



# ISPAD Clinical Practice Consensus Guidelines 2022: The diagnosis and management of monogenic diabetes in children and adolescents

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## 1 | WHAT IS NEW OR DIFFERENT

- Addition of recently described subtypes of monogenic diabetes, including causes associated with diabetes in infancy (*CNOT1*, *ONECUT1*, *YIPF5*, *EIF2B1*, *KCNMA1*); and genetic causes associated with diabetes later in life (*TRMT10A*, *DNAJC3*, *KCNK16*, *DUT*).
- The expanding list of genes causing monogenic diabetes further emphasizes comprehensive next-generation sequencing (NGS) as the best approach to allow for early molecular diagnosis that can guide treatment, rather than phenotype-based targeted testing, particularly for neonatal diabetes (NDM).
- Use of increasingly available publicly accessible information about specific variants to allow for the appropriate classification of pathogenicity of gene variants according to guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP), bolstered by the establishment of international Monogenic Diabetes Expert Panels for gene curation and variant curation with the

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**TABLE 1** Monogenic subtypes of neonatal and infancy-onset diabetes

Gene	Locus	Inheritance	Other clinical features	Reference
Abnormal pancreatic development:				
<i>PLAGL1/HYMAI</i>	6q24	Variable ( <i>imprinting</i> )	TNDM ± macroglossia ± umbilical hernia	20
<i>ZFP57</i>	6p22.1	Recessive	TNDM (multiple hypomethylation syndrome) ± macroglossia ± developmental delay ± umbilical defects ± congenital heart disease	29
<i>PDX1</i>	13q12.1	Recessive	PNDM + pancreatic agenesis (steatorrhea)	264
<i>PTF1A</i>	10p12.2	Recessive	PNDM + pancreatic agenesis (steatorrhea) + cerebellar hypoplasia/aplasia + central respiratory dysfunction	265
<i>PTF1A enhancer</i>	10p12.2	Recessive	PNDM + pancreatic agenesis without CNS features	133
<i>HNF1B</i>	17q21.3	Dominant	TNDM + pancreatic hypoplasia and renal cysts	23
<i>RFX6</i>	6q22.1	Recessive	PNDM + intestinal atresia + gall bladder agenesis	266,267
<i>GATA6</i>	18q11.1-q11.2	Dominant	PNDM + pancreatic agenesis + congenital heart defects + biliary abnormalities	134
<i>GATA4</i>	8p23.1	Dominant	PNDM + pancreatic agenesis + congenital heart defects	268
<i>GLIS3</i>	9p24.3-p23	Recessive	PNDM + congenital hypothyroidism + glaucoma + hepatic fibrosis + renal cysts	269
<i>NEUROG3</i>	10q21.3	Recessive	PNDM + enteric anendocrinosis (malabsorptive diarrhea)	270
<i>NEUROD1</i>	2q32	Recessive	PNDM + cerebellar hypoplasia + visual impairment + deafness	271
<i>PAX6</i>	11p13	Recessive	PNDM + microphthalmia + brain malformations	272
<i>MNX1</i>	7q36.3	Recessive	PNDM + developmental delay + sacral agenesis + imperforate anus	4
<i>NKX2-2</i>	20p11.22	Recessive	PNDM + developmental delay + hypotonia + short stature + deafness + constipation	273
<i>CNOT1</i>	16q21	Spontaneous	PNDM + pancreatic agenesis + holoprosencephaly	274
<i>ONECUT1</i>	15q21.3	Recessive	PNDM + pancreatic hypoplasia + gall bladder hypoplasia	275
Abnormal β-cell function:				
<i>KCNJ11</i>	11p15.1	Spontaneous or dominant	PNDM/ TNDM ± DEND	41
<i>ABCC8</i>	11p15.1	Spontaneous, dominant or recessive	TNDM/PNDM ± DEND	42
<i>INS</i>	11p15.5	Recessive	Isolated PNDM or TNDM	24
<i>GCK</i>	7p15-p13	Recessive	Isolated PNDM	107
<i>SLC2A2 (GLUT2)</i>	3q26.1-q26.3	Recessive	Fanconi-Bickel syndrome: PNDM + hypergalactosemia, liver dysfunction	276
<i>SLC19A2</i>	1q23.3	Recessive	Roger's syndrome: PNDM + thiamine-responsive megaloblastic anemia, sensorineural deafness	277
<i>KCNMA1</i>	10q22.3	Spontaneous	PNDM (not all cases) + developmental delay + intestinal malformations + cardiac malformations + bone dysplasia + dysmorphic features	278
Destruction of β cells:				
<i>INS</i>	11p15.5	Spontaneous or dominant	Isolated PNDM	90
<i>EIF2AK3</i>	2p11.2	Recessive	Wolcott-Rallison syndrome: PNDM + skeletal dysplasia + recurrent liver dysfunction	98
<i>IER3IP1</i>	18q21.2	Recessive	PNDM + microcephaly + lissencephaly + epileptic encephalopathy	279
<i>FOXP3</i>	Xp11.23-p13.3	X-linked, recessive	IPEX syndrome (autoimmune enteropathy, eczema, autoimmune hypothyroidism, elevated IgE)	280
<i>WFS1</i>	4p16.1	Recessive	PNDM <sup>a</sup> + optic atrophy ± diabetes insipidus ± deafness	189
<i>WFS1</i>	4p16.1	Dominant	PNDM or infancy-onset diabetes + congenital cataracts + deafness	281
<i>EIF2B1</i>	12q24.31	Spontaneous	PNDM + episodic hepatic dysfunction	282
<i>YIPF5</i>	5q31.3	Recessive	PNDM + severe microcephaly + epilepsy	283

(Continues)

TABLE 1 (Continued)

Gene	Locus	Inheritance	Other clinical features	Reference
STAT3	17q21.2	Spontaneous	PNPM + enteropathy + other autoimmunity such as cytopenias	116
CTLA4	2q33.2	Spontaneous	Lymphoproliferative syndrome + enteropathy + cytopenias + diabetes + thyroiditis	127
ITCH	20q11.22	Recessive	PNDM + facial dysmorphism + multi-system autoimmunity	128
IL2RA	10p15.1	Recessive	Lymphoproliferation + multi-system autoimmunity + diabetes	129
LRBA	4q31.3	Recessive	PNDM + enteropathy + hypothyroidism + autoimmune hemolytic anemia	118

<sup>a</sup>The mean age of diagnosis among persons with *WFS1* mutations is approximately 5 years.<sup>194</sup>

Source: modified from Reference 47.

TABLE 2 Most important subtypes of MODY and associated clinical features

Gene	Locus	Clinical features	Treatment	References
GCK	7p15-p13	Mild asymptomatic hyperglycemia	None	284
HNF1A	12q24.2	Renal glucosuria	Sulphonylurea	285
HNF4A	20q12-q13.1	Macrosomia and neonatal hypoglycaemia, renal Fanconi syndrome (mutation specific)	Sulphonylurea	286
HNF1B	17q12	Renal developmental abnormalities, genital tract malformations	Insulin	287
KCNJ11	11p15	Proband or relatives may have history of TNDM and/or neuropsychological difficulties	High-dose sulphonylurea	
ABCC8	11p15	Proband or relatives may have history of TNDM and/or neuropsychological difficulties	High-dose sulphonylurea	

elaboration of gene-specific rules (<https://clinicalgenome.org/affiliation/50016>).

- Further understanding of the neuroendocrine aspects of ATP-sensitive potassium channel (KATP) related NDM (KATP-NDM) is now included.
- Clarification that a small fraction of NDM is likely to be autoimmune type 1 diabetes (T1D) and autoimmune etiology distinct from T1D occurring in Trisomy 21.
- Among young persons with diabetes with a clinical diagnosis of type 2 diabetes (T2D), a low but significant fraction can be found to carry pathogenic MODY mutations; highlighting the importance of considering a monogenic cause even when obesity may be present.
- The rate of diabetes-related complications may be lower in HNF1A diabetes who have been treated with sulphonylureas (SU).
- Liver (with or without pancreas) transplantation can improve the outcomes of individuals with Wolcott-Rallison syndrome.

## 2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

### 2.1 | General aspects of monogenic diabetes

- Monogenic diabetes is uncommon, but accounts for ~2.5%–6.5% of pediatric diabetes **B**.

- NGS enables the simultaneous analysis of multiple genes at a lower cost per gene providing comprehensive testing **B**.
- NGS is the recommended methodology for study of suspected monogenic diabetes, unless a very specific and highly suggestive clinical scenario is present, such as glucokinase (*GCK*) mutations, which cause a distinct phenotype of asymptomatic and stable mild fasting hyperglycemia **B**.
- Results of genetic testing should be reported and presented to families in a clear and unambiguous manner **E**.
- Referral to a specialist in monogenic diabetes or an interested clinical genetics unit is suggested to guide specific management considerations and/or facilitate genetic testing of other related affected or pre-symptomatic individuals **E**.

### 2.2 | Neonatal diabetes

- All infants diagnosed with diabetes in the first 6 months of life are recommended to have immediate molecular genetic testing **B**.
- Genetic testing maybe be considered in infants diagnosed between 6 and 12 months, especially in those without islet autoantibodies or who have other features suggestive of a monogenic cause **C**.
- A molecular genetic diagnosis of NDM provides essential information regarding treatment options, associated features, and diabetes course that may have a significant clinical benefit **B**.

