Title of case study: Personalised medicine in patients with Maturity Onset Diabetes of the Young

1. Summary of the impact (indicative maximum 100 words)

The diagnosis and treatment of patients with Maturity Onset Diabetes of the Young (MODY) has been revolutionised by the research of Professors Andrew Hattersley (FRS) and Sian Ellard at Exeter. Prior to this research, up to 90% of patients with MODY were misdiagnosed as having type 1 or type 2 diabetes. To address this, the team developed new tests and integrated these into routine diagnosis. They showed that patients could be stratified to achieve delivery of the most appropriate therapy and, as a result, as many as 15000 patients worldwide have now gained a better quality of life.

2. Underpinning research (indicative maximum 500 words)

MODY is a familial form of diabetes whose molecular basis was elucidated in the 1990s. Genetic testing for MODY gene mutations was initially established in Exeter by Professor Sian Ellard (appointed in 1997). Identification of a mutation in the \textit{HNF1A} gene in a patient with an unexpected response to oral sulphonylureas led Professor Andrew Hattersley (appointed in 1995) to design a randomised controlled crossover study to investigate the response to sulphonylureas in a group of patients with \textit{HNF1A} MODY and a matched group with type 2 diabetes. The results showed a 4-fold improvement in blood glucose levels in \textit{HNF1A} MODY compared to type 2 diabetes \cite{1} and provided the first example of the successful application of pharmacogenetics (i.e. personalised medicine) in diabetes. The team then showed that patients with mutations in a related gene, \textit{HNF4A}, were also sensitive to sulphonylurea treatment and, in 2007, two novel phenotypes caused by \textit{HNF4A} mutations were defined; macrosomia and neonatal hypoglycaemia \cite{2}.

Another cause of MODY is mutation within the gene encoding glucokinase (\textit{GCK}) which leads to mild, stable, hyperglycaemia from birth. Although most individuals are asymptomatic and do not require treatment, \~20\% are misdiagnosed with type 1 or 2 diabetes and treated with insulin or oral hypoglycaemic agents. The research group has recently studied the effects of pharmacological treatment on glycaemic control and found no deterioration in glucose control in patients who stopped treatment after a \textit{GCK} mutation was diagnosed \cite{3}. In a separate study the researchers showed that these patients had no increased risk of diabetic complications compared to population controls \cite{4}.

On the basis of these studies it became clear that a strong case could be made to initiate routine genetic testing in diabetes to identify patients with MODY and to stratify them according to the optimal treatment (a personalised medicine approach). However, genetic testing is expensive and selection of patients for testing is historically based on recognition of key clinical characteristics by clinicians. Therefore, the team has now developed an entirely new approach to distinguish patients likely to have MODY from the more common type 1 diabetes. This is based on the measurement of C-peptide, a by-product of insulin biosynthesis. Tim McDonald (Exeter PhD student) found that C-peptide was stable in urine samples for up to 72 hours, thereby providing a new opportunity to develop an inexpensive but informative test. In 2011 Dr Rachel Besser (Exeter PhD student) demonstrated that this test is extremely useful for discriminating patients with MODY from those...
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with type 1 diabetes [5]. Additional research demonstrated the utility of measurement of two circulating autoantibodies, GAD and IA2, to refine the selection of patients for genetic testing [4]. Prof Hattersley and Dr Bev Shields (Exeter) then developed a clinical prediction model based on logistic regression analysis of large data sets to calculate the likelihood that an individual will have MODY based on their test results [6]. The “MODY Calculator” is available online (www.diabetesgenes.org) and to October 2013 had been used 5947 times by clinicians, patients and scientists throughout the world to refine the selection of patients for genetic testing.

3. References to the research (indicative maximum of six references)
Evidence of the quality of the research is provided via a selection of highly-cited, peer reviewed, publications and by the award of external grant support.


Grants:

1) Department of Health 2002-2007 £240K (Joint PIs: Prof Hattersley, Dr Shepherd, Prof Ellard) Title: Educational model for the integration of genetics into diabetes care
2) EU FP6 2006-2010 £6M (Prof Hattersley co-applicant with 16 others) Title: EURODIA
3) NIH via the University of Washington, Seattle 2006-2010 £192K (Joint PIs: Prof Hattersley and Prof Ellard) Title: SEARCH for diabetes in youth: monogenic diabetes
4) The Diabetes Foundation 2007-2014 £110K (Joint PIs: Prof Hattersley, Dr Shepherd, Prof Ellard) Title: The integration of genetics into diabetes care: The genetic diabetes nurse project
5) Wellcome Trust/NIHR Health Challenge Innovation Fund 2010-2013 £1.6M (PI Prof Hattersley and 9 others, including Prof Ellard).Title: Using pharmacogenetics to improve treatment in young–onset diabetes (UNITED).
6) Diabetes UK 2011-2014 £123K (Joint PIs: Prof Hattersley, Prof Ellard, Dr Weedon and Dr Shields) Title: Finding novel MODY genes using exome sequencing.
4. Details of the impact (indicative maximum 750 words)

