rady Children's, we started doing genome sequencing in the Children's Hospital of Wisconsin in 2010. I think it's the first place to do clinical genome sequencing for people that were sick. We sequenced about 22 children through that programme in the first year, and made some quite dramatic diagnoses. Then we moved towards more of a commercial diagnostic lab approach, where we were offering this testing more globally, worldwide. Over the next five-year period that I was in Wisconsin, we probably tested about 3,000 or 4,000 families and were making a diagnosis about a third of the time.

The trouble is that most of the children that were qualifying for the sequencing, were qualifying because people had failed to figure out what was going on and I think one of the worst feelings in the world is making a diagnosis on a child, when if you'd known earlier you could've prevented the child from getting sick. So, the real appeal of Rady Children's and what we're doing here is the fact that we're sequencing the children very early. Our target is to enrol kids within 96 hours of being born or arriving in our NICU, and the reason we've moved to that approach is that for many of these diseases that are treatable, they're only treatable within a limited time window. And so the real appeal of sequencing neonates is that you can actually get in early and change the long-term outcome.

As a clinician, you must be more involved with patients on a daily basis. How is it working somewhere where you're working with patients and research in such a tight combination?
There has been a huge increase in the number of potential treatments available for kids with rare diseases. One of the best parts of my day is being able to recommend new treatments for diseases for children who would otherwise die without the proper treatment. At Rady Children's I have the pleasure of being able to mix improving diagnosis with trying out new treatments for diseases that would otherwise lead to lifelong disability or death.

At Rady Children's one of the exciting things is that the research is currently being funded by an endowment. Previously, we've had to cobble together funding for the testing, either via insurance or the health care system, limiting the number of kids' lives you can impact. You spend almost as much time trying to figure out where the money's going to come from as you do actually taking care of the kid. But here, if kids meet our criteria we get to just go ahead and sequence them.

Previous studies looking at genetic testing in children have often selected kids to sequence because a clinical geneticist thought they had a genetic disease. What we're doing at Rady Children's now is sequencing almost all the kids that come into the NICU. I think the thing that has really shocked me is the fact that half the kids we're sequencing have a genetic disease.

That's a genetic disease that normally wouldn't have been noticed or at least not at that stage?
Yes, they wouldn't have seen clinical geneticists. Nobody would have tested them, nobody would have even thought that they had a genetic disease. What we're finding at Rady Children's is that so many of these kids have genetic diseases. Then think about the 80,000 to 100,000 kids a year in the US who fit the exact category of the kids we're sequencing and how a portion of those have a treatable, genetic condition. These are kids with genetic diseases that are being born in the US without a diagnosis and without appropriate early treatment. So, the reason we talk about going to five hospitals, and 50 hospitals, and 500 hospitals is because we have this huge passion to try and save as many kids as we can.

For those children where you can provide a diagnosis but it's not treatable, is there still a benefit, especially for the family, of knowing what it is?
I think that's an important question. When we talk about treatment, we mean that there is a specific therapy that is targeted at the underlying cause. That's an important concept because being able to tell a family what condition their child has, and therefore what to expect for the future is very helpful. With a portion of the kids we take care of, what the diagnosis does is provide a certainty to the parents around the prognosis. For example, I think for many parents, if they know that their child has a condition that is not compatible with long-term survival, it's emotionally a lot easier for them to choose not to do certain things that are potentially unpleasant to the baby. So even in the situations where there is not a treatment that is targeted to the underlying cause, having a diagnosis can be hugely useful in taking care of that child and deciding what should and shouldn't be done – you can make sure that the degree of harm or risk to which you're putting the baby is proportionate with the potential benefits.

Detail

RESEARCH OBJECTIVES
The team at Rady Children's Institute for Genomic Medicine focus on increasing the speed and availability of genomic medicine for children. This includes the most rapid whole genome sequencing technology for use on neonates in order to detect and treat genetic disorders at the earliest opportunity and with the greatest precision.

FUNDING
Rady Children's Institute for Genomic Medicine; National Human Genome Research Institute; Eunice Kennedy Shriver National Institute for Child Health and Human Development.

KEY TEAM MEMBERS
Illumina Inc., Edico Genome, OMICIA Inc., DNANexus, Children's Mercy Hospital (Kansas City), Sanford Children's Genomic Medicine Consortium

BIO
Led scientifically by Dr Stephen Kingsmore and Dr David Dimmock, the Rady Children's Institute for Genomic Medicine was established in 2014. Working alongside Rady Children's Hospital, San Diego and the University of California, San Diego, the Institute houses a team of world leaders in genomic medicine for children.

CONTACT
Rady Children's Institute
for Genetic Medicine
3020 Children's Way, MC 5129
San Diego
CA 92123
USA

W: www.RadyGenomics.org
E: rcigm_collaborations@rchsd.org

Rady Children's Institute
Genomic Medicine