**TABLE 3** Classification of Syndromes of severe insulin resistance

IR syndrome subtype		Gene (inheritance)	Leptin	Adiponectin	Other clinical features
Primary insulin signaling defects	Receptor defect	<i>INSR</i> (AR or AD)	Decreased	Normal or elevated	No dyslipidemia or hepatic sterosis
	Post receptor defects	<i>AKT2</i> , <i>TBC1D4</i> (AD)			Elevated fasting triglycerides and LDL-cholesterol, hepatic steatosis, diabetes ( <i>AKT2</i> )
Adipose tissue abnormalities	Monogenic obesity	<i>MC4R</i> (AD) <i>LEP</i> , <i>LEPR</i> , <i>POMC</i> (AR) Others	Increased (low in <i>LEP</i> )		Tall stature ( <i>MC4R</i> ) Hypogonadism ( <i>LEP</i> ) Hypoadrenalism ( <i>POMC</i> )
	Congenital generalized lipodystrophy	<i>AGPAT2</i> , <i>BSCL2</i> (AR) Others	Decreased	Decreased	Severe dyslipidemia (high triglycerides, low HDL-cholesterol) Hepatic sterosis
	Partial lipodystrophy	<i>LMNA</i> , <i>PPARG</i> , <i>PIK3R1</i> (AD) Others	Variable		Myopathy and cardiomyopathy ( <i>LMNA</i> ) Pseudo-acromegaly ( <i>PPARG</i> ) SHORT syndrome with partial lipodystrophy, and diabetes ( <i>PIK3R1</i> )
Complex syndromes	Alström	<i>ALMS1</i> (AR)			Cone-rod dystrophy leading to blindness, sensorineural hearing loss, diabetes and cardiomyopathy
	Bardet-Biedl	<i>BBS1</i> to <i>BBS18</i> (mostly AR)			Cone-rod dystrophy, obesity, renal dysfunction, polydactyly, learning disabilities, hypogonadism and diabetes
	DNA damage repair disorders	<i>WRN</i> (AR) <i>BLM</i> (AR)			Scleroderma-like skin changes, cataracts, increased cancer risk, atherosclerosis and diabetes; Sun-sensitive, telangiectatic skin changes; increased cancer risk and diabetes
	Primordial dwarfism	<i>PCNT</i> (AR)			Microcephalic osteodysplastic primordial dwarfism and diabetes

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

Source: modified from Parker et al. Reference 228.

- Treatment with SU, especially glibenclamide (also known as glyburide), is recommended for NDM due to *KCNJ11* and *ABCC8* abnormalities **B**.
- Glibenclamide significantly improved neurological and neuropsychological abnormalities in individuals with neonatal onset diabetes due to *KCNJ11* or *ABCC8* mutations. Earlier treatment initiation was associated with greater benefits **B**.

### 2.3 | Maturity onset diabetes of the young

- The diagnosis of maturity onset diabetes of the young (MODY) is recommended in the following scenarios:
  - A family history of diabetes in a parent and first-degree relatives of that affected parent in persons with diabetes who lack the characteristics of T1D and T2D **B**.
- Testing for GCK-MODY, which is the commonest cause of persistent, incidental hyperglycemia in the pediatric population, is recommended for mild stable fasting hyperglycemia that does not progress **B**.
- In familial autosomal dominant symptomatic diabetes, mutations in the *HNF1A* gene (*HNF1A*-MODY) should be considered as the first diagnostic possibility **B**.
- Specific features can suggest subtypes of MODY, such as renal developmental disease or renal cysts (*HNF1B*-MODY), macrosomia and/or neonatal hypoglycemia (*HNF4A*-MODY), exocrine pancreatic dysfunction or pancreatic cysts (*CEL*-MODY), or hearing impairment and maternal inheritance of diabetes (mitochondrial diabetes) **C**.
- Obesity alone should not preclude genetic testing in young persons, especially if: **C**
  - family history is strongly suggestive of autosomal dominant inheritance of diabetes
  - if some affected family members are NOT obese
  - and/or, there are no other features of metabolic syndrome.
- Some forms of MODY are sensitive to SU, such as *HNF1A*-MODY and *HNF4A*-MODY **B**
- Mild fasting hyperglycemia due to GCK-MODY is not progressive during childhood. These persons do not develop complications **B**

and do not respond to low dose insulin or oral agents C. They should not receive treatment.

- Establishing the correct molecular diagnosis of MODY is suggested for the following reasons: C
  - avoids misdiagnosis as T1D or T2D
  - may offer more accurate prognosis of risk of complications
  - may avoid stigma and limitation of employment opportunity (especially in the case of GCK-MODY)
  - may enable prediction of risk in relatives, including offspring
  - can be cost-effective when appropriately selected individuals are screened

### 3 | INTRODUCTION

Monogenic diabetes results from one or more defects in a single gene or chromosomal *locus*. The disease may be inherited within families as a dominant, recessive, or non-Mendelian trait or may present as a spontaneous case due to a *de novo* mutation.

Monogenic diabetes has been categorized as neonatal or early infancy diabetes (Table 1), MODY (Table 2), diabetes associated with extra-pancreatic features, and monogenic insulin resistance (IR) syndromes (Table 3).

### 4 | CLINICAL RELEVANCE OF DIAGNOSING MONOGENIC DIABETES

- Identification of children with monogenic diabetes usually improves their clinical care.<sup>1</sup>
- Making a specific molecular diagnosis helps predict the expected clinical course of the disease and guides the most appropriate management, including pharmacological treatment, in a particular person with diabetes.
- Characterizing the specific molecular diagnosis has important implications for the family as it informs genetic counseling. It also frequently triggers extended genetic testing in other family members with diabetes or hyperglycemia who may also carry a causal mutation, thereby improving the classification of diabetes.<sup>2,3</sup>

### 5 | SELECTING CANDIDATES FOR MOLECULAR TESTING

In contrast to T1D and T2D, where there is no single definitive diagnostic test, molecular genetic testing is both sensitive and specific for diagnosing monogenic diabetes. Appropriate informed consent/assent must be prospectively obtained from the affected person and/or legal guardians and should be strongly considered in persons with a suspected monogenic cause. Genetic testing is currently available (and may be free of charge on a research basis in certain academic institutions) in many countries around the world: <https://www.diabetesgenes.org>; <http://monogenicdiabetes.uchicago.edu>; [www.mody.no](http://www.mody.no); <http://euro-wabb.org>; <https://www.ospedalebambinogesu.it/test-genetici-89757/>; <https://robertdebre.aphp.fr/equipes-cliniques/pole-biologie/genetique/genetique-moleculaire/#1461944418-1-40> and several commercial laboratories.

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NGS enables the simultaneous analysis of multiple genes at a lower cost per gene and has mostly replaced single gene testing by Sanger sequencing or other methods.<sup>4–8</sup> Such NGS panels provide an efficient means of comprehensive testing that results in earlier genetic diagnosis, which in turn facilitates appropriate management as well as monitoring for other associated features before they become clinically apparent. It is important to note that NGS testing panels are still expensive, so it remains appropriate to use a judicious approach to selecting persons with diabetes for comprehensive molecular testing and in specific circumstances (such as living in a resource-poor setting), Sanger sequencing of a limited number of the most treatment-relevant genes may be the most practical approach. Moreover, some NGS panels have included genes lacking robust evidence for a causal role in monogenic diabetes and this can result in misdiagnosis and confusion for the person with diabetes and other affected family members; however, increasing international collaboration between testing laboratories has begun to limit such examples of inaccurately reported genetic testing results. Sanger sequencing remains appropriate as an efficient cost-effective method for testing of a variant found by NGS testing of the first individual in other affected or at-risk family members (cascade testing).

In NDM, genetic testing may be cost saving because of improved cheaper treatment; testing for MODY in appropriate populations can also be cost-effective.<sup>2,3,9</sup> Targeted gene sequencing, however, may still be appropriate for some persons with diabetes; for example, a pregnant female with mild fasting hyperglycemia, in whom a rapid test to identify a GCK mutation will inform management of the pregnancy. For most people with diabetes suspected to have a monogenic cause, NGS provides an optimal approach for clinical care as it provides a genetic diagnosis that often precedes the development of additional clinical features, informs prognosis, and guides clinical management.<sup>2,3,9</sup>

### 6 | WHEN TO SUSPECT A DIAGNOSIS OF T1D IN CHILDREN MAY NOT BE CORRECT?

Features that suggest monogenic diabetes in children initially thought to have T1D are listed below. Except for the age of diagnosis less than 6 months, none of these are pathognomonic and should be considered together rather than in isolation:

1. Diabetes presenting before 6 months of age (as T1D is extremely rare in this age group), or consider NDM if the diagnosis is between 6 and 12 months and there is no evidence of autoimmunity or if the person with diabetes has other features such as congenital defects, or an unusual family history.<sup>10,11</sup>
2. Family history of diabetes in one parent and other first-degree relatives of that affected parent.
3. Absence of islet autoantibodies, especially if checked at diagnosis.
4. Preserved  $\beta$ -cell function, with low insulin requirements and detectable C-peptide (either in blood or urine) over an extended partial remission phase (at least 5 years after diagnosis).

