Monogenic diabetes: importance of genetic testing

Rubena Ali Malik
Sabana Shaikh

Family Medicine Consultant, Primary Health Care Corporation, Qatar

Correspondence:
Dr. Rubena Ali Malik
Dr. Sabana Shaikh
Email: rmalik@phcc.gov.qa, sabanashaikh1234@gmail.com

Received: September 2020; Accepted:October 2020; Published: November 1, 2020.
Citation: Rubena Ali Malik, Sabana Shaikh. Monogenic diabetes: importance of genetic testing. World Family Medicine. 2020; 18(10): 78-86 DOI: 10.5742/MEWFM.2020.93893

Abstract

There are various forms of monogenic diabetes and these include neonatal diabetes mellitus, maturity-onset diabetes of the young (MODY), mitochondrial diabetes, and rare diabetes-associated syndromic diseases. Single gene forms of diabetes represent an uncommon heterogeneous group of conditions mainly characterized by functional defects of pancreatic beta cells with consequential moderate to severe hyperglycemia.

The body of the article will focus mainly on MODY. The classic presentation of MODY includes non-ketotic noninsulin-dependent diabetes with diagnosis before the age of 25 and with an affected parent. According to various studies, there is a substantial number of individuals with a confirmed genetic diagnosis of MODY that does not fit the classic clinical description and approximately > 80% of MODY cases are not diagnosed by molecular testing. Mutations in GCK, HNF1A, and HNF4A are the most common causes of MODY.

Differences in screening recommendations for diabetes varies across countries, but the reported prevalence of these causes in young people collectively accounts for almost 85–90% of all MODY cases. Incidence has increased in recent years due to greater understanding and wider accessibility of genetic testing. Unfortunately, there are no statistics on the incidence of monogenic diabetes in Saudi Arabia or other Middle Eastern countries, compared to their Western counterparts.

Diagnosis includes the use of a probability calculator and then genetic testing. There is much debate on availability and cost effectiveness of genetic testing. Accurate genetic diagnosis impacts treatment in the most common types of monogenic diabetes, including the use of sulfonylureas in place of insulin or other glucose-lowering agents, or discontinuing pharmacologic treatment altogether. However, it allows for precision medicine which in turn saves money, gives better quality of life to patients and postpones onset of diabetic complications.

There are plenty of advantages to genetic testing considering the increasing incidence of diabetes in young people and how the wrong type of treatment can cause physical and psychological impact.

Key words: monogenic diabetes,
maturity onset diabetes of the young (MODY),
mitochondrial diabetes,
diabetes-associated syndromic diseases

Introduction

Monogenic diabetes was first defined in mainstream literature by Tattersall and Fajans in 1975. They described it as a series of non-insulin dependent diabetes with autosomal dominant inheritance in young adults, as MODY. Further criteria mentioned was it occurs in early age, commonly less than 25 years, insulin independence for at least 5 years from diagnosis and absence of ketosis at any time were the clinical diagnostic criteria for MODY.

MODY is the most common type of monogenic diabetes and involves beta-cell dysfunction. There are some extra-pancreatic features that help as indicators of specific subtypes of MODY: presence of macrosomia and neonatal hypoglycemia in subtype HNF4A–MODY and renal cysts in subtype HNF1B-MODY. Other subtypes are categorized by stable levels of blood glucose throughout the patient's lifetime, others by a progressive waning of insulin secretion and poor glucose control. Additionally, patients with some subtypes are prone to develop micro- and macrovascular complications whereas those with other subtypes do not and it is this characteristic which drives the decision to treat or not, early in childhood. Intriguingly, the observable glycemic traits can vary among carriers of the same mutations and even within the same family generation.

Greater than 80% of patients with MODY are incorrectly diagnosed with type 1 and type 2 diabetes at presentation, with patients experiencing a delay of 12 years from the time of receiving a diabetes diagnosis to receiving a MODY diagnosis in a UK report. To prevent onset and progression of microvascular complications we need to achieve target glycemic control hence the need to detect at early age.

Maturity Onset Diabetes of the Young (MODY)

MODY is an uncommon form of diabetes with specific features that distinguish it from type 1 and type 2 diabetes and is caused by a defect in a single gene, is clinically heterogenous and characterized by impaired insulin secretion. MODY affects 1–6% of patients with diabetes. Primarily autosomal dominant, but a de novo mutation should be considered in those patients without a family history of diabetes but with clinical and biochemical findings highly indicative of MODY. There are 14 known subtypes of MODY, and mutations in three genes (HNF1A, HNF4A, GCK) which account for about 95% of all MODY cases with a detection rate that varies among different study populations.

At present, three main criteria define the disease: mild hyperglycemia or overt diabetes in at least three consecutive generations; onset usually before the age of 25 years; absence of islet autoantibodies and lack of characteristics of type 2 diabetes (i.e., insulin resistance, obesity).

