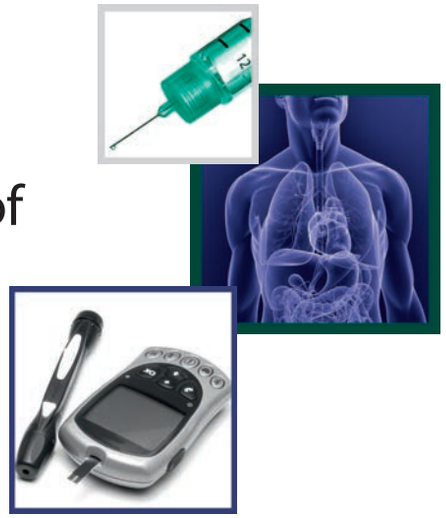
REVIEW

Biomarkers currently used for the diagnosis of maturity-onset diabetes of the young



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Practice Points

- Maturity-onset diabetes of the young (MODY) accounts for 1–2% of patients with diabetes, but the majority of cases are misdiagnosed as Type 1 or 2 diabetes.
- MODY should be part of the differential diagnosis of young adult-onset diabetes and initial diagnoses of Type 1 or 2 diabetes should be reconsidered if there is a clinical suspicion of MODY.
- Correct diagnosis of MODY alters treatment, informs clinical prognosis and helps identify at-risk family members.
- No treatment is required for *GCK*-MODY while low-dose sulfonylureas are the first-line treatment for *HNF1A*-/*HNF4A*-MODY.
- Nongenetic biomarkers such as high-sensitivity C-reactive protein, islet autoantibodies and C-peptide should be used in combination with clinical features to optimize the selection of patients for genetic testing.

SUMMARY Correct diagnosis of maturity-onset diabetes of the young (MODY) has a significant impact on selecting the optimal treatment, informing the clinical course of the disease and identifying at-risk family members. Despite the clinical value of an accurate diagnosis, many patients with MODY do not undergo confirmatory genetic testing and remain misdiagnosed as Type 1 or 2 diabetics. Possible reasons for this missed diagnosis include considerable overlap in the clinical features of MODY with other common types of diabetes, expense of genetic testing and lack of clinician awareness. It is highly desirable to identify nongenetic biomarkers that can help prioritize patients for genetic testing. This review updates the reader on the current state of biomarker development in MODY and discusses their possible application in clinical practice.

Diabetes is one of the leading causes of morbidity and mortality worldwide and is increasing in prevalence. Timely diagnosis and appropriate treatment of diabetes is a keystone of patient management to prevent or delay the complications of hyperglycemia. Updated American Diabetes Association guidelines recommend diabetes classification into four main categories: Type 1 diabetes (T1D), Type 2 diabetes (T2D), other specific types and gestational diabetes [1]. The 'other specific types' comprise various less common forms of diabetes, including monogenic disorders of

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β-cell function, also known as maturity-onset diabetes of the young (MODY). Correct molecular diagnosis of MODY allows optimal treatment, informs clinical course of diabetes and screening of family members. Despite the value of a correct diagnosis, etiologies outside classic T1D or T2D are frequently not considered in the clinical setting, leading to delayed or missed diagnosis and, hence, inappropriate treatment of rarer subgroups. This is particularly true for MODY where the majority of cases are inappropriately labeled as T1D or T2D [2].

Maturity-onset diabetes of the young

MODY is a clinically heterogeneous group of monogenic disorders characterized by autosomal dominant inheritance and young-onset non-insulin-dependent diabetes. A minimum population prevalence of MODY in the UK (based on MODY case referral to UK Genetic Testing Centres) is estimated to be approximately 100 cases per million [2]. Mutations in at least ten genes can cause a MODY-like phenotype [3]. The most common forms seen in clinical practice are due to heterozygous mutations in the gene encoding the glycolytic enzyme glucokinase (*GCK*), which account for approximately 30% of MODY cases in the UK, and genes encoding the transcription factors HNF-1α (*HNF1A*) and HNF-4α (*HNF4A*), which account for approximately 50 and 10% of MODY cases in the UK, respectively [2].

Clinical features of the common MODY subtypes

■ *GCK*-MODY

Patients with *GCK*-MODY have a defect in pancreatic β-cell glucose sensing that results in persistent, mild fasting hyperglycemia (5.5–8.0 mmol/l) from birth [4]. Glycated hemoglobin (HbA1c) is typically just above the normal range and there is a small increment in glucose levels after 2 h during an oral glucose tolerance test (<4.6 mmol/l corresponding to the 90th percentile) [5]. Most patients are asymptomatic and their hyperglycemia is frequently detected on routine blood screening. Patients do not suffer from microvascular complications [6]. Pharmacological treatment does not change HbA1c significantly, and therefore, apart from during pregnancy, these patients are treated by diet alone [7].