## 7 | WHEN TO SUSPECT A DIAGNOSIS OF T2D IN CHILDREN MAY NOT BE CORRECT

In young people, T2D often presents around puberty and the majority are obese. As there is no diagnostic test for T2D and because obesity has become so common in children, children and adolescents with monogenic diabetes may also be obese and can be very difficult to distinguish from T2D.<sup>1</sup> One recent study found that 3% of obese youth with presumed T2D in fact carried pathogenic monogenic diabetes variants.<sup>5</sup> Features that suggest monogenic diabetes in young people with suspected T2D are listed below:

1. Lack of consistent severe obesity among affected family members.
2. Lack of consistent acanthosis nigricans and/or other markers of metabolic syndrome (hypertension, low HDL-cholesterol, etc.) among affected family members.
3. Family history of diabetes in one parent and other first-degree relatives of that affected parent, especially if any affected family member lacks obesity and other markers of metabolic syndrome.
4. Unusual distribution of fat, such as central fat with thin or muscular extremities.

## 8 | INTERPRETATION OF GENETIC FINDINGS

Despite the obvious clinical benefits derived from genetic diagnostic services:

- Care needs to be exercised in the interpretation of genetic findings. The way the clinician interprets the genetic report will have a major effect on the future clinical management of the person with diabetes and his/her family.
- Results should be presented in a clear and unambiguous way to ensure that both clinicians and the person with diabetes and their families receive adequate and understandable information. Specific recommendations describing the information that should be included in the molecular genetics laboratory report for MODY testing have been published.<sup>12</sup>
- This includes the method used for mutation screening, limitations of the test, classification of the variant as pathogenic/likely pathogenic or of uncertain significance (with supporting evidence included where appropriate), and information about the likelihood of the disease being inherited by the offspring.
- The laboratory reporting the results should adhere to the ACMG/AMP variant classification guidelines.<sup>13</sup> Many genetic testing laboratories have been participating in the Monogenic Diabetes Variant Curation Expert Panel (<https://clinicalgenome.org/affiliation/50016/>) that has provided more definitive curation of hundreds of variants that are freely accessible and recognized by the US FDA. This resource can be utilized to check whether a variant in question has been deemed “pathogenic” or “likely pathogenic” in which case there should be confidence that this is the cause of diabetes, or if “benign” or “likely benign” that another cause should be considered.

Whether or not the testing report follows ACMG/AMP guidelines, when testing reveals a variant of uncertain significance (VUS), or when predictive testing of asymptomatic individuals is requested, consultation with an expert center with experience in monogenic diabetes can often provide additional insight on the interpretation and recommendations of how to proceed.

## 9 | SPECIFIC SUBTYPES OF MONOGENIC DIABETES AND THEIR MANAGEMENT

In children, the majority of cases of monogenic diabetes result from mutations in genes causing  $\beta$ -cell loss or dysfunction, although diabetes can rarely occur from mutations resulting in very severe IR. From a clinical perspective, specific scenarios when a diagnosis of monogenic diabetes should be considered include:

1. Diabetes presenting before 6 months of age, which is known as NDM.
2. Autosomal dominant familial mild hyperglycemia or diabetes.
3. Diabetes associated with extra-pancreatic features (such as, for example, congenital heart or gastrointestinal defects, brain malformations, severe diarrhea, or other autoimmune conditions in a very young child).
4. Monogenic IR syndromes (see below: characterized by high insulin levels or high insulin requirements; abnormal distribution of fat with a lack of subcutaneous fat, especially in extremities; dyslipidemia, especially high triglycerides; and/or significant acanthosis nigricans).

### 9.1 | Neonatal diabetes diagnosed within the first 6–12 months of life

- All infants diagnosed under 6 months should have genetic testing for a monogenic cause, regardless of islet autoantibody status.
- The clinical presentation of autoimmune T1D may rarely occur before age 6 months<sup>11,14</sup>; a recent study suggested approximately 4% of cases may be T1D (see section of autoimmune monogenic diabetes).<sup>15</sup>
- One recent study observed trisomy 21 in a much greater than expected fraction of NDM individuals, with the conclusion that trisomy 21 can cause an autoimmune form of diabetes that appears to be distinct from the more common autoimmune T1D.<sup>16</sup>
- Some cases of NDM can be diagnosed between 6–12 months<sup>17,18</sup> although the vast majority of these older infants with diabetes have T1D. Reasons to consider genetic testing in those diagnosed between 6–12 months include: negative autoantibody testing, extra-pancreatic features such as gastrointestinal anomalies or congenital defects, unusual family history, or even the development of multiple autoimmune disorders at a young age.
- Approximately half will require lifelong treatment to control hyperglycemia and are denominated as PNDM.
- In the remaining cases, known as transient neonatal diabetes (TNDM), diabetes will remit within a few weeks or months although it might relapse later in life.

- PNDM and TNDM present more frequently isolated or is the first feature to be noted.
- Some infants with diabetes show a variety of associated extra-pancreatic clinical features that may point to a particular gene; however, because these features often are not apparent initially, they will not always be helpful in guiding genetic testing and instead, early comprehensive testing will often allow for the genetic testing result to precede the recognition of other features (Table 1).

Many infants with NDM are born small for gestational age, which reflects a prenatal deficiency of insulin secretion as insulin exerts potent growth-promoting effects during intrauterine development.<sup>19</sup>

## 9.2 | Transient neonatal diabetes from imprinting anomalies on 6q24

- The genetic basis of TNDM has been mostly uncovered: approximately two-thirds of cases are caused by abnormalities in an imprinted region on chromosome 6q24.<sup>20,21</sup>
- Activating mutations in either of the genes encoding the two subunits of the ATP-sensitive potassium ( $K_{ATP}$ ) channel of the  $\beta$ -cell membrane (*KCNJ11* or *ABCC8*) cause the majority of the remaining cases (KATP-NDM).<sup>22</sup>
- A minority of cases of TNDM is caused by mutations in other genes, including *HNF1B*,<sup>23</sup> *INS*<sup>24</sup> among others.

Anomalies at the 6q24 locus, spanning two candidate genes *PLAGL1* and *HYMAI*, are the single most common cause of NDM and always result in TNDM.<sup>25</sup> In normal circumstances, this region is maternally imprinted so that only the allele inherited from the father is expressed. TNDM is ultimately associated with overexpression of the imprinted genes.<sup>26</sup> To date, three different molecular mechanisms have been identified: (1) paternal uniparental disomy of chromosome 6 (UPD6) either complete or partial; this accounts for 50% of sporadic TNDM cases, (2) unbalanced paternal duplication of 6q24 (found in most familial cases), and (3) hypomethylation of the maternal allele (found in sporadic cases).<sup>27</sup> Methylation defects may result from an isolated imprinting variant affecting only the 6q24 locus or may arise in the context of a generalized hypomethylation syndrome caused by multiple imprinting alterations across the genome, that is, multi-locus imprinting disturbance (MLIDs) along with other clinical features including congenital heart defects, brain malformations, and so forth.<sup>28</sup> Some cases of TNDM secondary to multiple methylation defects are caused by recessively acting mutations in *ZFP57*, a gene on chromosome 6p involved in the regulation of DNA methylation.<sup>29</sup>

Neonates with diabetes caused by 6q24 abnormalities are born with severe intrauterine growth retardation (IUGR) and one-third of them show macroglossia; more rarely, an umbilical hernia is present. They develop severe but nonketotic hyperglycemia very early, usually during the first week of life.<sup>27,30</sup>

- Despite the severity of the initial presentation, the insulin dose can be tapered quickly so that most infants do not require any

treatment by a median age of 12–14 weeks and the rate of remission is close to 100%.<sup>31</sup>

- Because most cases exhibit some degree of endogenous  $\beta$ -cell function, insulin therapy is not always necessary, and these infants may respond to oral SU or other drugs used for T2D.<sup>31–34</sup>
- In some, a transition to remission has been observed with no need for insulin therapy or initial SU treatment.<sup>34</sup>
- Some cases with TNDM have shown a positive response to SU.<sup>34,35</sup>
- Following remission, a low proportion of affected infants and children will exhibit clinically significant hypoglycemia that in some cases requires long-term treatment.<sup>36,37</sup> During remission, transient hyperglycemia may occur during intercurrent illnesses.<sup>38</sup>
- Over time, diabetes relapses in at least 50%–60% of these young people; in one large cohort followed until 18 years of age, relapse occurred in 85%.<sup>39</sup> Relapse usually occurs around puberty, although recurrences have been reported as young as 4 years of age.

Therefore, parents of children with TNDM should internalize the high risk of their child's future diabetes relapse and these children may benefit from annual HbA1c testing. Relapse clinically resembles early-onset T2D and is characterized by a loss of the first-phase insulin secretion.<sup>34</sup> Long-term metabolic and socio-educational follow-up has shown that these persons have decreased educational attainment, and those with diabetes have lower insulin secretion capacity.<sup>40</sup>

The phases described above do not present uniformly in every affected child. Interestingly, some carrier relatives develop T2D or gestational diabetes in adulthood without any evidence of having had NDM, as well as in a small fraction of people with early-onset, non-obese, non-autoimmune diabetes without a history of NDM. This suggests significant variability in phenotype, possibly related to other genetic or epigenetic factors that may influence the clinical expression of alterations of chromosome 6q24.<sup>20,31</sup>

The role of genetic counseling depends on the underlying molecular mechanism. Uniparental disomy of chromosome 6 is generally sporadic and, therefore, the risk of recurrence in siblings and offspring is low. When paternal duplication of the 6q24 region is found, affected newborn males have a 50% chance as adults of transmitting the mutation and the disease to their children. In contrast, newborn affected females will as adults pass on the duplication, but their children will not develop the disease. In this case, TNDM may recur in the next generation as their asymptomatic sons pass on the molecular defect to their own children. Some methylation defects (i.e., *ZFP57* mutations) show an autosomal recessive inheritance and hence the recurrence risk is 25% for siblings and almost negligible for the offspring of an affected individual.