Impacts on health and welfare

1) The research has impacted dramatically on the lives of an estimated 15,000 patients throughout the world who have MODY caused by mutations in the HNF1A, HNF4A or GCK genes. Up to 90% of patients with MODY were previously misdiagnosed with type 1 or 2 diabetes and received inappropriate treatment. The team’s research has shown that, for patients with HNF1A or HNF4A mutations, oral hypoglycaemic agents should be the first pharmacological intervention. They also showed that patients with GCK mutations can stop treatment, with no detrimental effect to their glucose control or long term health.

2) For most patients their genetic diagnosis has led to a complete change in their treatment such that they no longer rely on daily insulin injections but can control their blood glucose levels with tablets (HNF1A/4A MODY) or can stop all treatment (GCK MODY). This has led to a marked improvement in patient care and their quality of life.

Patient testimony 1, Mary: “It’s so much easier to take tablets each day rather than having to inject with all the inconvenience and discomfort”

Patient testimony 2, Margaret: “Even though I take these tablets I don’t feel like a diabetic anymore”

Impacts on public services

3) Sulphonylurea therapy for HNF1A/4A MODY has been adopted internationally such that more than 10,000 patients worldwide have had their diabetes therapy changed since this discovery.

4) A genetic testing service for the UK was established in Prof Ellard’s laboratory in 2000 and has continued throughout the REF period. To October 2013, a total of 2695 UK patients had been confirmed as having MODY. Patient samples are also referred from clinics worldwide to establish an accurate molecular diagnosis of MODY.

5) Prof Ellard introduced a European Quality Assessment Scheme that has run since 2006 under the auspices of the European Molecular Genetics Quality Network (http://www.emqn.org) and by 2013, included 43 laboratories from 15 countries in Europe and Australia. The scheme tests both genotyping and clinical interpretation, providing feedback to improve the quality of genetic testing.

Impacts on practitioners

6) This research has impacted on diabetes care through revision to clinical guidelines (Prof Hattersley led the 2009 ISPAD guidelines for monogenic diabetes that include MODY) and diagnosis/classification of diabetes through Prof Hattersley’s membership of the WHO Expert Committee. Prof Ellard led the development of best practice guidelines for molecular genetic testing in MODY. Originally published in 2008, these have been adopted by laboratories throughout Europe via the European Molecular Genetics Quality Network.

7) The group’s website provides information for patients and healthcare professionals. The online MODY calculator that predicts an individual’s risk of MODY from their clinical characteristics, family history and biochemical test results is used by clinicians, scientists and patients (>6000 hits to October 2013). It provides a systematic approach to selecting those patients most likely to benefit from genetic testing, an approach that is very much lacking for most other genetic tests.

8) The discovery that HNF4A mutations can cause macrosomia and neonatal hypoglycaemia has led to the inclusion of HNF4A testing into routine genetic testing for neonatal hypoglycaemia. This is important as it highlights a high risk of developing diabetes in adolescence/early adulthood for these babies. The risk of macrosomia in future
pregnancies has clinical application in decisions regarding timing and mode of delivery to avoid obstetric complications for the baby and mother.

**Impacts on education and training**

9) The researchers recognised that dissemination of the new knowledge about genetic forms of diabetes was crucial in order to benefit the maximal number of patients. An educational initiative to train UK Diabetes Specialist Nurses to recognise and manage patients with MODY started in 2002 and, to October 2013, 47 nurses have received training about monogenic diabetes. The Genetic Diabetes Nurse (GDN) network spans England, Scotland and Wales and an on-going evaluation indicates that GDNs have a higher positive pick up rate than patients referred from elsewhere (245/649, 38% v 726/3364, 22%, p<0.0001) and increased referrals of family members for genetic testing (157/245 (64%) v 317/733(43%), p<0.0001).

**5. Sources to corroborate the impact** (indicative maximum of 10 references)

**Impacts on health and welfare**

a) “Novel diabetes therapy paves way for personalised medicine for all” The Times June 2008 [http://www.thetimes.co.uk/tto/health/article1881329.ece](http://www.thetimes.co.uk/tto/health/article1881329.ece)


**Impacts on public services**

d) The Exeter website [www.diabetesgenes.org](http://www.diabetesgenes.org) provides information on genetic testing for neonatal diabetes and has received >115000 hits, including more than 10000 in the first 6 months of 2013.

**Impacts on practitioners**


h) US National Registry for MODY: Recommendations for treating MODY – available online at: [http://monogenicdiabetes.uchicago.edu/treatment/treatment-for-mody/](http://monogenicdiabetes.uchicago.edu/treatment/treatment-for-mody/)


**Impacts on education and training**