

CLINICAL REVIEW

Diagnosis and management of maturity onset diabetes of the young (MODY)

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Maturity onset diabetes of the young (MODY) comprises a heterogeneous group of monogenic disorders characterised by β cell dysfunction. It is estimated to be the underlying cause of diabetes in 1-2% of patients diagnosed with diabetes, but prevalence estimates will not be accurate until large population screening studies are performed.¹ It is important to distinguish MODY from type 1 and type 2 diabetes because optimal treatments are different. Furthermore, first degree relatives have a 50% probability of inheriting the same mutation, which confers a greater than 95% lifetime risk of developing diabetes.² Distinguishing people who have rare forms of diabetes such as MODY from those with type 1 or type 2 diabetes is a diagnostic challenge because clinical features are similar. In this review we discuss when the general physician might suspect MODY and how to identify which patients with diabetes should be offered genetic testing. We focus on the recognition of the common forms of MODY in people diagnosed with diabetes in the age range 10-45 years, drawing mainly on evidence from small trials and cross sectional and observational studies. Other causes of monogenic diabetes, including neonatal diabetes, are beyond the scope of this review.

What is MODY and who gets it?

Case reports in the 1970s described a familial form of non-insulin dependent diabetes that presented before the age of 25 years.³ The molecular genetic basis of MODY was recognised in the 1990s,^{w1-w6} and diagnostic genetic testing for common subtypes followed rapidly. Mutations in the genes encoding the enzyme glucokinase (GCK) and the nuclear transcription factors hepatocyte nuclear factor 1 α (HNF1A) and hepatocyte nuclear factor 4 α (HNF4A) are the most common causes of MODY, and in the United Kingdom they represent 32%, 52%, and 10% of MODY cases, respectively.⁴ The prevalence of MODY subtypes differs across countries: GCK mutations are more commonly diagnosed in countries where glucose testing of asymptomatic people is routine (such as France, Spain, and Italy), whereas in countries where random blood glucose tests

are seldom done HNF1A-MODY is more commonly diagnosed.^{w7-w12}

To date, mutations in 10 different genes have been associated with a MODY phenotype (table 1).^{w1-w6 w13-w15} On the basis of referrals to the UK diagnostic testing centre, the minimum UK population prevalence of all MODY subtypes is estimated as 68-108 cases per million.⁴ This figure is comparable with population based cross sectional studies in Oxfordshire, UK, and Nord-Trøndelag, Norway, which estimated minimum prevalences for HNF1A-MODY of 84 and 63 cases per million respectively.^{w16 w17}

Although cases of MODY have been described in most ethnic groups, only 0.5% of people referred for MODY testing in the UK were of Asian origin.^{w18} This low referral rate may reflect poor uptake of genetic testing by Asian patients, or that Asian patients, even with clinical features suggestive of MODY, are more readily assumed to have type 2 diabetes.

How does MODY present clinically?

Patients with MODY typically display one or more of the following features: a strong family history of diabetes (of any type), onset of diabetes in the second to fifth decade, insulin independence (although insulin may be needed for optimal control), absence of features of insulin resistance, and absence of β cell autoimmunity. The specific genetic subtype of MODY determines the clinical presentation, prognosis, and treatment response.

The recognition of MODY is challenging because of its relatively low prevalence and the overlap in presentation and clinical features between patients with MODY and those with other subtypes of diabetes. Table 2 summarises the similarities and differences between common MODY subtypes and type 1 and type 2 diabetes. The box lists the features to consider when assessing the cause of diabetes.

Summary points

One to two per cent of cases of diabetes have a monogenic cause but delayed diagnosis and misdiagnosis as type 1 and type 2 diabetes are common

Mutations in the glucokinase (*GCK*), hepatocyte nuclear factor 1 α (*HNF1A*), and hepatocyte nuclear factor 4 α (*HNF4A*) genes are the most common causes of maturity onset diabetes of the young (MODY)

Diagnostic and predictive genetic tests for the common causes of MODY are available

Consider a diagnosis of MODY in patients with diabetes whose features are atypical of their diagnostic label

A diagnosis of MODY has important clinical implications for patients and their families

Insulin and oral hypoglycaemic agents can usually be stopped in patients with GCK-MODY, and sulfonylureas are the optimal treatment in HNF1A/HNF4A-MODY

Sources and selection criteria

We conducted a PubMed database search using the key words "maturity onset diabetes of the young", "MODY", "monogenic diabetes", "hepatocyte nuclear factor 1 α ", "HNF1A-MODY", "glucokinase", "GCK-MODY", "hepatocyte nuclear factor 4 α ", and "HNF4A-MODY". We reviewed the reference lists of retrieved articles to ensure that we considered all relevant articles. Articles that, on the basis of our clinical experience, we considered to be the best evidence available were included in the review. Most of the included studies are cross sectional or observational because of the lack of clinical trials of patients with MODY.