## 9.3 | Permanent neonatal diabetes due to mutations in the $K_{ATP}$ channel genes (KATP-NDM)

KATP-NDM is the commonest cause of PNDM<sup>41–45</sup> and the second most common cause of TNDM.<sup>22</sup> The prevalence of KATP-NDM in a

specific group depends on the degree of consanguinity. In outbred populations the commonest known cause of PNDM are abnormalities in the  $K_{ATP}$  channel or *INS* genes.<sup>9,46</sup> If parents are related, Wolcott-Rallison syndrome or homozygous mutations in the *GCK* gene are the most common etiologies.<sup>47</sup> The causes of up to 20% of PNDM cases remain unknown.

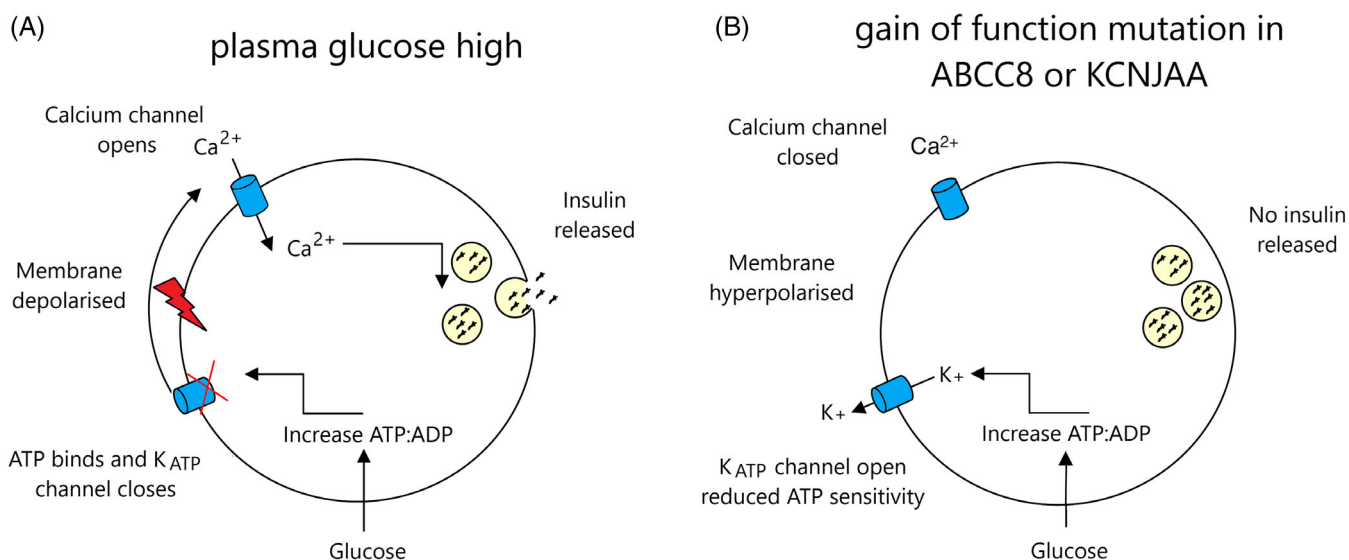
- $K_{ATP}$  channels are hetero-octameric complexes formed by four pore-forming Kir6.2 subunits and four SUR1 regulatory subunits, encoded by the genes *KCNJ11* and *ABCC8*, respectively.<sup>48</sup> They regulate insulin secretion by linking the intracellular metabolic state to the  $\beta$ -cell membrane electrical activity. Any increase in the intracellular metabolic activity induces a rise in the ATP/ADP ratio within the pancreatic  $\beta$ -cell. The high ATP/ADP ratio closes the  $K_{ATP}$  channels and leads to cell membrane depolarization which ultimately triggers insulin secretion.<sup>49</sup>
- Activating mutations in *KCNJ11* or *ABCC8*, prevent  $K_{ATP}$  channel closure and hence reduce insulin secretion in response to hyperglycemia, resulting in diabetes<sup>42,41,43,45</sup> (Figure 1). A loss-of-function nonsense mutation in *ABCC8*, resulting in gain-of-channel function, has also been reported.<sup>50</sup>

Approximately 90% of persons with *KCNJ11* mutations have PNDM while ~10% develop TNDM, whereas *ABCC8* mutations more frequently (~66%) cause TNDM.<sup>42,51</sup> There are no significant differences in the severity of IUGR or the age at diagnosis of diabetes between the two subtypes of NDM.<sup>22</sup>  $K_{ATP}$  channel mutations typically show milder IUGR and are diagnosed slightly later than infants with 6q24 abnormalities, indicating a less severe insulin deficiency during the last months of intrauterine development and at the time

birth. In  $K_{ATP}$ -TNDM, diabetes usually remits later and relapses earlier than in 6q24-TNDM.<sup>22</sup> The low or undetectable C-peptide levels and frequent presentation with diabetic ketoacidosis in  $K_{ATP}$ -NDM suggest insulin dependency.<sup>52</sup>

In addition to diabetes, about 20% of affected children with *KCNJ11* mutations present with associated neurological features<sup>41,53,54</sup> in keeping with the expression of  $K_{ATP}$  channels in neurons and muscle cells.<sup>49,55</sup> The most severely damaging mutations are also associated with marked developmental delay and early-onset epilepsy, known as DEND (developmental delay, epilepsy, and NDM) syndrome. An intermediate DEND syndrome characterized by NDM and less severe developmental delay without epilepsy is more common. Recent studies utilizing detailed testing have revealed that mild neurodevelopmental abnormalities occur even in those with milder mutations previously thought to cause only isolated diabetes. In some studies using sibling controls, mild but significant impairments were found in several domains, including IQ, measures of academic achievement, and executive function. Many of these children met criteria for developmental coordination disorder (particularly visual-spatial dyspraxia), attention deficit hyperactivity disorder, anxiety disorder, or autism, and/or had behavioral or sleep difficulties.<sup>39,56–58</sup>

- Approximately 90% of children with activating mutations in the  $K_{ATP}$  channel genes can be switched from insulin to off-label SU tablets.<sup>59–61</sup> A suspension of glibenclamide has shown to be safe and effective in individuals with NDM,<sup>62</sup> and received authorization for use in the European Union.<sup>63</sup>
- Treatment with SU dramatically improves glycemic management, which appears to be durable long-term with only minimal mild hypoglycemia.<sup>64,65</sup>



**FIGURE 1** Insulin secretion from the pancreatic beta cell in (A) normal cell in a high plasma glucose environment and (B) in a cell with a  $K_{ATP}$  channel mutation. Source: adapted from Reference 263. (A) Glucose enters the cell and is metabolized, causing an increase in ATP,  $K_{ATP}$  channel closure is induced via ATP binding, the membrane is depolarized, and calcium influx is triggered resulting in the release of insulin from its storage vesicles. (B) A gain of function mutation in the  $K_{ATP}$  channel results in the failure of ATP to bind to the channel, causing the channel to remain open, the membrane stays hyperpolarized and no insulin is released



- The glibenclamide doses required when calculated based on body weight are higher compared to the dose used in adults with T2D, typically needing around 0.5 mg/kg/day, although doses as high as 2.3 mg/kg/day have been occasionally reported.<sup>66–68</sup> The dose required depends mostly on the age at which the person starts SU, as well as the specific mutation.<sup>69,70</sup>
- Many persons have been able to progressively reduce the dose after transition while maintaining excellent glycemic management.<sup>71,72</sup> The only side effects reported to date are transient diarrhea and staining of the teeth.<sup>73,74</sup> Recently, it has been reported that celiac disease may cause secondary SU failure not explained by lack of adherence to therapy.<sup>75</sup>
- Insulin secretion in children with diabetes treated with adequate SU doses seems to be driven mostly by food intake via non-KATP dependent pathways. Meals composed of either all carbohydrate or only protein/fat resulted in similar insulin responses, highlighting the importance of carbohydrate intake with most meals to avoid post-prandial hypoglycemia.<sup>76</sup>
- Some studies have shown that SU may penetrate the blood–brain barrier, but maintenance of cerebrospinal fluid levels may limit the benefit of SU on neurodevelopmental outcome, and use of other agents could be considered.<sup>77–79</sup>
- Although SU appears to partially improve some of the neurological symptoms, the degree of improvement likely also depends on how early treatment is started.<sup>80–83</sup>
- Neurological features have been reported less frequently in persons with *ABCC8* mutations, who more often have TNDM.<sup>42,43</sup> However, those with PNDM due to *ABCC8* mutations had a similar range of difficulties as those with PNDM due to *KCNJ11* mutations.<sup>84</sup>
- The *ABCC8* encoded SUR-1 protein is crucial in retinal function and SU (glibenclamide) confers direct retinal neuroprotection through SUR-1 mediated mechanisms.<sup>85,86</sup>
- A recent study utilized patient-derived iPSCs to generate cerebral organoids and found major defects in early development of cortical neuronal network in V59M mutants compared to controls, that could partially be rescued by the SU tolbutamide.<sup>87</sup>

Activating mutations in *KCNJ11* causing NDM are always heterozygous. Since about 90% of these mutations arise de novo, there is usually no family history of NDM<sup>88</sup> but familial cases show an autosomal dominant pattern of inheritance. Recurrence risk for the offspring of an affected person is 50%. This is also true for most people with activating mutations in *ABCC8*. However, some persons are homozygous or compound heterozygous for two different mutations and NDM is recessively inherited.<sup>43</sup> In this case, the risk of NDM for future siblings is 25%, but almost non-existent for the offspring of the affected person unless the other parent is also a carrier for the same mutation. Germline mosaicism (mutations present in the gonads but not detectable in blood) has been reported in several families<sup>88</sup> and hence unaffected parents of a child with an apparently de novo mutation should be advised that the recurrence risk in siblings is low but not negligible.

