Institution: University of Exeter		
Unit of Assessment: UoA 1 Clinical Medicine		
Title of case study: A web/app based probability calculator is used worldwide to improve diagnosis and treatment of genetic diabetes		
Period when the underpinning research was undertaken: 2003 to 2020		
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:**
Dr Beverley Shields	Senior Lecturer in Medical Statistics	2001 to date
Prof Andrew Hattersley	Professor of Molecular Medicine & Consultant Physician	1995 to date
Prof Sian Ellard	Consultant Clinical Scientist and Professor of Genomic Medicine	1995 to date
Period when the claimed impact occurred: August 2013 to 31st December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Maturity Onset Diabetes of the Young (MODY), is a form of diabetes caused by mutation in a single gene that requires an expensive genetic diagnosis. It is difficult to recognise, so the majority of MODY patients are misdiagnosed as the more common Type 1 or Type 2 diabetes. Misdiagnosis matters because MODY has specific treatment requirements and importantly these patients do not need insulin injections. The Exeter 'MODY calculator' helps clinicians select patients who should have diagnostic genetic testing by giving a probability of MODY based on clinical features. It has been **used to improve diagnosis over 170,000 times in 187countries** and is **recommended in national and 3 international guidelines**. In the UK alone, 74% of clinicians referring for genetic testing report using the calculator. By increasing the number of patients with a correct MODY diagnosis the calculator leads to **better treatment and clinical care, improving outcomes for patients and saving money for the NHS**.

2. Underpinning research

People with diabetes need to know which subtype of the disease they have in order to receive the best treatment. Maturity Onset Diabetes of the Young (MODY) is distinct from the commoner Type 1 and Type 2 diabetes as it is caused by a mutation in a single gene (ie. monogenic). MODY accounts for 3.6% of young-onset diabetes **[3.1]**, amounting to more than 25,000 individuals in the UK alone. Exeter pioneered research into MODY, working in this field for over 20 years, and has led much of the work into the diagnosis, treatment, and management of this disease. A diagnosis of MODY is only confirmed by a genetic test, but this testing is expensive (about £650 per patient) so its use is limited. Therefore, approaches to help target testing at those most likely to have MODY have been needed.

2.1. Identifying patients with MODY is challenging

The vast majority of patients with MODY are misdiagnosed as Type 1 or Type 2 diabetes, with over 80% of cases estimated to be undiagnosed in the UK in 2010 **[3.2]**. Clinicians have limited experience of MODY as it is far less common than Type 1 or Type 2 diabetes and was only recently recognised (first genetic cause reported in 1992, NHS diagnostic testing did not commence until 2000). It can be difficult to distinguish from other forms of diabetes as many of the features overlap. Traditionally, MODY was defined by age at diagnosis below 25, strong family history of diabetes, and evidence of non-insulin dependence, but these criteria miss over half of MODY cases **[3.2]**.

2.2. Developing a calculator to determine the likelihood of MODY

To improve the detection of MODY in clinical practice Dr Beverley Shields led the development and validation of a probability algorithm for MODY, which incorporates clinical features such as a patient's sex, body mass index, glucose control (HbA1c), and age at diagnosis, in order to calculate the likelihood of them having MODY **[3.3]**. Combining information from multiple clinical features was highly effective in discriminating MODY from other forms of diabetes. The model was translated into an online calculator and app that enables users to input routinely available clinical characteristics and obtain an immediate probability score. This helps clinicians decide whether to send for molecular genetic testing to confirm the diagnosis.

2.3. A diagnosis of MODY influences treatment

Exeter researchers have demonstrated that patients with MODY do not require insulin injections and can successfully stop them **[3.4]**. Specific treatments are indicated depending on which MODY gene is found to be the cause. In individuals with MODY caused by mutations in the *HNF1A* gene, patients can be successfully treated with sulphonylurea tablets **[3.4]**. In a second subtype, caused by mutations in the *GCK* gene, patients can discontinue pharmacological treatment without any deterioration in control of blood sugar **[3.5]**. In addition, patients with *GCK* MODY who are not treated for 50 years have no greater risk of microvascular or macrovascular complications than people without diabetes, confirming that pharmacological treatment is unnecessary **[3.6]**.

3. References to the research

3.1. Shields BM, Shepherd M, Hudson M, McDonald TJ, Colclough K, Peters J, Knight BA, Hyde C, **Ellard S** , Pearson E, **Hattersley AT**, UNITED study team. Population-Based Assessment of a Biomarker-Based Screening Pathway to Aid Diagnosis of Monogenic Diabetes in Young-Onset Patients Diabetes Care. 2017 Aug;40(8):1017-1025. doi: 10.2337/dc17-0224.

3.2. Shields BM, Hicks S, Shepherd MH, Colclough K, **Hattersley AT**, **Ellard S**. Maturity-onset diabetes of the young (MODY): how many cases are we missing? Diabetologia. 2010;53:2504–2508. doi: 10.1007/s00125-010-1799-4.

