

Breakthroughs in children's medicine

Genetics





Welcome

Welcome to our breakthroughs in children's medicine guide, focusing on genetics. From Europe's first ever genetic counselling clinic to using the power of modern-day genetic technology, Great Ormond Street Hospital has always been at the forefront of improving care for children with genetic conditions and their families.

Genetic medicine has undergone a revolution over the past two decades. By understanding how our DNA causes genetic diseases, we have gone from knowing little about the underlying cause of genetic conditions to offering tests that accurately diagnose conditions in children and their families. Our doctors and researchers have kept pace with these remarkable changes and used cutting-edge techniques to benefit our patients.

But there's still a long way to go. In collaboration with our colleagues at the UCL Institute of Child Health, we are carrying out accurate diagnostic testing for rare diseases in order to develop life-saving treatments for children here at the hospital and worldwide. By understanding genetic mutations we can now begin to offer the hope of treatment to children with some of the rarest and most complex conditions.

I hope you enjoy reading about the breakthroughs in genetics at Great Ormond Street Hospital and that you continue to support our vital work.

A handwritten signature in black ink, reading 'Jane Hurst'.

Dr Jane Hurst
Consultant in Clinical Genetics
Great Ormond Street Hospital

Cover image: Five-year-old Maya has spinal muscular atrophy type 2.



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Yesterday 

The unknown world of inherited diseases

In the 19th century, life for sick children and their families was not easy. Doctors knew little or nothing about conditions that ‘ran in the family’. Genetic diseases resulted in chronic ill health, progressive disability and, in some cases, premature death. Parents were helpless as they wondered if their other children would endure a similar fate.

Nowhere was this more apparent than in a genetic bleeding disorder known as haemophilia. Dubbed the ‘royal disease’ because of its prevalence in Queen Victoria’s family, haemophilia was considered life-threatening at that time. Children experienced terrible pain caused by bleeding into their joints and muscles, and in the most severe

form of the condition, parents were informed that their child might not see their next birthday. Doctors were unable to stem excessive bleeding beyond bandaging cuts and injuries in cotton wool.

Medical knowledge about inherited conditions was still limited in the 1800s. Doctors had little idea how diseases were transmitted from healthy parents to their children – the word ‘gene’ hadn’t even been invented. But when the Hospital for Sick Children at Great Ormond Street – now Great Ormond Street Hospital – first opened its doors in 1852, children had an environment where they could receive dedicated paediatric care for the first time ever.

Right: A hospital ward in the early 1900s.





First understanding of genetic diseases

On 3 May 1901, Thomas Poole, a young boy from Bethnal Green, was admitted to Great Ormond Street Hospital with a rare but harmless disorder known as alkaptonuria. Two years later, his brother, Albert Poole, was also admitted to the hospital with exactly the same symptoms. Dr Archibald Garrod saw both brothers and his notes for Albert revealed: “Elder brother has alkaptonuria.”

Through exemplary record-keeping of the children he treated, Dr Garrod saw a pattern where alkaptonuria emerged more frequently in children of first-cousin marriages. He put forward a concept that is now fundamental to modern-day genetics. Dr Garrod concluded that alkaptonuria was the

result of a defect in the body that was present from birth – what he referred to as an ‘inborn error’. His work was the first to connect human diseases with the laws of heredity, that physical characteristics are passed down from parent to child. Dr Garrod subsequently went on to discover a whole group of these ‘inborn errors’.

His work did not excite great interest among his contemporaries. Children like the Poole brothers were considered to have rare disorders that doctors seldom saw in their clinics. But as our understanding of the role that genetics plays in determining our physical traits has improved, Dr Garrod’s work has become widely recognised as ahead of its time.

Left: Dr Archibald Garrod.