### 9.3.1 | Neonatal diabetes due to mutations in *INS* gene

Mutations in the proinsulin gene (*INS*) are the second most common cause of PNDM after KATP channel mutations.<sup>46,89–92</sup> Individuals with diabetes due to *INS* mutations lack any extra-pancreatic features and are insulin dependent.<sup>89,91,93</sup> Dominant heterozygous mutations are most common and usually result in a misfolded proinsulin molecule that is trapped and accumulates in sub-cellular compartments, leading to endoplasmic reticulum stress and  $\beta$ -cell apoptosis.<sup>93–95</sup> Recessive biallelic (homozygous or compound heterozygous) mutations lead to loss or inactivation of proinsulin.<sup>24</sup> These mutations do not cause slowly progressive  $\beta$ -cell destruction but result in a lack of insulin biosynthesis before and after birth, which explains much lower birth weights and earlier presentation of diabetes in affected children. Since the disease is recessively inherited, there will be a 25% recurrence risk in siblings when each parent has been confirmed to be a carrier of a causal *INS* variant.

The severity of IUGR in children with heterozygous *INS* mutations is similar to those with  $K_{ATP}$  channel mutations, but they present at somewhat later ages.

- Although the diabetes is still diagnosed most often before 6 months of age, it can also occur up to a year of age or even later; therefore genetic testing should be considered in children with autoantibody negative diabetes presenting at early ages,<sup>89,91,93,96</sup> as well as in those with a MODY-like phenotype.
- Most heterozygous *INS* mutations are sporadic de novo mutations but about 20% of probands have a family history of autosomal dominant NDM.<sup>91</sup>

### 9.3.2 | Wolcott–Rallison syndrome

This rare autosomal recessive syndrome is the commonest cause of PNDM in highly inbred populations and characterized by early-onset diabetes mellitus, spondyloepiphyseal dysplasia, and recurrent hepatic and/or renal dysfunction.<sup>97,98</sup> Wolcott–Rallison syndrome (WRS) is caused by biallelic mutations in the *EIF2AK3* (eukaryotic translation initiation factor alpha 2-kinase 3) gene, which encodes a protein involved in the regulation of the endoplasmic reticulum (ER) stress response. Pancreatic development is rather normal in the absence of the functional protein, but misfolded proteins accumulate within the endoplasmic reticulum after birth and eventually induce  $\beta$ -cell apoptosis. Although diabetes usually manifests during infancy, it might not present until 3–4 years of age. Diabetes may be the first clinical manifestation of the syndrome and, therefore, this diagnosis should be considered even in children with isolated PNDM, especially if they were born to consanguineous parents or from a highly inbred population.<sup>99,100</sup> Since the disease is recessively inherited, there is a 25% recurrence risk in siblings. Fulminant hepatic failure is the main cause of death in persons with WRS and currently there is no agent to reverse this abnormality<sup>101</sup>; however, recent reports indicate that liver

(with or without pancreas) transplantation can be life saving and improve the outcomes of individuals with this syndrome.<sup>101-104</sup>

### 9.3.3 | Neonatal diabetes due to GCK mutations

The enzyme glucokinase is considered the glucose sensor of the  $\beta$ -cells, as it catalyzes the rate-limiting step of glucose phosphorylation and therefore enables the  $\beta$ -cell to respond appropriately to the degree of glycemia.<sup>105</sup>

- Complete glucokinase deficiency secondary to mutations in both alleles, either homozygous or compound heterozygous, prevents the  $\beta$ -cells from secreting insulin in response to hyperglycemia.<sup>106,107</sup>
- Neonates present with severe IUGR, are usually diagnosed with diabetes during the first few days of life, and require exogenous insulin therapy. Apart from diabetes, they do not show any relevant extrapancreatic features.<sup>106-113</sup>

GCK is responsible for not more than 2%–3% of cases of PNDM overall,<sup>47</sup> but has an increased prevalence in regions with a high degree of consanguinity.<sup>114</sup> This type of PNDM is inherited in a recessive manner so the recurrence risk for future siblings is 25%. This diagnosis should be strongly considered in probands born to parents with asymptomatic mild hyperglycemia; therefore, measuring fasting blood glucose in the parents of any child with NDM, even when there is no known consanguinity or family history of diabetes, is often recommended.

Few studies have evaluated the risk of microvascular complications in NDM, but one study showed that individuals with KATP/PNDM or abnormalities in the insulin gene (*INS*) do not seem prone to severe eye complications even after a median diabetes duration of 24 years.<sup>115</sup>

## 10 | IPEX SYNDROME AND OTHER MONOGENIC CAUSES OF AUTOIMMUNE DIABETES

- Mutations in at least nine different genes are now known to cause autoimmune syndromes that can include neonatal and infancy-onset diabetes associated with pancreatic islet autoantibodies: *AIRE*, *CTLA4*, *FOXP3*, *IL2RA*, *ITCH*, *LRBA*, *STAT1*, *STAT3*, and *STAT5B*.
- These monogenic conditions that do cause autoimmune diabetes share basic features with pediatric T1D<sup>15,116-118</sup> and account for the previously mentioned rare cases of T1D in the first months of life.
- Rarely, some cases of diabetes with onset during the first 6 months of life have an autoimmune basis; it is now accepted that mutations in a range of genes related to immune function (such as *FOXP3*, *STAT3*, or *LRBA*) are at least as likely as T1D.

Mutations in the *FOXP3* gene are responsible for the immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)

syndrome.<sup>119,120</sup> IPEX syndrome is clinically heterogeneous ranging from severe intrauterine forms to moderate phenotypes, as has been recently described in different cohorts.<sup>117,121,122</sup> Among male infants who present with diarrhea, eczema, autoimmune diabetes, immune deficiency, and/or life-threatening infection, mutations in *FOXP3* should be considered.<sup>123,124</sup> Treatment with immunosuppressive agents (sirolimus or steroids),<sup>123,124</sup> Alternatively, allogeneic hematopoietic stem cell transplantation (HSCT) with reduced-intensity conditioning is recommended.<sup>125</sup> Survival is similar with both immunosuppressant treatment and HSCT, but higher rates of disease-free survival and improved quality of life have been shown with HSCT.<sup>126</sup>

In addition to mutations in *FOXP3* “classic IPEX,” there is a group with an “IPEX-like” phenotype with defects in other genes. Examples include individuals with heterozygous mutations in *CTLA4* causing autoimmune lymphoproliferative syndrome which can include autoimmune diabetes, enteropathy, cytopenias, and thyroiditis<sup>127</sup>; individuals with recessive mutations in the ubiquitin ligase gene (*ITCH*) present with multisystem autoimmune disease and facial dysmorphism<sup>128</sup>; individuals with bi-allelic mutations in *IL2RA* (interleukin 2 receptor subunit alpha) resulting in immunodeficiency 41 syndrome, with lymphoproliferation, other autoimmunity, and autoimmune diabetes,<sup>129,130</sup> as well as individuals with recessively inherited mutations in *LRBA* reported as a cause of immunodeficiency-8 with autoimmune enteropathy, T1D, autoimmune hypothyroidism, and autoimmune hemolytic anemia.<sup>118</sup>

The proteins encoded by the *STAT3*, *STAT1*, and *STAT5B* genes are transcription factors involved in the cellular response to cytokines and growth factors. Activating mutations in *STAT3* cause multiple autoimmune disease with enteropathy, hematological autoimmune disorders, autoimmune cytopenia, and autoimmune diabetes which often presents in the neonatal period.<sup>116,131</sup> Persons with gain of function mutations in *STAT1* present with chronic fungal infections including respiratory tract infections with a subset of people developing severe organ specific autoimmunity including T1D.<sup>132</sup> On the other hand, loss of function mutations in *STAT5B* are associated with disorders characterized by allergic or autoimmune manifestations.

Loss of function mutations in the *AIRE* gene cause polyendocrine autoimmune syndrome type 1 (APS1), characterized by chronic mucocutaneous candidiasis, hypoparathyroidism, and autoimmune adrenal insufficiency. In addition, 13% of individuals present with diabetes by 30 years of age.<sup>128</sup>

## 11 | OTHER CAUSES OF NEONATAL DIABETES

More than 30 genetic subtypes of NDM have been described. The clinical features seen in the more common causes of neonatal and infancy-onset diabetes are shown in Table 1. Pancreatic scanning is unreliable in neonates and so it is best to use functional tests of exocrine pancreatic function (fecal elastase and fecal fats) when assessing if pancreatic aplasia is present.<sup>133,134</sup> Apart from KATP-PNDM and some persons with *SLC19A2* mutations causing thiamine-responsive

megaloblastic anemia (TRMA) syndrome,<sup>135</sup> all other causes need to be treated with subcutaneous insulin. Children with pancreatic aplasia/hypoplasia will also require exocrine pancreatic supplements.

