Institution: University of Exeter

Unit of Assessment: UoA 1 Clinical Medicine

Title of case study: Revolutionising diagnosis and clinical care in neonatal diabetes patients worldwide

Period when the underpinning research was undertaken: 2004-2019

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
De Franco E	Senior Research Fellow	2011-present
Hattersley AT	Professor	1995-present
Ellard S	Professor	1997-present
Flanagan S	Associate Professor	2005-present

Period when the claimed impact occurred: 31 August 2013- 31 July 2020

Is this case study continued from a case study submitted in 2014? Y

1. Summary of the impact

The discoveries of the Exeter Diabetes Genetics group have revolutionised the way neonatal diabetes is diagnosed and treated worldwide. They have discovered 18 of the 28 known genes which cause diabetes diagnosed in the neonatal period and optimised the clinical management of the commonest subtypes. The genes they discovered are now included in a comprehensive diagnostic test provided by the NHS and international laboratories in over 30 countries. This molecular genetic test has been adopted and used to test children from 106 countries in 5 continents **providing a diagnosis in over 85% of patients**. **The 2018 International Society for Pediatric and Adolescent Diabetes guidelines** and the 2020 NHS testing criteria for rare and inherited disease, recommend genetic testing should be performed whenever diabetes is diagnosed in the first 6 months of life and use treatment guidelines based on the Exeter group's work. In ~40% of cases there is a mutation in the potassium channel genes and the Exeter group has shown that these patients get long-lasting, outstanding glucose control by replacing insulin injections with sulphonylurea tablets. This optimised care has **improved patients' quality of life and reduced costs to healthcare providers** through optimisation of testing, treatment changes and reduced incidence of severe long-term complications.

2. Underpinning research

Exeter is the world-leading centre for research into monogenic diabetes. The Exeter Diabetes Genetics group has led the way in identifying novel genetic causes and in translating the genetic discoveries into improved treatment and clinical care for the subtype which presents in babies, called neonatal diabetes.

Mutations in only 3 genes, found in 15% of patients, were known to result in neonatal diabetes prior to the Exeter Diabetes Genetics work in this area. Since 2002 Prof Ellard and Prof Hattersley have performed genomic analyses to identify the disease-causing genes in nearly 2,400 patients with neonatal diabetes. As a result, the Exeter group has identified 18 novel genetic causes (**3.1-3.4**) with a further 4 found through collaborative projects. Genes discovered by the Exeter team explain over 50% of all neonatal diabetes cases and 90% of cases born without a pancreas (a condition called pancreatic agenesis). The Exeter group has developed a diagnostic panel to analyse the 28 known neonatal diabetes genes and shown that mutations in these genes explain the diabetes in over 85% of patients (**3.4**).

For each new genetic type of neonatal diabetes identified, the Exeter group has characterised the clinical features associated with defects in the gene (**3.4**-**3.6**) The team has reported in detail the clinical features of the diabetes and treatment response, highlighting the diabetes remission and relapse in some subtypes and the need for supplementary pancreatic enzymes to help digestion in others (**3.4**). They have carefully described the extra-pancreatic clinical

features found in the different subtypes which they have shown usually develop after the diabetes and so can be anticipated with an early genetic diagnosis (**3.4**).

In REF2014 the group reported the impact of discovering two genes causing neonatal diabetes (*KCNJ11* and *ABCC8* (also called *SUR1*)) and how patients with mutations in these genes can stop insulin injections and be treated with oral sulphonylurea drugs, resulting in improved disease management (**3.1**). New research since REF2014 has shown that these patients maintain excellent glucose control without having serious hypoglycaemia and with no evidence of deterioration over time (**3.5**). Recent research by the Exeter team has shown that the majority of patients with this form of neonatal diabetes have some form of cognitive, neurological, or psychiatric features. Recognising these features is essential for the patients' families to be able to access proper support (**3.5**, **3.6**). For non-potassium channel genes, the genetic diagnosis is essential to identify the children who are likely to require treatment for pancreatic exocrine insufficiency (6% of subjects) and those who require monitoring for developmental delay and neurological disorders (26% of subjects).

The Exeter group's discoveries have resulted in patients with neonatal diabetes being referred for genetic testing much earlier than they used to be (>5 years after diagnosis in 2004 vs less than 2 months in 2013) (**3.4**). This shift in age at referral has resulted in patients with neonatal diabetes usually receiving a genetic diagnosis before developing the full clinical spectrum of features associated with their genetic subtype.

