Improving patient care in monogenic diabetes through research and education

Maggie Shepherd
RGN, PhD, Honorary Clinical Professor, University of Exeter Medical School; Lead Nurse for Research, Royal Devon and Exeter NHS Foundation Trust; NHRF 70@70 Senior Nurse Research Leader, Exeter, UK

Correspondence to:
Maggie Shepherd, RGN, PhD, Honorary Clinical Professor, University of Exeter Medical School, RILD – Level 3, Barrack Road, Exeter EX2 5DQ, UK; email: M.H.Shepherd@exeter.ac.uk

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Abstract
The 2019 Arnold Bloom lecture reviewed the progress in monogenic diabetes since the start of the service in Exeter in 1995 to present day.

The impact of a correct molecular genetic diagnosis has been profound for many patients who have been able to stop insulin injections even after many years on this treatment. However, there remain many patients who are still not correctly diagnosed and long delays between initial diabetes diagnosis and correct genetic diagnosis remain. Raising awareness of monogenic diabetes across the UK has been aided by a national network of genetic diabetes nurses (GDNs). GDNs educate health care professionals about genetic forms of diabetes and are able to provide advice to patients and their families following a positive genetic diagnosis.

Challenges in the management of monogenic diabetes still remain. Systematic approaches are being instigated to ensure correct molecular genetic diagnosis is made as close to the initial diabetes diagnosis as possible, and research is being undertaken to identify what support is needed for those receiving ‘unexpected’ genetic results. Management of monogenic diabetes pregnancy can be complex as many women with the most common forms of monogenic diabetes are best treated with sulphonylureas outside pregnancy and fetal genotype can affect birthweight so there are a number of issues to consider. Future management of pregnancy in these cases may be aided by use of cell free fetal DNA testing. Further information on monogenic diabetes can be found at www.diabetesgenes.org. Copyright © 2019 John Wiley & Sons.

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Key words
monogenic diabetes; neonatal diabetes; maturity onset diabetes of the young (MODY); genetic testing

Introduction
Prior to 1995 only the glucokinase (GCK) gene had been identified as a genetic cause of hyperglycaemia with just 31 families ascertained. The author’s initial role in Exeter involved meeting families thought to have ‘genetic forms of diabetes’, collating family histories, clinical details and collecting blood samples for the molecular genetics team at the Royal Devon and Exeter NHS Foundation Trust to search for causal genes. To date, more than 29 different genes have been identified as causing monogenic diabetes. Each of these have different clinical characteristics and many require different treatments. The key genes causing maturity onset diabetes of the young (MODY) and neonatal diabetes provide examples: individuals with GCK MODY require no treatment or follow up; those with HNF1A and HNF4A MODY are sensitive to low doses of sulphonylureas with babies inheriting the affected HNF4A gene at high risk of macrosomia (birth weight >4kg) and neonatal hypoglycaemia. Individuals with HNF1B MODY usually require insulin treatment and have renal developmental abnormalities (predominantly renal cysts). Mutations in the KCNJ11 gene are a key cause of neonatal diabetes and around 20% of these patients have learning difficulties in addition to their diabetes, which is optimally treated with high doses of sulphonylureas.

Recognition of different forms of monogenic diabetes has led to new scientific insights, but also highlighted the importance of making sure the impact for individuals and their families was understood to ensure support and information provided was appropriate. Innovative means of ensuring this new genetic knowledge was swiftly and effectively translated into clinical care were also required. This lecture used case studies to illustrate the impact of a genetic diagnosis, issues around misdiagnosis, the importance of raising awareness of monogenic diabetes, and future challenges.
**Case study**

Jen was diagnosed with ‘type 1 diabetes’ as a baby. She presented in diabetic ketoacidosis. She is now 43 years of age and runs a transport business with her husband. In 2015, a genetic diabetes nurse (GDN) was appointed in the North West of England and, as part of her role, presented a talk on MODY and neonatal diabetes to health care professionals in her region. As a direct consequence of this talk, Jen’s consultant, who was in the audience, realised the significance of Jen’s diabetes diagnosis below the age of six months and referred her for genetic testing. The Exeter molecular genetic team identified Jen had a mutation in the KCNJ11 gene which caused her diabetes. As a result of this diagnosis Jen was able to stop all her insulin and transfer to high-dose glibenclamide (35mg bd), she improved her HbA1c from 64mmol/mol to 53mmol/mol, was able to lose 16kg in weight (now 61kg), her pre-proliferative retinopathy reversed and the DVLA restrictions were lifted. Jen has described the impact of getting the correct genetic diagnosis. ‘I’m so happy to stop insulin after 43 years on this treatment. I feel so much better. My blood sugar is more stable and I’ve managed to lose weight, something I was never able to do on insulin. I’ve also gained my HGV licence, something I never dreamed I’d be able to do.’

