Institution: University of Exeter

Unit of Assessment: UoA 3 Allied Health Professions, Dentristry, Nursing and Pharmacy

Title of case study: Recognising and improving treatment in monogenic diabetes globally through educational initiatives

Period when the underpinning research was undertaken: 2002 to date

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:
Professor Maggie Shepherd	Lead Nurse for Research / NIHR 70@70 Senior Nurse Research Leader / Honorary Clinical Professor	1995 to date
Professor Sian Ellard	Professor of Genomic Medicine	1995 to date
Dr Beverley Shields	Senior Lecturer in Medical Statistics	2002 to date

Period when the claimed impact occurred: 2013 to date

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Diabetes UK estimates there are over 4.7 million people in the UK living with diabetes. Diabetes caused by single gene mutations (monogenic diabetes) accounts for 3.6% of diabetes diagnosed under the age of 30 and approximately 2% of all cases of diabetes in the UK. It causes neonatal diabetes and Maturity Onset Diabetes of the Young. Our research to understand monogenic diabetes led to the creation and delivery of the national Genetic Diabetes Nurse (GDN) initiative, and directly informs the work of the ten specialist monogenic diabetes clinics now established across the UK.

This work has increased international understanding of monogenic diabetes among clinicians, through an annual training course (>130 specialist clinicians from 40 different countries trained since 2014). Together these award-winning initiatives have resulted in:

- Training in monogenic diabetes of over 10,000 clinicians in the UK
- 196% increase in referrals for genetic testing
- More diagnoses of monogenic diabetes, including 308 by UK's GDNs since 2014
- More patients changing to effective, non-invasive treatments for their diabetes
- Significant estimated NHS cost savings, due to life-long switching of patients to much cheaper tablet-based treatments, or for some, to no treatment at all.

2. Underpinning research

Monogenic diabetes (diabetes caused by a genetic change in a single gene) accounts for approximately 2 per cent of cases of diabetes in the UK (3.6% of diabetes diagnosed under the age of 30, approximately). This form of diabetes can cause neonatal diabetes (presenting in the first 6 months of life) and Maturity Onset Diabetes of the Young (MODY). Research shows that eighty percent of individuals with monogenic diabetes are initially misdiagnosed as having Type 1 or Type 2 diabetes. This often means a lifetime of unnecessary insulin treatment. Healthcare professionals need to know about the existence of monogenic diabetes, understand the need for genetic testing, and know how to support those correctly diagnosed to change treatment. Research led by Professor Shepherd has pioneered and evaluated the education programmes for health professionals, and has tested, devised and evaluated the new patient pathways for successful treatment change.

Shepherd first conducted qualitative research to understand the impact of the correct diagnosis for patients with MODY **[3.1]** and neonatal diabetes **[3.2]**. The 2010 paper generated understanding of the impact of a genetic diagnosis and highlighted how insulin treatment had

often become a part of an individual's identity, meaning some patients find it a greater challenge to stop insulin.

In 2010, there was also widespread variation in the identification of monogenic diabetes across the UK **[3.3]** revealing a lack of awareness of the condition in many regions. The Genetic Diabetes Nurse (GDN) network was established by University of Exeter researchers (Shepherd, Ellard and Hattersley) to raise awareness of monogenic diabetes and ensure patients likely to have monogenic diabetes were referred for genetic testing. The GDN initiative was rigorously evaluated and shown to be an effective means of rapidly disseminating knowledge about monogenic diabetes into clinical care. (see Corroborating Evidence, **[5.1]**)

Exeter research has also increased understanding of the clinical characteristics of different types of monogenic diabetes, which has enabled better understanding of the likely success of different treatments **[3.4; 3.5]**. For example, the nationwide study of treatment change in MODY **[3.4]** established that patients with particular genotypes of MODY with a shorter duration of diabetes, lower BMI and lower HbA1c at time of genetic diagnosis, were more likely to be successfully managed on sulphonylurea tablets alone.

Shepherd and her team also developed and evaluated methods to identify those patients likely to have monogenic diabetes, and who should therefore be referred for genetic testing **[3.6]**. This research showed how using a systematic approach using biochemical markers aided detection of monogenic diabetes in children and provided the first data on its prevalence in the UK.

