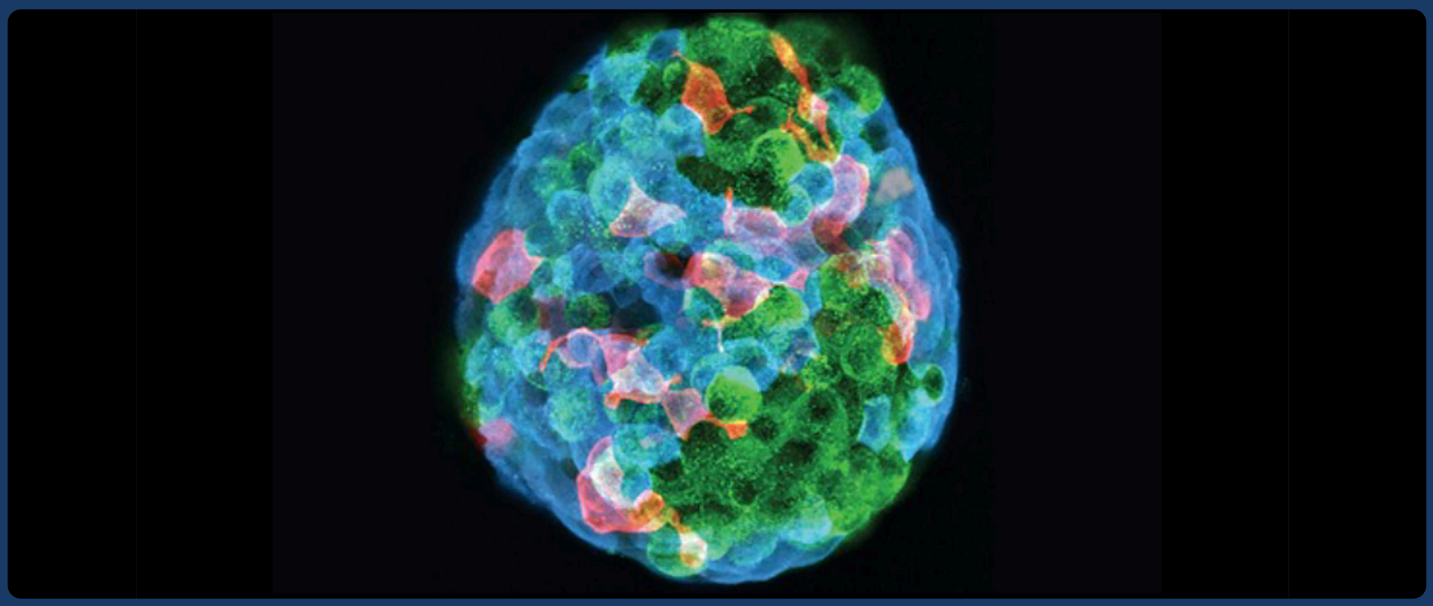
SMART-MD

Volume 2 / Issue 2
Spring 2025

Journal of

Precision Medicine



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SMART-MD Journal of Precision Medicine 2025; Vol 2. No 2.

SMART Medical Review

Precision Diagnostics for Monogenic Diabetes in Children

Hector I. Ortega, MD[1], Anna L. Gloyn, DPhil[1,2,3]

1 *Department of Pediatrics, Division of Endocrinology, Stanford School of Medicine, Stanford, CA, USA.*
2 *Department of Genetics, Stanford School of Medicine, Stanford, CA, USA.*
3 *Stanford Diabetes Research Center, Stanford School of Medicine, Stanford, CA, USA.*

Abstract: Monogenic diabetes, caused by a single-gene defect, accounts for roughly 1–5% of pediatric diabetes cases. Although relatively uncommon, correct identification of these subtypes is critical, as accurate classification can markedly influence both treatment and prognosis. However, distinguishing monogenic forms from type 1 (T1D) or type 2 diabetes (T2D) remains challenging due to overlapping features, such as early onset and variable insulin requirements. Many children with monogenic diabetes are misdiagnosed and, consequently, may not receive optimal therapy. Advances in sequencing technologies, combined with growing knowledge of the underlying genetic causes, now enable earlier, more precise diagnoses and offer opportunities to tailor therapy—often avoiding insulin in favor of targeted interventions. In this review, we summarize key categories of monogenic diabetes, including maturity-onset diabetes of the young (MODY), neonatal diabetes mellitus (NDM), and syndromic forms and outline current recommended diagnostic workflows and genetic testing strategies. Ultimately, we aim to provide clinicians with a clear, actionable framework for recognizing and managing these significant but often under recognized forms of pediatric diabetes.