### 11.1 | Genetic testing should be performed as soon as diabetes is diagnosed in a child aged less than 6 months

- All infants diagnosed with diabetes in the first 6 months of life should have immediate molecular genetic testing to define their subtype of monogenic NDM, as T1D is extremely rare in this subgroup.
- Genetic testing will allow diagnosis of a specific type of monogenic diabetes in over 80% of children whose diabetes is diagnosed before the age of 6 months. As discussed above, this will influence treatment as well as prediction of clinical features.
- It is no longer necessary to wait to see if diabetes resolves or for other features to develop, as major laboratories will offer comprehensive testing of all NDM subtypes as well as very rapid testing of subtypes that alter treatment.

## 12 | AUTOSOMAL DOMINANT FAMILIAL MILD HYPERGLYCEMIA OR DIABETES (MODY)

A familial form of mild diabetes presenting during adolescence or in early adulthood was first described many years ago.<sup>10,136</sup> Even though diabetes presented in young people, the disease clinically resembled elderly-onset non-insulin dependent diabetes and the newly recognized subtype of familial diabetes became known by the acronym MODY (maturity-onset diabetes of the young).<sup>137</sup> As MODY persons passed on the disease to their offspring following an autosomal dominant pattern of inheritance, it was quickly suspected that it might be a monogenic disorder.<sup>138</sup> MODY is by far the commonest type of monogenic diabetes. All currently known subtypes of MODY are caused by dominantly acting heterozygous mutations in genes important for the development or function of  $\beta$ -cells. Over the last few years, however, a number of forms of monogenic diabetes clinically and genetically different from MODY have been identified.<sup>1</sup> Individuals may harbor dominant mutations arising de novo; in such cases, a family history suggesting a monogenic condition is lacking.<sup>41,90,139</sup> These facts, along with a widespread lack of awareness, hinder clinical diagnosis so that the majority of children with genetically proven monogenic diabetes are initially misdiagnosed as having T1D<sup>140,141</sup> or T2D.<sup>142,143</sup> Although monogenic diabetes is uncommon, it accounts for 2.5%–6% of pediatric diabetes cases.<sup>144–149</sup>

- MODY syndromes are forms of monogenic diabetes characterized by impaired insulin secretion, with minimal or no defects in insulin action.<sup>150</sup>

- Most cause isolated diabetes and therefore may be misdiagnosed as either familial T1D or T2D.<sup>142,151</sup>
- Classic criteria for MODY include family history of diabetes; however, sporadic de novo mutations in several causative genes have been reported.<sup>152</sup>
- The different genetic subtypes of MODY differ in age of onset, pattern of hyperglycemia, and response to treatment.
- Three genes are responsible for the majority of MODY cases (GCK, HNF1A, and HNF4A) and will be described in some detail below.
- Most MODY subtypes will have a phenotype of isolated diabetes or stable mild fasting hyperglycemia, but some MODY genes have additional features such as renal cysts (see HNF1B below) or pancreatic exocrine dysfunction.<sup>153</sup>

At least 14 different genes have been reported to cause diabetes with a MODY-like phenotype (Table 2), and some panels will include all these genes or, possibly, also many other genes associated with exceedingly rare recessive causes. It is reasonable to consider including syndromic causes such as mitochondrial diabetes, as diabetes can often be the first presenting feature and a molecular diagnosis can thereby guide monitoring and treatment of other associated features. In the modern era of expanded testing by many different laboratories, caution must be used when interpreting test results, as often there is very little information available to support the causality of rare variants in uncommon subtypes.

## 13 | MILD FASTING HYPERGLYCEMIA DUE TO GLUCOKINASE GENE MUTATIONS (GCK-MODY, MODY2)

- GCK-MODY is the commonest subtype of monogenic diabetes in the pediatric diabetes clinic and its clinical phenotype is remarkably homogeneous among affected persons.
- In contrast to other subtypes of monogenic diabetes, persons with GCK-MODY regulate insulin secretion adequately but around a slightly higher set point than other people. As a result, they show nonprogressive mild hyperglycemia from birth.<sup>154</sup>
- HbA1c is mildly elevated but usually below 7.5% (59 mmol/mol).<sup>155</sup>
- Despite the mild fasting hyperglycemia, there is usually a small increment in blood glucose during an oral glucose tolerance test (OGTT) (<60 mg/dl or <3.5 mmol/L)<sup>156</sup> although this should not be considered an absolute criterion because of the variability of the OGTT.
- Since the degree of hyperglycemia is not high enough to cause osmotic symptoms, most cases are usually diagnosed incidentally when blood glucose is measured for another reason.
- The incidental finding of mild hyperglycemia (5.5–8 mmol/L or 100–145 mg/dl) in otherwise asymptomatic children and adolescents raises the possibility that they will subsequently develop T1D or T2D. In the absence of concomitant islet autoimmunity,

the risk of future T1D is minimal,<sup>157</sup> and a significant proportion will have a heterozygous mutation in *GCK*.<sup>158</sup> In peripubertal children and adolescents with a diagnosis of T2D, the lack of obesity or other signs of IR should raise concern about the diagnosis of MODY.

- Since blood glucose does not deteriorate significantly over time, this subtype of monogenic diabetes is rarely associated with chronic microvascular or macrovascular complications of diabetes.<sup>159,160</sup> and affected individuals do not generally require any treatment<sup>161</sup> except in the setting of pregnancy where an affected mother has an unaffected fetus and there is in utero evidence of accelerated growth.<sup>162</sup>
- When the clinical features of asymptomatic, long-standing, stable mild fasting hyperglycemia are present, specific testing of *GCK* is appropriate.

Very often, the affected parent remains undiagnosed or has been misdiagnosed with early-onset T2D. Measuring fasting glucose concentrations in apparently unaffected parents is important when considering a diagnosis of a *GCK* mutation. *GCK*-MODY may first be diagnosed during pregnancy; it represents ~2%–6% of cases of gestational diabetes and can be differentiated from gestational diabetes based on clinical characteristics and fasting glucose concentration.<sup>163,164</sup>

Of note, the presence of a *GCK* mutation does not protect against the concurrent development of polygenic T2D later in life, which occurs at a similar prevalence as in the general population.<sup>165</sup> *GCK*-PNDM may manifest in *GCK*-MODY families especially in the setting of consanguinity.

## 14 | FAMILIAL DIABETES DUE TO *HNF1A*-MODY (MODY3) AND *HNF4A*-MODY (MODY1)

- The possibility of monogenic diabetes should be considered whenever a parent of a child with diabetes also has diabetes, even if they are thought to have T1D or T2D.
- Glucose intolerance associated with *HNF1A*- and *HNF4A*-MODY usually becomes evident during adolescence or early adulthood. In the early stages of the disease, fasting blood glucose concentration may be normal, but there may be a large increment in blood glucose (>80 mg/dl or 5 mmol/L) after meals or at 2 h during an OGTT.<sup>156</sup>
- Over time, fasting hyperglycemia and osmotic symptoms (polyuria, polydipsia) present but they rarely develop ketosis because some residual insulin secretion persists for many years.
- Chronic complications of diabetes are frequent, and their development is related to the degree of glycemic management.<sup>166</sup>
- *HNF1A*-MODY is the most common form of monogenic diabetes that results in familial *symptomatic* diabetes, with heterozygous *HNF1A* mutations being about 10 times more frequent than heterozygous mutations in *HNF4A*.<sup>167</sup> Therefore, *HNF1A*-MODY is

the first diagnostic possibility to be considered in families with autosomal dominant symptomatic diabetes.

- Persons with *HNF1A*-MODY demonstrate an impaired incretin effect and inappropriate glucagon responses to OGTT.<sup>168</sup>
- Despite the association of *HNF1A* mutations with microvascular complications, recent data suggest that timely initiation of treatment with SUs is associated with lower rate of microvascular complications than T1D.<sup>169</sup> *HNF1A* mutations are also associated with an increased frequency of cardiovascular disease and mortality.<sup>170</sup>

Mutations in *HNF1A* show a high penetrance so that 63% of mutation carriers develop diabetes before 25 years of age, 79% before age 35, and 96% before 55 years.<sup>1</sup> The age at diagnosis of diabetes is partly determined by the location of the mutation within the gene.<sup>171,172</sup> Persons with mutations affecting the terminal exons (8 to 10) are diagnosed, on average, 8 years later than those with mutations in exons 1 to 6. On the other hand, exposure to maternal diabetes in utero (when the mutation is maternally inherited) brings forward the age at onset of diabetes by about 12 years.<sup>156</sup> In the pediatric population, diabetes in *HNF4A* mutation carriers tends to appear at a similar age to persons with mutations in *HNF1A*.<sup>146</sup>

Some differential clinical characteristics may be noted between persons with mutations in *HNF4A* and *HNF1A*; however, they do not often help in the choice of genes to be sequenced and it would be preferable to test all genes simultaneously with NGS whenever possible.<sup>173</sup>

- Persons with *HNF1A* mutations typically have a low renal threshold for glucose reabsorption due to impaired renal tubular transport of glucose and may present postprandial glycosuria before developing significant hyperglycemia.<sup>174</sup>
- In addition to diabetes, carriers of the p.Arg76Trp (R76W) mutation in *HNF4A* present with an atypical form of Fanconi syndrome including hypercalciuria and nephrocalcinosis.<sup>175</sup>
- About 50% of *HNF4A* mutation carriers are macrosomic at birth and 15% have diazoxide-responsive neonatal hyperinsulinemic hypoglycemia.<sup>176</sup> In this case, hyperinsulinism typically remits during infancy and individuals develop diabetes from adolescence.<sup>177,178</sup> Hyperinsulinemic hypoglycemia has also been reported in *HNF1A* mutation carriers<sup>179</sup> but this is very uncommon.