The above research and evaluations of related developments in clinical education were variously supported by research funding from the *Wellcome Trust* (Using pharmacogenetics to improve treatment in young-onset diabetes 2010-2015, PI: Hattersley, £1.25 million), a *Department of Health Research Capacity Development PhD Fellowship* (Shepherd, 2006-2010, £276,000), and service and capacity development funding from the *Department of Health* (4 grants from 2002-07, total £259,000), *Health Education England* (4 grants from 2014-18, total £582,000) and other grants from the *Scottish Executive* and the *Diabetes Foundation*.

3. References to the research

3.1 **Shepherd M,** Hattersley AT. 2004. 'I don't feel like a diabetic anymore': The impact of stopping insulin in patients with maturity onset diabetes of the young (MODY) following genetic testing. *Clinical Medicine*. 4, 2, 144-147. doi: 10.7861/clinmedicine.4-2-144

3.2 **Shepherd M.** 2006. Transforming lives: transferring patients with neonatal diabetes from insulin to sulphonylureas. *European Diabetes Nursing*. 3, 3, 137-142. https://doi.org/10.1002/edn.60

3.3 **Shields BM,** Hicks S, **MH Shepherd MH**, Colclough K, Hattersley AT, **Ellard S.** 2010 Maturity-onset diabetes of the young (MODY) in the UK; how many cases are we missing? *Diabetologia*. 53(12):2504-8. doi: 10.1007/s00125-010-1799-4

3.4 **Shepherd MH, Shields BM**, Hudson M et al. A UK nationwide prospective study of treatment change in MODY: genetic subtype and clinical characteristics predict optimal glycaemic control after discontinuing insulin and metformin. *Diabetologia*. 2018 Dec;61(12):2520-2527. doi: 10.1007/s00125-018-4728-6. Epub 2018 Sep 18.

3.5 **Shepherd M,** Shields B, **Ellard S**, Rubio-Cabezas O, Hattersley AT. 2009. A genetic diagnosis of HNF1A diabetes alters treatment and improves glycaemic control in the majority of insulin treated patients. *Diabetic Medicine*. 26, 437-441. doi: 10.1111/j.1464-5491.2009.02690.x

3.6 **Shepherd M, Shields B**, Hammersley S et al. Systematic population screening, using biomarkers and genetic testing, identifies 2.5% of the UK pediatric diabetes population with monogenic diabetes. *Diabetes Care*. 2016. Nov;39(11):1879-1888. DOI: 10.2337/dc16-0645.

4. Details of the impact

Research shows there are between 20,000-40,000 cases of monogenic diabetes in the UK. Shepherd investigated its screening and referral pathways and reported an average of nine years from diabetes diagnosis to correct molecular genetic diagnosis. This highlighted the unwarranted variation in awareness of the condition – and that low awareness of monogenic diabetes was contributing to low levels of service provision across the country. Getting the correct genetic diagnosis for a patient can result in reduced or less invasive treatment needs, reduced need for blood glucose monitoring, and crucially, improvements in quality of life.

Research and service evaluation by Prof Shepherd and the Exeter team led to the creation and ongoing success of a specialist clinical network of Genetics Diabetes Nurses (GDNs), a related clinical education programme with global reach, and ten specialist monogenic diabetes clinics across the UK. The national GDN educational initiative has improved awareness and recognition of monogenic diabetes **[5.1]**. In addition, health and quality of life has been enhanced through nurse-led initiatives for clinical education and service development. This has substantially reduced the incorrect diagnosis and inappropriate treatment of people with diabetes, and enabled hundreds of patients to change to effective treatments in a safe and acceptable way.

4.1 Ongoing care delivery by the Genetics Diabetes Nurse network

The GDN network was established by Exeter researchers and clinicians (2002) to raise awareness of monogenic diabetes and ensure patients likely to have monogenic diabetes were referred for genetic testing. The GDN project has grown to be an effective, innovative means of disseminating research-based genetic knowledge from a centre of excellence. Since 2013, it has also become an established, more securely funded and successful element of how the NHS cares for people affected by rarer, genetic forms of diabetes **[5.2]**. GDNs are existing diabetes specialist nurses who receive additional training in monogenic diabetes such as: skills in differential diabetes diagnosis; recognition of monogenic diabetes; treatment requirements in monogenic diabetes and genetic counselling. **[5.3]** They also play a key role in spreading awareness and knowledge of monogenic diabetes amongst other healthcare professionals and support families receiving a genetic diagnosis.

Sixty-two GDNs have been trained since the project started (including 22 new GDNs trained from 2014; and 23 are currently in post, in early 2020) **[5.5]**. Ten dedicated monogenic diabetes clinics have been set up by GDNs across the UK since 2002, and our research enables them to provide specialised effective and safe care for diabetes patients with a genetic diagnosis, and also specialised support for other local healthcare teams.