Mutations in the genes causes β-cell dysfunction, which leads to the development of types of MODY described in Figure 3.

Focus must be placed on correct diagnosis to ensure a strengthened link to important treatment benefits, such as a more accurate prognosis of the risk of complications, avoidance of stigma and limitations to the patients, and appropriate genetic counseling for family members, especially children, but most importantly it directs the choice of the best treatment. The personalizing of medical treatment to the characteristics of each patient has been termed "Precision Medicine". Precision medicine refers to the use of combined knowledge of a person to predict susceptibility to a specific disease identifying etiologic mechanisms, prognosis of the disease and response to a specific treatment. Benefits in being able to determine with some degree of accuracy the most appropriate treatment includes cost-saving and the avoidance of ineffective therapy with its possible side effects. Specifically, for diabetic patients, precision medicine refers to determining the most appropriate method for self-monitoring blood glucose and avoiding the burden of insulin injections when unnecessary.

Misdiagnosis of type 1 and 2 diabetes can be avoided if clinicians are able to establish a correct molecular diagnosis and with progress now in genetic testing, assisted by the development of new techniques (i.e., Next Generation Sequencing) and increased accessibility to genetic testing facilities they can achieve this more accurately. MODY can be diagnosed by direct sequencing with up to 100% sensitivity. Testing is increasing throughout the world and most developed countries have at least one academic, health service or commercial laboratory providing testing. There are of course regions with limited resources but there needs to be a target population for necessary molecular genetic testing to improve detection rates. There are various algorithms that aid molecular diagnosis by using clinical and laboratory parameters to highlight individual candidates. Interestingly, one developed model revealed that a useful discriminator between MODY and T2DM is age of diagnosis below 30 years. Also, a family history of diabetes increased the probability of MODY diagnosis by 23 times in those who had been initially categorized as T1DM.

The University of Exeter has created a calculator to assess the probability of MODY and it is currently available online. The Exeter laboratory have gone from approximately 50 patients being diagnosed with MODY in 1996 to approximately 5,000 diagnoses in 2016. It can be a helpful tool to learn more about the factors that can influence a suspicion of monogenic diabetes. The tool calculates a Positive Predictive Value (PPV) which varies substantially based on the BMI of the patient, current insulin treatment, and if the patient has an affected parent. The only criticism is that this tool was created based on a primarily Caucasian European population hence it may not be as useful for patients from ethnic minorities who may have shifted BMI curves or for the possibility of a de novo mutation.

A urine C-peptide creatinine ratio (UCPCR) test can be useful in distinguishing type 1 diabetes from a monogenic form of diabetes but does not distinguish from type 2 diabetes. However, at this time it is used mainly for research purposes and this method is less invasive than blood c-peptide testing.

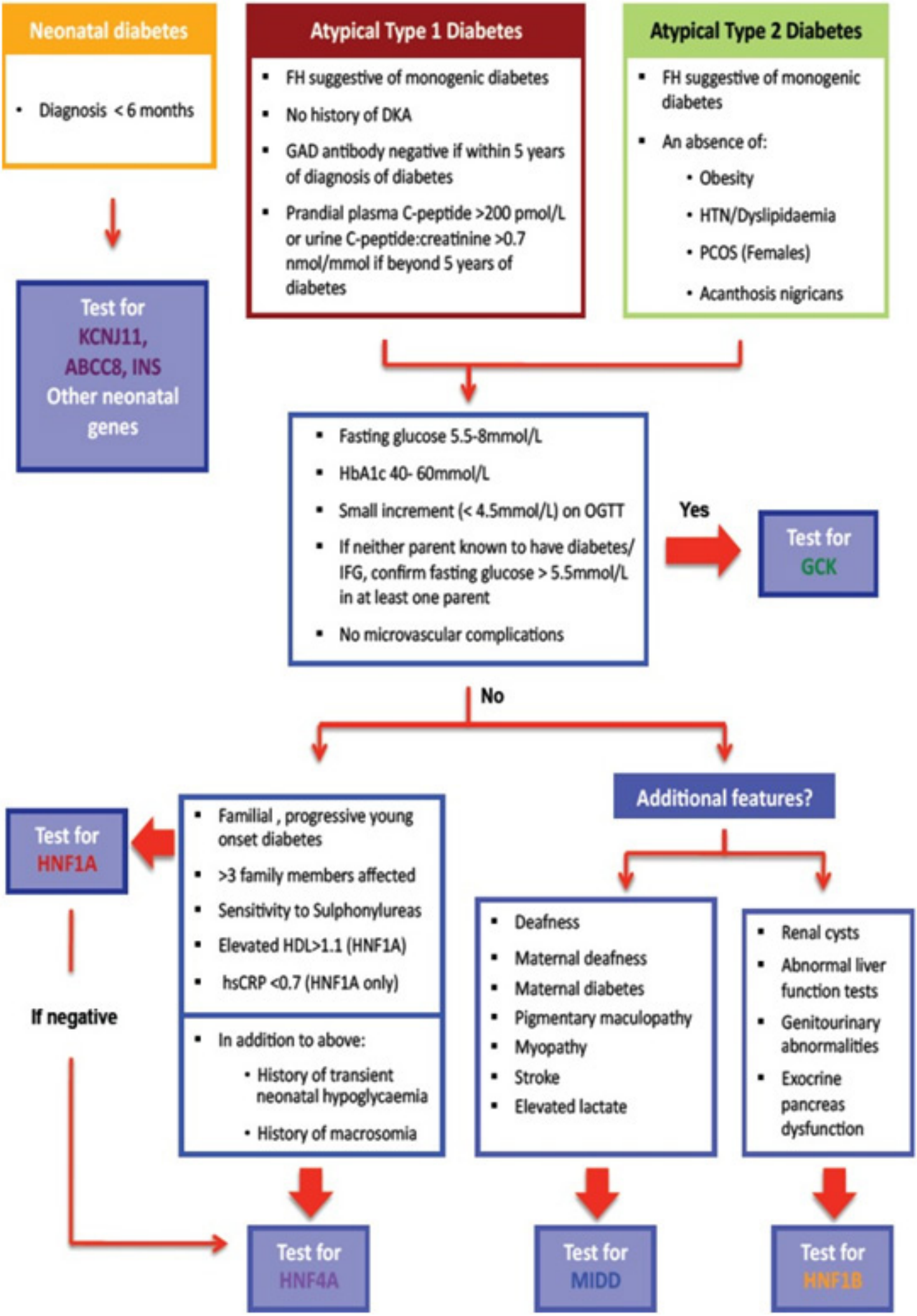
Figure 1: Characteristic phenotypes of the commonly encountered diabetes subtypes, illustrating clinically useful differences between type 1, 2 and monogenic diabetes.