1902 Archibald Garrod links alkaptonuria disorder to inheritance at the hospital.

Europe's first support clinic for genetic conditions

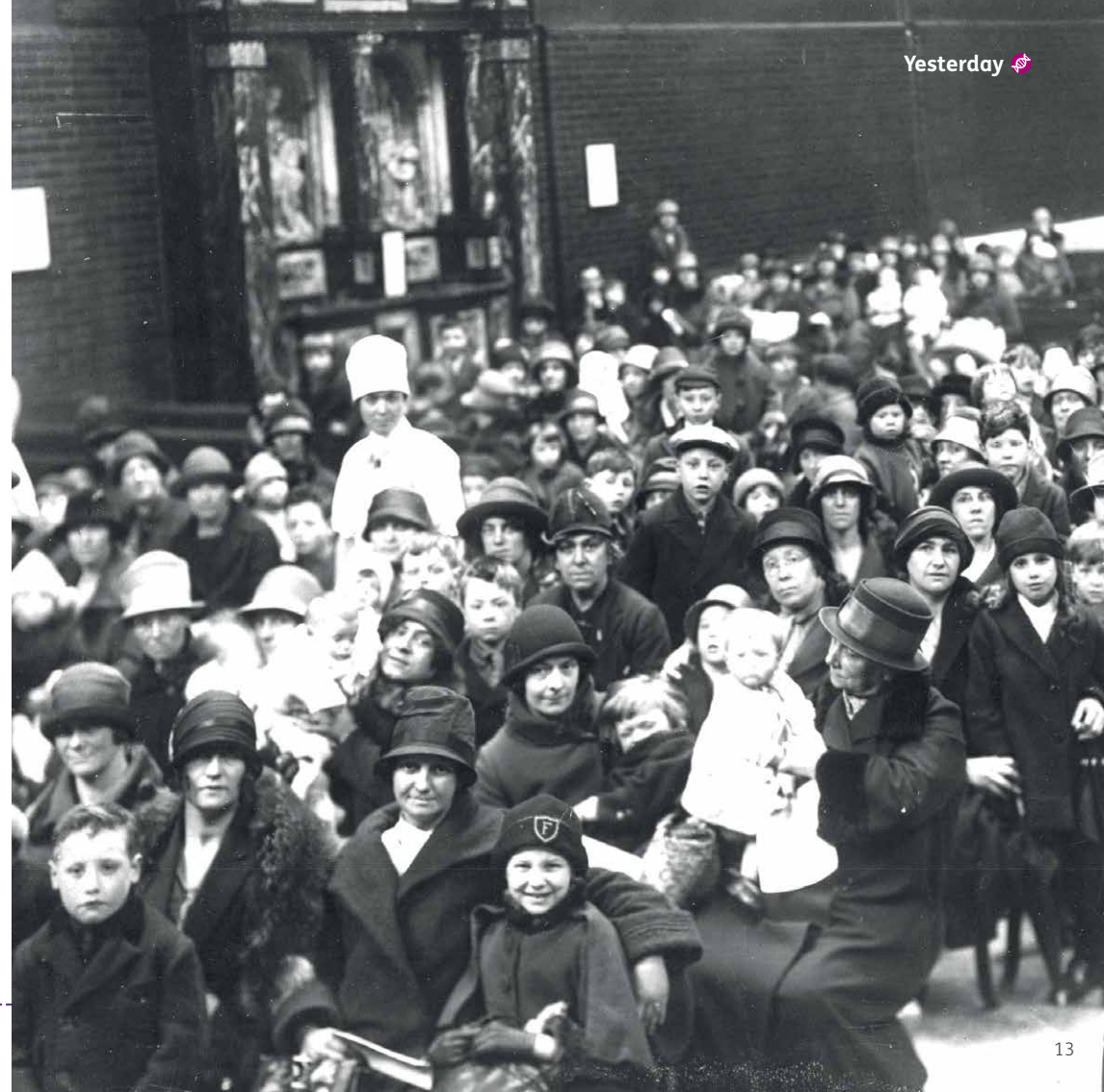
In the 1940s, parents of children with genetic conditions had no idea if any future children they might have would be similarly affected. Doctors were slow to fully grasp the concept of inherited conditions in the same way that Dr Garrod had and they were unable to answer anxious parents' questions on the risk of illness in any additional children they may have in the future.

Recognising the support these families required, Dr John Fraser Roberts founded Europe's first ever genetic counselling clinic in 1946 at Great Ormond Street Hospital. His weekly clinics provided expert advice about the likelihood of a disease re-occurring to those parents who wanted to have more children.

Right: A busy waiting room in the Hospital for Sick Children.