This case study powerfully illustrates the impact of the correct molecular genetic diagnosis, the issues of misdiagnosis and the importance of raising awareness of monogenic diabetes.

**Impact of a genetic diagnosis HNF1A/HNF4A MODY**

Individuals with HNF1A MODY are sensitive to low doses of sulphonylureas; however, the majority are often assumed to have type 1 diabetes due to the young age at presentation. For example, Dan was diagnosed at 16 years of age and despite his mother drawing out a family history indicating three generations of autosomal dominantly inherited diabetes they were told: ‘We’ll never take him off insulin so what’s the point in testing?’ Once Dan finally underwent genetic testing, HNF1A MODY was confirmed which meant he was able to stop all insulin injections and transfer to just 20mg of gliclazide and achieve an HbA1c of 44mmol/mol. The following quotation clearly illustrates how Dan initially found it hard to believe he did not need his insulin injections. ‘It was May 2005, the “big day” where I just didn’t take insulin at all. I tested my blood 48 times over 24 hours. I can’t emphasise enough how different it’s been, it’s fantastic.’

Stopping insulin injections contradicted previous advice and beliefs in those who had originally been told they had type 1 diabetes. Many individuals with HNF1A/HNF4A MODY were initially unsure about transferring from insulin to tablets: ‘I was anxious about stopping insulin. I was told I needed it to survive but it’s fantastic not to have to inject and the worry of hypos has gone,’ (Thomas). For those who had been on insulin for many years these concerns persisted for some time: ‘I carried my insulin pen around for 6 months. One day I realised it had expired and I finally threw it away,’ (Mary). This gave clear evidence for the need to provide support to patients transferring from insulin to tablets following a positive genetic diagnosis. However, not all patients chose to stop their insulin treatment following a positive genetic diagnosis and in some cases related to the duration of that treatment: ‘I was afraid of the tablets. I’m dependent on the safety net of insulin. I feel in control with insulin. I think mentally I wasn’t ready to stop injecting.’ (Jean).

Early data indicated that those with HNF1A/HNF4A MODY could successfully transfer from insulin to sulphonylureas, but the first prospective, observational study of treatment change post genetic test across the UK indicated that, although all those with GCK MODY could stop all treatment with no deterioration in HbA1c, of the 36/44 with HNF1A/HNF4A MODY who changed treatment only 21 of them (58%) remained on either diet or sulphonylurea alone at two-year follow up. Focusing on these 36 individuals with HNF1A/HNF4A MODY in more detail indicated that diabetes duration predicted success of sulphonylurea treatment (Figure 1). This reinforces the importance of an early, correct genetic diagnosis as HNF1A/HNF4A MODY are characterised by a progressive beta-cell dysfunction. Although treatment change can be considered at any duration of diabetes, it is important to recognise that those with a longer duration are less likely to be successful on sulphonylurea alone and background insulin may be needed in addition to sulphonylureas. Those with a higher BMI or higher HbA1c at time of genetic test were also less likely to be successful on sulphonylurea treatment alone.

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**Figure 1.** Diabetes duration predicts success of sulphonylurea treatment in HNF1A/HNF4A MODY at 2-year follow up