The results have provided a new framework for personalised treatment management and clinical care, with an early genetic diagnosis preceding development of clinical features and guiding clinical management (**3.4**).

3. References to the research

3.1. Pearson ER, Flechtner I, Njølstad PR, Malecki MT, **Flanagan SE**, Larkin B, Ashcroft FM, Klimes I, Codner E, Iotova V, Slingerland AS, Shield J, Robert JJ, Holst JJ, Clark PM, **Ellard S**, Søvik O, Polak M, **Hattersley AT**; Neonatal Diabetes International Collaborative Group.: Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med.* 2006 355: 467-777. doi: 10.1056/NEJMoa061759

3.2. Flanagan SE, Haapaniemi E, Russell MA, Caswell R, Allen HL, **De Franco E**, McDonald TJ, Rajala H, Ramelius A, Barton J, Heiskanen K, Heiskanen-Kosma T, Kajosaari M, Murphy NP, Milenkovic T, Seppanen M, Lernmark A, Mustjoki S, Otonkoski T, Kere J, Morgan NG, **Ellard S**, **Hattersley AT**: Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune disease. *Nat Genet* 2014; 46:812-814. doi: 10.1038/ng.3040

3.3. Weedon MN, Cebola I, Patch AM, **Flanagan SE**, **De Franco E**, Caswell R, Rodriguez-Segui SA, Shaw-Smith C, Cho CH, Allen HL, Houghton JA, Roth CL, Chen R, Hussain K, Marsh P, Vallier L, Murray A, **Ellard S**, Ferrer J, **Hattersley AT**: Recessive mutations in a distal PTF1A enhancer cause isolated pancreatic agenesis. *Nat Genet* 2014; 46:61-64. doi: 10.1038/ng.2826

3.4. De Franco E, **Flanagan SE**, Houghton JA, Lango Allen H, Mackay DJ, Temple IK**, Ellard S**, **Hattersley AT**: The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. *Lancet* 2015; 386:957-963. doi: 10.1016/S0140-6736(15)60098-8

3.5. Bowman P, Sulen Å, Barbetti F, Beltrand J, Svalastoga P, Codner E, Tessmann EH, Juliusson PB, Skrivarhaug T, Pearson ER, **Flanagan SE**, Babiker T, Thomas NJ, Shepherd MH, **Ellard S**, Klimes I, Szopa M, Polak M, Iafusco D, **Hattersley AT**, Njølstad PR; Neonatal Diabetes International Collaborative Group: Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. Lancet Diabetes Endocrinol. 2018 ;6:637-646. doi: 10.1016/S2213-8587(18)30238-9

3.6. Bowman P, Day J, Torrens L, Shepherd MH, Knight BA, Ford TJ, **Flanagan SE,** Chakera A**, Hattersley AT**, Zeman A.: Cognitive, Neurological, and Behavioral Features in Adults With *KCNJ11* Neonatal Diabetes. Diabetes Care. 2019 ;42:215-224. doi: 10.2337/dc18-1060.

4. Details of the impact

In REF2014 we reported the discovery of neonatal diabetes-causing mutations in 2 genes coding for the potassium channels in the pancreatic beta-cells. Our research allowed these insulin-dependent patients to be treated with sulphonylurea tablets and improve glucose control. We now report the new impact of these discoveries, and the discovery of an additional 16 genetic causes of neonatal diabetes.

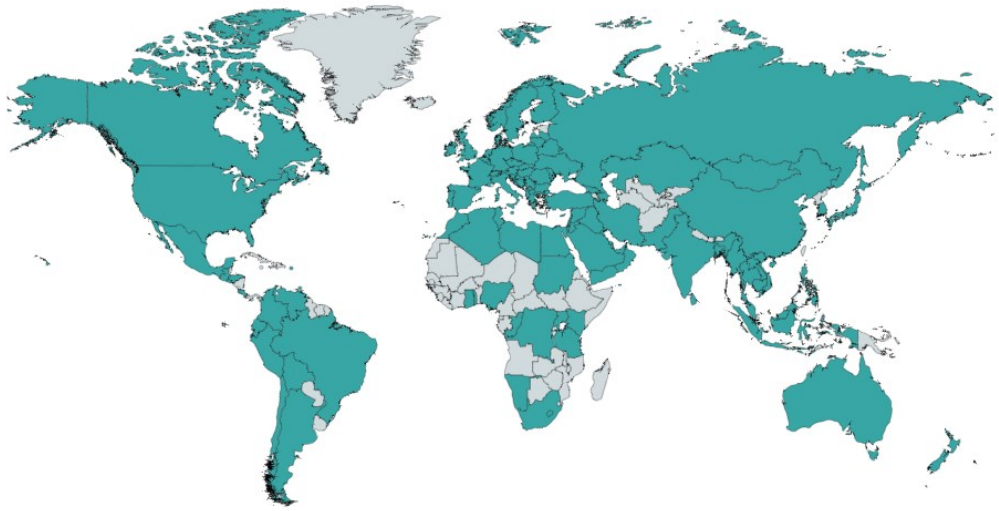
The research conducted at the University of Exeter has revolutionised the way neonatal diabetes is understood and treated leading to increased access to genetic testing for neonatal diabetes worldwide, improved patient outcomes, optimised new clinical guidelines, and a reduction in the cost of testing.