Characteristic Phenotypes of the commonly encountered diabetes subtypes, illustrating the clinically useful differences between type 1 and type 2 diabetes, and monogenic forms of diabetes.

Features associated with diabetes	Type 1 diabetes	Young onset Type 2 diabetes	Monogenic diabetes					
			GCK *	HNF1A #	HNF4A #	HNF1B #	Neonatal diabetes	MIDD ≠
DKA	Yes	No	No	No ∞	No ∞	No	Yes	Yes/No
Parent affected	2%–4%	Yes	Yes =	Yes	Yes	Yes	variable	Mother
Age of onset	6 months to adulthood	Adolescence and young adulthood	Birth	Teens to young adulthood	Teens to young adulthood	Teens to young adulthood	<6 months	Young adulthood
Obesity	Population frequency	Increased frequency	Population frequency	Population frequency	Population frequency	Population frequency	Population frequency	Rare
Glycaemic pattern	Acute General hyperglycaemia	Progressive hyperglycaemia	Stable, mild fasting glycaemia	Post-prandial hyperglycaemia initially, progressing to general hyperglycemia	Post-prandial hyperglycaemia initially, progressing to general hyperglycemia	Post-prandial hyperglycaemia initially Progressing to general hyperglycemia	Acute General hyperglycaemia	Variable dysglycaemic pattern either acute or slowly progressive
β cell antibodies ¥	Yes	No	No	No	No	No	No	No
C-peptide ¥	Very low/Absent (>5 years)	Raised/Normal	Normal	Low but Detectable	Low but Detectable	Low but Detectable	Absent but detectable once treated with SU	Low but detectable
hsCRP	Normal	High/High normal	Normal	Very low	Normal	Normal	Normal	Normal
Additional clinical features	Other autoimmune disease (Thyroid, coeliac etc.)	Dyslipidaemia, PCOS, Hypertension, Acanthosis Nigricans	Absence of microvascular and macrovascular complications	Low renal threshold for glucose in early stages of diabetes	Macrosomia and transient neonatal hypoglycaemia	High renal involvement e.g., cysts etc.	Transient in 50% of cases, although may relapse	Deafness, short stature, macular dystrophy

* = Glucokinase; # = Hepatocyte nuclear factor; ≠ = Mitochondrial diabetes and deafness; ∞ = Excellent responses to Sulphonylurea therapy are commonly noted; = = whilst the autosomal dominant inheritance pattern requires that at least one parent must be a carrier of the mutated gene, GCK mutations are frequently subclinical and an absence of a known family history of diabetes is not uncommon; ± = β cell antibodies are detected in approximately 90% of patients with type 1 diabetes at onset of dysglycaemia although the sensitivity declines later in the disease. Absent autoantibodies >5 years following onset are commonly seen in confirmed type 1 diabetes. Conversely, a small number of patients with type 2 diabetes and monogenic diabetes will have one or more detectable β cell antibodies; ¥ = PCOS = Polycystic ovary syndrome.

