For the kids: innovation in paediatric screening and diagnostics

A recent GSTS Innovation Academy meeting included coverage of the latest laboratory developments in child health. Tony Sackville reports.

Newborns, children and young people are particularly vulnerable to a wide range of infectious diseases and other life-threatening conditions. Unfortunately, healthcare monitoring services show that significant markers of child health – cancer survival rates and markers of diabetic control, for example – are worse in the UK than in comparable countries. Politicians and policy-makers may demand improvements, but it is most often physicians and clinical diagnostic scientists who hold the key to innovation and improvement on the ground.

Earlier this year, GSTS Pathology held the inaugural one-day Innovation Academy event in London, where more than 100 laboratory scientists from Guy's and St Thomas' and King's College Hospitals NHS Foundation Trusts (partner trusts in GSTS Pathology) shared the latest diagnostic innovations in four areas: child health, keeping people healthy, infectious diseases and next-generation diagnostics.

This report covers three examples of the innovative science in the area of child health, highlighting recent innovations in creating a 24/7 metabolic biochemistry service, newborn screening for metabolic disease, and developing a steroidomic service.

RECOMMENDATIONS FROM THE DEPARTMENT OF HEALTH

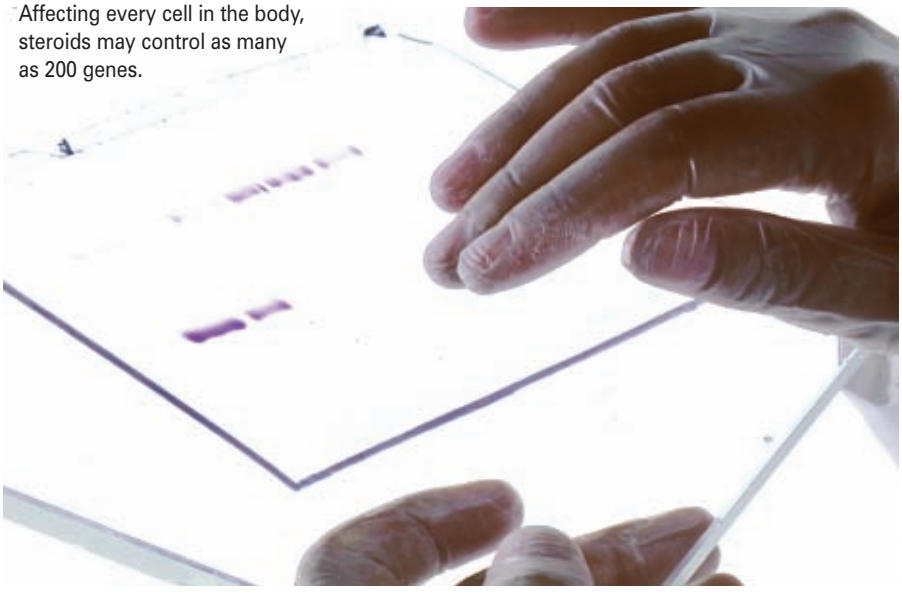
In July 2012, the Children and Young People's Health Outcome Forum published proposals for how health-related care for children and young people can be improved,[1] a key message being that poor or delayed diagnosis of conditions impacts on patient outcomes. The report explained that while there have been some "notable improvements in measured outcomes for children and young people over recent years, the evidence is telling us that this is at a slower rate in the UK than in comparable countries in northern and western Europe."

The Department of Health responded in February 2013,[2] setting out the first stage of its collaborative work to improve health outcomes for children and young people. Under consideration for inclusion in the NHS Outcomes Framework are four new outcome indicators recommended by the Forum, including time from first NHS presentation to diagnosis or start of treatment.

With this in mind, those involved in delivering diagnostic services are ideally placed to review current practices and to generate innovative new approaches that reduce the time through to diagnosis and treatment, with the aim of improving the patient pathway and reducing hospital stays.

SEVEN-DAY METABOLIC BIOCHEMISTRY SERVICE

The GSTS Pathology metabolic biochemistry service at Guy's and St Thomas' NHS Foundation Trust is one of the largest centres in England, providing adult testing and specialist paediatric services for the Evelina Children's Hospital. In collaboration with Great Ormond Street Hospital, it is seeking to establish the UK's first seven-day metabolic biochemistry service. This is in line with the NHS Improvement report *Equality for All: Delivering Safe Care – Seven Days a Week*,[3] which states: "There is a growing body of



Affecting every cell in the body, steroids may control as many as 200 genes.