Persons with both *HNF1A* and *HNF4A*-diabetes can initially be treated with diet although they will have marked postprandial hyperglycemia with high carbohydrate food.<sup>156</sup>

- Most will need pharmacological treatment as they show progressive deterioration in glycemic management. They are extremely sensitive to SUs,<sup>180</sup> which usually allow better glycemic management than that achieved with insulin, especially in children and young adults.<sup>181</sup>
- The initial dose of SUs should be low (one-quarter of the normal starting dose in adults) to avoid hypoglycemia. As long as there are

no problems with hypoglycemia, they can be maintained on low-dose SUs (e.g., 20–40 mg gliclazide daily) for decades.<sup>182,183</sup>

- If there is hypoglycemia despite dose titration of a once or twice daily SU preparation, a slow-release preparation or meal time doses with a short-acting agent such as a meglitinide may be considered.<sup>184</sup> A randomized controlled trial comparing a glucagon-like peptide receptor agonist (GLP1RA) with a SU demonstrated lower fasting glucose in those treated with the GLP1RA.<sup>168</sup>

## 15 | DIABETES ASSOCIATED WITH EXTRA-PANCREATIC FEATURES

A monogenic disorder should be considered in any child with diabetes associated with multi-system extrapancreatic features,<sup>185</sup> or in young-onset diabetes when consanguinity is known or suspected, even when syndromic features are not obvious.<sup>186</sup> These syndromes may either cause NDM (Table 1) or present later in life (see below). The Online Mendelian Inheritance in Man website ([www.ncbi.nlm.nih.gov/omim](http://www.ncbi.nlm.nih.gov/omim) or [www.omim.org](http://www.omim.org)) can help with clinical features and to know if the gene for a particular syndrome has been defined hence molecular genetic testing is available. Genetic testing for some of these conditions is available on a research basis at [www.euro-wabb.org](http://www.euro-wabb.org).<sup>187</sup> The most common syndromes usually presenting beyond infancy are described in some detail below. A number of rare syndromes that include diabetes may also be tested through a gene panel approach (for example, see <https://www.diabetesgenes.org/>).

### 15.1 | Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD) syndrome (WFS)

The combination of diabetes and progressive optic atrophy below 16 years of age is diagnostic of this autosomal recessive syndrome.<sup>188</sup> Non-autoimmune, insulin requiring diabetes, presenting at a mean age of 6 years, is usually the first manifestation of the disease.<sup>189</sup> Other reported features, including sensorineural deafness, central diabetes insipidus, urinary tract dysfunction, and neurological symptoms that develop later in a variable order even within the same family.<sup>190–192</sup> Many individuals with WFS are initially diagnosed as having T1D and subsequent loss of vision, which occurs ~4 years after diabetes diagnosis, may be misdiagnosed as diabetic retinopathy.<sup>193,194</sup> Persons with WFS die at a median age of 30 years, mainly from neurodegenerative complications. At least 90% of these people harbor biallelic mutations in the *WFS1* gene.<sup>195</sup> This gene encodes WFS1, which is an endoplasmic reticulum (ER) transmembrane protein important for the negative regulation of ER stress and the maintenance of cellular calcium homeostasis.<sup>196</sup> Preclinical studies in cell and animal models suggest that therapeutic strategies targeting ER calcium homeostasis may be beneficial. However, a recent trial of using dantrolene sodium in 19 WFS subjects showed no significant improvement in  $\beta$ -cell, retinal or neurological function.<sup>197</sup>

A second variant of the syndrome (WFS2) has been described in association with mutations in *CISD2* gene.<sup>198</sup> Persons with this rare variant do not develop diabetes insipidus but present with additional symptoms including a bleeding diathesis and peptic ulcer disease.

The current management of WFS involves symptomatic treatment of the associated features with no agents to cure or slow the disease progression.

### 15.2 | Renal cysts and diabetes (RCAD) syndrome (HNF1B-MODY or MODY5)

Although initially described as a rare subtype of familial diabetes, it is now clear that persons with heterozygous mutations in *HNF1B* rarely present with isolated diabetes.<sup>199</sup> In contrast, renal developmental disorders (especially renal cysts and renal dysplasia) are present in almost all persons with *HNF1B* mutations or gene deletions<sup>139</sup> and constitute the main presentation in children, even in the absence of diabetes.<sup>200–202</sup> Genital tract malformations (particularly uterine abnormalities), hyperuricemia, and gout can also occur, as well as abnormal liver function tests.<sup>199</sup> Diabetes develops later, typically during adolescence or early adulthood<sup>203,204</sup> although TNDM has been reported in a few cases.<sup>23,203</sup> In addition to insulin deficiency related to pancreatic hypoplasia,<sup>205</sup> affected persons also show some degree of hepatic IR,<sup>206</sup> which explains why they do not respond adequately to SU treatment and require early insulin therapy.<sup>1</sup> Moreover, mutation carriers have lower exocrine pancreatic function with reduced fecal elastase; this involves both ductal and acinar cells.<sup>207</sup> Therefore, the phenotype of RCAD is highly variable even within families sharing the same *HNF1B* mutation and therefore this diagnosis should be considered not only in the diabetes clinic but also in other clinics (nephrology, urology, gynecology, etc.). In people with diabetes found to have renal cysts, imaging of the pancreas is indicated, since the absence of the pancreatic body and/or tail is highly indicative of HNF1B-MODY.<sup>208</sup> Fecal elastase should also be measured, as this is always abnormal in persons with HNF1B-MODY.<sup>207</sup> Importantly, a family history of renal disease or diabetes is not essential to prompt genetic testing, as de novo mutations and deletions of this gene are common (one-third to two-thirds of cases).<sup>139,200</sup>

### 15.3 | Mitochondrial diabetes

Diabetes due to mitochondrial mutations and deletions is rarely seen (<1%) in children and adolescents<sup>209</sup> as most affected persons develop diabetes as young or middle-aged adults. The most common form of mitochondrial diabetes is caused by the m.3243A>G mutation in mitochondrial DNA. Diabetes onset is usually insidious but ~20% may have an acute presentation, including diabetic ketoacidosis.<sup>210</sup> Although it typically presents in adulthood, some cases have been reported in adolescents with a high degree of heteroplasmy.<sup>209,211,212</sup> Mitochondrial diabetes should be suspected in persons presenting

with diabetes and maternally inherited sensorineural hearing loss, or diabetes and progressive external ophthalmoplegia. Interestingly, the same m.3243A>G mutation also causes a much more severe clinical syndrome known as MELAS (myopathy, encephalopathy, lactic acidosis, and stroke).<sup>213</sup>

Persons with mitochondrial diabetes may initially respond to diet or oral hypoglycemic agents but often require insulin treatment within months or years. Metformin should be avoided as it interferes with mitochondrial function and may trigger episodes of lactic acidosis.<sup>214</sup>

The penetrance of diabetes in mutation carriers depends on age, but is estimated to be above 85% at 70 years.<sup>210</sup> Affected males do not transmit the disease to their offspring. In contrast, females transmit the mutation to all their children, although some may not develop the disease.<sup>1</sup> In addition to the m.3243A>G mutation, early-onset diabetes (even in infancy) has been reported in other less common mitochondrial disorders such as Kearns-Sayre syndrome<sup>215</sup> and Pearson syndrome.<sup>216</sup>

#### 15.4 | Diabetes secondary to monogenic diseases of the exocrine pancreas

Heterozygous mutations in *CEL*, which encodes a pancreatic lipase, cause CEL-MODY or MODY8, an autosomal dominant disorder of pancreatic exocrine insufficiency and diabetes.<sup>153</sup> Importantly, the exocrine component of the syndrome is evident in childhood, 10–30 years before diabetes develops, and can be revealed by reduced fecal elastase and/or pancreatic lipomatosis.<sup>217,218</sup> Diabetes typically develops in the 30–40s together with pancreatic cysts.<sup>218</sup> The *CEL* gene is highly polymorphic and extremely difficult to sequence. El Jellas et al recently described how to diagnose CEL-MODY.<sup>219</sup> The disease mechanism of CEL-MODY involves protein misfolding/aggregation, endoplasmic reticulum stress, and proteotoxicity.<sup>220–223</sup> Other autosomal dominant monogenic diseases mainly affecting the exocrine pancreas that can lead to diabetes sooner or later include cystic fibrosis (*CFTR*), hereditary pancreatitis (*PRSS1* and *SPINK1*)<sup>224</sup> and pancreatic agenesis/hypoplasia (*GATA6*).<sup>134</sup>

#### 15.5 | Syndromic diabetes due to TRMT10A and DNAJC3 deficiencies: oxidative stress, apoptosis in $\beta$ -cells

Mutations in *TRMT10A*, a nuclear tRNA methyltransferase, are associated with a novel syndrome of young-onset diabetes mellitus or impaired glucose metabolism, microcephaly, intellectual disability, short stature, and delayed puberty (OMIM 616013). To date, five families are described in the literature with a total of 11 people with a mutation. Phenotypes are heterogenous with most individuals presenting with impaired glucose homeostasis, microcephaly, short stature, seizures, and intellectual disability.<sup>225</sup>

DNAJC3 mutation, which is associated with DM and multisystemic neurodegeneration, have been described. Familial case of

DNAJC3 mutation manifesting as juvenile-onset DM, hypothyroidism, multisystemic neurodegeneration, short stature, and sensorineural hearing loss with the new finding of pancreatic fibrosis and atrophy.<sup>226</sup>

## 16 | MONOGENIC INSULIN RESISTANCE SYNDROMES

- The cardinal features of IR syndromes include moderate to severe acanthosis nigricans in association either with markedly increased insulin concentrations (fasting insulin >150 pmol/L) or, where there is diabetes, increased insulin requirements, usually in the absence of a corresponding degree of obesity.
- Three different subtypes are described, based on the underlying pathogenic mechanism: primary insulin signaling defects, IR secondary to adipose tissue abnormalities, and IR as a feature of complex syndromes.<sup>227</sup>
- Clinical and biochemical characterization of persons with severe IR may be used to guide genetic testing (Table 3).
- In contrast with monogenic syndromes of  $\beta$ -cell failure, hyperglycemia and diabetes tend to occur later in the genetic syndromes of severe IR and may not be a feature before the onset of puberty,<sup>228</sup> except for Donohue syndrome.