Figure 2: Diagnostic algorithm for assessment of suspected monogenic diabetes diagnosed at <35 years old



Clinical characteristics of maturity onset diabetes of the young (MODY) genetic subtypes

MODY type	Gene name (locus)	Protein function	Prevalence	Other features	Treatment	OMIM*
MODY 1	*HNF4A* (20ql2)	Transcription factor	5–10%	Neonatal hyperinsulinemia and hypoglycemia with associated macrosomria, low serum levels of cholesterol	Sensitive to sulfonylureas	125850, 600281
MODY 2	*GCK* (7pl3)	Glycolytic enzymre	30–60%	Mild fasting hyperglycemia throughout life, often asymptomatic, gestational diabetes, low birth weight (with unaffected mother)	No treatment outside of pregnancy	138079,125851
MODY 3	*HNFIA* (12q24.2)	Transcription factor	30–60%	Glycosuria	Sensitive to sulfonylureas	600496,142410
MODY 4	*PDXI* (13ql2.1)	Transcription factor	<1%	Homozygote: pancreatic agenesis	Diet, OAD, or insulin	606392,600733
MODY 5	*HNFIB* (17q21)	Transcription factor	5–10%	Diabetes in association with renal and genito-urinary abnomralities	Insulin	137920, 189907
MODY 6	*NEUROD I* (2q31.3)	Transcription factor	<1%	Obesity and insulin resistance	OAD or insulin	606394, 601724
MODY 7	*KLF11* (2p25)	Transcription factor	<1%	Impaired glucose tolerance to overt diabetes	OAD or insulin	603301,610508
MODY 8	*CEL* (9p34)	Lipase enzymre	< 1%	Diabetes and pancreatic exocrine. Endocrine deficiency	OAD or insulin	114840,609812
MODY 9	*PAX4* (7q32)	Transcription factor	< 1%	Ketosis prone diabetes	Diet, OAD, or insulin	167413,612225
MODY 10	*INS* (llpl5.5)	Homrone	<1%	May result in neonatal diabetes, antibody-negative diabetes, and MODY	OAD or insulin	613370, 176730
MODY 11	*BLK (8p23)*	Tyrosine kinase	<1%	Obesity common	Diet, OAD, or insulin	191305, 613375
MODY 12	*ABCC8* (llpl5.1)	SURI (KATP channel regulatory subunit)	<1%	Usually associated with neonatal diabetes, rare cause of MODY	Sensitive to sulfonylureas	600509
MODY 13	*KCNJ11* (1 lp 15.13	Kir6.2 (KATP channel regulatory subunit)	<1%	Usually associated with neonatal diabetes, rare cause of MODY	Sensitive to sulfonylureas	616329, 600937
MODY 14	*APPL1* (3pl4.3)	Serine\threonine kinase	<1%	Adult-onset diabetes	Diet, OAD, or insulin	616511, 604299

ABCC8 ATP-binding cassette, subfamily C (CFTR/MRP), member 8, *APPL1* adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1, *BLK* B lymphocyte kinase, *CEL* carboxyl ester lipase enzyme, *GCK* glucokinase, *HNF1A* hepatocyte nuclear factor-lα, *HNF1B* hepatocyte nuclear factor-lβ, *FLNF4A* hepatocyte nuclear factor-4α, *INS* preproinsulin, *KATP* ATP-sensitive potassium channel, *KCNJ11* potassium channel, inwardly rectifying subfamily J, member 11, *KLF11* Kriippel-like factor 11, *NEUROD 1* neurogenic differentiation factor 1, *OAD* oral anti-diabetic, *PAX4* paired box gene 4, *PDX1* pancreas/duodenum homeobox protein 1, *SURI* sulfonylurea receptor 1

*The Online Mendelian Inheritance in Man (OMIM; http://omim.org) numbers indicate the descriptive entry of the phenotype and/or gene

Figure 3: Classical characteristics of MODY genetic subtypes.

Figure 4. Molecular genetics-based approach for precision diabetes in monogenic and type 2 diabetes