■ *HNF1A*-MODY

Patients with *HNF1A*-MODY have a progressive decrease in insulin secretion. In contrast to *GCK*-MODY, patients with *HNF1A*-MODY are normoglycemic in childhood, with diabetes presenting in adolescence or early adulthood. Pharmacological treatment is required to maintain glycemic control. Patients with *HNF1A*-MODY have been shown to be exquisitely sensitive to low-dose sulfonylurea therapy compared with metformin in a randomized-controlled trial [8]. Sulfonylureas are, therefore, recommended as first-line therapy, maintaining good glycemic control for a number of years; although insulin treatment may eventually be required [8]. Patients with *HNF1A*-MODY have a protective lipid profile with normal or high HDL [9]. There is a low renal threshold for glucose and they often have glycosuria following a carbohydrate load, before the clinical features of diabetes become apparent [10]. Patients with *HNF1A*-MODY can develop severe diabetes-related complications and require regular medical follow-up comparable with that employed in T1D.

■ *HNF4A*-MODY

Patients with *HNF4A*-MODY have a similar clinical presentation to *HNF1A*-MODY and also demonstrate sulfonylurea sensitivity. Unlike *HNF1A*-MODY, they have a normal renal threshold. Alterations of lipid profile have been reported, which may vary with the type of mutation, but low ApoA2 is a consistent finding [11]. Mutations in *HNF4A* are associated with macrosomia and neonatal hypoglycemia caused by fetal hyperinsulinemia [12].

Why diagnose MODY?

As outlined above, a correct diagnosis of MODY has significant clinical implications for the patient. Low-dose sulfonylureas are the first-line treatment for patients with *HNF1A*-MODY and *HNF4A*-MODY [8], while no treatment is required for *GCK*-MODY [7]. This is different from both T1D and T2D, where insulin and metformin, respectively, are the treatments of choice. A correct diagnosis also makes it easier to predict the course of the hyperglycemia and allows genetic testing of family members who either already have diabetes or are at risk of having inherited the mutation.

Biomarkers & diagnosis of diabetes subtypes

It is estimated that the majority (>80%) of MODY cases remain undiagnosed or misdiagnosed as T1D or T2D [2,13]. Possible reasons

for this include overlap in clinical features with the more common forms of diabetes, high cost of genetic testing (~£350 per gene) and a low level of awareness among clinicians. The current diagnostic guidelines for MODY emphasize that genetic testing should be offered to individuals who have a young age at diagnosis of diabetes (<25 years), family history of diabetes (at least two consecutive generations) and evidence of endogenous insulin secretion [5]. It is clear that most individuals meeting these criteria are not referred for diagnostic genetic testing, and approximately 50% of proven MODY cases do not match these criteria [2,14]. The use of non-genetic biomarkers in combination with clinical features could enhance identification of MODY cases and help prioritize patients for molecular diagnostic testing.

■ Characteristics of an ideal biomarker

Biomarkers are adjunct tools that help clinicians to predict, diagnose, monitor or screen for a specific disease. Results of measuring biomarkers can be compared with a gold-standard test, which in the case of MODY is genetic sequencing. A biomarker is considered clinically useful if it demonstrates a high sensitivity and specificity for the disease in question, is cheap and locally available, is not operator or assay dependent, and has the potential to discriminate subjects with and without the disease. For tests that yield a continuous outcome, an optimum threshold or cut-off value is used for discriminating diseased from healthy individuals. This optimum cut-off value, as well as the discriminant potential of a biomarker, can be determined by receiver operating characteristic (ROC) curve analysis, as illustrated in Figure 1. A ROC curve is a graphical display of sensitivity versus 1 – specificity for every possible cut-off point of a test result. The area under the ROC curve (also known as the C-statistic) is a summary measure of the discriminatory potential of the diagnostic test. The C-statistic can range from 0.5 (which means the diagnostic test is as good as a random guess in discriminating cases with and without disease) to 1.0 (perfect discrimination). There is usually a trade-off between high sensitivity (to detect most affected cases) and high specificity (to exclude most noncases). Cut-off values can be selected by the point on the ROC curve that combines the optimal sensitivity and specificity, or selected according to whether high sensitivity or specificity is desired. For example, for a disease such as MODY with a relatively low prevalence among all those with diabetes, a higher specificity may be set, to prevent investigating large numbers of individuals with other forms of diabetes. However, this will be at the expense of missing a small proportion of MODY cases.