<table>
<thead>
<tr>
<th>Diabetes duration (no.) of cohort</th>
<th>Diet or SU only</th>
<th>SU + other OHA</th>
<th>Insulin + SU or other OHA</th>
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<tr>
<td>0–4 years (n=12)</td>
<td>20%</td>
<td>25%</td>
<td>55%</td>
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<td>4.1–18 years (n=12)</td>
<td>70%</td>
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<tr>
<td>&gt;18 years (n=12)</td>
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OHA = oral hypoglycaemic agent; SU = sulphonylurea.
type 1 diabetes, due to the young are initially misdiagnosed as either the vast majority, 80% or more, less than 30 years of age. 3.6% of UK diabetes diagnosed at Monogenic diabetes accounts for Misdiagnosis clinically appear less favourable this cations of a genetic diagnosis may implications of a genetic diagnosis may explain other features in addition to cases, monogenic diagnosis can be helpful even when treatment A positive genetic diagnosis can also Other forms of monogenic diabetes A positive genetic diagnosis can also be helpful even when treatment change may not be possible. In some cases, monogenic diagnosis can explain other features in addition to diabetes. For example, in individuals with HNF1B MODY renal cysts might not previously have been considered to have the same genetic cause as the diabetes, and even though the implications of a genetic diagnosis may clinically appear less favourable this information may still be regarded positively by families. Misdiagnosis Monogenic diabetes accounts for 3.6% of UK diabetes diagnosed at less than 50 years of age. However, the vast majority, 80% or more, are initially misdiagnosed as either type 1 diabetes, due to the young age at diagnosis, or type 2 diabetes, and therefore inappropriately managed. On average there is a 13-year delay from the initial diabetes diagnosis to the correct molecular diagnosis. Early work from the Exeter team indicated that diabetes health care professionals were unfamiliar with the key characteristics of MODY and may have failed to recognise the condition as they were unfamiliar with the importance of family history: ‘I’ve no recollection of thinking about the rest of the family at all’ (diabetes registrar), ‘I don’t understand what I’m looking for in the family tree’ (diabetes specialist nurse). It was clear that widespread education was needed to increase recognition of monogenic diabetes across the UK. Raising awareness of monogenic diabetes through a national network of genetic diabetes nurses In 2002, the Exeter monogenic diabetes team initiated the national genetic diabetes nurse (GDN) project (formerly known as the MODY link nurses project) to raise awareness of monogenic diabetes across the UK. This initiative trains diabetes specialist nurses (DSNs) to become regional experts who increase recognition of monogenic diabetes through presentations to other health care professionals across their region. They liaise with local diabetes teams to aid differential diagnosis and advise on which patients may benefit from genetic testing. Following a positive genetic diagnosis they are also able to provide advice regarding treatment change and family follow up. GDNs attend an initial two-day basic training in monogenic diabetes followed by ongoing specialised training three times a year. The GDNs continue to work as DSNs but are seconded to the project 3.5 hours a week. GDNs have now established specialist monogenic clinics in 10 centres nationwide and have given >1000 presentations to more than 13 200 health care professionals across the UK who may otherwise not have been familiar with monogenic diabetes; 97% of these presentations have been rated as very good or excellent for educational quality. This model of training specialist nurses in genetics has been highlighted by Health Education England as a model for the integration of genetics into clinical care in other disease areas.

Diagnosis of monogenic diabetes is increasing, with over 4000 individuals now confirmed with a monogenic cause of their diabetes (Figure 2). In the regions with a GDN in post there are increased rates of referrals of new cases and more family members are followed up, compared to areas without a GDN. The GDN role is hugely rewarding for DSNs who are able to gain new skills and knowledge and share these skills with other health care professionals. All GDNs have identified cases of monogenic diabetes within their own clinics and across their regions following training, leading to improvements in treatment and quality of life.

Future challenges There remain a number of challenges in monogenic diabetes and this lecture focused on three key areas: (i) Identifying monogenic diabetes at diagnosis, (ii) ‘Unexpected’ genetic results, and (iii) Pregnancy management.

Identifying monogenic diabetes at diagnosis The UNITED study identified that 2.5% of the UK paediatric population have monogenic diabetes. The systematic screening used within that study provided a practical approach to identify patients for genetic testing (who were c-peptide positive and islet autoantibody negative) and one
in four of these paediatric patients were confirmed with monogenic diabetes. However, identifying the correct diabetes type at initial diabetes diagnosis is important to prevent unnecessary insulin treatment. A new study starting shortly within the South West of England will aim to recruit all newly-diagnosed children with diabetes and test them for three islet autoantibodies (GAD, IA2 and ZnT8). Those who are negative to all three islet autoantibodies will proceed to targeted next generation sequencing of all genes known to cause monogenic diabetes, enabling identification within three months of the initial diabetes diagnosis.

### ‘Unexpected’ genetic results

Increasing genetic technology has resulted in the possibility of targeted next generation sequencing (tNGS), testing for all genes known to cause monogenic diabetes in a single test.\(^2\) Previously, a decision regarding which individual gene to test would be based on an individual’s clinical characteristics; for example, those with a 2–3 generation family history of diabetes with at least one family member diagnosed below 25 years of age, a low renal threshold for glucose and evidence of sulphonlurea sensitivity may have been tested for mutations in the HNF1A gene. However, a move to a more systematic approach to testing, through use of islet autoantibodies and c-peptide in combination with use of tNGS has led to identification of what might be described as ‘unexpected’ results in some patients who were previously thought to have ‘diabetes only’.