Features to consider when assessing the cause of young onset diabetes

History

Duration and severity of symptoms

History of obesity, hypertension, or dyslipidaemia (suggests metabolic syndrome)

History of pancreatic disease

Family history of diabetes, noting the age of diagnosis and treatment in relatives (it is helpful to draw a family tree)

Family history or personal history of early onset deafness (associated with mitochondrial diabetes) and renal cystic disease (associated with *HNF1B* mutations)

Personal history or family history of neonatal diabetes or neonatal hypoglycaemia

Clinical features

Signs of insulin resistance, such as acanthosis nigricans, abnormal fat distribution (lipodystrophy), central obesity, and dyslipidaemia

Signs suggesting other endocrine disorders (such as Cushing's disease or acromegaly)

Investigations

Measurement of autoantibodies to β cells (antibodies to glutamic acid decarboxylase and islet cells)

Measurement of C peptide in patients taking insulin—serial measurements may be helpful

Biomarkers for specific types of maturity onset diabetes of the young, such as high sensitivity C reactive protein (currently mainly a research tool, but likely to enter clinical use in near future)

Genetic testing

Mutations within the *GCK* gene

Patients with GCK-MODY have a raised threshold for the initiation of glucose stimulated insulin secretion.^{w19} This leads to lifelong, mild, stable hyperglycaemia, with fasting plasma glucose values of 5.5–8 mmol/L. A large observational study showed that patients with GCK-MODY have a low rise in blood sugar after a glucose challenge,⁵ and that their glycated haemoglobin (HbA_{1c}) is normally below 8%.^{5,6} Patients are generally asymptomatic, and hyperglycaemia is commonly discovered during routine screening—for example, in pregnancy. Thus GCK-MODY can be diagnosed at any age. Evidence from observational studies (including a study of 95 people with GCK-MODY who were exposed to hyperglycaemia for an average of 50 years) suggests that these patients do not develop diabetes related microvascular complications.^{7,8} No large studies have assessed long term macrovascular outcomes, but patients with *GCK* mutations seem to have normal cardiovascular risk profiles.^{8,9}

Mutations within *HNF1A* and *HNF4A* genes

Patients with HNF1A-MODY and HNF4A-MODY are typically normoglycaemic in childhood but have a progressive defect of insulin secretion, with diabetes usually diagnosed in the second

to fifth decades. Treatment requirements usually increase over their lifetime, and they are vulnerable to the microvascular and macrovascular complications associated with diabetes.^{w20 w21}

Tight glycaemic control and management of other cardiovascular risk factors are essential aspects of these patients' long term care.

How is the condition diagnosed?

Diagnostic genetic testing for MODY, by direct sequencing of the genes, is widely available. The sequencing technique used in the UK diagnostic testing centre has greater than 99% sensitivity to detect a heterozygous base substitution.^{w22} Genetic testing should be performed after informed consent, with the implications of both a positive or negative result discussed with the patient. Predictive and diagnostic genetic testing for MODY was welcome to most adults,^{w23} but less satisfactory to adolescents, despite previous counselling.^{w24} General practitioners may prefer to refer patients to the local diabetes or clinical genetics team to discuss MODY genetic testing rather than to organise testing themselves. In general, we recommend genetic counselling before predictive genetic testing (when the person does not have diabetes), especially for children.^{w24 w25} Offer diagnostic genetic testing to relatives of patients with