4.2 Training and education of diabetes professionals

All our research findings to aid the recognition, diagnosis and correct treatment of those with monogenic diabetes have been incorporated into our training courses and disseminated through the GDN network and international training course.

Since 2014, our annual 2-day training course on monogenic diabetes has been attended by 516 clinicians (382 UK and 134 worldwide) from 40 countries **[5.5]**. The course is always over-subscribed, with a waiting list each year, and is highly evaluated: 91% rated the course 5/5 as being “highly relevant to their practice”. In turn, these trained Genetic Diabetes Nurses have gone on to give presentations to more than 10,000 attendees at their own training sessions since January 2014 **[5.5]** The research-based clinical knowledge has also been disseminated online via the Diabetes Genes website in order to educate healthcare professionals involved in diabetes care worldwide. (with 420,885 visitors as of 20 July 2020) **[5.6]**.

4.3 Increased referrals and diagnosis of monogenic diabetes

Partly as a result of these service developments and professional education, referrals for genetic testing are increasing, and a total of 1,689 patients have been referred for genetic testing by the GDNs since January 2014 **[5.7]**. Over three hundred (308) of these have had a confirmed diagnosis of monogenic diabetes. **[5.7]** The specialised skills and knowledge of GDNs have also led to a higher positive pick-up rate of monogenic diabetes in counties with GDNs than patients referred from elsewhere and have also increased referrals of family members compared with

areas with no GDNs **[3.5]**. Data supplied by the (NHS) Exeter Genomic Laboratory's monogenic diabetes testing registry **[5.6]** has been analysed to show this:

Counties with GDN activity:	**Before GDN in post**	**After GDN in post**	**% change**	**P value**
Referrals (median)	26	77	+196%	0.004
Positive Cases (median)	9	21	+133%	0.01
Pick-up rate (median)	26%	26%	-	>0.05
Counties with no GDN activity	**Jan 2011 – Feb 2015**	**Feb 2015 – Oct 2018**	**% change**	**P value**
Referrals (median)	31	37	+19%	>0.05
Positive Cases (median)	10	9	-10%	>0.05
Pick-up rate (median)	20%	23%	+3%	>0.05

4.4 Treatment change and related health and economic outcomes

Neonatal Diabetes: Diabetes during early childhood creates a psychosocial challenge to the families of those children. Insulin injection technique, blood glucose monitoring, appropriate infant feeding, and recognition and treatment of hypoglycaemia can be traumatic for both the babies and their parents. One dramatic example of the success of our precision medicine approach is in neonatal diabetes. Previously, these babies were diagnosed with Type 1 diabetes and expected to remain on insulin injections for their whole lives, often with poor outcomes. Our research demonstrating that these patients could be treated with oral sulphonylurea therapy, has enabled babies to transfer off insulin and onto tablets. The discovery has fundamentally changed treatment and prognosis for children with neonatal diabetes worldwide leading to beneficial impacts on their health and well-being and family life **[5.4].** As a mother, who was a participant in one of our published studies shared (p.141 of **[3.2]**):

> *"Family life has completely changed. Before we were unable to live the life of a normal family as he had 2-3 hypos a day, now he is more independent, he is generally well and has not had one hypo. I even had the courage to let him go to a friend's for tea."*

Monogenic diabetes: Of the 308 patients with a confirmed diagnosis of monogenic diabetes since 2014 it is estimated that two-fifths have been able to stop insulin treatment due to the support from these new services **[5.6].** The benefits to patients of receiving the correct genetic diagnosis have been profound; not only have many patients been able to stop daily insulin injections completely, but the diagnosis and simpler treatment regimens have also led to improvements in glycaemic control, quality of life and regained personal identity **[5.7][3.1][3.2][3.6]**. One MODY patient in an early study said:

> *"I can't describe how it feels. It's just a huge relief not being on insulin … The best thing about it is that you felt like you weren't a diabetic."* p.146 in **[3.1]**

Also, a Lead Diabetes Nurse Specialist at an NHS Trust in England said:

> "*I have now been involved in the GDN project for five years and … We regularly see patients whose lives have been changed by more appropriate treatment, in some cases stopping insulin entirely. I hear multiple soundbites. One that springs to mind is: "it's like a dream - not being on the insulin". Equally as satisfying is stopping unnecessary treatment and diabetes reviews for those with glucokinase MODY* - as in the case of an elderly man on triple oral therapy for his 'diabetes' who was able to stop treatment once his [genetic] diagnosis was confirmed. The project has benefitted patients, made me a better clinician*." **[5.3]**

*****A diagnosis of glucokinase MODY, a particular type of monogenic diabetes, means people can stop all their diabetes drug treatments and remain healthy.