For example, Oliver was diagnosed at 29 years of age with an HbA1c of 15.4mmol/mol, he was slim, BMI 23kg/m² and he had no family history of diabetes and was therefore assumed to have type 1 diabetes and started on insulin. However, through a process of systematic testing Oliver was found to be negative to GAD, IA2 and ZnT8 and had significant endogenous insulin, 2.2nmol/mol five years post diagnosis and so underwent tNGS. This identified that Oliver had an HNF1B whole gene deletion which explained his diabetes and autism, the latter being a feature of those with whole gene deletions.\(^24\) As HNF1B is known to cause renal developmental abnormalities,\(^7\) Oliver subsequently underwent a renal ultrasound which identified he had multiple cysts in his left kidney. Those with HNF1B MODY usually have a small pancreas and so Oliver had a faecal elastase test which confirmed moderate pancreatic insufficiency and he was started on Creon. Both of Oliver’s parents were tested and this indicated neither had the same gene deletion, indicating this was ‘de novo’ in Oliver. The consequence of this ‘unexpected’ genetic result has consequences for Oliver’s own future health; he currently has normal renal function, but the renal phenotype in HNF1B MODY is variable, ranging from normal renal function to individuals who have needed dialysis and transplant. This genetic result also has an impact if Oliver decides to start a family of his own as this is an autosomal dominant condition and so each child would have a 50% chance of inheriting the same genetic change.

Identifying ‘unexpected’ genetic results has the potential to uncover a number of other clinical features depending on the gene identified; research is being undertaken to identify the best way to support patients and their families receiving such results which can impact on their own and their children’s health.

### Pregnancy management

There are many issues to consider when managing pregnancy in individuals with monogenic diabetes. In each case there is a 50% chance of the offspring inheriting the genetic mutation, and fetal genotype affects birthweight in a number of different types of monogenic diabetes, e.g. HNF4A, GCK, HNF1B MODY and KCNJ11 neonatal diabetes, so specialist advice is required. In addition, many women with monogenic diabetes are optimally treated with sulphonylureas outside pregnancy (e.g. HNF1A, HNF4A MODY and KCNJ11 neonatal diabetes) but, as glibenclamide crosses the placenta and birthweight can be affected in HNF4A MODY and KCNJ11 neonatal diabetes, treatment of the mother requires careful consideration.\(^25\)

Usually, fetal genotype is only known if chorionic villus sampling or amniocentesis has been performed for another reason but cell free fetal DNA (cffDNA) testing, which simply requires a venous sample from the mother during pregnancy, has the potential to aid pregnancy management by identifying the fetal genotype during pregnancy with >99% accuracy.\(^26\) Currently, this testing is available on a research basis when the mother is affected, but the aim is to introduce this as a clinical test within the next 12 months.

Use of cffDNA testing can currently aid management of pregnancy in monogenic diabetes when the father is affected, in cases where birthweight may be affected by fetal genotype. For example, a family where the father has HNF4A MODY was referred to the Exeter team by their local GDN when his wife became pregnant. Venous samples were taken from the unaffected mother at 12 and 20 weeks gestation and it was identified that the fetus had inherited the affected HNF4A gene. Knowing this result in advance enabled the local team to manage the pregnancy as high risk for macrosomia and neonatal hypoglycaemia, and early delivery was arranged with a paediatrician present. The baby was born at 38 weeks gestation before macrosomia developed, with a birthweight of 3.25kg but still had a low blood glucose (<2.0mmol/L) and required intravenous glucose, transfer to neonatal intensive care and ongoing treatment with diazoxide and chlorothiazide for the first eight months of life. The family felt well prepared for what happened and reassured that necessary steps were taken to ensure a safe delivery and follow up during the neonatal period.

The Exeter monogenic diabetes team are happy to be contacted directly regarding management of pregnancy in monogenic diabetes.

### Conclusions

This lecture focused on four key areas and illustrated how the correct genetic diagnosis can transform the lives of individuals, particularly when it is possible to stop insulin treatment. Misdiagnosis of monogenic diabetes is common but recognition is improving and systematic approaches including use of comprehensive islet autoantibody testing can help ensure that
the correct diagnosis is made closer to the initial diabetes diagnosis. Caution is needed when changing treatment in those with HNF1A/HNF4A MODY if they have a long duration of diabetes or high BMI or high HbA1c at time of genetic test as they are likely to need basal insulin in combination with a sulphonylurea.

The national network of GDNs has successfully raised awareness of monogenic diabetes and provides regional support to diabetes health care professionals and patients with monogenic diabetes. There remain a number of challenges in monogenic diabetes where further research is needed. More information about monogenic diabetes is available via www.diabetesgenes.org, and details of the national network of GDNs and a two-day training course on monogenic diabetes can be found via the ‘training’ link on the website.

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Declaration of interests

There are no conflicts of interest declared.

References