3.3. Shields BM, McDonald TJ, **Ellard S**, Campbell MJ, Hyde C, **Hattersley AT**. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. *Diabetologia*. 2012 55(5):1265-72. doi: 10.1007/s00125-011-2418-8.

3.4. Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM**, Hattersley AT** Genetic cause of hyperglycaemia and response to treatment in diabetes. Lancet. 2003 Oct 18;362(9392):1275-81. doi: 10.1016/S0140-6736(03)14571-0.

3.5. Stride A, **Shields B**, Gill-Carey O, Chakera AJ, Colclough K, **Ellard S**, **Hattersley AT**. Cross-sectional and longitudinal studies suggest pharmacological treatment used in patients with glucokinase mutations does not alter glycaemia. *Diabetologia*. 2014 Jan;57(1):54-6. doi: 10.1007/s00125-013-3075-x.

3.6. Steele AM, **Shields BM**, Wensley KJ, Colclough K, **Ellard S**, **Hattersley AT**. Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia. *JAMA*. **2014** Jan 15;311(3):279-86. doi: 10.1001/jama.2013.283980.

4. Details of the impact

4.1 MODY probability calculator has improved diagnosis of MODY

The impact on improving diagnosis is seen in the referrals for UK genetic testing for MODY. The MODY calculator is very widely used by UK healthcare professionals with 74% of UK referrals since August 2014 stating that they have used the calculator **[5.1].** The referrals that have used the calculator are more likely to receive a positive diagnosis of MODY than those who do not use it (32% v 24%, p=0.001) **[5.1].** The number of cases of MODY diagnosed in the UK has increased threefold since the online calculator/app has been made available to clinicians and 3860 individuals have now received a genetic diagnosis.

- **MODY probability calculator is widely used in clinical practice worldwide**

The value of the MODY calculator to clinical decision making is best demonstrated by its widespread use worldwide. Exeter's online MODY calculator can be accessed for free on computers and mobile devices via the Exeter Diabetes Research website (www.diabetesgenes.org/exeter-diabetes-app) **[5.2]**. Since February 2015, the website calculator has had been used over 170,000 times, with 65% of users of the calculator being from outside the UK **[5.3]**. The MODY probability calculator has been accessed by people from 187 countries across 6 continents **[5.3].**

- **Mobile phone App incorporating the MODY probability calculator is extensively used.**

An App developed for use on mobile phones to help clinicians get rapid access to the MODY probability calculator in clinic has been extensively used. The calculator is available as part of the Diabetes Diagnostics App on both iOS and Android platforms and has been downloaded over 14,000 times in over 70 countries worldwide. **[5.3]**.

- **MODY probability calculator is a CE marked device**

The calculator constitutes a medical device and has a CE marking that demonstrates its compliance with strict regulations. CE marking involved a rigorous process of clinical evaluation, thorough software testing, user testing, and risk mitigation and thus provides reassurance of quality to healthcare providers **[5.4]**.

4.2. Recommended in national and international guidelines

The MODY calculator is widely recommended for clinical use in national and international guidelines to ensure the correct diagnosis is made for young people with diabetes. The calculator is promoted in four independent guidelines: the 2019 World Health Organisation guidelines for the Classification of Diabetes Mellitus, the 2020 Association for British Clinical Diabetologists (ABCD) Standard of Care guidelines, the 2020 American Diabetes Association's position statement on paediatric diabetes, and the 2018 International Society of Paediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines **[5.5]**.

The 2020 NHS UK National Genomic testing criteria for monogenic diabetes use the MODY calculator to identify which patients with diabetes should have NHS diagnostic genetic tests as an appropriate and accurate approach to identify patients most likely to have monogenic diabetes **[5.6]**.

4.3. Outcome for patients with MODY has improved, as a result of correct diagnoses

The significance of the MODY calculator is that it helps patients get the correct diagnosis, and this means patients get the right treatment plus other important clinical benefits:

- **Improved treatment** – The clearest improvement in treatment is to be able to stop insulin and maintain excellent glucose control in the commonest subtypes of MODY. Patients with *HNF1A*-MODY or *HNF4A*-MODY are very sensitive to sulphonylurea tablets and those diagnosed with the *GCK* subtype of MODY require no pharmacological

treatment. In a prospective observational UK wide study carried out by the Exeter team, 78% of MODY patients on insulin successfully stopped their insulin treatment with no deterioration in blood sugar control **[5.7]**.