Key Words: Diabetes mellitus type 1; Maturity-onset diabetes of the young; Neonatal diabetes mellitus, Mitochondrial diabetes, Wolfram syndrome, lipodystrophy, precision medicine, genetic testing, insulin.

Outline

Abbreviations used in this paper. AAB, Diabetes-related autoantibodies; ABCC8, ATP-binding cassette subfamily C member 8; BMI, Body Mass Index; GCK, Glucokinase; GDM, Gestational Diabetes Mellitus; GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonist; HNF1A, Hepa-tocyte Nuclear Factor 1 Alpha; HNF1B, Hepatocyte Nuclear Factor 1 Beta; HNF4A, Hepatocyte Nuclear Factor 4 Alpha; KCNJ11, Potassium Inwardly Rectifying Channel Subfamily J Member 11; MODY, Maturity-Onset Diabetes of the Young; NDM, Neonatal Diabetes Mellitus; NGS, Next-Generation Sequencing; PNDM, Permanent Neonatal Diabetes Mellitus; SU, Sulfonylurea; T1D, Type 2 Diabetes; TNDM, Transient Neonatal Diabetes Mellitus.

ISSN 2997-2876 (online)
ISSN 2997-2868 (print)
DIO: https://doi.org/10.69734/1e8v6h36
Website: www.SMART-MD.org

1. Introduction

Monogenic diabetes (MONDO:0015967) arises from a single pathogenic variant in one of over 40 genes. The most prevalent subtype, maturity-onset diabetes of the young (MODY), was first characterized by Tattersall and Fajans in the 1970s as an autosomal dominant, early-onset, non–insulin-dependent diabetes.[1,2] Since that seminal description, investigators have identified over a dozen genes involved and expanded the monogenic spectrum to include neonatal diabetes mellitus (NDM) and several syndromic forms.[3]

Monogenic diabetes can be misdiagnosed in children as T1D, especially during the "honeymoon period"—a transient phase after T1D diagnosis when residual β-cell activity reduces or eliminates the need for exogenous insulin. Likewise, non-obese young adults are often categorized as T2D because they present with non-ketotic hyperglycemia, preserved C-peptide, and negative diabetes-related autoantibodies (AAB) leading clinicians to often default to a diagnosis of T2D.[3,4] Making the correct diagnosis matters because it influences treatment, informs prognosis, and has implications for family members (see Table 1).

This review synthesizes current knowledge on the principal pediatric forms of monogenic diabetes, highlights their genetic and clinical hallmarks, and outlines practical diagnostic and management strategies that frontline clinicians can readily incorporate into practice.

2. Maturity-Onset Diabetes of the Young (MODY)

MODY typically presents with mild-to-moderate, non-ketotic hyperglycemia in childhood or early adulthood—often before 25 years though later onset is well-described—and is characterized by preserved endogenous insulin secretion. The "classical" autosomal-dominant pedigree remains a valuable clue, but inheritance is variable: *de novo* mutations occur, maternal transmission is seen with the mitochondrial m.3243A>G variant, and rare autosomal-recessive cases involving hypomorphic alleles in the same genes (e.g. biallelic *GCK* or *HNF1A*) have been reported.[4,5,18,43,46]

More than a dozen genes have been approved by the ClinGen Monogenic Diabetes Gene Curation Expert Panel, with additional, less-validated candidates pushing the reported total beyond twenty. Pathogenic variants in *GCK* (HGNC:4195), *HNF1A* (HGNC:11621), *HNF4A* (HGNC:5024), and the mitochondrial m.3243A>G rare variant together explain roughly 75% of molecularly confirmed cases, whereas *HNF1B* and other loci each contribute only a small fraction.[3,5,6] Gene-based nomenclature (e.g., GCK-MODY, HNF1A-MODY, etc.) underscores this mechanistic diversity and provides a flexible framework as new, less-common subtypes continue to be validated.

