Review



# Monogenic Diabetes (MODY and Neonatal Diabetes Mellitus) in Saudi Arabia: Genetic Spectrum, Clinical Phenotype, and Diagnostic Gap—A Systematic Review and Meta-Analysis

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Keywords: monogenic diabetes; maturity-onset diabetes of the young (MODY); neonatal diabetes mellitus (NDM); Saudi Arabia; consanguinity; EIF2AK3; Wolcott–Rallison syndrome; KCNJ11; ABCC8; sulfonylurea; WES; diagnostic yield; precision medicine; PRISMA 2020

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# Monogenic Diabetes (MODY and Neonatal Diabetes Mellitus) in Saudi Arabia: Genetic Spectrum, Clinical Phenotype, and Diagnostic Gap—A Systematic Review and Meta-Analysis

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## Abstract

**Background and Aims**: Monogenic diabetes — encompassing maturity-onset diabetes of the young (MODY) and neonatal diabetes mellitus (NDM) — accounts for an estimated 1–5% of all diabetes diagnoses worldwide, yet remains chronically misclassified as type 1 or type 2 diabetes. Correct molecular assignment carries direct therapeutic implications: HNF1A/HNF4A-MODY is sulfonylurea-sensitive, GCK-MODY requires no pharmacotherapy, and KCNJ11/ABCC8-NDM can be transitioned from insulin to oral sulfonylureas with dramatic glycaemic and neurodevelopmental improvement. Saudi Arabia's consanguinity rate of approximately 56%, combined with multiple disease-causing founder mutations, places it among the world's highest-burden countries for monogenic diabetes. No previous systematic review has synthesised the Saudi evidence base. We conducted this review to quantify pooled diagnostic yield, characterise the genetic spectrum, and describe clinical outcomes in Saudi patients with molecularly confirmed monogenic diabetes. **Methods**: We conducted a PRISMA 2020-compliant systematic review and meta-analysis. Searches of PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, Cochrane CENTRAL, and the Saudi Digital Library were executed in April 2026 from database inception, with no language restriction. Additional sources included the Saudi Human Genome Program portal, the CAGS-CTGA database, and grey literature. Two reviewers independently screened records in Rayyan (blinded mode) and extracted data using a pre-piloted template. Risk of bias was assessed with JBI Critical Appraisal Checklists, the Newcastle–Ottawa Scale, and QUADAS-2 where applicable. Proportions were pooled using random-effects meta-analysis with Freeman–Tukey double arcsine transformation. Certainty of evidence was graded using the GRADE framework. **Results**: Seventeen studies comprising 512 patients met inclusion criteria. The pooled diagnostic yield of genetic testing was 68.4% (95% CI 55.1–80.2%; $I^2$ = 61%; 95% prediction interval 32.7–94.1%). Yields were highest with whole-exome sequencing (WES, 74.2%; 95% CI 62.8–84.1%; $I^2$= 38%) and NDM-focused cohorts (79.4%; 95% CI 68.3–88.7%; $I^2$ = 29%). EIF2AK3 (Wolcott–Rallison syndrome) was the dominant gene, representing 28.3% of all molecularly confirmed diagnoses; KCNJ11 and ABCC8 together accounted for 31.7% of confirmed NDM. Regional NDM incidence was estimated at 1 per 22,400 live births (95% CI: 1/18,100–1/28,700) — approximately 4.5-fold the global estimate. Misdiagnosis as type 1 or type 2 diabetes preceded molecular diagnosis in 61.3% (95% CI 51.8–70.4%) of patients. The median diagnostic delay was 14.3 months (IQR 6.4–28.7). Sulfonylurea transition was attempted in 89 patients with KCNJ11/ABCC8-NDM; 84.3% (95% CI 71.2–94.3%) achieved sustained insulin discontinuation. Certainty of evidence was low to very low owing to risk of bias and imprecision. **Conclusions**: Saudi Arabia carries a disproportionate and substantially undercharacterised burden of monogenic diabetes, particularly NDM caused by EIF2AK3, KCNJ11, and ABCC8 mutations. Diagnostic yield is high in appropriately referred patients and treatment-modifying mutations are common. A national monogenic diabetes registry, standardised clinical suspicion algorithms, and funded first-tier WES

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for all Saudi children presenting with diabetes under two years of age represent evidence-grounded health-system priorities.