Although his tools were limited, Dr Fraser Roberts drew detailed family charts based on the clinical notes of hundreds of children and families he saw, and also from the excellent record-keeping of the hospital. For the first time ever parents were counselled on the risk of having a child with the same condition in the future.

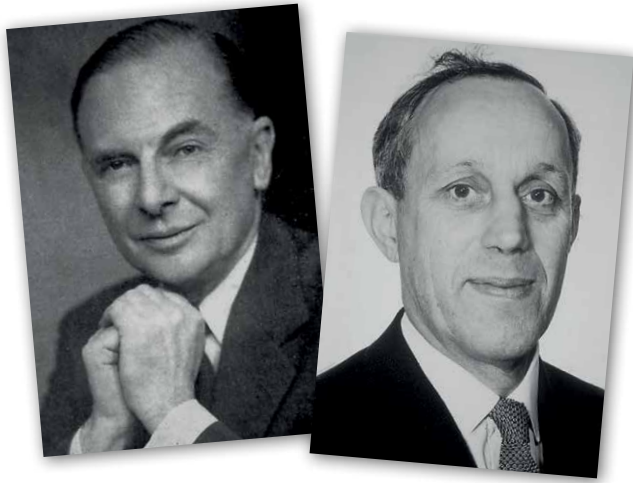
The precision, clarity and empathy Dr Fraser Roberts brought to his clinics formed the foundation of genetic counselling as we know it today. His clinics were able to dispel unfounded fears, provide a much-needed support service for families and consider the welfare of the unborn child.



The UK's first genetics research department

In 1953, Dr James Watson and Sir Francis Crick made a discovery at the University of Cambridge that would revolutionise the field of genetics. They uncovered the structure of DNA, often referred to as the 'blueprint for life'. Recognising the need to bring such

vital science and medicine together to benefit patients, The Clinical Genetics Research Unit was established at the UCL Institute of Child Health (ICH). Founded in April 1957 by the Medical Research Council, it was the first genetics research department of its kind in the UK.



Dr John Fraser Roberts (left) and Dr Cedric Carter (right).

Led initially by Dr John Fraser Roberts and then by Dr Cedric Carter – both of whom were prominent doctors at Great Ormond Street Hospital – the work of the departments forged the practical and long-lasting link between genetic science and medicine. Keen to extend the support that counselling offered to families, they conducted high-quality research on genetic conditions such as Down's syndrome and spina bifida in order to work out the precise chance of these conditions recurring in a future pregnancy.

Previously, doctors had to study family medical records in order to determine the likelihood of parents passing on a genetic condition. But Professor Marcus Pembrey, who worked alongside Dr Carter, later led the transition from observational genetic studies to the application of DNA technology for research. He then established a diagnostic genetic laboratory at the ICH in the 1980s with Professor Sue Malcolm, which improved clinical care for children and their families.



By the late 1980s, genetics as a medical specialty was becoming more widely understood and doctors began receiving specialist training in this field. Yet most doctors were still presented with the challenge of diagnosing genetic conditions. The difficulty lay in trying to recall the thousands of conditions that had been described across many different medical journals. Keen to address this situation, Robin Winter, Professor of Clinical Genetics at Great Ormond Street Hospital, developed an award-winning computer-based database that helped doctors quickly diagnose children with complex and rare genetic conditions.

and compiled information on thousands of genetic conditions based on the children under their care. Known as the London Dysmorphology and Neurogenetics Database, and still widely used by doctors today, this database has proved an invaluable diagnostic tool for more than 4,700 conditions. It has served as a useful reference tool for clinical geneticists faced with identifying an unknown genetic condition.

Professor Winter worked on the database largely in his spare time, which epitomises his commitment and dedication. He had the foresight to bring the latest computer technology together with genetics, a pioneering approach that has helped to benefit children and families all over the world.

Today 

Life outside the bubble

In 2001, Rhys Evans became one of the first people in the world to be treated with gene therapy at just nine months old. To this day, Rhys remains a healthy teenage boy, able to go to school and play with his friends, which is an extraordinary feat for someone with his condition who has undergone such pioneering treatment.