HNF1A-MODY & HNF4A-MODY

Pathogenic variants in the transcription factors *HNF1A* and *HNF4A* blunt glucose-stimulated insulin release by disrupting pancreatic β-cell development and the regulation of key genes involved in mature function.[7,8] Diabetes usually develops in the late teens or early twenties, and mimics T2D but at a lower BMI and without evidence of insulin resistance.[6,9,10] A distinctive clue for *HNF4A* is neonatal macrosomia or transient neonatal hypoglycemia, reflecting in-utero hyperinsulinism.[11]

Marked sulfonylurea (SU) sensitivity is the therapeutic hallmark: a pivotal cross-over study, showed that low-dose gliclazide lowered glucose far more than metformin in HNF1A-MODY—an effect not seen in matched T2D controls. Later studies have consistently confirmed that roughly half of genetically confirmed *HNF1A/HNF4A* patients achieve good glycemic control on low dose sulfonylureas, especially when treatment starts early after diagnosis; although response diminishes with longstanding insulin use.[12–14]

Small but growing evidence suggests glucagon-like peptide-1 receptor agonists (GLP-1RA) can help when sulfonylurea therapy is inadequate or contraindicated. In a randomized 6-week cross-over trial, liraglutide matched glimepiride for glucose lowering in HNF1A-MODY but caused far fewer hypoglycemic episodes.[15] More recently, a 12-year-old with HNF1A-MODY achieved additional weight loss, normalized liver enzymes and reduced HbA1c to 4.7% after a year of liraglutide therapy, supporting GLP-1RAs as a useful alternative—or additive—option in management.[16]

GCK-MODY

GCK encodes glucokinase, the pancreatic β-cell "glucose sensor." Heterozygous loss-of-function variants raise the glucose threshold for insulin secretion, producing lifelong, mild fasting hyperglycemia (HbA1c typically <7.5%) with virtually no vascular sequelae. In contrast, biallelic (homozygous or compound-heterozygous) loss of function variants abolish enzyme activity and present as permanent neonatal diabetes mellitus with severe intra-uterine growth restriction and lifelong insulin dependence.[17]

With regards to pregnancy, about 1–6 % of women with gestational diabetes mellitus (GDM) carry a heterozygous GCK variant, but the yield rises to 20% when testing non-obese women (BMI <25 kg/m^2) whose fasting plasma glucose is ≥100 mg/dL (5.5 mmol/L). Current consensus guidelines therefore recommend offering GCK testing to GDM patients who satisfy those two simple criteria.[4]

Outside pregnancy, glucose-lowering therapy is seldom required; long-term studies show stable glycemia and unchanged outcomes after insulin or oral agents are withdrawn. Management changes only in pregnancy, where fetal genotype guides intervention—if the fetus has **not** inherited the variant, maternal insulin is recommended to prevent macrosomia; if the fetus **does** inherit the variant and growth remains normal, treatment

Table 1. Key genes associated with monogenic diabetes

Gene / Locus (inheritance; mechanism, HGNC ID)	*Typical age of onset*	*Key clinical clues*	*First-line (or most effective) therapy*	*Long-term / special notes*
GCK *(AD; LOF; HGNC:4195)*	Mild fasting hyperglycemia from birth; often detected in childhood when labs first drawn	Stable HbA1c <7.5%; minimal post-prandial rise	**None** in most cases	Treat only in pregnancy if fetus is unaffected; micro-/macro- vascular risk very low
HNF1A *(AD; LOF; HGNC:11621)*	Teens–20s (sometimes childhood)	Glycosuria at relatively low glucose, low hs-CRP	**Sulfonylurea**	Early SU switch improves durability; monitor for hypoglycemia
HNF4A *(AD; LOF; HGNC:5024)*	Teens–20s; history of neonatal macrosomia ± transient neonatal hypoglycemia	Same phenotype as HNF1A plus macrosomia history	**Sulfonylurea**	Pregnancy counselling (macrosomia risk)
HNF1B *(AD, de-novo common;* LOF; *HGNC:11630)*	Childhood–early adulthood (broad)	Renal cysts/dysplasia, hypomagnesemia, genital tract malformations	Start with **SU/repaglinide** but **often need insulin**	Screen kidneys & liver; progressive β-cell loss expected
KCNJ11 *(AD/AR, de-novo*; GOF; *HGNC:6257)*	< 6 mo (PNDM, TNDM), childhood/adolescence (MODY)	IUGR; DKA rare, +/- neurodevelopmental delay	**Sulfonylurea**	Earlier switch → better glycemic & neuro outcomes
ABCC8 *(AD/AR; GOF; HGNC:59)*	< 6 mo (PNDM, TNDM), childhood & adolescence (MODY)	Similar to *KCNJ11*; transient form may remit	**Sulfonylurea**	Watch for relapse at puberty in transient cases
INS *(AD/AR; LOF; HGNC:6081)*	< 6 mo (PNDM, TNDM), childhood & adolescence (MODY)	Low birthweight, no extra pancreatic signs	**Insulin** (SU ineffective)	Educate families on lifelong insulin need
6q24 (*PLAG1 / HYMAI / ZFP57 imprinting; loss of imprinting causes overexpression****)***	Birth–few weeks (transient NDM)	Severe IUGR, macroglossia, umbilical hernia	**Insulin** initially; some tolerate SU in relapse	50–60 % relapse in adolescence/adulthood
WFS1 *(AR*; *LOF*; *HGNC:12762)* **–** *Wolfram Syndrome 1*	~6yo (diabetes often first sign)	Optic atrophy, DI, deafness (DIDMOAD), urologic abnormalities	**Insulin**; consider GLP-1RA for β-cell sparing (off-label)	Multisystem surveillance (vision, audiology, urology)
CISD2 *(AR; LOF; HGNC:24212)* **–** *Wolfram Syndrome 2*	Childhood	Diabetes, optic atrophy, GI dysmotility and ulcers, no DI	**Insulin**	Similar management to WFS1; watch GI complications
INSR *(AR/AD; LOF; HGNC:6091)*	Infancy (Donohue), puberty (Type A)	Extreme insulin resistance, acanthosis; +/- growth defects	**Metformin + insulin-sensitizers**; high-dose **insulin**	Consider rhIGF-1 in severe forms; manage PCOS features
AGPAT2 / BSCL2 *(AR; LOF; HGNC:325 / 15832)*	Infancy (CGL)	Near-total fat loss, hepatomegaly, hyper-triglyceridemia	**Metreleptin** + **insulin-sensitizers** ± insulin	Aggressive TG & NAFLD management; cardiac screening
LMNA *(AD/AR; LOF; HGNC:6636)*	Childhood–teens (FPLD)	Fat loss from limbs/buttocks, muscular arms, PCOS	**Metreleptin**; **insulin-sensitizers**	Cardiomyopathy risk; monitor lipids, liver

