By Leah Kaminsky

DECODING MASSIMO

THE QUEST TO FIND A DIAGNOSIS FOR ONE BOY'S RARE GENETIC DISEASE LED TO A DISCOVERY "NO LESS MONUMENTAL THAN LANDING A MAN ON THE MOON"

As soon as the midwife placed my newborn son on my belly, moments after a 23-hour labour brought him into the world, I started counting his fingers and toes. I checked his fontanelle wasn't too big. Or too small. Or bulging. Or sunken. I looked closely for a squint, unusual lumps on his ears, a receding chin, any sign of respiratory distress. I ran my hand slowly along his spine. Most parents I have spoken to over the years describe the first meeting with their baby as it emerges into the world in radiant or spiritual terms; a moment of exaltation. I, on the other hand, spent those precious moments at the starting line of our life together, scanning my son's tiny 2.9kg body for imperfections. It's how I roll. I have dedicated much of my working life to routinely checking newborn babies.

One wintry day back in 2008, Stephen and Sally Damiani walked into my GP clinic in Melbourne, proudly holding their first newborn son. It was particularly frantic at the clinic, so I bypassed the chit-chat and went straight over to little Massimo. There is a fixed routine for examining a neonate head to toe. You need to completely undress the baby. First weigh them. Measure length and head circumference. Check the colour – pink is good, blue is definitely not. Palpate the fontanelles, look

These loving arms: Stephen and Sally Damiani with son Massimo

for symmetry of the face, insert a gloved finger into the mouth and use a torch to make sure there is no cleft palate, feel the tiny space between the skull bones, listen to the rapid *lubdub* of the fledgling heart. Feel for clicks in the hips as you splay their legs out like a frog. The stepping reflex is always good for a laugh – I tell parents their baby is a genius who already knows how to walk. Leave the Moro reflex for last, because as you hold the baby's hands together and then let go, it will inevitably startle and let out a shriek. In essence, when you examine a baby, always look for something you don't want to find.

Until recently I've been in the habit of breathing a sigh of relief at the end of a normal examination as I say to the parents, "Your child is perfect." It rolls off the tongue easily and is the quickest way to engender beaming grins all around. But lately I've been thinking about this seemingly innocuous phrase and have substituted the watered-down "Everything seems to be OK". I remember, while working as a young paediatric resident at Prince of Wales Children's Hospital in Sydney, calling a senior consultant when I had found an abnormality during an examination. He told me to check for two more imperfections – "Things come in threes with FLKs." In those days we used this coded term in front of parents whose baby in some way seemed unusual and warranted further investigation. FLK: Funny Looking Kid.

Massimo Damiani had a 2mm skin tag at the base of his spine. I remembered my professor's warning of the Trinity of Affliction and so spent time scouring the baby's body for any other signs or anomalous structures. The rest of his examination was unremarkable, but an X-ray revealed unusual tethering at the base of his spinal cord, a malformation that would most likely need surgery further down the track. Stephen and Sally were devastated. None of us realised then that it was only the start of this little guy's journey into the world of the unknown.

Notes in medical record: Parents have been trawling the internet for information. They have multiple questions I cannot answer.

Stephen Damiani is a friendly, unassuming guy. He has no college-level medical training but from his home-base "mission control" in Elsternwick, Melbourne, he has been the architect of a complex family genetic project – organising to have his wife Sally's, son Massimo's and his own genomes – the complete set of genetic

Breakthrough: "This is the future of medicine," says Dr Ryan Taft

material (DNA) carried within each cell of the body – mapped and compared. Inspired by his childhood astronaut heroes, Stephen was driven by the need to find a diagnosis for his son's unknown genetic condition, which became apparent after his first birthday when his development deteriorated rapidly – he could no longer crawl or sit and began to choke on food and water. He was presumed to have some form of leukodystrophy, which is characterised by a lack of myelin, the substance that coats nerve fibres, enabling transmission of electrical impulses throughout the nervous system. The rare degenerative disorder robs sufferers of their sight and eventually all senses; there is no treatment or cure.