A patient's perspective

I was diagnosed with type 1 diabetes in 2003 at the age of 18. It was a surreal experience because, although I have a strong family history of diabetes, I never expected to be diagnosed myself. After diagnosis I did all that I could to adjust to having to take insulin each day but found this very hard, especially given how much exercise I did and all the associated complications for balanced control. At one point, I needed eight injections a day to help support my rugby training. I have learnt to live with diabetes for the past eight years but it has not been easy. My re-diagnosis this year with maturity onset diabetes of the young (MODY) has completely changed my lifestyle. I currently take just 40 mg of oral gliclazide each day and have been able to exercise regularly with no problems. My recent glycosylated haemoglobin results show that with this pill I still have good glucose control. I no longer have to worry about carrying around and administering insulin, and I have had no hypoglycaemic events since taking the pill. Although I have received excellent care in this transition period and am thankful that it is working, it is not easy to live with the memory of the hardships of taking insulin for eight years because of the misdiagnosis. It is frustrating that the lack of awareness about MODY among health professionals led to this option for diagnosis never being considered.

MODY who have diabetes. Do not assume that all family members will have MODY, because different types of diabetes can occur within the same family.^{w26}

Why is diagnosis often delayed?

Currently, testing for MODY is largely opportunistic. The UK diagnostic testing centre recently reported an average delay of 13 years from diagnosis of diabetes to establishing a definitive genetic diagnosis in patients with MODY, and it reported considerable variation in referral rates for MODY testing across the UK.⁴ It also estimated that more than 80% of MODY cases in the UK are currently misdiagnosed as type 1 or type 2 diabetes.⁴ Explanations for this variation include financial restraints on accessing genetic testing and differences in local clinical expertise in MODY. Knowledge and experience of MODY is limited outside of specialist diabetes centres; a diagnosis of MODY is therefore rarely considered in most patients with diabetes who are managed in primary care.

Can diagnosis of MODY be improved?

Genetic testing is too expensive for indiscriminate use in all patients with diabetes. In 2008 best practice guidelines were produced for the diagnosis of MODY secondary to mutations in the *GCK*, *HNF1A*, and *HNF4A* genes.¹⁰ These guidelines recommend genetic testing for people who match specific clinical criteria: diabetes presenting before the age of 25 years, a strong family history of diabetes, and evidence of insulin independence. The extent of underdiagnosis described above suggests that genetic testing is not routinely offered to patients meeting these testing criteria. Furthermore, more than half of patients with confirmed mutations identified in European countries do not meet these clinical criteria for referral, so even adherence to current guidelines will continue to miss a large proportion of patients with MODY.^{4 11}

Which patients diagnosed with type 1 diabetes should be referred for genetic testing?

Patients with MODY who present at a young age may be misdiagnosed as having type 1 diabetes and inappropriately treated with insulin.

In type 1 diabetes, autoimmune destruction of the β cells results in complete insulin deficiency within three to five years of diagnosis (the "honeymoon period"), whereas some β cell function is maintained in MODY.¹²⁻¹⁵ Consider MODY in patients with evidence of continued endogenous insulin secretion (for example, persistent C peptide production, low insulin dose (<0.5 units/kg/day), and no tendency to ketoacidosis when insulin is omitted) three to five years after diagnosis with apparent type 1 diabetes.

C peptide is co-secreted with insulin from the β cell and can be measured in blood or urine. Urinary C peptide to creatinine ratio can be measured in urine with boric acid preservative that has been sent by post.^{w27} A case-control study found that this test provided excellent discrimination 97 patients with MODY and 69 patients with long duration type 1 diabetes.¹⁵

However, assessment of C peptide is less useful for distinguishing MODY from type 1 diabetes close to diagnosis, when endogenous insulin production is still present.

At diagnosis of type 1 diabetes, most patients have pancreatic autoantibodies, including antibodies to glutamic acid decarboxylase and to islet cells. Patients with MODY are not thought to have pancreatic autoantibodies, and their absence is often part of the selection strategy for genetic testing. A recent case-control study reported that less than 1% of 508 patients with a confirmed genetic diagnosis of MODY had antibodies to β cells.¹⁶ A paediatric survey, however, found that 17% of patients with confirmed MODY mutations had positive antibodies.⁹ The difference between the studies probably relates to different laboratories and methods of antibody testing used, but the results suggest that the presence of pancreatic antibodies should not preclude genetic testing in cases where there is high clinical suspicion.

Parental history of diabetes is more common in MODY than in type 1 diabetes, although family history alone does not discriminate well between type 1 diabetes and MODY.^{w28}

Which patients diagnosed with type 2 diabetes should be referred for genetic testing?