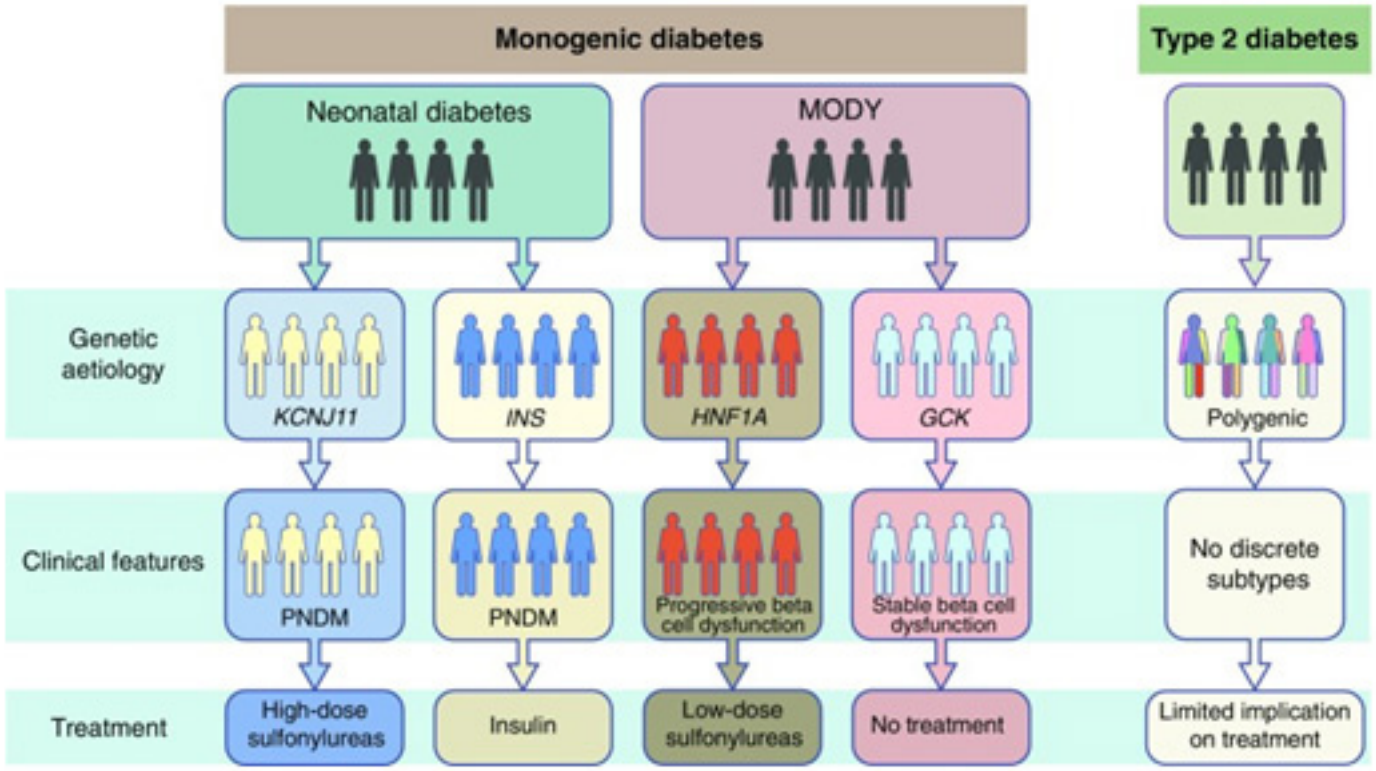
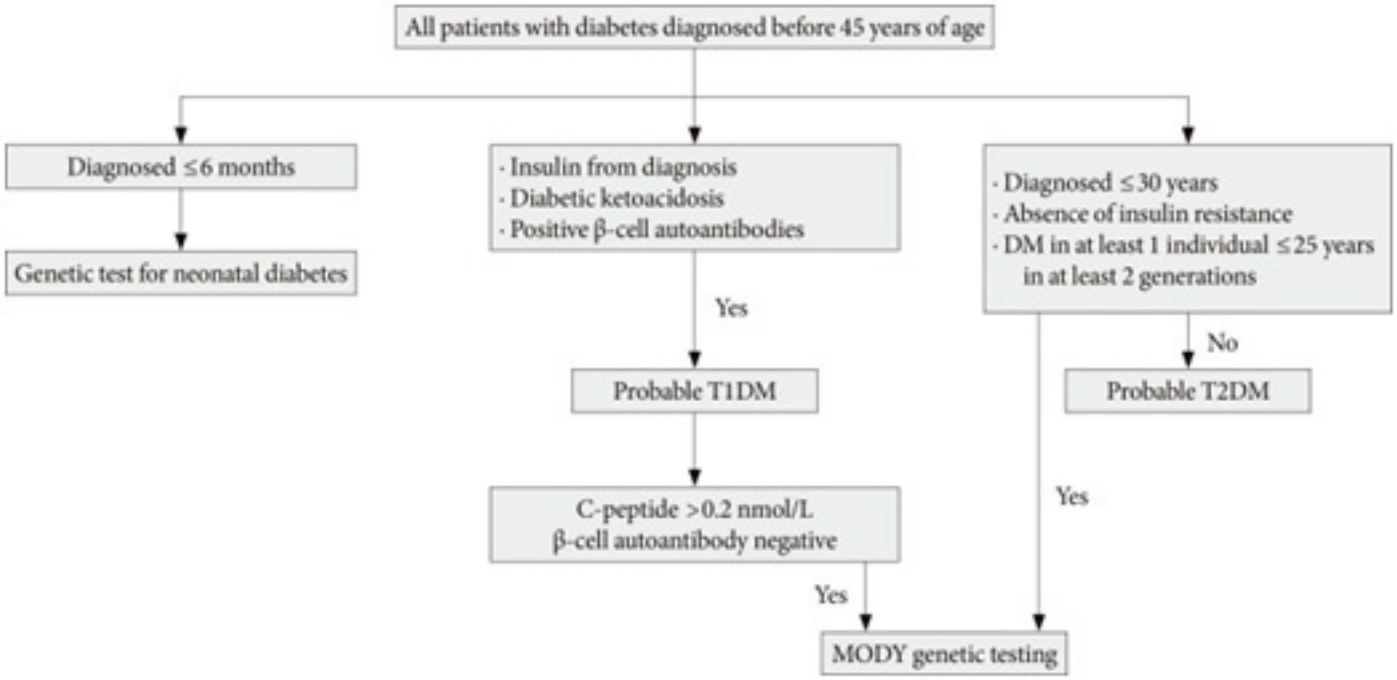