As a baby, Rhys was diagnosed with rare X-linked severe combined immune deficiency (X-SCID), which means his body was unable to produce the white blood cells that are essential for fighting infections. In the past, this disease could not be treated at all until bone marrow transplant (BMT), became an accepted form of treatment in the late 1970s. Before

that time, some patients were kept permanently in a sterile environment to protect them from infections that their genetically weakened immune systems would not be able to fight, prompting the label of ‘bubble babies’. Inevitably, being kept apart from direct human contact was psychologically damaging for these patients.

BMT was a major step forward, but still children with X-SCID rarely survived beyond two years old. Rhys was put forward for a new gene therapy treatment under the care of Adrian Thrasher, Professor in Paediatric Immunology. This was a process that added a correctly-functioning version of the faulty gene into Rhys’ blood.

Right: Rhys Evans today, aged 13.



Within just a fortnight, Rhys’ immune system was beginning to respond.

Rhys will require follow-up for the rest of his life in order to check on his progress. Nonetheless, the signs to date have been highly encouraging.

“We were ecstatic about his progress,” said Professor Thrasher. “We’d been working on the technique for years in the lab, and it was great to take that work into the clinic and see therapeutic success.”





Benefits of early diagnosis

Technology to accurately diagnose genetic conditions became available in the 1990s, following global efforts to map out the entire DNA code of a human.

Early diagnosis helps improve the outcomes for children with genetic conditions. This impact can be seen in conditions like Usher syndrome – a disorder that causes the loss of two vital senses; hearing at birth and vision later on in childhood. At Great Ormond Street Hospital, Professor Maria Bitner-Glindzicz has developed the UK's first dedicated genetic test for children with Usher syndrome using the latest technology. The test allows an accurate and rapid diagnosis of Usher syndrome, something that would have previously taken years to do.

Following diagnosis children are given powerful implanted hearing aids early

to support their communication. This is essential as communicating through sign language can become challenging as vision deteriorates.

Professor Bitner-Glindzicz, who specialises in genetic causes of deafness, says: “Although the confirmation of Usher syndrome is a difficult diagnosis to give to families, we can now offer the early support required to help them manage their child’s hearing and vision.”

As well as Usher syndrome, Professor Bitner-Glindzicz has identified a number of genes responsible for other forms of deafness. She is working closely with the diagnostic team to ensure her research benefits the children seen at the hospital.

Left: Khadeeja is now 13 and was born with nonsyndromic deafness.

Infantile parkinsonism-dystonia

The ability to read a patient's DNA code has led to the discovery of new genetic conditions, some of which were previously misdiagnosed. Infantile parkinsonism-dystonia (IPD) is just one recently discovered genetic condition, by Dr Manju Kurian in 2011. This rare childhood neurological disorder is a life-threatening condition where children experience movement difficulties similar to those seen in adults with Parkinson's disease.

Dr Manju Kurian, a Paediatric Neurologist at Great Ormond Street Hospital, made the vital discovery that IPD is caused by a faulty gene in the brain. Children with the condition were previously misdiagnosed with cerebral palsy and trialled on a combination of drugs to

control their symptoms, some with little effect. This ground-breaking discovery has resulted in more children around the world being correctly diagnosed.

Dr Kurian is now looking to develop the first effective treatment for IPD: "We are better placed to manage the movement difficulties children experience through knowing what causes this condition," she says. "Yet none of these treatments are life-saving. I am continually driven by the children that I see to find a way of fixing the faulty gene and developing the first effective treatment for IPD. We hope that our efforts will one day allow children and their families with IPD to lead a normal life."

Right: Two-year-old Shira was recently diagnosed with IPD as a result of Dr Manju's recent research.



Gene discovery

Great Ormond Street Hospital sees more children with rare diseases than any other hospital in the UK. The rarity of conditions seen by our doctors can sometimes be as low as one in 100,000. In 75 per cent of these conditions, the faulty genes responsible remain unknown, meaning children and families face the uncertainty of not knowing the cause of their condition.

Determined to provide the best outcomes for children with even the rarest conditions, doctors at the hospital, together with leading scientists at the UCL Institute of Child Health, founded GOSgene in 2010. A unique genetic facility, GOSgene uses cutting-edge methods to pinpoint the faulty gene responsible for a child's condition.

GOSgene harnesses the power of modern-day DNA technology by providing a readout of a child's DNA code, using methods that were not previously available. Working closely with world-leading doctors, in-house genetic experts meticulously search the 20,000 genes in the human body in order to pinpoint the faulty one.