- **Improved clinical care** –Patients diagnosed with *GCK*-MODY are at no greater risk of microvascular or macrovascular complications than the non-diabetic population, even 50 years after diagnosis and consequently they do not need any clinical follow-up **[5.8]**.
- **Family member follow-up** – As MODY is a genetic disease and runs in families, a diagnosis of one individual can help determine the cause of diabetes in other family members. A recent audit **[5.1]** identified that a median of 3 further family members are referred for genetic testing following each diagnosis of a MODY index case. Eighty six percent of these family members subsequently receive a genetic diagnosis for their own diabetes and are able to modify their treatment.

4.4. Cost savings to the NHS

The MODY calculator is saving money for the NHS by reducing the numbers of expensive inappropriate genetic tests and by helping patients get better cheaper care once a diagnosis of MODY is made.

Using the MODY calculator, which is free and easily accessible, allows a rapid assessment by a non-expert healthcare provider to assess if testing or referral to secondary care is appropriate. In the UK with the assistance of the MODY calculator the positive diagnostic rate for NHS testing is 32% almost 10x higher than the 3.6% that would be seen with non-selective testing. By targeting testing at only those at the highest probability of MODY, fewer expensive genetic tests are negative, increasing value for money. The ability of the MODY calculator to do this is why it is now incorporated into the NHS UK National Genomic testing criteria for monogenic diabetes **[5.5]**.

Targeted MODY testing using the calculator helps increase the diagnosis of monogenic diabetes which saves the NHS money by reducing the cost of treating and monitoring raised blood glucose levels and avoiding the additional expense associated with treating diabetes complications. A health economic model published in 2015 from the Exeter team, showed that a targeted testing approach based on using the MODY calculator in all patients diagnosed with diabetes under 30, could save the NHS £20-40 million due to the substantial savings from change in treatment over the lifetime of patients **[5.8]**. Correctly diagnosing *HNF1A* MODY in a patient previously thought to have Type 1 diabetes can result in considerable direct cost savings ranging from £400-£2300 (mean £660) per year, because they can be treated with tablets in place of insulin therapy. Diagnosing *GCK*-MODY results in substantial savings as treatment, monitoring and healthcare appointments are not needed for the remainder of a patient's life.

5. Sources to corroborate the impact

5.1. Genomic testing for monogenic diabetes in the UK: A three-fold increase in diagnoses since 2010, but how many are we still missing? Lewis Pang, Kevin Colclough, Maggie H R Shepherd, Ewan Pearson, **Sian Ellard**, **Andrew T Hattersley**, **Beverley Shields.**

5.2 MODY Probability calculator https://web.archive.org/web/20201013141759/https://www.diabetesgenes.org/exeter-diabetes-app/

5.3. Report of the web hits and app downloads for the MODY probability calculator, overall and split by country.

5.4. Certificate of CE marking for the Exeter Diabetes App R1

5.5. (i) World Health Organization (2019) guidelines 'Classification of diabetes mellitus'. Available

at: https://web.archive.org/web/20201013142117/https://www.who.int/publications/i/item/classification-of-diabetes-mellitus

5.5. (ii) Association for British Clinical Diabetologists (ABCD) guidelines. Children and Adolescents: Standards of Medical Care in Diabetes−2020. https://web.archive.org/web/20201218112045/https://abcd.care/sites/abcd.care/files/resources/Standards_of_Care_T1DM_ABCD_FINAL.pdf

5.5. (iii) Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association https://web.archive.org/web/20201218112128/https://care.diabetesjournals.org/content/43/Supplement_1/S163

5.5. (iv) International Society of Paediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatric Diabetes* 19 (Suppl. 27), 47–63. DOI:10.1111/pedi.12772

5.6. National Genomic Test Registry. Testing Criteria for Rare and Inherited Disease (August 2020). https://web.archive.org/web/20201218111914/https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-Inherited-Disease-Eligibility-Criteria-November-2020-21.pdf

5.7. A UK nationwide prospective study of treatment change in MODY: genetic subtype and clinical characteristics predict optimal glycaemic control after discontinuing insulin and metformin. Shepherd MH, **Shields BM**, Hudson M, Pearson ER, Hyde C, **Ellard S**, **Hattersley AT**, Patel KA; UNITED study. *Diabetalogia* (2018) Dec;61(12):2520-2527. DOI: 10.1007/s00125-018-4728-6

5.8. Recognition and Management of Individuals With Hyperglycemia Because of a Heterozygous Glucokinase Mutation. Chakera AJ, Steele AM, Gloyn AL, Shepherd MH, **Shields B**, **Ellard S**, **Hattersley AT.** *Diabetes Care*. 2015 Jul;38(7):1383-92. DOI: 10.2337/dc14-2769.

5.9. Strategies to identify individuals with monogenic diabetes: results of an economic evaluation. Peters JL, Anderson R, **Shields B**, King S, Hudson M, Shepherd M, McDonald TJ, Pearson E, **Hattersley AT**, Hyde C. *BMJ Open*. 2020 Mar 18; 10(3): e034716. DOI: 10.1136/bmjopen-2019-034716.