Figure 5. Diagnostic algorithm for MODY, T1DM AND T2DM



Genetic testing can be not only expensive, available in only specialized laboratories but also time consuming. Focus needs to be on Diabetologists to increase their expertise in this area, and suspected cases should be referred to a specialist in monogenic diabetes or a clinical geneticist working in this field to maximize the diagnostic yields. Results from recent simulation modeling suggest that testing for MODY genes is cost-effective in targeted individuals.

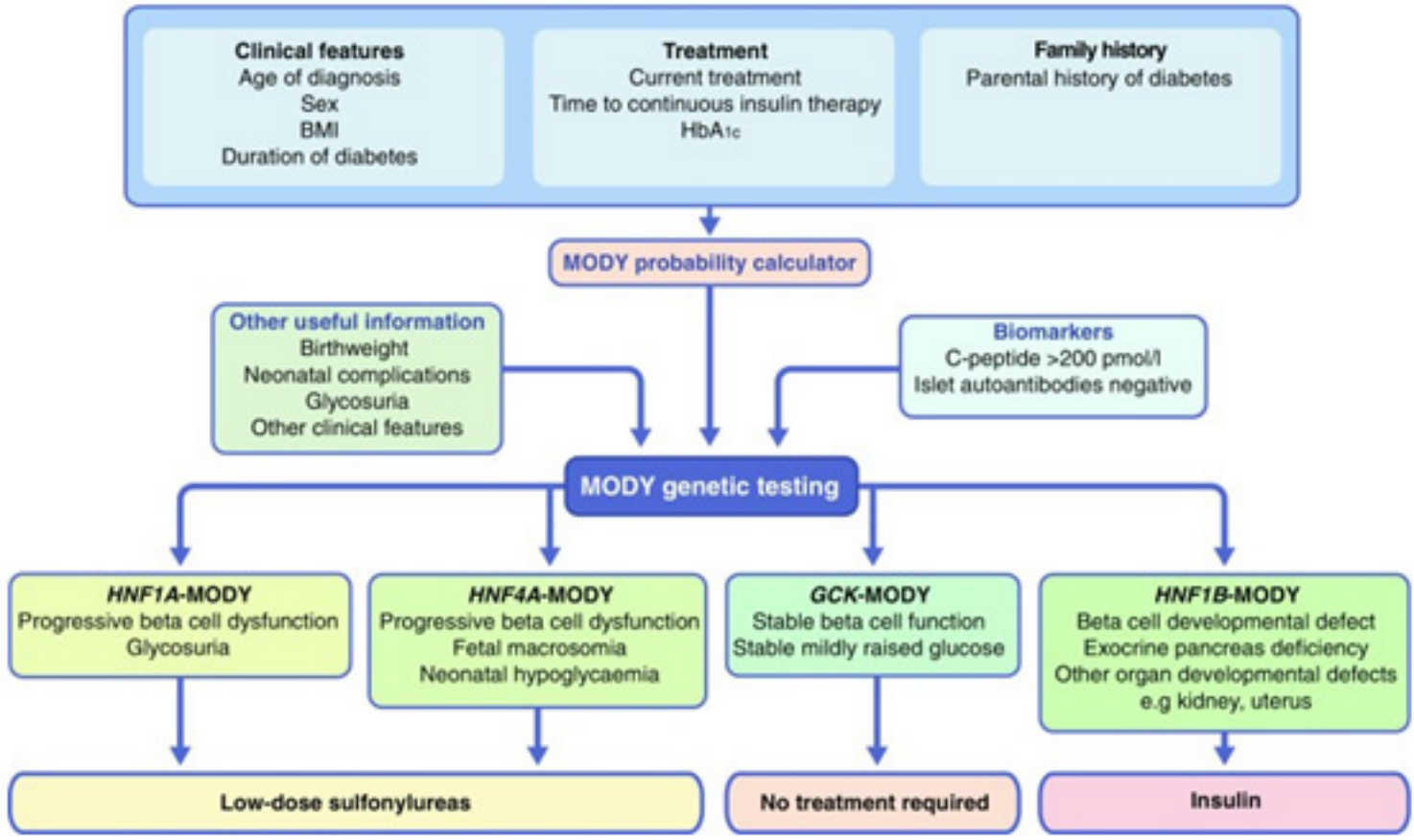
Results from the UK suggest that within the context of the National Health Service (NHS), the additional costs of genetically testing (a relatively large number of) individuals are likely to be offset by the lifetime savings from the subsequent treatment changes in a very small proportion of individuals. However, lifetime cost savings are approximately only £100–£200 (UK). If we assume around 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 have applied beneficial strategies, between £20 million and £40 million savings are possible. To be able to apply these findings to other populations the cost of the testing especially will need to be updated. If the genetic test costs are significantly higher than predicted, then it is unclear whether the Clinical Prediction Model Testing and Biomarker Testing strategies could be considered cost saving, or even cost neutral. However, further collection of treatment patterns, home blood glucose monitoring frequency, HbA1c and quality of life data are needed to aid model development including the incident cohort. Once feasibility has improved to detect those with monogenic diabetes only then can evaluation for effectiveness and cost effectiveness be done.