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Dr Rachel Carling is consultant scientist and Deputy Director of Biochemical Sciences at St Thomas' Hospital, London.

evidence to suggest that where there is a lack of access to clinical services over a seven-day period, patients do not always experience parity of access to the optimum treatment or diagnostic test. This can result in delays to their treatment that can contribute to less-favourable clinical outcomes".

Dr Rachel Carling, consultant scientist and Deputy Director of Biochemical Sciences, explained that: "Although inherited metabolic diseases are a diverse group of disorders, many patients present acutely, often in early life. Without appropriate intervention and management, such disorders can result in permanent disability and many are life-threatening. Currently, UK metabolic biochemistry services are only available weekdays, 9.00 am to 5.30 pm. Outside of this, analysis of urgent samples relies entirely upon the goodwill and availability of a small number of highly specialised staff." The following example provided by Dr Carling demonstrates why an out-of-hours metabolic biochemistry service would be beneficial.

A previously healthy four-day-old baby became floppy, lethargic and started vomiting. He collapsed on day 5 and was admitted with suspected sepsis, but he deteriorated rapidly. The metabolic paediatrician suspected an inborn error of metabolism (IEM) and requested an urgent metabolic screen consisting of plasma amino acids, urine organic acids and blood spot acylcarnitines. These tests have minimum turnaround times (TATs) of four, six and two hours, respectively.

On receiving the urgent request on Good Friday, the laboratory made numerous telephone calls until a biomedical scientist agreed to go in on the Saturday to run the organic acids. This result was finally available at 7.00 pm on Saturday evening; 36 hours after the patient presented. Propionic acidaemia was diagnosed and treatment commenced.

It is clear that had a seven-day service been available it would have improved the patient's care in this case. However, initial challenges to establishing a seven-day metabolic biochemistry service are that analysis takes too long, the laboratory is too small, and there are insufficient highly trained staff to support a formal seven-day service. A service developed in partnership between two laboratories could overcome these difficulties; GSTS Pathology and Great Ormond Street Hospital are working together to establish a collaborative metabolic biochemistry service that will provide analysis of urgent samples seven days a week.

Professor Simon Heales from chemical pathology at Great Ormond Street Hospital said he is "delighted to be part of this collaborative project that has the clear potential to have a significant positive effect with regards to achieving timely diagnosis for children with life-threatening metabolic disorders".

EXPANDED NEWBORN SCREENING SERVICE

Over the past 30 years, the newborn screening programme has been highly successful in preventing significant mortality and morbidity. Every baby born in the UK is offered screening for five inherited disorders within their first week of life (ie phenylketonuria, congenital hypothyroidism, sickle cell disease, medium-chain acyl-CoA dehydrogenase deficiency [MCADD] and cystic fibrosis). Technologies such as mass spectrometry have revolutionised screening with the ability to analyse multiple biomarkers simultaneously from just a single blood spot.

In 2011, in an effort to improve the health of newborns, six laboratories began a pilot to explore the potential of this technology in expanding the range of conditions screened to include five more metabolic disorders. Dr Fiona Carragher, Director of Biochemical Sciences at St Thomas' Hospital, said: "For this expansion to be viable an effective treatment for each of the conditions screened must be available and there must be a window of clinical opportunity. It should require no additional blood to be taken and no extra laboratory equipment."

The pilot study screened for five additional disorders from the existing blood spot sample (ie maple syrup urine disease, homocystinuria, glutaric aciduria type I, isovaleric acidaemia, and long-chain acyl-CoA dehydrogenase deficiency). Individually these are rare but as a group are likely to affect one child in 30,000.

"We already have the technology for these tests," added Dr Carragher. "Using a multiplex approach, different analytes can be tested from a single 3-mm blood spot punch, and in just a few minutes. By adding these five new tests, we now have the capability of detecting many more conditions for no additional analytical time, all from the original blood sample."

This expanded screening has already yielded benefits; for example, in July 2012,

Dr Fiona Carragher is Director of Biochemical Sciences at St Thomas' Hospital, London.

a baby screened in Sheffield was diagnosed with maple syrup urine disease. As the results became available, the child was already lethargic and not crying, and just hours from death. This disease is so rare, and symptoms are initially so broad, that any number of ailments could have been causing the symptoms. The diagnosis was made much earlier through screening, and life-saving treatment was commenced.