Gene / Locus (inheritance; mechanism, HGNC ID)	Typical age of onset	Key clinical clues	First-line (or most effective) therapy	Long-term / special notes
m.3243A>G mtDNA *(maternal; LOF)*	Teens–20s (variable)	Sensorineural deafness, short stature, macular dystrophy	**Insulin** (avoid metformin if renal/hepatic compromise)	Screen hearing, kidneys, heart; family testing
EIF2AK3 *(AR; LOF; HGNC:3255) – Wolcott-Rallison syndrome*	Birth – 6 mo (permanent NDM)	Consanguinity; epiphyseal dysplasia, hepatic dysfunction, intermittent episodes of multi-organ failure	**Insulin** (high dose often required); manage stress hyperglycemia aggressively	Multisystem surveillance: liver enzymes, skeletal imaging, thyroid, kidneys; high mortality in early childhood

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CGL, congenital generalized lipodystrophy; DI, diabetes insipidus; DKA, diabetic ketoacidosis; FPLD, familial partial lipodystrophy; GI, gastrointestinal; GLP-1RA, glucagon-like-peptide-1 receptor agonist; GOF, gain-of-function; HbA1c, glycated hemoglobin A1c; HGNC, HUGO Gene Nomenclature Committee; hsCRP, high-sensitivity C-reactive protein; IUGR, intra-uterine growth restriction; LOF, loss-of-function; MODY, maturity-onset diabetes of the young; mtDNA, mitochondrial DNA; NAFLD, non-alcoholic fatty liver disease; NDM, neonatal diabetes mellitus; PCOS, polycystic ovary syndrome; rhIGF-1, recombinant human insulin-like growth factor 1; SU, sulfonylurea; TG, triglycerides; TNDM, transient neonatal diabetes mellitus.

Note: The table highlights the most frequent or clinically actionable genetic causes of pediatric monogenic diabetes. Other rare or syndromic forms are not listed here but should be considered when the presentation and first-tier testing do not establish a diagnosis.[3,4,6,13,36,37,45]

can generally be withheld, as the variant-positive fetus shares the mother's higher glucose set point, so hyperglycemia does not promote overgrowth, and added insulin can precipitate growth restriction.[13,14,18] When the fetal genotype is unknown, perform ultrasounds every two weeks after 26 weeks' gestational age and start maternal insulin only if the fetal abdominal circumference exceeds the 75th percentile, indicating likely macrosomia in a variant-negative fetus; otherwise, surveillance can be continued without pharmacotherapy.[51]