■ Biomarkers & MODY

Given the high cost of genetic testing for MODY, biomarker discovery has been an area of major interest in the last decade with particular focus on *HNF1A*-MODY. *HNF1A* encodes the transcription factor HNF-1α, which regulates gene expression in the pancreas as well as several extra-pancreatic sites such as the liver, kidney and gastrointestinal tract. As all types of diabetes have an underlying β-cell defect, a biomarker utilizing the specific extra-pancreatic features could be better equipped to differentiate *HNF1A*-MODY from other forms of diabetes. A number of different approaches have been used for biomarker discovery. These include knockout mouse models, human studies, bioinformatics and metabonomics.

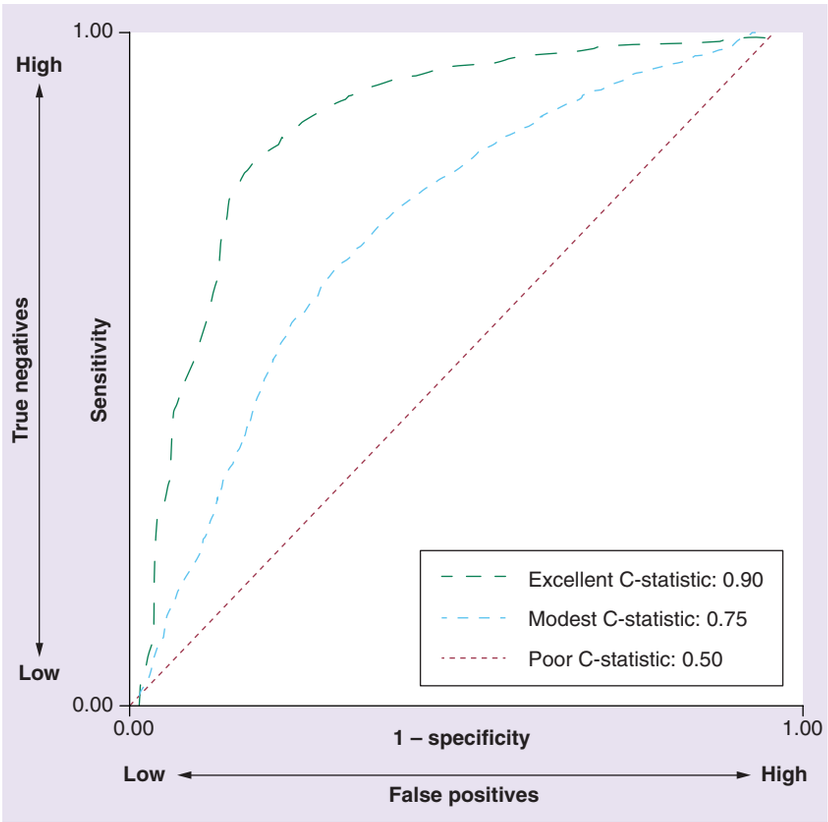

Figure 1. Example of receiver operating characteristic curves illustrating different C-statistics. The closer a curve follows the upper left hand border the more clinically useful the test is.

■ High-sensitivity C-reactive protein

Of all the biomarkers investigated for *HNF1A*-MODY, the most promising biomarker to date is high-sensitivity C-reactive protein (hsCRP).

In 2008–2009, three independent genome-wide association studies discovered that common variation near *HNF1A* was reproducibly associated with modest differences in C-reactive protein (CRP) levels in healthy adults [15–17]. This has now been replicated in numerous populations. This finding from genome-wide association studies is supported by the fact that the *CRP* promoter contains binding sites for HNF-1α [18,19] and that *CRP* expression is downregulated in *Hnf1a* knockout mice [20]. This observation led to the hypothesis that loss-of-function *HNF1A* mutations could lead to lower hsCRP levels in *HNF1A*-MODY. This was confirmed in an initial pilot study that showed significantly lower baseline levels of hsCRP in *HNF1A*-MODY patients compared with autoimmune diabetes, T2D and *GCK*-MODY, as well as healthy controls [21]. These initial results were then replicated in two large independent studies [22,23] that also tested the rarer MODY subgroups caused by *HNF4A* and *HNF1B* mutations, and assessed a total of four different common hsCRP assays. The hsCRP levels from these studies are illustrated in **Figure 2**. Taken together, these studies show that hsCRP is significantly lower in *HNF1A*-MODY than any other group (the median value of hsCRP generally being at the lower reporting range of the assay being used). The largest difference is seen between *HNF1A*-MODY and T2D, where the chronic low-grade inflammation seen in T2D tends to lead to a higher hsCRP in this group (nearly 20% of the T2D group had >10g/l CRP in one study from Oxford [21]). Overall the studies show that hsCRP can usefully discriminate *HNF1A*-MODY from young-onset T2D (C-statistic: 0.79–0.97) and *HNF4A*-MODY (C-statistic: 0.79–0.97) [22].