"The benefits of screening should always be weighed against potential negatives," said Dr Carragher. "False positives can cause significant anxiety, while confirmation of diagnosis may take up to a week. The study also assessed the impact on parents and considered the best approach to minimise emotional impact. In addition, it was interesting to note that areas where the least number of parents declined the tests were where scientists were part of a multiprofessional screening network. It is believed that informed and confident midwives were the key, and a training programme led by the laboratory really helped with this."

With the backing of the National Screening Committee, the pilot has been extended to March 2014 and has the potential for national roll out by 2014–15.

DEVELOPING A STEROIDOMIC SERVICE

Efficient and timely steroid analysis is a vital step in ensuring the right care for newborn babies who, for a variety of reasons, may not always produce sufficient steroids to develop essential functions fully. Such deficiencies can result in disease and death. At KingsPath, considerable work has taken place to evaluate different methods of steroid analysis, and new service approaches include the proposed establishment of a specialised steroidomic centre.

Affecting every cell in the body, steroids may control as many as 200 genes. Steroid analysis is challenging as they have a large number of alternative chemical structures, many having the same molecular weight. Furthermore, steroids show a huge range of physiological concentrations in the blood. While tests for steroid hormone are commonly available, other steroids are less so.

Dr Norman Taylor, Director of the Supra-Regional Assay Service (SAS) for urinary steroid profiling at King's College Hospital, explained: "Until now, the core of every steroid testing service has been based on immunoassay kits for particular steroid molecules. However, some of these have limited specificity and for the steroids behind some rarer inborn errors of metabolism there may not be an assay kit available at all. Many of these disorders first appear in the newborn baby, which is a time of life when steroid metabolism has some unique features, making the use of standard assays even more problematic."

Dr Norman Taylor is Director of the Supra-Regional Assay Service (SAS) for urinary steroid profiling at King's College Hospital, London.

GSTS Pathology's long-established urine steroid profiling service at KingsPath has developed methods using GC-MS, which provides good specificity and covers a potentially limitless range of compounds, enabling nearly all of these disorders to be identified both in babies and children. However, this technique may not be appropriate for routine use in clinical laboratories, due to the need for extensive urine sample preparation as well as analytical expertise. In terms of accuracy, precision and sensitivity, LC-MS/MS compares well to GC-MS, but allows simplified sample preparation.

Dr Taylor continued: "We have been working on three developments that bring us closer to providing a service that examines the totality of steroid production and so has the potential to provide a 'one stop' service for steroid-related disorders that would provide an excellent fit with the other paediatric metabolic services provided. First, we are using tandem mass spectrometry to discover new steroid metabolites. Our recent study identified more than 400 previously unreported steroids in samples from babies with a single steroid disorder. Second, we have developed statistical methods that have become standard in the wider field of metabolomics to integrate very large sets of metabolic data. And third, we have developed high-performance liquid chromatography/tandem mass spectrometry to target chosen steroids in blood. We are close to offering a panel of 14 steroids. Coupling these analyses with new-generation DNA sequencing for genes related to steroid metabolism could enable us to provide a world-class service."

Dr Taylor's proposal for a world-class steroidomic centre combines highly accurate and specific analytical methods with next-generation sequencing of steroid-related genes, allied to a research and development programme and the academic development of scientific staff to provide a one-stop world-class service.

INNOVATION AND COLLABORATION

The three examples above clearly illustrate how innovations in paediatric diagnostics at GSTS Pathology could significantly enhance patient care by providing an accurate diagnosis earlier. With many of the patients affected being in the first few days of life, this is particularly effective and important. The examples also clearly demonstrate how the laboratory service can be configured more efficiently to provide quicker results with resources that are already in place, thus becoming more cost-effective. This is especially true of collaborative projects and services. ■

REFERENCES

1 Report of the Children and Young People's Health Outcomes Forum, July 2012 (www.gov.uk/government/uploads/system/uploads/attachment_data/file/216852/CYP-report.pdf).

2 Department of Health. *Improving Children and Young People's Health Outcomes: a system-wide response*. London: DH, 2013 (www.gov.uk/government/uploads/system/ uploads/attachment_data/file/214928/9328-TSO-2900598-DH-SystemWideResponse.pdf).

3 NHS Improvement. *Equality for All: Delivering Safe Care – Seven Days a Week*. (www.improvement.nhs.uk/documents/SevenDayWorking.pdf).

Tony Sackville is head of sales and marketing at GSTS Pathology. GSTS provides services to NHS organisations around the UK, to the private sector and to other public sector services in the UK, and to International clients. More information about GSTS Pathology, and the Innovation Academy, is available on the GSTS website (www.gsts.com).