GOSgene has generated early successes. More than 52 children have been given an accurate diagnosis, and in over 50 per cent of these cases, the discovery of the faulty gene is a new one that has not been previously reported in medical literature. The dedicated efforts of GOSgene mean that children with the rarest genetic conditions are offered hope at Great Ormond Street Hospital.



Meet the team

Much of the pioneering work carried out by our doctors and researchers is multidisciplinary, involving nurses, genetic counsellors, laboratory scientists and many more. Working as part of a team is essential in pooling everyone's skill and knowledge in order to ensure the best outcome for children and their families.



“ We are in the midst of an exciting time for genetics. The early promise genetics held a decade or so ago is finally coming to fruition and we can already see it transforming care for patients. We are working closely with doctors and researchers to develop more genetic tests in order to rapidly and accurately diagnose conditions. These tests weren't even possible a few years ago. Consequently, children have the earliest access to care and, where possible, treatment. ”

Nick Lench, Director of North East Thames Regional Genetics Service at Great Ormond Street Hospital

“ Only a small percentage of cancers are inherited. In these families the chances of developing cancers are increased. By identifying these families we can offer support and advice to help them manage their risks.

I meet so many people who have been through difficult and life-altering experiences, and yet they remain positive and inspirational. In the genetic clinics, we are able to take the time to offer advice in a manner that is hopefully simple and clear, empowering families to make informed decisions. ”