Treatment options

Personalized medicine approach can be implemented with earlier detection of monogenic diabetes in children and adolescents. In young people there is an accumulation of long duration of hyperglycemia and suboptimal control. Also, the aggressive nature of certain mutations makes it more prone for them to develop disease complications.

Target treatment to a single genetic mutation has shown to result in improvements in glycemic control, fewer diabetic complications, and decreased cost as well as burden of treatment. Regarding surveillance of complications and associated extra-pancreatic disorders and identification of affected and at-risk family members it is imperative to differentiate between monogenic diabetes and type 1 or type 2 diabetes.

Figure 6. Identification, important clinical features and treatment implications for common subtypes of MODY



Precision diabetes in MODY patients has an important clinical feature which is the differential treatment response in discrete genetic groups.

• GCK-MODY patients do not require any treatment and there is no response to treatment.
• HNF1A- and HNF4A-MODY patients can be treated with low-dose sulfonylureas. Additional treatment if required: dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonist and insulin in addition to sulfonylureas.
• HNF1B-MODY requires insulin treatment as response to oral hypoglycemics is limited.

There can be large implications on the differences in treatment response in MODY. The best example is in HNF1A-MODY where there is enhanced sensitivity to sulfonylureas, the consequence being severe hypoglycemic with even standard doses and that discontinuing sulfonylureas results in a marked deterioration in blood glucose (a 5%-point reduction [31 mmol/mol] in HbA1c). A randomized trial displayed that sulfonylureas led to a four-fold greater reduction of fasting blood glucose in HNF1A-MODY patients compared with age, BMI and blood glucose level-matched type 2 diabetes patients.
The sensitivity recognition of sulphonylureas was not a prediction from gene function but actual clinical observation.

In patients with GCK-MODY strikingly, there is a lack of glycemic response with oral hypoglycemic agents or low-dose insulin. There is a lack of efficacy with insulin administration at its median dose with no difference in birthweight of babies born to mothers who used or did not use insulin in GCK-MODY. There are some situations where a pregnant GCK-MODY woman will need insulin, but even at very high doses, its ability to lower the mother's blood glucose levels is partial. Interestingly, as a result of insulin and counter-regulatory hormones GCK-MODY patients have a regulated blood glucose set to a higher level so the lack of response to therapy may be predicted due to this.

GCK-MODY:
• Stable, mild fasting hyperglycemia.
• Treatment not recommended as no significant change in glycemic level.
• A study of 117 probands with GCK mutations found that nearly 50% of subjects were inappropriately given oral hypoglycemics prior to genetic testing, with hypoglycemia as the most commonly reported side-effect. Following genetic diagnosis, nearly 80% of subjects stopped medications with no change in HbA1c levels at follow-up.
• No increase in diabetes-related complications.
• Identifying early is important to avoid unnecessary pharmacological risks and costs.

HNF1A- and HNF4A-MODY:
• Most display a pronounced sensitivity to sulfonylureas (sometimes with hypoglycemia).
• Can maintain target glycemic control on very small oral doses.
• Patients on insulin therapy before obtaining a correct genetic diagnosis often have poorer glycemic control.
• Additional therapies such as GLP-1 receptor agonists, may help in lowering glucose levels without significant risk of hypoglycemia.
• Glinide therapy has a shorter duration of action compared to sulphonylureas hence reduced risk for hypoglycemia therefore beneficial for active adolescents.