The phenotypes of monogenic IR syndromes tend to be more pronounced in females, who may present during adolescence with significant ovarian hyperandrogenism. The physical appearance of the partial lipodystrophies can also be less pronounced in males and so the presentation is more common in females who can present with features similar to those seen in polycystic ovarian syndrome.

### 16.1 | Primary insulin signaling defects due to mutations in the insulin receptor (*INSR*) gene

*INSR* mutations are responsible for a number of rare IR syndromes.<sup>229,230</sup> Leptin levels are low, but adiponectin levels are paradoxically normal or elevated since insulin normally inhibits adiponectin secretion.<sup>231</sup> There is a spectrum of severity, depending on the effect of the mutation on the signaling function of the receptor. The most severe forms are associated with either homozygous or compound heterozygous mutations in the *INSR* gene responsible for Donohue and Rabson-Mendenhall Syndromes. In Donohue Syndrome this leads to almost complete loss of insulin action at the cellular level and in Rabson-Mendenhall Syndrome, where there is some residual insulin signaling, the phenotype can be milder.<sup>232</sup> Infants with Donohue Syndrome are born small for gestational age and develop diabetes in infancy with insulin concentrations over 1000 pmol/L, often in association with cardiomyopathy and hypertrichosis. Postprandial hyperglycemia may be severe, and present early in life, but is usually accompanied by fasting hypoglycemia. There is no effective treatment, and the majority of infants sadly succumb to infection, or

cardiac complications during the first year of life. Children with Rabson–Mendenhall Syndrome may not present until later in childhood, with failure to thrive, gingival hyperplasia, acanthosis nigricans, hyperandrogenism, and insulin resistant diabetes requiring very high doses of insulin developing during adolescence.<sup>229,233</sup>

Type A IR Syndrome is the mildest form and results most commonly from a heterozygous mutation in the *INSR* gene and is inherited in an autosomal dominant manner.<sup>229</sup> Diabetes is rare before adolescence, but there can be significant ovarian hyperandrogenism and acanthosis nigricans during puberty.

The management of hyperglycemia in persons with *INSR* mutations can be challenging as insulin is largely ineffective even at high doses. Insulin sensitizers such as metformin may be tried initially but most will need extraordinarily high doses of insulin, with limited effect.<sup>229</sup> As an alternative therapeutic method for young children, recombinant human IGF-I has been reported to improve both fasting and postprandial glycemia although long-term effects on survival remain unclear.<sup>234,235</sup> Recently, a trial showed benefits of long-term treatment with metreleptin in persons with Rabson-Mendenhall Syndrome.<sup>236</sup> Use of SGLT2i has also been reported to be beneficial in improving hyperglycemia.<sup>237,238</sup> For females, the hirsutism resulting from ovarian hyperandrogenism should be managed using similar strategies as for polycystic ovarian syndrome.<sup>239</sup>

## 16.2 | Monogenic lipodystrophies

Lipodystrophies are characterized by a partial or complete reduction in adipose tissue, which results in decreased adipokine levels and IR.<sup>240,241</sup> Mutations in either *AGPAT2* or *BSCL* account for ~80% of cases of congenital generalized lipodystrophy (Berardinelli–Seip syndrome).<sup>242</sup> These are recessively inherited disorders characterized by an almost complete absence of subcutaneous and visceral fat. The clinical features are often apparent at birth. Inability to store excess dietary fat results in ectopic fat deposition in the liver, with hepatic steatosis that may progress to cirrhosis.<sup>241</sup> Diabetes can manifest in early infancy, but there then can be a period of remission until late childhood.

In contrast, a clinical diagnosis of familial partial lipodystrophy (FPLD) is usually made after puberty where there is failure to gain subcutaneous fat in the extremities and lower trunk during puberty, in combination with progressive accumulation of subcutaneous adipose tissue in the face and around the neck.<sup>241,243</sup> Heterozygous mutations in *LMNA* or *PPARG* account for ~50% of cases.<sup>240</sup> Visceral fat is greatly increased in addition to hyperinsulinemia, hypertriglyceridemia, and decreased HDL-cholesterol levels.<sup>244</sup> Diabetes usually appears in late adolescence or early adulthood. More recently, there has been opportunity to make a genetic diagnosis in the offspring of persons with FPLD. In theory, this permits early intervention with lifestyle recommendations and screening for co-morbidities in the hope that the development of co-morbidities can be delayed but it is too early to tell whether this approach will be effective.

More rarely, lipodystrophy may occur as part of a multi-system disorder. A mutation in *POLD1*, a universal DNA polymerase causes subcutaneous lipodystrophy in combination with diabetes, deafness, mandibular hypoplasia, and hypogonadism in males.<sup>245</sup> SHORT syndrome (short stature, hypermobility of joints, ocular depression, Rieger's anomaly, teething delay) with partial lipodystrophy, is caused by a hot spot mutation in *PIK3R1* which has a central role in the insulin-signaling pathway and growth factor resistance.<sup>246–248</sup> Mutation carriers of the dominant-negative mutation in *PIK3R1* seem to be protected from obesity and hepatic steatosis but not diabetes,<sup>249</sup> and the disease mechanisms is associated with unfolded protein response and reduced sensitivity to ER stress-dependent apoptosis.<sup>250</sup>

The mainstay of therapy for lipodystrophy is dietary intervention with a low-fat, calorie-neutral diet,<sup>241</sup> and an expert dietician as part of the multidisciplinary team is of paramount importance. In partial lipodystrophy, insulin sensitizers such as metformin and glitazones may be initially effective<sup>251</sup> but glitazones may exacerbate accumulation of ectopic fat in the face and neck.<sup>228</sup> More recently, therapy with recombinant leptin, given by daily subcutaneous injection, has been shown to be well tolerated, with sustained improvements in hypertriglyceridemia, glycemic management, and liver volume.<sup>252</sup> Efficacy in the partial forms of lipodystrophy is less clear, but where conventional therapy for diabetes and hypertriglyceridemia has not been successful, adjunctive therapy with metreleptin should be considered.<sup>253</sup>

## 16.3 | Ciliopathy-related insulin resistance and diabetes

### 16.3.1 | Alström syndrome

This autosomal recessive disorder shares symptoms with Bardet-Biedl syndrome (see below), including progressive visual impairment related to cone-rod dystrophy, sensorineural hearing loss, obesity, and diabetes mellitus. It can be distinguished from the latter syndrome by the lack of polydactyly and hypogonadism and by the absence of cognitive impairment.<sup>254</sup> More than 60% of individuals with ALMS develop cardiomyopathy. The syndrome is caused by mutations within the *ALMS1* gene of unknown function.<sup>255</sup> Persons with Alström syndrome (ALMS) usually show many features of the metabolic syndrome including acanthosis nigricans, hyperlipidemia, hyperuricemia, hypertension, and slowly-progressive insulin-resistant diabetes.<sup>256</sup> Lifestyle intervention can initially ameliorate the metabolic abnormalities.<sup>257</sup>

### 16.3.2 | Bardet-Biedl syndrome (BBS)

This disorder is characterized by intellectual disability, progressive visual impairment due to cone-rod dystrophy, polydactyly, obesity, diabetes mellitus, renal dysplasia, hepatic fibrosis, and hypogonadism. Obesity is found in almost every affected individual, while diabetes

affects less than 50%.<sup>258</sup> While the syndrome shares some similarities with Lawrence-Moon syndrome, these two disorders can be distinguished by the presence of paraplegia and the absence of polydactyly, obesity, and diabetes mellitus in Lawrence-Moon syndrome. Terms such as Lawrence-Moon-Bardet-Biedl or Lawrence-Moon-Biedl syndrome should therefore be avoided. Bardet-Biedl syndrome has been linked to 18 different genetic loci, referred to as *BBS1* to *BBS18*.<sup>259,260</sup> The majority of cases are autosomal recessive,<sup>261</sup> but triallelic inheritance has been reported.<sup>262</sup> Genetic diagnostic laboratories and detailed clinical recommendations for persons with ALMS and BBS are present at <http://www.euro-wabb.org>.

## 17 | CONCLUSIONS

Advances in molecular genetics have led to the identification of genes associated with many clinically identified subgroups of diabetes. Molecular genetic testing should now be considered an essential clinical diagnostic tool that can help define the diagnosis and determine the appropriate treatment of children with diabetes. Although the cost of NGS continues to drop, diagnostic genetic testing should be limited to those persons with diabetes who are likely to harbor a mutation based on the suggestive clinical features described above.

### CONFLICT OF INTEREST

Dr Michel Polak MD, PhD has acted as scientific advisor for the development of the glibenclamide-glyburide suspension named AMGLIDIA in the European Union. The other authors have declared no conflicts of interest.

### DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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