Cheryl Berlin, Cancer Genetic Counsellor

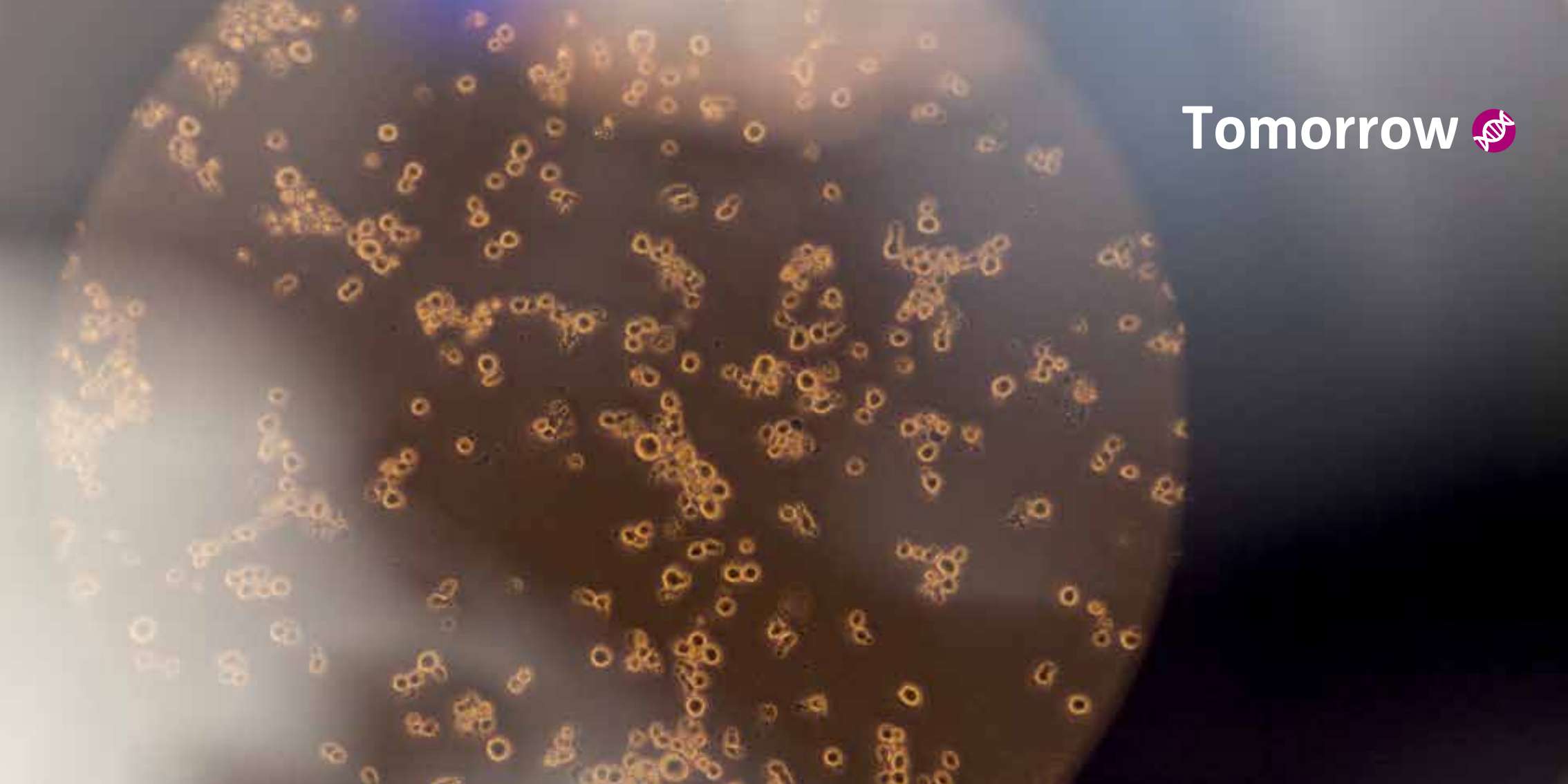


“ At Great Ormond Street Hospital we see children with some of the most complex and rare conditions. Some of these children come to us as a last resort. We are committed to supporting these children and their families, taking away the unknown – through unique facilities like GOSgene – and providing them with a clear cause for their condition. But we don't want to stop there. As we improve our understanding of genetic diseases we want to press ahead in developing vital treatments. ”

Phil Beales, Professor of Medical and Molecular Genetics



Tomorrow 



A brighter future

Genetics has come a long way since Great Ormond Street Hospital first opened in 1852. Doctors have gone from knowing nothing about genetic conditions to providing children and their families with a starting point by using accurate diagnosis. As the field of genetics continues to move at an extraordinary pace and more genetic tests become available, we can do even more to provide support and information to families.

We are continually driven by the fact that there is still a long way to go. By building up a picture of which genetic

errors cause each condition, for the very first time we are positioned to develop vital and life-saving treatments for disorders where no treatment or cure currently exists. Furthermore, thanks to the developments in genetic technology, the ability to read a patient's entire DNA code means we can potentially move to an era where treatments will be tailored to each child's needs.

Only with the ongoing generosity of our supporters can we continue to advance research that will improve the lives of children with genetic conditions across the UK and beyond.

Right: Zoe was born with Crouzon syndrome, a rare genetic condition that causes the craniofacial bones to fuse prematurely. The craniofacial surgery team at Great Ormond Street Hospital could develop life-changing new techniques to help children like Zoe.



Safer prenatal diagnosis

Prenatal diagnosis of genetic conditions is a routine part of care offered to women at high risk during pregnancy. Work led by Lyn Chitty, Professor in Genetics and Fetal Medicine, has been at the forefront of efforts to develop and implement safer tests that assist in determining the health of the unborn baby.

Until recently, diagnosing a genetic condition during pregnancy usually required invasive testing that carries a small risk of miscarriage. Professor Chitty's work has reduced the number of invasive tests required by leading implementation of a non-invasive genetic test into clinical practice in the NHS. The technique measures tiny

quantities of the baby's DNA in the mother's blood. Known as non-invasive prenatal diagnosis (NIPD), this simple blood test also has the advantages of being offered earlier in pregnancy than traditional invasive testing.

The work has transformed prenatal testing for many women. Professor Chitty's research has led to the adoption of NIPD nationally to aid the prenatal diagnosis of a number of genetic conditions. For example, women at risk of gender-linked genetic conditions such as Duchenne muscular dystrophy, which only affects baby boys, are now offered this test to determine whether the mother is carrying a boy or a girl. Only those mothers carrying a baby



boy need to have an invasive test to see whether or not the baby is affected. The team have also developed this test for other genetic conditions

associated with a variety of ultrasound abnormalities and are working now to extend it to conditions such as cystic fibrosis.

Right: A 20-week scan of a fetus.