"Like any small boy I was always fascinated with aviation, aerospace and all things pointy and fast," says Stephen. "It was an era when science was inspired by imagination and anything was possible. When we reached the end of the road in trying to diagnose Massimo in December 2009 we needed to engineer a miracle. If we were to achieve a diagnosis we needed to separate science from finance and allow researchers to be inspired by imagination, rather than be hindered by ivory tower ethics, bureaucracy and budgets." He set up a charitable fund called Mission Massimo.

Stephen follows in the footsteps of parents like Augusto Odone, whose story inspired the 1992 film *Lorenzo's Oil*, starring Nick Nolte and Susan Sarandon. Augusto was told that his son Lorenzo suffered from a rare genetic disease called adrenoleukodystrophy and had at most two years to live. He and his wife were determined to find a cure for him despite being told it may be impossible; they were warned that they would be unable to understand the specialised medical literature and, like the Damiani family, there was little hope for their son.

What Stephen Damiani has achieved over the past three years is nothing short of the wildest science fiction. The discovery of Massimo's defective gene, allowing a more specific diagnosis than had been possible before, together with the parent-driven nature of this advance, marks a huge turning point in medicine, no less monumental than landing a man on the moon. It's fitting that Massimo's favourite toy is a NASA space shuttle.

Dr Adeline Vanderver, a paediatric neurologist who specialises in leukodystrophies at the Children's National Medical Centre in Washington DC, is part of the international team that found the gene causing Massimo's illness. "Before genomic medicine, the patient and their family were very isolated," she says. "Several times a week I get an email from someone out there who has a child with an unsolvable leukodystrophy. This is all played out in Massimo's story. Once the gene responsible for his condition was found, we started looking at a series of images in other patients."

The man responsible for the discovery is Dr Ryan Taft, a genomics researcher from the University of Queensland's Institute for Molecular Bioscience. "We asked Ryan to analyse their genomes too and immediately found two patients who also had the DARS gene defect," says Vanderver. "Instantaneously, we had a domino effect, with a whole cohort of patients. Since the paper was published in *The American Journal of Human Genetics*, even more are coming out of the woodwork. Genomics, coupled with the link-up and collaboration around the world, made this possible. This shrinks the isolation of these families, from Michigan and Colorado to Melbourne."

It took 11 years and billions of dollars for the first complete human genome to be read back in 2001. The Human Genome Project set out to decipher the code of human DNA – our genetic blueprint, comprising more than 25,000 genes and three billion letters of DNA – with the ultimate goal of identifying how each gene might contribute to disease.

To date, there are around 8000 known genetic diseases. However, the faulty gene responsible for a particular disease has been identified in only 40 per cent of cases and of these known genetic causes, only a fraction can

be treated in some way. Statistically, you are probably more likely to find a needle in a haystack than an unknown gene that is causatively linked to a disease. "If each letter of Massimo's raw genome data was 1cm by 1cm it would stretch to the moon and back 4.6 times," Stephen Damiani says. "We were searching for two letters and found a compound heterozygous variation in the DARS gene."

Genomic medicine, also known as personalised medicine, where whole genome sequencing and other screening technologies are employed, is rapidly changing the future of health care. Researchers are using the vast amount of data that can be gathered on an individual's genetic make-up to tailor prevention, diagnosis and treatment plans for various diseases.

The exciting thing about personalised medicine is that as these methods are refined and become cheaper, much earlier diagnosis is possible. This enables clinicians to better predict the course of a disease and give better treatment options. Or simply give parents a name for their child's mystery illness, so they know what they're dealing with. "This is the future of medicine," says Dr Taft, who led Massimo's team of doctors from around the world – including the Children's National Medical Centre in Washington DC, The Royal Children's Hospital in Melbourne and VU Medisch Centrum in Amsterdam. "Although in this new age of genomic medicine we are getting better at finding mutations, translating these discoveries into specific treatment is still a huge leap, especially when it comes to a newly recognised genetic disorder in a gene like DARS, the one we found responsible for Massimo's disease, that has previously not been described as being associated with any disease."

