



Monogenic Diabetes Misdiagnosed as Type 1: A Narrative Review of When to Test for MODY

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Abstract

Monogenic diabetes accounts for roughly 1 to 3 per cent of diabetes diagnosed before the age of 25, and the diagnosis matters because it changes treatment: several subtypes respond to sulfonylurea rather than insulin, and one usually requires no treatment at all. It is nonetheless missed. In a diabetes centre cohort of 97 patients with onset before 25, detectable C-peptide and negative autoantibodies, 22 were found to carry a pathogenic variant, and only one of those 22 had been given the correct diagnosis before genetic testing. Yield depends almost entirely on how patients are selected: 2.1 per cent in an unselected childhood cohort, 8.2 per cent among those who were autoantibody-negative with detectable C-peptide, and 21 per cent under narrow clinical criteria. About 10 per cent of people with type 1 diabetes of European ancestry have no detectable islet autoantibodies, rising to 28 per cent in other populations, and in one cohort of 482 such patients MODY accounted for 2.5 per cent. This review sets out who should be tested and what the testing does not settle.

Keywords: Monogenic diabetes; MODY; Misdiagnosis; C-peptide; Genetic testing

Introduction

Monogenic diabetes results from a single gene defect and accounts for approximately 1 to 3 per cent of diabetes diagnosed in young people, with paediatric series reporting 1 to 6 per cent [1,2,3]. The commonest form is maturity-onset diabetes of the young, which follows autosomal dominant inheritance and typically presents in late childhood, adolescence or early adulthood [1,4].

The diagnosis is worth making because it changes management. Variants in HNF1A and HNF4A respond to low-dose sulfonylurea, often allowing insulin to be withdrawn; GCK variants produce mild stable hyperglycaemia that usually requires no treatment outside pregnancy; and neonatal diabetes from KCNJ11 or ABCC8 variants responds to high-dose sulfonylurea [1,5,6,24,25]. Glucokinase variants carry a low burden of vascular complications despite lifelong hyperglycaemia, which is why treatment is usually unnecessary

[26,27].

Because the clinical picture overlaps with type 1 diabetes, many of these patients are treated as type 1 for years [2,7]. This review examines how often that happens, which patients should be tested, and what the genetic result does and does not resolve [29,32].

Material and Methods

Search strategy: PubMed and the archives of the major diabetes, endocrinology and clinical genetics journals were searched for studies of monogenic diabetes misclassified as type 1. Search terms combined monogenic diabetes, MODY and maturity-onset diabetes of the young with misdiagnosis, autoantibody-negative, C-peptide, genetic testing and diagnostic yield. Reference lists of clinical overviews [1,2] and national testing criteria [8] were screened by hand for primary sources.

Eligibility: Studies were included if they reported the yield of genetic testing in a described population, characterised biomarkers used to select patients for testing, or reported treatment change following diagnosis. Registry reports are cited for the relative frequency of subtypes and are identified as such.

Data extraction and handling: Design, population, the selection criteria applied before testing, the genes sequenced and the reported yield were extracted as published. The selection criteria are stated alongside every yield figure, because the same test applied to differently selected groups produces results differing by an order of magnitude. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

How often the diagnosis is missed: A large diabetes centre enrolled 97 patients with diabetes onset before age 25, a random C-peptide of 0.1 ng/mL or above and negative testing for all four islet autoantibodies. Genetic testing identified 22 patients with a pathogenic variant: 10 in HNF1A, eight in GCK and four in HNF4A. Only one of those 22 had been given the appropriate diagnosis before testing (Figure 1) [9].

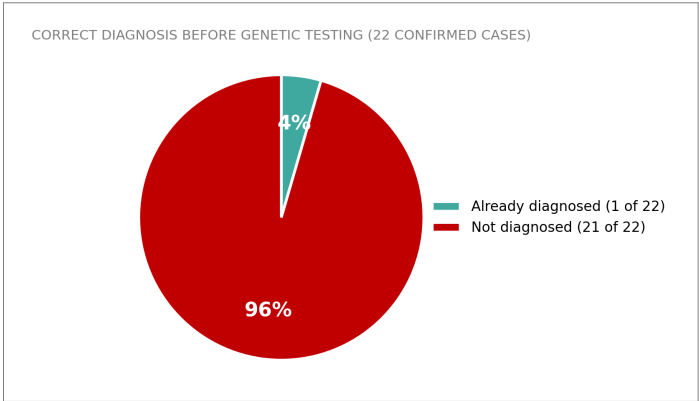


Figure 1: Correct diagnosis before genetic testing among 22 confirmed cases [9]

Why the overlap arises: Approximately 10 per cent of people of European ancestry with a clinical diagnosis of type 1 diabetes have no detectable islet autoantibodies, and that proportion reaches 28 per cent in non-European populations (Figure 3) [10,11]. Antibody-negative type 1 diabetes is a provisional diagnosis rather than a positive one, and a proportion of those patients have monogenic disease [10,12].