4.1. *Comprehensive genetic testing has been adopted resulting in >85% of patients with neonatal diabetes now receiving a genetic diagnosis worldwide.*

A targeted genomic sequencing assay was developed by the Exeter team and offered as a diagnostic test since 2013 (**5.1**). As new genes were discovered they were added to the panel, resulting in the current single test for all 28 known neonatal diabetes genes. This approach allows for comprehensive and rapid genetic testing, providing a faster genetic diagnosis for patients (**3.4**). As a result of Exeter research, this test is now being offered routinely by the NHS (**5.2**). Genetic testing for neonatal diabetes, including the 18 novel genes identified by the Exeter group, is now also routinely offered by genetic laboratories in over 30 countries world-wide (**5.3**).

This comprehensive testing of all the genetic causes of neonatal diabetes has been offered to >4000 patients from 106 countries in 5 continents with over 85% of patients receiving a genetic diagnosis as a result (see figure). The majority of these patients have been diagnosed since REF2014.

Countries where patients have received neonatal diabetes genetic testing for the genes discovered in the Exeter laboratory (shaded dark green)



4.2. *Patient outcomes and quality of life have dramatically improved.*

Diabetes management is extremely challenging in new-borns and infants. Exeter research has shown that treatment, clinical features and prognosis vary greatly between genetic

aetiologies and an early genetic diagnosis of neonatal diabetes can be used to lead and improve clinical management (**3.4**). This is particularly important for almost half of the patients with neonatal diabetes who can achieve optimal glucose control when treated with tablets rather than insulin injections (**3.1, 3.5**). For such patients treatment change results in a life free from insulin injections and minimises the risk of developing life-limiting complications associated with sub-optimal blood glucose control (**5.4, 5.5**). This has been effectively life-saving for children living in developing countries, where access to insulin is often limited and too expensive, and optimal blood glucose control is hindered by the lack of a controlled diet due to limited economic resources. Because of this, children with diabetes in developing countries are at high risk of life-threatening severe ketoacidosis episodes and tend to develop severe diabetes-related complications (including blindness and neuropathy affecting their movements) which often results in social stigma and inability to work. Sulphonylurea tablets are cheaper than insulin and result in greatly improved blood sugar control, meaning that children with neonatal diabetes treated with these tablets are less likely to develop ketoacidosis and severe complications. As a clinician of a patient in Rwanda noted, 'I am forwarding this good news (*of the successful transfer from insulin to tablets*) that makes all efforts feel worthwhile. Again, for a child in a developing country, not depending on insulin is a huge thing. Moreover, the change in A1C could mean the difference between developing complications in a country where there is almost no resources for addressing complications and living a healthy and productive life. So thank you.' (**5.6, 5.7**).

Following our first report of the safety and efficacy of sulphonylurea tablets treatment in patients with the most common subtypes of neonatal diabetes (**3.1**), over 2000 patients with neonatal diabetes worldwide are now successfully treated with sulphonylurea rather than insulin.