Of all the biomarkers investigated for identifying *HNF1A*-MODY, hsCRP is the only biomarker where initial results have been confirmed by replication studies. It has also been found useful for discriminating *HNF1A*-MODY from other diabetes subtypes at an individual case selection level [24]. Given the good discriminative capacity and common use in clinical practice, hsCRP has excellent potential to be used as a biomarker for prioritization of patients with young-onset diabetes for molecular diagnostic testing. One limitation of using hsCRP as a biomarker is that CRP is an acute-phase protein. High hsCRP levels can be misleading in someone with a clinical suspicion of *HNF1A*-MODY but who is suffering from a concurrent infection. It is advisable to repeat the test after a few weeks in a patient with high clinical suspicion of MODY and an elevated hsCRP.

■ Urinary amino acids

The *Hnf1a* knockout mouse has a striking phenotype of renal Fanconi syndrome with polyuria, glycosuria and increased renal fractional excretion of amino acids [25]. The severe renal phenotype of *Hnf1a* knockout mice led to the hypothesis that aminoaciduria would be seen in human *HNF1A* mutation carriers. The urinary levels of 16 amino acids were analyzed in patients with *HNF1A*-MODY, T1D, T2D and patients with coexisting diabetes and chronic renal failure. This study found that generalized aminoaciduria was not specific to *HNF1A*-MODY and was a common feature of all diabetes groups due to glycosuria [26].

The above results were independently confirmed in a recent study that compared the metabolic urine profiles of subjects with *HNF1A*-MODY, *GCK*-MODY and young-onset T2D [27]. Urine samples were analyzed using liquid chromatography mass spectrometry and ^{1}H-nuclear magnetic resonance spectroscopy (NMR). Examination of NMR-acquired data revealed significant difference in valine and glycine levels in subjects with *HNF1A*-MODY compared with T2D. Direct quantification of these amino acids was undertaken to confirm the findings of the NMR data. The urine samples were matched for urinary glucose to control for the effect of glycosuria. No difference in the levels of urinary amino acids was observed among the diabetes subtypes when the subjects were matched for urine glucose. This confirms the previous reports that any difference in urinary amino acid profile between the diabetes subtypes was driven by glycosuria.

■ Serum amino acids

Hnf1a knockout mice also exhibit alteration in serum levels of amino acids, in particular demonstrating raised levels of phenylalanine. Serum amino acids in *HNF1A*-MODY patients were compared with healthy controls [28]. However, the specific changes seen in serum amino acids of mouse models were not observed in subjects with *HNF1A*-MODY.