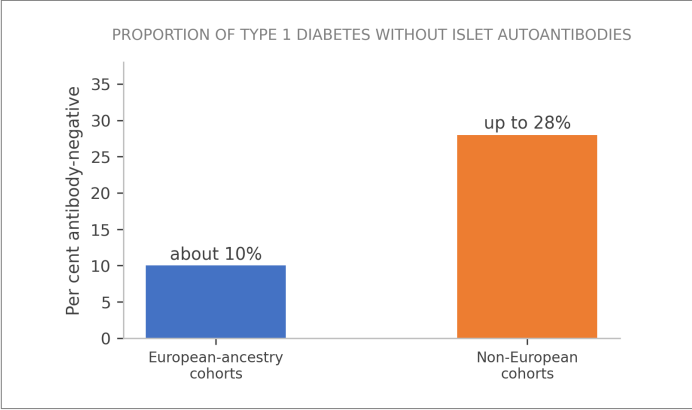


Figure 3: Proportion of clinically diagnosed type 1 diabetes without detectable islet autoantibodies [10,11]

What testing that group finds: Targeted sequencing of 482 antibody-negative patients using a 36-gene panel plus the mitochondrial 3243A>G variant identified MODY in 2.5 per cent and mitochondrial diabetes in 1.7 per cent (Figure 4). HLA genotype was the key distinguishing factor, and persistent C-peptide secretion in the monogenic cases supported the case for screening this group [10].

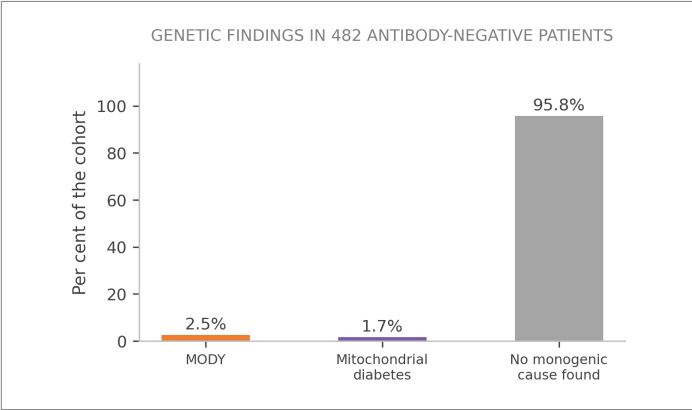


Figure 4: Genetic findings in 482 antibody-negative patients [10]

Yield depends on selection: An unselected childhood diabetes cohort of 821 reported a prevalence of 2.1 per cent. Among paediatric patients without autoantibodies the reported range is 4 to 15 per cent, rising to 8 to 24 per cent when residual C-peptide secretion is also present [11,13]. In the SEARCH analysis, 730 of approximately 5,000 newly diagnosed young people (14.5 per cent) were autoantibody-negative and fasting C-peptide-positive; of the 586 sequenced for GCK, HNF1A and HNF4A, 48 (8.2 per cent) carried a likely pathogenic variant. Narrow clinical selection raises the figure to around 21 per cent (Figure 2) [9,12,14].

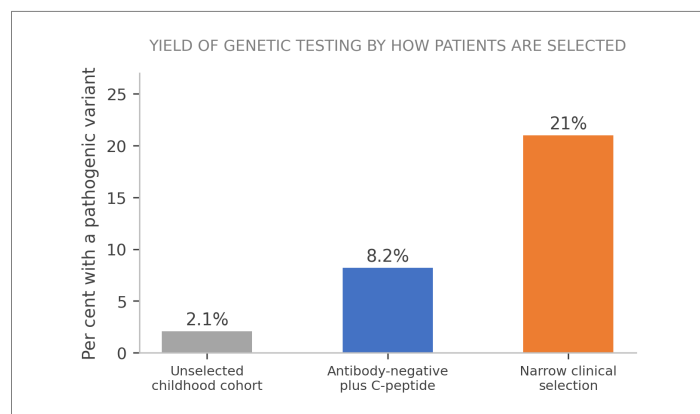


Figure 2: Yield of genetic testing by how patients are selected [9,12,14]

Study	Selection applied	Yield
Unselected cohort [14]	All childhood diabetes, n = 821	2.1%
SEARCH analysis [12]	Antibody-negative, C-peptide-positive	8.2% of 586
Diabetes centre [9]	Onset under 25, antibody-negative, C-peptide detectable	21% of 97
Antibody-negative cohort [10]	482 patients, 36-gene panel	2.5% MODY, 1.7% mitochondrial
Italian paediatric series [15]	8.4% of 275 were antibody-negative	10.5% of those
Finnish register [11]	Children without autoantibodies at diagnosis	Over 10%