HNF1B-MODY

Pathogenic *HNF1B* (HGNC:11630) variants couple diabetes with various combinations of renal cysts, congenital anomalies of the kidney and urinary tract, and Mullerian and Wolffian duct malformations; many children therefore initially present to nephrology rather than endocrinology clinics.[19] Metabolically, carriers show a 2- to 3-fold reduction in insulin-sensitivity with compensatory hyperinsulinemia, accompanied by low-HDL/highpertriglyeridimic dyslipidaemia—evidence that insulin resistance, not just β-cell dysfunction, drives the phenotype.[19] Sulfonylureas and repaglinide may provide transient benefit but most patients progress to insulin, and therapeutic data remain confined to case series; no randomized trials have evaluated HNF1B-specific treatment.[13]

3. Neonatal Diabetes Mellitus (NDM)

NDM is defined by persistent hyperglycemia diagnosed before six months of age.[20] Roughly half of cases are transient (TNDM) whereas the rest are permanent (PNDM). Regardless of subtype, neonates typically present with intrauterine growth restriction, dehydration, and failure to thrive.

Transient NDM (TNDM)

About 70% of TNDM is caused by 6q24 imprinting defects (collectively termed 6q24-TNDM); the remainder are explained by activating variants in *KCNJ11* (HGNC:6257) or *ABCC8* (HGNC:59), or more rarely, pathogenic *INS* (HGNC:6081) or *GATA6* (HGNC:4174) variants. Affected newborns are typically growth-restricted at birth and may display macroglossia or umbilical hernias. Hyperglycemia usually remits by 18 months but can relapse in adolescence or adulthood.[21,22] Initial treatment is almost always insulin, but there is some evidence to suggest sulfonylureas may maintain glycemic control during relapse or prolonged hyperglycemic phases.[13] Case reports of post-remission hyper-insulinemic hypoglycemia managed with diazoxide further underscore the central role of the 6q24 locus in insulin secretion.[52,53]

Permanent Neonatal Diabetes Mellitus (PNDM)

The most common cause of PNDM is caused by activating variants in K_{ATP}-channel genes *KCNJ11 and ABCC8*; loss-of-function variants in *INS* account for another 10-20% with the remainder split among rarer loci. PNDM does not remit and may be syndromic: biallelic *EIF2AK3* (HGNC:3255) variants produce Wolcott-Rallison syndrome (neonatal diabetes, epiphyseal dysplasia, liver failure), notably the most common genetic cause of PNDM in consanguineous families[23], whereas *FOXP3* (HGNC:6106) variants underlie IPEX (acronym for immune dysregulation, polyendocrinopathy, enteropathy, x-linked-syndrome). Because most non-K_{ATP} forms are

marked by absolute insulin deficiency, lifelong insulin therapy remains standard; multidisciplinary follow-up is essential when extra-pancreatic features are expected. [22]

K_{ATP}-Channel–Related Neonatal Diabetes Mellitus (K_{ATP} NDM)

Activating *KCNJ11* or *ABCC8* variants prevent closure of the β-cell K_{ATP} channel and subsequent membrane depolarization impairing insulin release. They span the clinical spectrum from TNDM to PNDM and in severe *KCNJ11* genotypes, the DEND phenotype (developmental delay, epilepsy, and neonatal diabetes). [24,25] Remarkably, up to 90% of K_{ATP}-NDM patients can transition from insulin to high-dose sulfonylureas, with earlier transfer correlating with better glycemic, and in some series, neuro-developmental outcomes. [13] Notably, although pathogenic variants in KCNJ11 and ABCC8 are most often inherited in an autosomal-dominant fashion, rare autosomal-recessive cases have been reported and are typically associated with a more severe clinical phenotype. [47,48]

Wolfram Syndrome

The Wolfram spectrum illustrates how a single gene can underlie more than one clinical entity, with inheritance pattern and allele type shaping the phenotype. Classic Wolfram syndrome (WS1) most often results from biallelic loss-of-function of *WFS1* (HGNC:12762), typically presenting around six years old with diabetes followed by optic atrophy and progressive neurological deterioration including arginine vasopressin deficiency (central diabetes insipidus).[26] By contrast, heterozygous missense variants in the same gene give rise to an autosomal-dominant "Wolfram-like" condition that shares optic and metabolic features but usually presents later and with milder neurologic involvement.[50] A rarer form (WS2), caused by *CISD2* (HGNC:24212) mutations, shares many features but includes peptic ulcers and lacks diabetes insipidus. Recognizing these genotype-phenotype distinctions enables timely, multidisciplinary care.[6,26]