In contrast to type 2 diabetes, patients with MODY have β cell dysfunction that typically occurs in the absence of insulin resistance. Thus, patients with young onset (<45 years) of apparent type 2 diabetes, who do not have features of insulin resistance, may have MODY. Clinical features such as acanthosis nigricans, central obesity, hypertension, and dyslipidaemia can be used as surrogate markers of insulin resistance in everyday clinical practice. In a cross sectional study of patients with a clinical diagnosis of type 2 diabetes, two of 15 patients without insulin resistance were found to have *HNF1A* mutations.^{w29} In a second cross sectional study, 12 of 291 (4%) patients with young adult onset type 2 diabetes were found to have a mutation in the *HNF1A* or *HNF4A* genes using age of diagnosis of diabetes 30 years or less or absence of metabolic syndrome as a strategy to identify subjects for genetic testing.¹⁴ Type 2 diabetes in adolescents is almost always associated with obesity and features of insulin resistance, so the clinical contrast with MODY is more distinct than in adults with type 2 diabetes.^{w30}

A family history of diabetes is common in people with young onset type 2 diabetes.^{w31} Parental history of diabetes does not discriminate well between patients with type 2 diabetes and those with MODY; a case-control study of 44 patients with

HNF1A-MODY and 44 age matched patients with type 2 diabetes found no difference in reported parental diabetes.¹⁷

Another clinical clue is marked sensitivity to sulfonylurea agents (see below); patients who have hypoglycaemia on low or normal doses of sulfonylureas may have an *HNF1A* or *HNF4A* mutation.

How are patients with MODY treated?

GCK-MODY

There are no large published studies, but no change in HbA_{1c} was seen in a small observational study of 20 subjects who had been treated with insulin or oral hypoglycaemic agents when treatment was discontinued after the diagnosis of GCK-MODY.¹⁸ This, plus the mild increase in HbA_{1c} generally seen in GCK-MODY,^{5,6} suggests that drugs do not improve glycaemic control in GCK-MODY. Therefore the consensus is that antidiabetic drugs can be stopped in most patients.¹⁹

HNF1A-MODY and HNF4A-MODY

Anecdotal reports that patients with HNF1A-MODY were sensitive to sulfonylurea drugs were confirmed in a randomised controlled crossover trial that found a five times greater drop in fasting plasma glucose in patients with HNF1A-MODY treated with low dose gliclazide compared with metformin.^{20,32} Patients with HNF4A-MODY showed similar sensitivity to sulfonylureas in a subsequent observational study.²¹ On the basis of these findings, low dose sulfonylureas are recommended as first line treatment for patients with HNF1A/HNF4A-MODY, and observational evidence suggests that patients can be switched safely from insulin to a sulfonylurea. A case study of 43 patients reported that 34 changed from insulin to a sulfonylurea after diagnosis of HNF1A-MODY, and 24 remained off insulin for 39 months with no deterioration in glycaemic control.²² Good control may be maintained for many years, although eventually most patients progress to insulin treatment.

Nateglinide reduced postprandial glucose excursions acutely in 15 patients with HNF1A-MODY, suggesting that prandial secretagogues are a useful therapeutic alternative.²³

Special case 1: children with hyperglycaemia

As discussed, type 1 diabetes can be distinguished from MODY by examining several disease markers. The initial management will depend on the severity of hyperglycaemia at presentation. MODY is more common than type 1 diabetes in children who have asymptomatic hyperglycaemia; *GCK* mutations were found in 11-43% of children presenting with incidental hyperglycaemia.^{24,25} In children with few or no symptoms we recommend genetic testing (*GCK* sequencing first) along with serial blood glucose monitoring. In children with more severe hyperglycaemia, it is safer to start insulin treatment and re-evaluate the causes later. This approach should prevent most children with *GCK* mutations from starting unnecessary treatment with insulin.