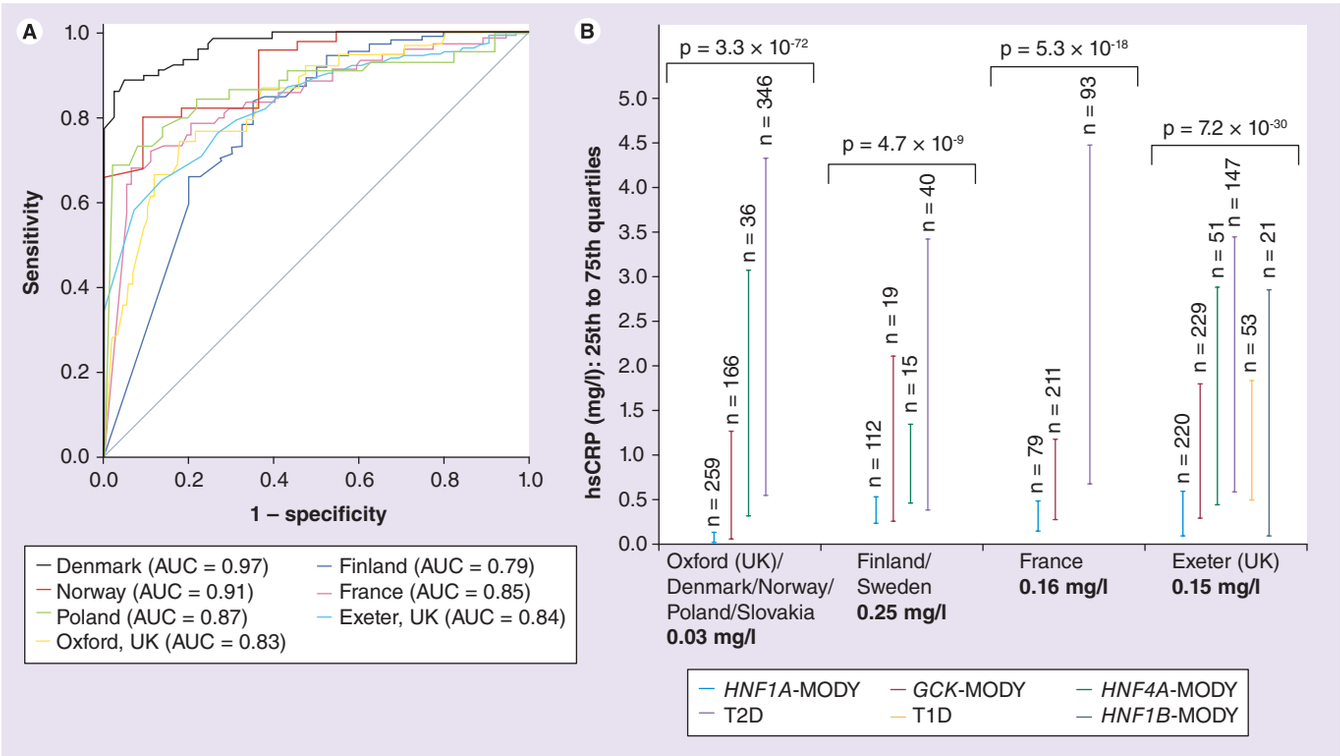

Figure 2. Combined results of two large independent studies examining high-sensitivity C-reactive protein in subtypes of diabetes. (A) Receiver operating characteristic curve illustrating the discriminative capacity of hsCRP to distinguish between subjects with *HNF1A*-MODY and T2D across seven European centers. **(B)** hsCRP levels in different forms of diabetes. The interquartile range is plotted for four different hsCRP assays, with the median value for *HNF1A*-MODY cases given on the x-axis.
AUC: Area under the curve; hsCRP: High-sensitivity C-reactive protein; MODY: Maturity-onset diabetes of the young; T1D: Type 1 diabetes; T2D: Type 2 diabetes.

■ Complement 5 & 8, & transthyretin

Both *HNF1A* and *HNF4A* regulate the genes encoding complement 5 (C5), complement 8 (C8) and transthyretin. *Hnf1a* knockout mice fail to express C5 and C8. C5, C8 and transthyretin were evaluated as potential biomarkers for *HNF1A*-/*HNF4A*-MODY [29]. Although sensitivity was quite good (60–90%), these candidate biomarkers had extremely poor specificity (2–10%).

■ Urine glucose

HNF-1α regulates the transcription of the high-affinity low-capacity sodium–glucose transporter-2 in the proximal renal tubule. *HNF1A* haploinsufficiency results in reduced expression of sodium–glucose transporter-2, decreased glucose reabsorption from the proximal tubule and a low renal threshold for glucose with glycosuria inappropriate for the blood glucose levels [30]. This feature is used in clinical practice to identify nondiabetic mutation carriers who are developing hyperglycemia [10]. 1,5-anhydroglucitol (1,5 AG) is a non-metabolized dietary monosaccharide with structural similarity to glucose. Usually, 1,5 AG is reabsorbed in the proximal renal tubule by a anhydroglucitol/fructose/mannose common transport system. However, when glycosuria is present, glucose competes with 1,5 AG for reabsorption via this monosaccharide transport system, leading to loss of 1,5 AG in the urine and a lowered plasma concentration of 1,5 AG. Skupien *et al.* hypothesized that the glycosuria seen in *HNF1A*-MODY would lower levels of 1,5 AG, and thus, 1,5 AG could serve as a biomarker for *HNF1A* mutations. It was found that plasma levels of 1,5 AG in *HNF1A*-MODY patients were 50% lower than T2D subjects with matched glycemic control [31]. A later study validated the results by Skupien *et al.*; again noting that the difference in plasma levels of 1,5 AG between *HNF1A*-MODY and T2D subjects was evident only after adjustment for HbA1c [32]. The unadjusted C-statistic was only 0.60

for *HNF1A*-MODY versus T2D, suggesting poor discrimination in everyday clinical use. An interesting finding in this study was that levels of 1,5 AG provided a good discrimination between *GCK*-MODY and *HNF1A*-MODY (C-statistic: 0.86). It was proposed that 1,5 AG could be used as an alternative to the oral glucose tolerance test, which is currently being used to discriminate between *GCK*- and *HNF1A*-MODY [32]. 1,5AG is available commercially as a marker of post-prandial hyperglycemia (and is an alternative to HbA1c for measuring glycemic control in diabetes), but is not yet widely available in Europe.