Insulin Receptor Defects

Pathogenic *INSR* (HGNC:6091) variants produce a continuum of rare monogenic insulin-resistance syndromes that are mechanistically distinct and clinically more profound than the obesity-linked resistance of the metabolic syndrome. Type A insulin-resistance syndrome, usually appears after puberty in otherwise lean adolescents with marked hyperinsulinemia, hirsutism, and acanthosis nigricans. Autosomal-recessive, biallelic loss-of-function variants give rise to progressively more severe phenotypes: Rabson-Mendenhall syndrome emerges in early childhood with growth failure, coarse facies, dental and nail dysplasias, and extreme insulin resistance, whereas Donohue syndrome manifests in the neonatal period with profound failure to thrive and is typically fatal in infancy.[6,27,28]

Lipodystrophy Syndromes

Defects in adipose genes [e.g., *AGPAT2* (HGNC:325), *BSCL2* (HGNC:15832), *LMNA* (HGNC:6636)] disrupt fat-cell development, driving ectopic lipid storage and severe insulin. These mutations give rise to two main phenotypes: congenital generalized lipodystrophy (CGL), marked by near-total fat absence from birth and early-onset diabetes, and familial partial lipodystrophy (FPLD), in which limb fat is lost but visceral fat accumulates, still producing major metabolic derangements.[29,30] Although LMNA variants are classically inherited in an autosomal-dominant fashion, rare autosomal-recessive cases have also been reported.[49] Metreleptin replacement, the only FDA approved disease-specific therapy, can normalize glycemia and triglycerides in most CGL and some severe FPLD cases.[31,32]

Mitochondrial Diabetes

Most mitochondrial diabetes cases are maternally inherited diabetes and deafness (MIDD) caused by the tRNA m.3243A>G mitochondrial DNA mutation. The classic triad—maternal inheritance, non-autoimmune diabetes emerging in late childhood or young adulthood, and progressive bilateral sensorineural hearing loss—may be joined other extra pancreatic features including macular pattern dystrophy, focal-segmental glomerulosclerosis, gastrointestinal dysmotility, or neuromuscular and encephalopathic signs when affected organs contain a higher share of variant versus normal mitochondrial genomes.[33] More than three-quarters of patients eventually require insulin and metformin is usually avoided because defective oxidative phosphorylation heightens risk of lactic acidosis.[33–35]

4. Syndromic Diabetes

Syndromic diabetes involves hyperglycemia plus specific multisystem features. Accurate diagnosis can expedite targeted management and screening for associated comorbidities.

5. Diagnostic Workflow

Timely recognition of monogenic diabetes can greatly impact management. The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends genetic testing for all infants diagnosed before six months or before 12 months if AAB are negative, given the high likelihood of identifying K_{ATP}-channel variants amenable to sulfonylurea therapy.[36]

The American Diabetes Association (ADA) similarly advises testing individuals who do not fit classic T1D or T2D profiles.[37] Complementing these, the Precision Medicine in Diabetes Initiative (PMDI) provides a graded framework for genetic testing, with Grade A recommendations for infants diagnosed <6 months,

individuals with mild stable hyperglycemia (suggestive of GCK-MODY), and those with atypical features such as negative AAB, non-obesity, or a strong family history.[4] Broadening testing criteria in clinical practice has been shown to significantly increase diagnostic yield, especially for MODY among young adults misclassified as having T2D (see Figure 1).[38]

consideration for MODY or other non-autoimmune forms. Notably, 1–2% of MODY patients can test positive for GAD, underscoring the importance of genetic testing when suspicion remains high. Several experimental biomarkers are being evaluated but are not yet recommended for routine diagnosis.[37] Multivariable tools that estimate monogenic diabetes probability— blending age at