Most children with symptomatic hyperglycaemia have type 1 diabetes. However, infants who present with diabetes before 6 months are likely to have a genetic rather than autoimmune basis for their diabetes, and specialist investigation should be instigated.²⁶

Special case 2: pregnancy

Women with asymptomatic hyperglycaemia secondary to GCK-MODY may present with gestational diabetes during

routine screening in pregnancy. A cross sectional study found GCK-MODY in 12 of 15 white women with gestational diabetes who met four additional criteria—fasting hyperglycaemia outside pregnancy, low glucose increment during an oral glucose tolerance test, diet controlled diabetes outside pregnancy, and a family history of diabetes.^{w33} Other studies suggest that GCK-MODY and HNF1A-MODY explain 2-5% and around 1% of gestational diabetes, respectively.^{w34,w35} Clinical experience of treating patients with MODY in pregnancy is limited, so there is a lack of consensus about treatment between specialist centres. Although many clinicians use insulin routinely, some centres treat women with GCK-MODY with insulin only if fetal monitoring suggests development of macrosomia and treat with glibenclamide in HNF1A/HNF4A-MODY if patients were previously well controlled with sulfonylureas.

Future strategies for diagnosing MODY

A cost effective biomarker that could be used to screen all patients with young onset diabetes to pick out those most likely to have MODY would improve rates of diagnosis. Most candidate biomarkers investigated so far have had insufficient sensitivity and specificity to be useful for screening.^{w36-w40} High sensitivity C reactive protein, which is under transcriptional control by *HNF1A*, has recently been reported to be significantly lower in patients with *HNF1A* mutations than in those with other types of diabetes.²⁷ This finding has now been replicated in two large European studies of around 1500 patients with MODY.^{28,29} Low concentrations of this protein (<0.25-0.75 mg/L, depending on the assay used) discriminated well between patients with HNF1A-MODY and those with young onset type 2 diabetes, with receiver operator characteristic curve derived C statistics of more than 0.8. Given its wide availability and modest costs, this test could be readily incorporated into diagnostic pathways to facilitate the identification of patients with HNF1A-MODY.

Conclusion

Despite the wide availability of molecular genetic testing, identification of patients with MODY remains a challenge for clinicians. An accurate genetic diagnosis of MODY has important clinical implications for individual patients and their relatives. Therefore, clinicians should be aware of the rarer causes of diabetes, particularly MODY, and should not be afraid to challenge existing diabetes diagnostic labels. We propose that a systematic assessment of the underlying cause of diabetes is incorporated into diabetes care plans for patients with diabetes diagnosed between the ages of 10 and 45 years, using a simple diagnostic algorithm such as that outlined in the figure. Otherwise most patients with MODY will continue to be misdiagnosed and forgo the opportunity of individualised care, tailored to the underlying genetic causes.

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Questions for future research

- What effect will cheaper and faster genetic testing (via high throughput sequencing techniques) have on diagnosis rates of maturity onset diabetes of the young (MODY)?
- What new biomarkers can facilitate the distinction between MODY subtypes and common types of diabetes?
- What are the health economics of establishing an accurate molecular diagnosis of MODY?
- Are newer treatments for type 2 diabetes, such as glucagon-like peptide 1 agonists, effective in patients with MODY?

Tips for non-specialists

- Don't be afraid to challenge existing diagnostic labels; patients with diabetes may benefit from a comprehensive review of the cause of their condition
- It is important to take a detailed family history of diabetes including gestational diabetes
- Consider specialist review for patients with clinical features that are atypical of their current diagnostic label of diabetes
- Evidence of endogenous insulin secretion more than a few years after diagnosis is unusual in people with type 1 diabetes, and it may be useful to measure C peptide in insulin treated patients
- Absence of clinical markers of insulin resistance (such as central obesity, acanthosis nigricans, hypertension, and dyslipidaemia) is unusual in those with a clinical label of type 2 diabetes

Additional educational resources for healthcare professionals and patients

- Diabetes Gene (maintained by the UK diagnostic testing centre in Exeter) (www.diabetesgenes.org)—Provides information on clinical care and research into genetic types of diabetes including maturity onset diabetes of the young (MODY) for patients and professionals
- Diabetes UK (www.diabetes.org.uk/Guide-to-diabetes/Introduction-to-diabetes/What_is_diabetes/mody/)—Information for patients on the different types of diabetes including MODY
- University of Chicago (www.monogenicdiabetes.org/what-is-monogenic-diabetes)—Provides information on different types of diabetes with an underlying genetic cause including MODY
- Diabetes Genes (<http://beta.diabetesgenes.org/content/genetic-diabetes-nurses-locations-map>)—Locations of regional genetic diabetes nurses in the UK, some associated with specialist MODY clinics, who can offer advice
- International Society for Paediatric and Adolescent Diabetes (ISPAD; <http://www.ispad.org/>)—Provides clinical details on rare types of diabetes and serves as a repository of stored DNA for research

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Patient consent obtained.