Urinary glucose was directly measured in a study investigating the metabolic urine profile of *HNF1A*-MODY, *GCK*-MODY and young-onset T2D [27]. Urine glucose was highest in the *HNF1A*-MODY subjects and lowest in the *GCK*-MODY cases on both liquid chromatography mass spectrometry and direct urinary glucose measurement. Urine glucose-derived parameters were found to be significantly different across the diabetes subtypes. However, there was a huge variation in urine glucose levels, and the C-statistic for these measures was less than 0.60, indicating that parameters based on urine glucose will not be very useful clinical discriminators of *HNF1A*-MODY.

■ apoM

apoM is an approximately 25-kDa apolipoprotein found in all major lipoprotein classes but mainly associated with HDL [33]. *apoM* is transcriptionally regulated by HNF-1α [34]. In 2003, Richter *et al.* reported 50% reduced expression of apoM in mice heterozygous for *Hnf1a* and undetectable levels of apoM in *Hnf1a* knockout mice [34]. This finding was then followed up in subjects with *HNF1A*-MODY, healthy controls and those with T2D in three separate studies [34–36]. Initially, significantly reduced plasma apoM was reported in subjects with *HNF1A*-MODY compared with controls [34]. In a second study, no significant difference in apoM levels was observed between subjects with *HNF1A*-MODY, T2D and controls [35]. Finally a third study found 10% lower apoM serum concentration only in women with *HNF1A* mutations compared with controls, while no difference was observed between *HNF1A*-MODY and T2D [36]. Different techniques used for apoM analysis and different ascertainment of samples in the three studies could have led to the observed inconsistency between the results. Further work is needed to investigate the role of apoM as a biomarker for *HNF1A*-MODY.

■ Lipid profile

T2D is characterized by diabetic dyslipidemia, which includes elevated plasma triglyceride levels and low levels of HDL. Previous studies investigating phenotypic characteristics of *HNF1A*-MODY have shown that fasting triglyceride levels are lower in patients with *HNF1A*-MODY compared with patients with young-onset T2D [37]. Moreover, patients with *HNF1A*-MODY have normal HDL similar to nondiabetic individuals. HDL has also been investigated as a candidate biomarker for discriminating *HNF1A*-MODY and T2D [38]. HDL was found to be significantly lower in patients withT2D compared with those with *HNF1A*-MODY, with a C-statistic of 0.76 indicating modest discrimination. The difference in HDL between diabetes subtypes disappeared when adjusted for covariates, such as age at diagnosis and BMI, suggesting that HDL does not add much further discrimination to that which is available from clinical features.

Research in human subjects has shown that single-nucleotide polymorphisms in the *GCK* promoter are associated with changes in HDL levels [39,40]. It was hypothesized by Fendler *et al.* that HDL could be used as a biomarker for *GCK*-MODY [41]. The study group included both adult and pediatric populations. HDL levels were found to be lower in *GCK*-MODY than both T1D and *HNF1A*-MODY. The C-statistic was 0.81 for discriminating *GCK*-MODY from T1D, and was 0.79 for discriminating *GCK*-from *HNF1A*-MODY. These results suggest that HDL provides modest discrimination between *GCK*-MODY, *HNF1A*-MODY and T1D; however, this requires confirmation by further replication studies.

■ Cystatin C

Cystatin C, a low-molecular-weight protein, is a marker of glomerular filtration rate and renal function. CRP is one of the factors that affects cystatin C levels in the blood [42]. Given the observation that patients with *HNF1A*-MODY have lower baseline levels of CRP [21,43], Nowak *et al.* hypothesized that cystatin C levels might be altered in *HNF1A*-MODY [44]. Cystatin C was analyzed in Polish and British subjects with *HNF1A*-MODY, T1D, T2D and normal

controls. Cystatin C levels were found to be significantly lower in the Polish *HNF1A*-MODY subjects, but this was not replicated in the British subjects [44]. Cystatin C is unlikely to be a useful biomarker for *HNF1A*-MODY.