4.3. ***Clinical guidelines have changed to emphasise the importance of early genetic testing.***

Recent national NHS guidelines and international guidelines have emphasised that genetic testing should be performed for every patient diagnosed with diabetes in the first 6 months of life and this testing should include all 18 genes discovered by the Exeter group (**5.8**). Clinical guidelines also emphasise that this testing is a priority and should be performed immediately after the diagnosis of diabetes (**5.8**)

The Exeter group raises awareness of the importance of an early genetic diagnosis of neonatal diabetes through yearly workshops and our online MOOC (Massive Open Online Course) launched in 2016 and has enrolled 31,406 learners to date (**5.9**)***.***

4.4. ***Reduced costs to healthcare providers for diagnostic testing, treatment and long-term complications.***

The implementation of the targeted capture assay since 2013 has resulted in a fall in the cost of comprehensive genetic testing. Testing all the 28 known neonatal diabetes genes costs the NHS £750 per sample. This is cheaper than traditional Sanger sequencing testing of just the 3 most common genes (costing £1050) which would provide a genetic diagnosis in only 55% of patients. Testing all the other genes in the remaining 45% by Sanger sequencing would cost an additional £8750 per patient.

Switching babies from insulin injections to oral medication has a substantial cost saving for healthcare systems worldwide. The cost saving is partly directly reduced treatment costs because sulphonylurea tablets are cheaper than insulin therapy. The estimated annual cost saving to the NHS of this switch in treatment is ~£1,400 per patient. This means that for the 93 UK patients, switching to sulphonylureas has resulted in a direct saving of ~ £130,000 per year (approximately £9,000,000 for their lifetime). A second major saving results from the improved diabetes control achieved on tablets, leading to reduced incidence of severe long-term complications and diabetes related hospitalisations. A cost effectiveness analysis conducted in the USA has shown that genetic testing for neonatal diabetes resulted in quality of life benefits that enlarged over time (0.32 QALYs at 10 years, 0.70 at 30 years) with an increasing mean cost saving per patient ($12,528 at 10 years, $30,437 at 30 years) (**5.10**).

5. Sources to corroborate the impact

5.1. The diabetesgenes website provides information on genetic testing for patients worldwide. https://bit.ly/2P3291m

5.2. The NHS is providing testing using the targeted capture method we developed for monogenic diabetes (including neonatal diabetes) https://bit.ly/39dR6td

5.3. Laboratories in over 30 countries worldwide offer genetic testing for neonatal diabetes some of them listed at the following link: https://bit.ly/3rkYFV5

5.4. A documentary entitled "Journey to a Miracle: Freedom from Insulin" was released in 2015 https://web.archive.org/web/20200501161729/http://journeytoamiraclemovie.com/. It has won 10 national and international awards and was screened in 26 film festivals.

5.5. There have been numerous reports on the TV news and in newspapers about the improved quality of life for patients. One example can be seen on the https://bit.ly/3vWRwxU (February 2015).

5.6. The Exeter team were awarded The BMJ Award- Diabetes Team of the Year for their impact on changing clinical care for patients with diabetes (2016).

5.7. Testimonials from Clinicians: Genetic testing changes neonatal diabetes patients' clinical management, allowing optimal treatment and targeted management. In addition to the above are some testimonials from clinicians who have referred their patients with neonatal diabetes to Exeter for genetic testing:

- 'Thank you very much for the results of your brilliant work. We are very glad to know such an excellent laboratory in Exeter which is able to help us with these difficult patients.' *Clinician of patient from Germany who switched from insulin to tablets*
- 'Thank you very much for sending your formal report. This will be an important basis for formal genetic counselling which we will now offer the family. Once more congratulations for your outstanding scientific workup in this case!' *Clinician of patient from Germany with mutation in novel gene found by the Exeter team.*

5.8. The 2018 ISPAD (International Society for Pediatric and Adolescent Diabetes) guidelines and the 2020 NHS National genomics testing directory eligibility criteria recommend immediate referral for neonatal diabetes genetic testing in individuals diagnosed with diabetes before 6 months https://doi.org/10.1111/pedi.12772. https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-Inherited-Disease-Eligibility-Criteria-November-2020-21.pdf

5.9. The Exeter team has developed the free online course on Genomic Medicine: Transforming Patient Care in Diabetes https://bit.ly/3w05e39 which has had 31,406 enrolments and 12,256 active learners between 22/02/2016 and 22/12/2020) and organises a yearly course for clinicians to raise awareness on monogenic forms of diabetes (including neonatal diabetes). The course has been running once a year since 2014 and has had 516 delegates so far from 41 different countries https://bit.ly/2QCITIF

5.10. The cost-effectiveness of personalized genetic medicine: the case of genetic testing in neonatal diabetes. S.A.W Greeley, P.M John, A.N Winn, J. Ornelas, R.B Lipton, L.H Philipson, G.I Bell, E.S Huang. *Diabetes* Care 2011 34(3):622-7. doi: 10.2337/dc10-1616.