Because monogenic diabetes disproportionately affects younger people with diabetes, and treatment is life-long, correct diagnosis and treatment is also a cost-effective use of NHS resources. A recently published (Exeter University) model-based economic evaluation of genetic screening for MODY **[5.8]** concluded: "Although the estimated cost savings are relatively small per person screened (approximately £100–£200 over a lifetime), assuming there are

approximately 200,000 individuals in England and Wales who are <50 years old and have had a diagnosis of diabetes before the age of 30 years, between £20 million and £40 million could be saved if such strategies are used." **[5.8].** While the scale of screening is not yet at these levels, this suggests NHS cost savings are already being achieved.

4.5 National and international recognition of these impacts

The GDN project was winner of a Quality in Care Diabetes Award for innovation in 2015, as the 'Best innovation in integrated commissioning, or integrated care model' **[5.9]**. The GDN project has since been suggested by *Health Education England* as a model for the translation of genetic findings into clinical care, and Prof. Shepherd's contributions to diabetes care globally have been recognised through being named as one of the 'Women in Global Health's 100+ Outstanding Women Nurses and Midwives' (2020 Year Of the Nurse and Midwives) for "notable nurses and midwives doing extraordinary work in their field and communities" **[5.10]**.

5. Sources to corroborate the impact

5.1 The Atlas of Shared Learning Case study: Developing a national Genetic Diabetes Nurse educational initiative. https://www.england.nhs.uk/atlas_case_study/developing-a-national-genetic-diabetes-nurse-educational-initiative/

5.2 Shepherd M, Colclough K, Ellard S, Hattersley AT. Ten years of the national Genetic Diabetes Nurse network: a model for the translation of genetic information into clinical care. *Clinical Medicine* 2014. 14(2):117-21. DOI: 10.7861/clinmedicine.14-2-117

5.3 PDF document with testimonial statements from clinicians and patients.

5.4 Number of Genetics Diabetes Nurses, training course attendees and data on their subsequent training activity, supplied by the *Royal Devon & Exeter Hospital* Molecular Genetics department. https://www.diabetesgenes.org/training/genetic-diabetes-nurses/

5.5 Letter of Testimony - Evidence on the activity and scale of the GDN network and Monogenic Diabetes training courses. The *Exeter NIHR Clinical Research Facility* provides the infrastructure and administrative base for both the GDN and the annual international training courses and holds all the records for both.

5.6 Numbers of referrals, positive diagnoses and treatment changes have been supplied by the Principal Clinical Scientist at the *Royal Devon & Exeter Hospital* Molecular Genetics Laboratory's monogenic diabetes testing registry. The registry contains the testing details of all UK NHS patients referred for monogenic diabetes genetic testing.

5.7 Shepherd M. 2010. Stopping insulin injections following genetic testing in diabetes: impact on identity. *Diabetic Medicine*. 27, 1-6. https://doi.org/10.1111/j.1464-5491.2010.03022.x

5.8 Peters JL, Anderson R, Shields B, King S, Hudson M, Shepherd M, et al. Strategies to identify individuals with monogenic diabetes: results of an economic evaluation. *BMJ Open* 2020;10:e034716. doi: 10.1136/bmjopen-2019-034716

5.9 Quality in Care (QiC) - Diabetes Award, 2015: The award was for the 'Best innovation in integrated commissioning, or integrated care, model'. The judges further commented: '*this is a rare form of diabetes, which is often misdiagnosed and a difficult topic to teach. This initiative was beautifully presented and there were some great comments from the patients themselves*.' http://www.qualityincare.org/diabetes/awards/results/qic_diabetes_2015_results/best_innovation_in_integrated_commissioning,_or_integrated_care,_model

5.10 Prof Shepherd was named in December 2020 as one of the 'Women in Global Health's 100+ Outstanding Women Nurses and Midwives' (as part of the *2020 Year Of the Nurse and Midwives*). Women in Global Health in partnership with WHO, UNFPA, the International Confederation of Midwives, and Nursing Now. Details at: https://yonm.org/nominees/maggie-shepherd-rgn-phd/