Markers specific for T1D: absence of C-peptide & β-cell antibodies

■ C-peptide

C-peptide is cosecreted with insulin from β-cells and measurable levels indicate residual β-cell function. In T1D, due to autoimmune destruction of β-cells, C-peptide levels gradually decline while patients with MODY retain their endogenous β-cell function. In a cross-sectional study of subjects diagnosed with diabetes up to 45 years of age, clinically labeled T1D subjects with residual serum C-peptide were investigated for MODY [45]. Subjects with a C-peptide increment of ≥0.2nmol/l on glucagon simulation test or a random serum C-peptide level of ≥0.2nmol/l underwent genetic testing for MODY. Out of all of those sequenced, 10% (two subjects) were found to have *HNF1A*-MODY. In another study, a urinary C-peptide:creatinine ratio was found to be lower in long-standing T1D than *HNF1A*-/*HNF4A*-MODY with a C-statistic of 0.98 [46]. Serum C-peptide needs to be analyzed within a few hours of sampling, while the urinary C-peptide:creatinine ratio can be measured in urine collected with boric acid preservative and sent by post [46].

During the 'honeymoon period' of T1D, C-peptide is still present for a variable length of time postdiagnosis. During this period of endogenous insulin production, any measure of C-peptide would be less useful in discriminating MODY from T1D. This is a major disadvantage of C-peptide, as identifying MODY close to diagnosis of diabetes is highly desirable to prevent long periods of taking endogenous insulin in those with MODY.

■ Islet autoantibodies

T1D is characterized by the presence of pancreatic islet autoantibodies, including glutamic acid decarboxylase (GAD) and islet cells (IA-2). In those with T1D, 85–90% have the presence of one or more pancreatic islet autoantibody at the time of diagnosis [1]. MODY subjects would not be expected to have pancreatic islet autoantibodies and diagnostic guidelines for MODY suggest testing those who are antibody negative [5]. Data are mixed, however, and a recent study from UK Diagnostic Testing Centres reported less than 1% prevalence of GAD and IA-2 antibodies in MODY [47], while in a registry-based German pediatric cohort, Schober *et al.* reported the presence of pancreatic islet autoantibodies in 17% patients with confirmed MODY mutations [48]. In another two Swedish and British studies, GAD antibodies were detected in 4.8 and 21% of MODY patients, respectively [45,49]; however, no IA-2 antibodies were detected [45].

Table 1. Biomarkers of maturity-onset diabetes of the young subtypes investigated to date and their differential diagnosis potential.

Biomarkers	*HNF1A*-MODY vs T1D	*HNF1A*-MODY vs T2D	*HNF1A*- vs *HNF4A*-MODY	*HNF1A*- vs *GCK*-MODY	*GCK*-MODY vs T1D	Approximate cost (£)	Routinely available?	Ref.
hsCRP	X	✓	✓	X	X	2	✓	[21,22]
Urinary amino acids	X	X				75	✓	[26,27]
Serum amino acids						75	✓	[28]
C5, C8 and TTR		X	X			Unknown	Unknown	[29]
apoM		X	X			Unknown	Mainly research	[34–36]
1,5 AG		✓		✓†		20	USA/Japan; not widely used in UK	[31,32]
Islet autoantibodies	✓				✓	15	✓	[47]
C-peptide	✓	X	X	X	✓	10	✓	[46]
Cystatin C	X	X				10	✓	[44]
HDL		✓			✓†	2	✓	[38,41]

†Needs replication
✓: Good discrimination between subtypes of diabetes; 1,5 AG: 1,5-anhydroglucitol; C5: Complement 5; C8: Complement 8; GCK: Glucokinase; HDL: High-density lipoprotein; hsCRP: High-sensitivity C-reactive protein; MODY: Maturity-onset diabetes of the young; T1D: Type 1 diabetes; T2D: Type 2 diabetes; TTR: Transthyretin; X: Not clinically relevant, reproducible discrimination demonstrated.