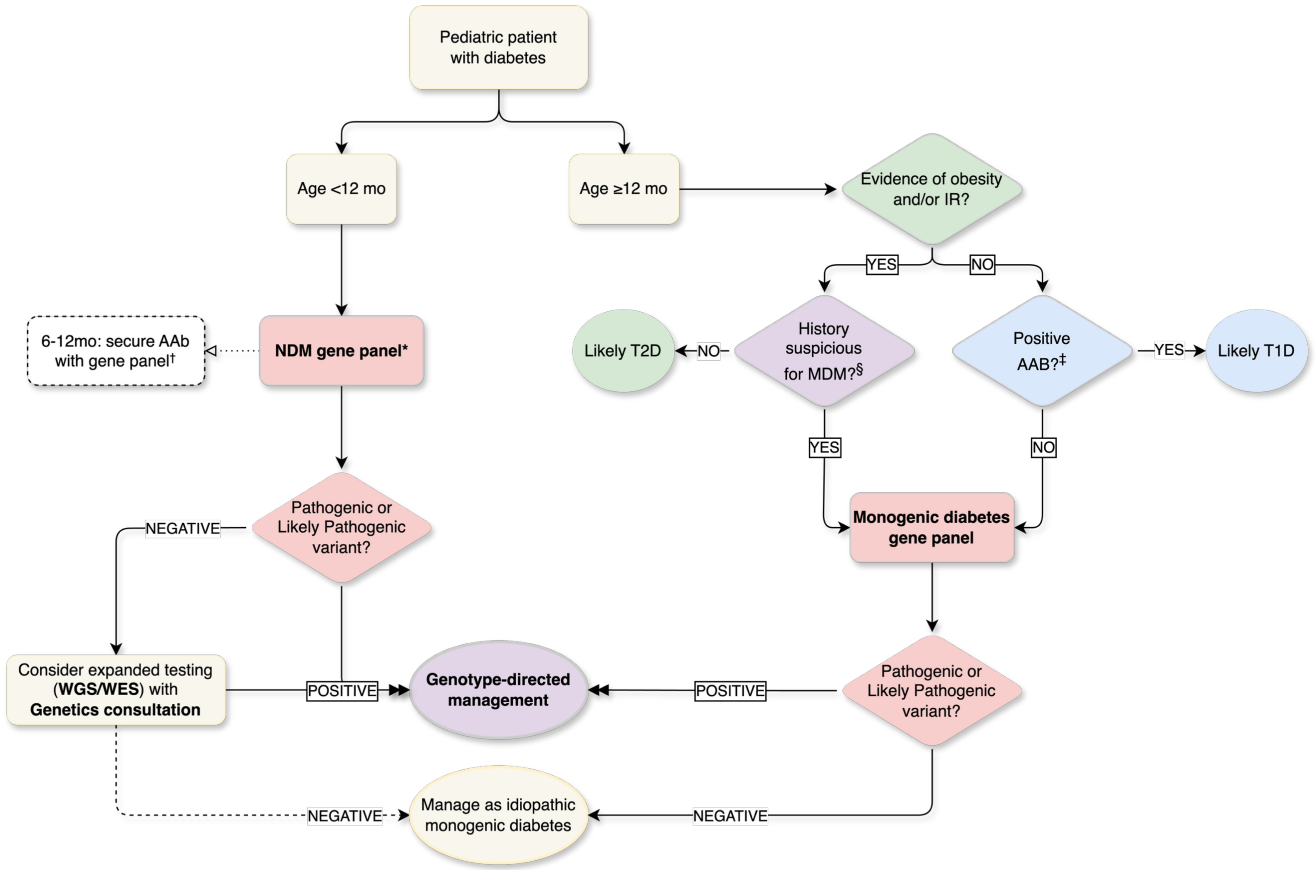

Figure 1. Diagnostic workflow for identifying monogenic diabetes in pediatric patients

Abbreviations: AAB, diabetes-related autoantibody; IR, insulin resistance; MDM, monogenic diabetes mellitus, NDM, neonatal diabetes mellitus; WES, whole exome sequencing; WGS, whole genome sequencing.

*: Neonatal diabetes mellitus large gene panel should include at minimum ***ABCC8, KCNJ11, INS,*** plus less common causes like *GCK, EIF2AK3, PDX1, and PTF1A* (some laboratories extend to >20 genes) with an additional targeted test for 6q24 methylation defects.[4]

†: Patients aged 6–12 months should have both a NDM gene-panel and diabetes-autoantibody screening. In infants < 6 months autoantibodies are rare, but testing can be reconsidered if the NDM panel is negative—particularly in those ≥ 5 months.[4]

‡: Diabetes-related autoantibodies (AAB) include glutamic acid decarboxylase 65 (GAD65), insulin autoantibody (IAA), islet antigen-2 autoantibody (IA-2A), and zinc transporter 8 autoantibody (ZnT8).