Taft worked on the Damiani project during his free time, often through the night and on weekends, without any pay. It was a steep learning curve for him with many ups and downs, he says. "It's very rare for a basic research scientist to be on the receiving end of a call from the father of a sick child asking, 'Can you help us?' Knowing there was even a remote possibility that I could have some small effect on someone's life was hugely motivating. Then, to actually get what I thought was 'it' was incredible. I convinced Illumina [a US biotoech company] to take a shot with sequencing Sally and Stephen's genome. Once we had the findings, it took a couple of weeks before the clinicians reacted and then months went by before we could really validate everything. Soon after, though, the team in Amsterdam identified two more patients with mutations in the DARS gene and within 48 hours, 18 months of hard work was completed. It felt surreal. We got to discover a new disease. Who gets to do that?"

Vanderver says recent advances in genomics have completely changed her life as a physician. Being able to identify a child's genetic illness is a relief for most parents, she says. "In one way a diagnosis robs parents of the hope that there's nothing wrong, the lingering thought that maybe the doctors are misguided in their bleak prognostications. But most find a huge sense of relief at the end of their diagnostic odyssey… It is always better to fight an enemy you can name."

As to whether there is any imminent treatment breakthrough in sight, she muses: "That's why I get up every morning. We are searching for a global cure for leukodystrophies, looking at replacing defective cells in the body with normally functioning ones. We are hoping to minimise the disease process for sufferers and improve their symptoms, hopefully improving their life expectancy. But we are still a long way away from this."

How does working in this field affect Vanderver personally? "I keep a stack of condolence cards in my desk drawer. I have to use them far more often than I would like. There are days when that's really hard. I go to patients' funerals if I think it's meaningful for the families to have me there. We have palliative care paediatricians attached to our unit, disguised as what we call "complex care" doctors. Together with grief counsellors, they help both the families and the medical team to cope with accepting that often there is nothing we can do to save these children. Everyone's life has an arc – a beginning, middle and end – but even though these children's arcs may be much shorter, they can still be packed with meaning."

In the US it is now possible to have a sick child's exome sequenced within 72 hours. Exomes are a specific region of DNA that specifies the genetic code for proteins. Although exomes account for only 1 per cent of the entire human genome, they are thought to be implicated in more than 80 per cent of mutations that cause disease. In Europe, this procedure has become a standard of care for suspected paediatric genetic disorders.

In Australia, funding is scarce and the pull for top scientists to enter private industry is financially far more attractive. As the Damianis' GP, I have witnessed the family's ongoing struggle as they have negotiated with various high-level players, trying to enlist their assistance and backing in finding a diagnosis for Massimo. They ended up paying for a lot of the testing themselves. I have been ashamed at times to see the turning-up of some of my genetics peers' noses, the unwillingness to take risks into the unknown, or to simply keep up with research and development happening in the field of genomics. Like many other visionaries, Stephen Damiani has met with a fair amount of resistance along the way. Thankfully, he is a stubborn and determined man and has followed those who were able to see beyond the tremendous obstacles, to have faith in his ability to facilitate the process.

The journey towards a cure has just started for little Massimo. What has been the hardest thing all along, according to his parents, is living with the uncertainty of their son's future. They can take solace in knowing they are not alone. The Damianis are realistic in their expectations, but determined to take another leap into the unknown towards developing a therapy and maybe a cure for their son, and for others around the world with this condition. As they say, "We have something tangible to fight, now that the disease has a name." ●

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Vision: "We needed to engineer a miracle," says Stephen Damiani

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