Table 1: Diagnostic yield by the selection applied before testing, as reported by the original investigators

The biomarker pathway: Cost-effectiveness analysis supports measuring islet autoantibodies and C-peptide in all paediatric patients and referring those who are antibody-negative with preserved C-peptide for genetic testing (Figure 5) [1,12]. A fasting C-peptide below 0.60 ng/mL indicates insulin deficiency consistent with type 1 diabetes, while a detectable C-peptide alongside a glucose above 8 mmol/L three to five years after diagnosis is unusual in type 1 diabetes and favours monogenic disease [16,17]. National testing criteria add a body mass index threshold and a family history requirement to direct resources [8]. A validated probability model combines these features into a single estimate [21], a type 1 genetic risk score discriminates monogenic from polygenic disease [19,20], and Swedish national data support testing where autoantibodies are absent and glucose only modestly raised [22].

What follows a confirmed diagnosis: National prospective follow-up of treatment change has examined which patients achieve good control after stopping insulin, and reports that genetic subtype and clinical characteristics predict the outcome [33]. Withdrawal is therefore not uniformly successful, and the diagnosis changes the treatment options rather than guaranteeing the result. Registry data describe the relative frequency of subtypes, with glucokinase variants the most common among those producing a MODY phenotype [28].

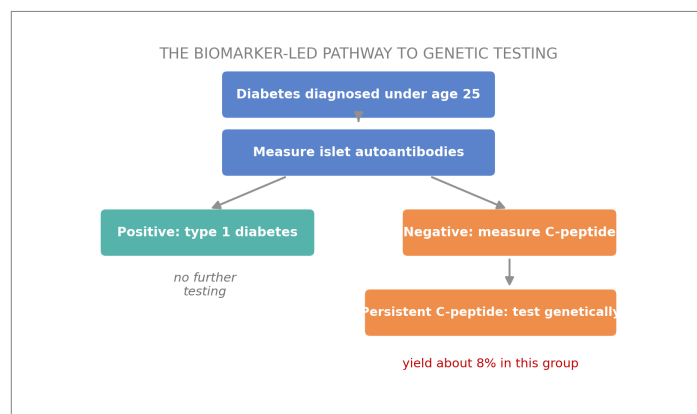


Figure 5: The biomarker-led pathway to genetic testing [1,12,16]

Feature	Favours type 1 diabetes	Favours monogenic diabetes
Islet autoantibodies	Present	Absent
C-peptide after 3-5 years	Undetectable or very low	Persistently detectable
Family history	Usually sporadic	Often across three generations
Presentation	Frequently with ketoacidosis	Often incidental hyperglycaemia
Genetic risk score	High for type 1	Low for type 1

Table 2: Clinical and laboratory features distinguishing the two diagnoses [1,2,16,17]

What the result does not settle: Of the 22 variants identified in the diabetes centre cohort, 13 were known to be pathogenic and nine, 41 per cent, were novel and predicted to be pathogenic (Figure 6) [9]. Variant interpretation is therefore a substantial part of the work, and one large analysis identified over 300 variants of uncertain significance alongside its positive findings [12]. Benign variants are common in some genes, so a reported variant is not automatically a diagnosis [2,18,30,31]. Registry data describe the relative frequency of each subtype [23,28], national follow-up has examined who achieves good control after insulin is withdrawn [33], and referral series report yields of a similar order [34].

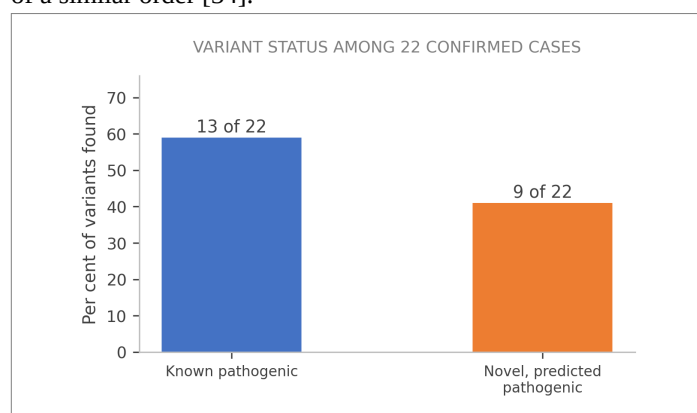


Figure 6: Variant status among the 22 confirmed cases [9]