§: History suspicious for monogenic diabetes includes a strong family history of diabetes mellitus, only mildly elevated blood glucose level, age <30 years-old.[4,36,37]

Biomarkers and Risk Calculators

Baseline testing should always include fasting (or stimulated) C-peptide together with the four standard diabetes-related autoantibodies (AAB)—glutamic acid decarboxylase (GAD65), insulin (IAA), islet antigen 2 (IA-2), and zinc transporter 8 (ZnT8)—because the combination effectively separates classic T1D (low C-peptide, ≥1 positive AAB) from cases that warrant

diagnosis, BMI, C-peptide, auto-antibody data, etc.—are also being refined and show promise in identifying individuals in need of monogenic diabetes testing, but lower accuracy in non-European ancestry groups underscore the need for local validation and further refinement.[39–42]

Genetic Testing

Historically, Sanger sequencing of a single candidate gene—like *GCK* or *HNF1A*—was ordered based on a patient's clinical phenotype. Modern next-generation sequencing (NGS) panels now interrogate multiple loci at once, ranging from focused sets to comprehensive assays that cover all currently recognized monogenic-diabetes genes; nonetheless, deep-intronic or other non-coding variants may still be missed. Variant classification relies on population databases (e.g. gnomAD), segregation analyses, and when available, functional assays and is summarized with the ACMG/AMP five-level system (pathogenic to benign). Incomplete penetrance and variable expressivity continue to pose counselling challenges.[4] Crucially, when a pathogenic or likely pathogenic variant consistent with monogenic diabetes is identified, results should be conveyed directly by a clinician experienced in monogenic diabetes or by a genetic counsellor, rather than released through an electronic medical record (EHR) portal or communicated by non-clinical staff. This approach ensures accurate interpretation, psychosocial support, and coordinated management planning.[4,36] Afterward, cascade testing is gene-specific: autosomal-dominant or otherwise actionable variants warrant screening of all first-degree relatives, whereas GCK variants are usually tested only in relatives who already show persistent mild hyperglycemia or gestational diabetes; carrier testing for recessive or de-novo findings follows standard Mendelian counselling.[4]

Monogenic Diabetes, Ancestry, and Health Disparities

Emerging evidence demonstrates that ancestry influences both the presentation and detection of monogenic diabetes. In a large UK study, South Asian patients referred for MODY testing had a significantly lower mutation pick-up rate compared to white Europeans; however, this disparity likely reflects a combination of factors, including a higher background prevalence of young-onset type 2 diabetes and systemic biases embedded in diagnostic pathways.[43,44] Similar challenges have been observed in other underrepresented populations, where social, economic, and healthcare access barriers further compound disparities in genetic testing and diagnosis.[44] These findings underscore the need for ancestry-inclusive studies, tailored diagnostic thresholds, and validation of existing tools like the MODY probability calculator to ensure equitable application of precision medicine in monogenic diabetes.

6. Conclusion

Monogenic diabetes is a prime opportunity for the application of precision medicine in pediatric practice. Early, accurate diagnosis—driven by clinical vigilance and increasingly accessible genomic testing—can replace lifelong insulin or suboptimal therapies with targeted, lower-burden options. By contrast, syndromic forms require coordinated surveillance for extra-pancreatic sequelae. Ongoing advances in NGS, biomarker diversity, and variant-interpretation frameworks are steadily refining diagnostic workflows, yet important challenges remain: detecting non-coding or structural variants, clarifying variant pathogenicity, and ensuring equitable implementation across diverse populations. Sustained collaboration that integrates large-scale genomic data with carefully phenotyped clinical cohorts will be essential for honing genotype–phenotype correlations and, ultimately, for delivering truly personalized care to every child with these rare but consequential disorders.

Acknowledgements

HIO is supported by the Maternal Child Health Research Institute Clinical (MD) Trainee Grant (July 2023–June 2024) & the Ruth L. Kirschstein National Research Service Award (NRSA) T32 Training Program (DK007217-47)

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Further Reading

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   Provides essential guidance on managing the three most common MODY subtypes during pregnancy, emphasizing fetal genotype considerations.

2. Greeley SAW, Hattersley AT, Rubio-Cabezas O, et al. ISPAD clinical practice consensus guidelines 2022: the diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes*. 2022;23(8):1188-1211. DOI: 10.1111/pedi.13427.

   Gold-standard consensus guidelines offering evidence-based algorithms for pediatric monogenic diabetes diagnosis and management.

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   Synthesizes latest evidence on targeted treatments for monogenic diabetes subtypes with practical guidance for transitioning from insulin to specific therapies.

Corresponding Author

Hector I. Ortega (hio@stanford.edu)

Author Contributions

HIO and ALG both contributed to the conception and design of the review. HIO performed the literature search and drafted the initial manuscript. ALG provided critical revision of the manuscript for important intellectual content. Both authors approved the final version for publication.

Conflicts of Interest

HIO has no conflicts of interest to disclose. ALG's spouse is an employee of Genentech and holds stock options in Roche.