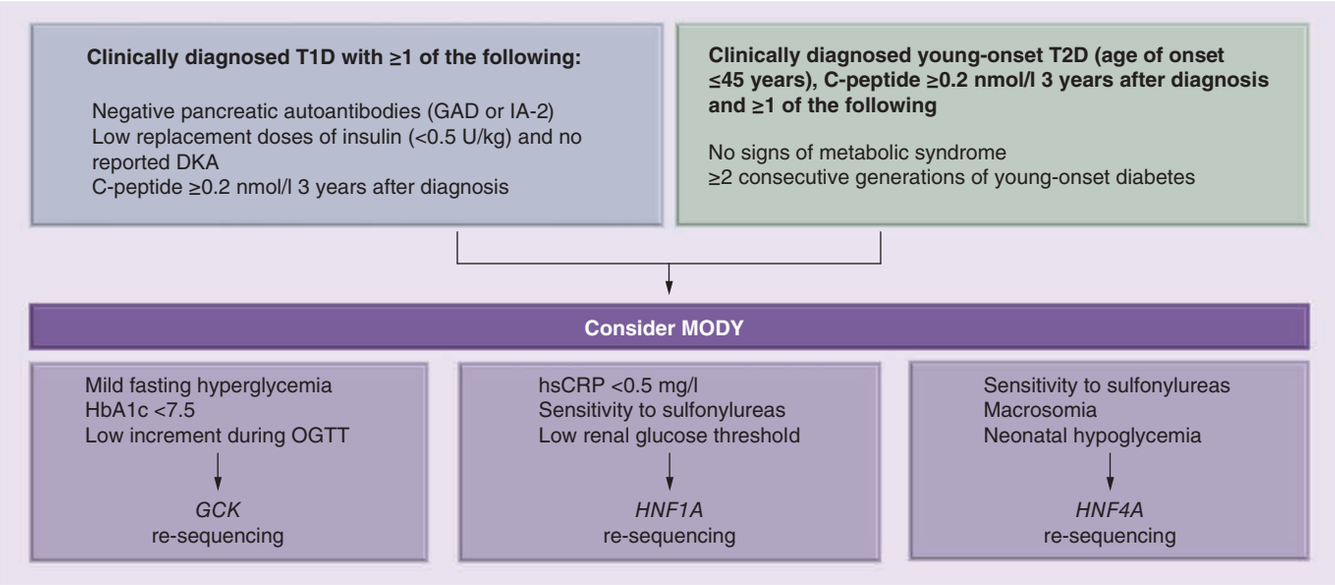

Figure 3. Suggested algorithm for investigation of maturity-onset diabetes of the young.
DKA: Diabetic ketoacidosis; GAD: Glutamic acid decarboxylase; hsCRP: High-sensitivity C-reactive protein; MODY: Maturity-onset diabetes of the young; OGTT: Oral glucose tolerance test; T1D: Type 1 diabetes; T2D: Type 2 diabetes.

This suggests that in the case of strong clinical suspicion, presence of islet autoantibodies should not preclude genetic testing.

■ Biomarkers in combination with clinical features

Table 1 shows the biomarkers investigated to date for MODY, the types of diabetes they distinguish and the cost and availability of the assays.

Current diagnostic criteria are highly specific but have poor sensitivity, missing many cases of MODY [2]. Clinical prediction models utilizing the combination of extended clinical criteria and emerging biomarkers could provide improved sensitivity. Studies evaluating hsCRP in *HNF1A*-MODY observed improvement in the sensitivity and specificity using a combination of hsCRP and existing diagnostic criteria rather than either of them alone [21]. Recently, a prediction model based on most discriminant clinical characteristics was developed by Shields *et al.* [50]. This model uses easily available clinical features such as HbA1c, gender, age at diagnosis, parent with diabetes and treatment to calculate the probability of having MODY. Combinations of these clinical features resulted in an improved sensitivity and specificity (both reaching up to 91%). However, this model remains to be tested in a wider population. hsCRP, C-peptide, islet autoantibodies and HDL, which have been shown to discriminate *HNF1A*-MODY from T1D or T2D, are now being tested in this model [51].

Conclusion & future perspective

Personalized medicine, although not yet achievable in the majority of diseases, is feasible for the more common MODY subtypes, and has a huge clinical impact on patient management. However, the majority of MODY cases remain misdiagnosed as T1D or T2D, and hence are denied appropriate treatment. A systematic approach, as suggested in **Figure 3**, to assessing the underlying etiology of young adult-onset diabetes should be adopted to avoid this diagnosis delay.

Several nongenetic biomarkers that can help prioritize patients for genetic testing have been studied over the last decade. The most promising biomarker to emerge from this research is hsCRP, which is observed to be low in *HNF1A*-MODY. hsCRP provides good discriminatory power between *HNF1A*-MODY and T2D, and can also discriminate *HNF1A*- from *HNF4A*-MODY. Further replication in unselected datasets and health economic assessment is required before this biomarker can be fully translated into clinical practice. Moreover, for efficient use of biomarkers, biomarker development should be accompanied by clinician education so that they can order the appropriate tests, interpret them correctly and identify patients for molecular diagnostic testing.

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- ■ of interest
- ■■ of considerable interest

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