Subtype	Typical management	Consequence of the diagnosis
HNF1A	Low-dose sulfonylurea	Insulin often withdrawn
HNF4A	Low-dose sulfonylurea	Insulin often withdrawn
GCK	Usually none outside pregnancy	Treatment may be stopped
Neonatal, KCNJ11 or ABCC8	High-dose sulfonylurea	Insulin often withdrawn

Table 3: Management implications by subtype [1,5,6]

Tools that improve selection: Two instruments narrow the group worth testing. A clinical prediction model combining age at diagnosis, sex, body mass index, treatment and family history returns a probability of monogenic diabetes [21]. A type 1 diabetes genetic risk score, built from the HLA and non-HLA variants that confer autoimmune risk, is low in monogenic disease and helps separate it from polygenic type 1 diabetes, and the same score aids discrimination from type 2 diabetes in young adults [19,20]. Urinary C-peptide creatinine ratio offers a practical outpatient alternative to serum sampling [17].

Discussion

One statistic frames this literature. Of 22 patients found to carry a pathogenic variant, one had the right diagnosis beforehand [9]. The remaining 21 were being managed as something they did not have, and for several of them that meant insulin for a condition treatable with a tablet, or treatment for a condition needing none.

The reason is not clinical carelessness. Monogenic diabetes presents in the same age range as type 1 diabetes, and the feature that would distinguish it, absence of autoimmunity with preserved endogenous insulin, is only visible if someone measures autoantibodies and C-peptide and then acts on a negative result [1,12]. A negative antibody test is easy to record and easy to leave unexamined, and antibody-negative type 1 diabetes remains a provisional label applied to about one patient in ten [10,11].

The yield figures should be read as a statement about selection rather than about biology. Two point one per cent in an unselected childhood cohort, 8.2 per cent among those antibody-negative with C-peptide, and 21 per cent under narrow criteria describe the same disease encountered through three different filters [9,12,14]. Any claim about how common monogenic diabetes is requires the selection to be stated, and a testing policy is really a choice about which of those yields is acceptable against the cost.

There is a genuine tension in that choice. The SEARCH investigators reported that no trait or combination of traits reliably distinguished carriers from non-carriers without testing [12]. That argues against relying on clinical criteria to decide who gets sequenced, and simultaneously against testing everyone, since 91.8 per cent of even the well-selected group in that analysis had no variant. The biomarker pathway is the available compromise rather than a solution.

Finally, a positive result is not always an answer. Forty-one per cent of the variants in one cohort were novel, and a separate analysis reported more than 300 variants of uncertain significance [9,12]. Withdrawing insulin on the strength of a variant whose significance is uncertain would be a serious error, and the interpretation step requires genetics input rather than a report read at a diabetes clinic [2,18].

A separate consideration is what a diagnosis means for relatives. Because these conditions are autosomal dominant, a confirmed variant identifies a family rather than an individual, and first-degree relatives have a one in two prior probability of carrying it [2,4]. That multiplies the value of testing the index case and also the consequences of getting the interpretation wrong, since a misclassified variant propagates through a pedigree [18,31].

Set against the enthusiasm for testing, the base rate deserves respect. Monogenic diabetes accounts for a small minority of young-onset diabetes, and rare variants in the same genes are found in the general population without diabetes [30,31]. Testing a poorly selected group will therefore generate more uncertainty than it resolves, which is the argument for the biomarker filter rather than for universal sequencing [3,12].

Study limitations

The limitations belong to the underlying literature. Yields are not comparable across studies because selection criteria, the genes sequenced and the variant classification thresholds all differ [9,10,12]. The diabetes centre cohort includes 97 patients, of whom 22 tested positive, and two were siblings, so the effective sample is smaller than it appears [9]. Gene panels vary in breadth, so a negative result excludes only what was sequenced [10,15]. Variant interpretation is unresolved in a substantial minority of positives, and predictions of pathogenicity are not diagnoses [2,9]. Most cohorts are of European ancestry, while the proportion of antibody-negative diabetes is higher in other populations, so both the yield and the appropriate thresholds may differ [10,11]. C-peptide thresholds derive from small studies and assay standardisation varies. And no randomised evidence establishes that a systematic testing policy improves outcomes compared with testing on clinical suspicion [1,8].

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Conclusion

Monogenic diabetes is uncommon, treatable differently from type 1 diabetes, and routinely missed: in one cohort of 22 confirmed cases, one patient had the correct diagnosis before genetic testing. The patients in whom it should be suspected are identifiable from two tests already available in most clinics, since absence of islet autoantibodies with persistent C-peptide raises the yield from around 2 per cent to around 8. What the evidence does not support is deciding on clinical grounds alone, because no combination of features reliably separates carriers from non-carriers. Nor does a positive result end the matter, with four in ten variants in one series novel and of predicted rather than established significance.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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