Genetic technologies to pioneer new treatments

Every year, over 100 children will be diagnosed in the UK with Duchenne muscular dystrophy (DMD) – a genetic muscle-wasting disease that mainly affects boys. A life-limiting condition, boys lose their ability to walk by the ages of eight to 12 because of a fault in a gene vital for muscle function – dystrophin. Great Ormond Street Hospital, together with the UCL Institute of Child Health, is the largest national referral centre in the UK for children with this condition.

Through years of painstaking and dedicated work, we are now taking advantage of clever genetic technology to pioneer urgently required treatment. Our team of experts, led by Professor Francesco Muntoni, Clinical Paediatric

Neurologist, have already made an early breakthrough.

The team have shown that an innovative genetic-based technology – exon skipping – is able to restore some of the missing dystrophin gene. This early success means the team are now poised to test whether the drug brings about longer-term improvements in muscle function for children.

While momentum is building in this area, it is just one in a spectrum of muscular dystrophies – others urgently require new therapies. But we can say with confidence that we've made a significant breakthrough towards finding a treatment for boys with DMD.

Left: Matthew, aged nine, with mum Claire and dad Michael. Matthew has DMD.



Cancer genetics

Survival rates in certain types of childhood cancers have vastly improved over the past 20 years, using a successful combination of treatments such as surgery, radiotherapy and chemotherapy. However, not all children's cancer treatments lead to cures, and there is an urgency to produce better treatments with fewer long-term and unpleasant side effects.

Currently, cancer treatment involves a one-size-fits-all approach, meaning some patients may not respond and others are overtreated. Our doctors and researchers are committed to using advances in genetics to develop more precise ways of knowing which children are likely to respond to a particular treatment.

Left: Isolated cancer cell.

In the same way that modern genetic technologies can decipher the entire DNA code of a human, we can use the same sophisticated methods to unravel the specific genetic faults in a cancer. Armed with this information, we can now begin to understand who should receive which treatments.

Dr Darren Hargrave, Consultant Paediatric Oncologist, says: "The potential to use the advances in genetics for cancer treatments is enormous. By knowing the genetic make-up of a cancer and how certain cancer drugs work, we hope to be able to accurately predict how children will respond to treatment, so that we can tailor a treatment directly to a child's needs."

The Centre for Research into Rare Disease in Children

Young patients, from babies to teenagers, come to Great Ormond Street Hospital from all over the UK and across the globe with rare life-threatening conditions. At least 75 per cent of rare diseases affect children and, tragically, 30 per cent of children diagnosed with a rare condition die before their fifth birthday.

We are committed to doing even more and make a step change in rare disease research by building the Centre for Research into Rare Disease in Children. The centre, which is a unique partnership between Great Ormond Street Hospital and the UCL Institute of Child Health, offers an unrivalled opportunity to tackle rare diseases and provide much-needed help for these often-neglected conditions.

Right: Mia was born with a rare abdominal wall defect.

The site will be a world-leading centre of excellence that will address some of the most challenging scientific questions regarding rare diseases. It will provide state-of-the art facilities for world-leading researchers and doctors, allowing them to do even more towards developing new and better ways to diagnose and treat children with rare conditions.

Scientific breakthroughs, new technologies and fresh thinking offer hope to these children, which was unimaginable a few years ago. The centre will accelerate our research, aiming to help thousands of families and children with rare diseases from the UK and around the world.



Thank you

We have come a long way since the Hospital for Sick Children opened in 1852. Our dedicated and passionate staff have pioneered many new and better ways of treating some of the sickest children. But we are yet to find a cure for all of the patients we see.

Throughout the hospital's history, it has been the continued and generous support of our donors that has helped to fund the research that provides new breakthroughs. With your ongoing generosity we seek to give hope to all children that need our specialist help.

Right: Five-year-old Ronni has cystic fibrosis and visits Great Ormond Street Hospital every six months for treatment.





Find out more

Our website has more information about the specialists, patients and treatments you've read about in this guide, as well as the pioneering research the hospital carries out.

If you'd like to find out more, or you have your own stories that you'd like to share with us, please visit **gosh.org/breakthroughs**

To continue the legacy of breakthroughs at Great Ormond Street Hospital, we need to raise £50 million every year. This helps to rebuild and refurbish the hospital, buy vital equipment and fund pioneering research. As well as the developments in this guide, amazing things happen at Great Ormond Street Hospital every day.