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Tables

Table 1 | Clinical features associated with mutations in genes that cause maturity onset diabetes of the young (MODY)

Gene	Relative prevalence	Other clinical features
HNF1A	Common (30-70% of MODY)	Low renal threshold for glycosuria; marked sensitivity to sulfonylureas
HNF4A	5-10% of MODY	Normal renal threshold; marked sensitivity to sulfonylureas; neonatal hyperinsulinaemia and hypoglycaemia with associated macrosomia; low concentrations of high density lipoprotein/high concentrations of low density lipoprotein
GCK	Common (30-70% of MODY)	Mild fasting hyperglycaemia throughout life; often detected during screening; small incremental glucose rise after carbohydrate load
HNF1B	5-10% of MODY	Malformations of the genitourinary tract (especially renal cysts and other renal developmental abnormalities); pancreatic atrophy; exocrine insufficiency
IPF1	Very rare	Pancreatic agenesis in homozygotes/compound heterozygotes
INS	Rare: <1% of MODY	More usually associated with neonatal diabetes
CEL	Very rare: fewer than 5 families reported	Exocrine pancreatic dysfunction
NEUROD1	Very rare: fewer than 5 families reported	
KCNJ11	Rare: <1% of MODY	More usually associated with neonatal diabetes; sulfonylurea responsive
ABCC8	Rare: <1% of MODY	More usually associated with neonatal diabetes; sulfonylurea responsive

Table 2| Clinical and biochemical features associated with type 1 diabetes, type 2 diabetes, and the common subtypes of maturity onset diabetes of the young (MODY)

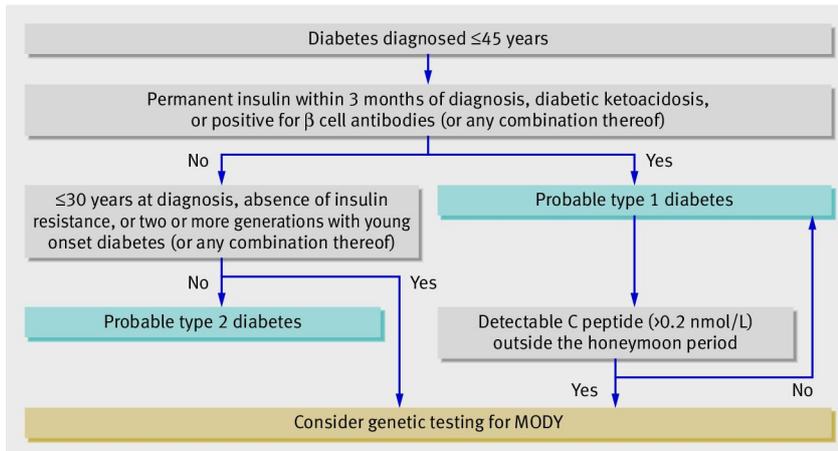
Features	Type 1 diabetes	Type 2 diabetes	GCK-MODY*	HNF1A/4A-MODY†
Typical age of diagnosis (years)	10-30	>25	Present from birth; presents at any age	15-45
Diabetic ketoacidosis	Common	Rare	Rare	Rare
Insulin dependent	Yes	No	No	No
Parental history of diabetes	<15%	>50% in young onset type 2 diabetes	If tested one parent usually has impaired fasting glycaemia (may not be previously known)	60-90%‡
Obesity	Uncommon	Common	Uncommon	Uncommon
Insulin resistance	Uncommon	Common	Uncommon	Uncommon
Presence of β cell antibodies	>90%	Negative	Rare	Rare
C peptide concentrations	Undetectable/low	Normal/high	Normal	Normal
Optimal first line treatment	Insulin	Metformin	None	Sulfonylurea

*GCK=glucokinase.

†HNF1A/4A=hepatocyte nuclear factor 1 α /4 α .

‡Family history is often part of the criteria for testing. Some reports cite a parental history of 60-70%.^{15 18}

Figure



Algorithm to aid diagnosis of maturity onset diabetes of the young (MODY) in patients with young adult onset diabetes