HNF1B-MODY:
• Oral hypoglycemics work in over 50% of patients from diagnosis, the others do need insulin.
• Insulin also appears to be needed after 5-6 years of oral therapy.
• Changing from insulin to oral hypoglycemics has a low success rate.

Psychology:
Changing medication regimes from insulin to tablets can have a positive impact on people's lives but they do need support on this adjustment as it can take months. It is a major decision for some who have accepted for a long time they will use insulin for life. Feelings experienced can be a combination of excitement and anxiety; when reflecting on their journey on insulin they can feel annoyed, especially when the need for insulin treatment had been questioned at diagnosis. Patient' responses are influenced by previously received messages from healthcare professionals on the importance of insulin treatment and the length of time on insulin; it can be difficult for some to 'let go'. Some patients are likely to need insulin again at some stage in the future due to the progressive nature of certain genetic mutations and they will be followed up. In contrast, others can feel an improvement in their lifestyle and self-image with feelings of relief and normality again.

Conclusion

Identification of monogenic forms of diabetes among children and adolescents remains a challenge, and as a result, these conditions are largely underdiagnosed with missed opportunities for genetically targeted management. Even though monogenic forms of diabetes are uncommon overall, the clinical implications of the diagnosis for the individual and their family support the use of genetic testing in appropriate cases.

Factors contributing to misdiagnosis include:
• clinical and genetic heterogeneity of the different subtypes
• clinical overlap with the more common polygenic forms of diabetes
• high cost of genetic testing
• limited knowledge of the condition by health care professionals

However, the probability calculator that combines biomarkers with phenotype is a promising approach to target individuals that need testing. In particular, the absence of the classic features of type 1 or type 2 diabetes, early onset, family history, and presence of extra pancreatic features should warrant consideration of an underlying genetic form of diabetes.

Further information is needed to reduce uncertainties in the modeling such as data collection on longer-term treatment plans and frequency of HBGM data. Future work to evaluate the use of genetic testing strategies soon after diagnosis of diabetes can support policy makers also.

Raising awareness of monogenic diabetes and making the diagnosis more accessible will improve disease prognosis and disease management in children and their families. Not only are there cost saving benefits but also the impact this has on the patient from a physical and emotional perspective.

Current data does not address ethnic diverse populations but more so Caucasians. Increasing the research population will give better understanding of impact to all populations.

Unfortunately, the diagnosis of diabetes is often delayed (except in type 1) leading to prolonged periods of uncontrolled hyperglycemia and consequent risk of acute and chronic complications, and rarely misclassification. Timely and accurate diagnosis, combined with regular follow-up and maintenance of optimal glycemic and risk factor control by cautious use of the available therapies will ensure that these young people have a normal life expectancy with minimal impact of diabetic complications.

Finally, one thing that we have learnt from monogenic diabetes, particularly MODY, is that even when there is a clear case, both clinically and economically, for a precision diabetes approach, implementation may be difficult.

References

1. Update on clinical screening of maturity-onset diabetes of the young (MODY).Diabetol Metab Syndr. 2020 Jun 8;12:50. doi: 10.1186/s13098-020-00557-9.
2. Treatment Options for MODY Patients: A Systematic Review of Literature. Diabetes Therapy. 2020 Aug; 11(8): 16 67–1685.
3. Variation in Maturity-Onset Diabetes of the Young Genes Influence Response to Interventions for Diabetes Prevention. J Clin Endocrinol Metab. 2017 Aug 1; 102(8): 2678–2689.
4. Monogenic Diabetes in Children and Adolescents: Recognition and Treatment Options. Curr Diab Rep. 2018 Jun 22; 18(8): 58.
5. Precision diabetes: learning from monogenic diabetes. Diabetologia. 2017; 60(5): 769–777.
6. Monogenic Diabetes: the Impact of Making the Right Diagnosis. Curr Opin Pediatr. 2018 Aug; 30(4): 558–567.
7. Monogenic Diabetes: A Diagnostic Algorithm for Clinicians. Genes (Basel). 2013 Dec; 4(4): 522–535.
8. Challenges in diagnosis and management of diabetes in the young. Clin Diabetes Endocrinol. 2016; 2: 18.
9. Maturity-Onset Diabetes of the Young: What Do Clinicians Need to Know? Diabetes Metab J. 2015 Dec; 39(6): 468–477.
10. Strategies to identify individuals with monogenic diabetes: results of an economic evaluation. BMJ Open. 2020; 10(3): e034716.
11. ‘I don’t feel like a diabetic anymore’: the impact of stopping insulin in patients with maturity onset diabetes of the young following genetic testing. Clin Med (Lond). Mar-Apr 2004;4(2):144-7. doi: 10.7861/clinmedicine.4-2-144.
12. A Systematic Review of Childhood Diabetes Research in the Middle East Region. Front Endocrinol (Lausanne). 2019; 10: 805.