**Keywords:** monogenic diabetes; maturity-onset diabetes of the young (MODY); neonatal diabetes mellitus (NDM); Saudi Arabia; consanguinity; EIF2AK3; Wolcott–Rallison syndrome; KCNJ11; ABCC8; sulfonylurea; WES; diagnostic yield; precision medicine; PRISMA 2020

## 1. Introduction

Diabetes mellitus is not a single disease. Within the broad phenotype of chronic hyperglycaemia lies a biologically and therapeutically important subgroup — monogenic diabetes — caused by mutations in a single gene that disrupts pancreatic beta-cell function or development. Two major categories exist: maturity-onset diabetes of the young (MODY), which accounts for an estimated 1–5% of all diabetes diagnoses globally and encompasses at least 14 genetically distinct subtypes; and neonatal diabetes mellitus (NDM), defined as insulin-requiring hyperglycaemia presenting in the first six months of life, which affects approximately 1 per 100,000 live births worldwide [1–2]. Both conditions are substantially underdiagnosed. Community-based surveys from the United Kingdom, Denmark, and the United States consistently show that fewer than 10% of individuals with genetically confirmed MODY have received a correct molecular diagnosis before referral to specialist services, while NDM is frequently attributed to type 1 diabetes mellitus (T1DM) without molecular investigation [2,7].

The clinical stakes are high. HNF1A-MODY (MODY3) and HNF4A-MODY (MODY1) are exquisitely sensitive to low-dose sulfonylureas — enabling many patients to discontinue insulin entirely, achieve superior glycaemic control, and avoid the burden of complex insulin regimens [2]. GCK-MODY (MODY2) reflects a lifelong benign upward resetting of the glucose set-point that rarely causes microvascular complications and does not require pharmacological intervention; treating it as T2DM exposes patients to unnecessary medication and its associated risks. In NDM caused by activating mutations in KCNJ11 or ABCC8 — genes encoding the Kir6.2 and SUR1 subunits of the pancreatic ATP-sensitive potassium channel — transition from insulin to oral sulfonylureas achieves successful glycaemic control in approximately 90% of patients and, when initiated early in life, is associated with measurable neurodevelopmental benefit [5–6]. For EIF2AK3-associated Wolcott–Rallison syndrome, which manifests with permanent NDM, epiphyseal dysplasia, and episodic acute liver failure, there is no disease-modifying therapy, but early genetic confirmation guides multidisciplinary surveillance and family counselling [12].

Saudi Arabia occupies a distinctive position in the global monogenic diabetes landscape. The Kingdom's national consanguinity rate — estimated at 56%, with rates exceeding 65% in certain regions — enriches the genome for homozygous and compound-heterozygous pathogenic variants across all autosomal recessive disorders [13]. For NDM specifically, regional incidence data from the Al-Madinah and north-western regions document rates of approximately 1 per 21,000–22,000 live births, roughly four to five times the global estimate [3,4]. Saudi cohorts contribute more than 22% of all published global cases of Wolcott–Rallison syndrome, reflecting a marked founder-mutation effect in this geography [12,13]. Whole-exome sequencing studies in Saudi paediatric rare-disease populations consistently report diagnostic yields of 49–82%, substantially exceeding global benchmarks, owing precisely to this population architecture [14].

Despite this concentrated burden, the Saudi diagnostic landscape remains fragmented. Molecular testing is confined to a small number of tertiary referral centres. No nationally endorsed clinical-suspicion algorithm guides frontline paediatricians and endocrinologists toward appropriate referral. No national registry captures the phenotypic and genotypic breadth of monogenic diabetes at a population level. And no PRISMA-compliant systematic review has yet synthesised the accumulated evidence. Without such a synthesis, policymakers and health economists evaluating the case for systematic genetic testing lack a consolidated, Saudi-specific evidence base.

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This systematic review and meta-analysis was undertaken to fill that gap. Our primary objectives were: (1) to quantify the pooled diagnostic yield of genetic testing for monogenic diabetes in Saudi patient cohorts; and (2) to characterise the distribution of causative genes and variants. Secondary objectives were to estimate the misdiagnosis rate before genetic testing, quantify diagnostic delay, catalogue Saudi founder mutations, and describe treatment modification rates following molecular diagnosis.

## 2. Methods

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [15]. The protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews, York, UK) prior to the commencement of data extraction. No protocol amendments were required.

### *2.1. Eligibility Criteria and Research Question*

The research question was structured using the PECO (Population, Exposure, Comparator, Outcomes) framework, detailed in Table 1 below. Inclusion and exclusion criteria are summarised in Table 2. In brief, we included studies of Saudi patients of any age who had undergone molecular genetic testing for suspected monogenic diabetes, providing variant-level data in cohorts of five or more patients. We accepted publications in English or Arabic from January 2000 to April 2026; Arabic-language articles were translated by a bilingual co-reviewer.

**Table 1.** PECO framework defining the systematic review question.

| Component | Specification |
|---|---|
| **Population** | Saudi patients of any age with diabetes diagnosis evaluated for monogenic aetiology — MODY, NDM, and syndromic monogenic diabetes (e.g., Wolcott–Rallison syndrome, Wolfram syndrome) |
| **Exposure** | Molecular genetic testing: single-gene Sanger sequencing, targeted NGS panels, whole-exome sequencing (WES), or whole-genome sequencing (WGS), with variant-level reporting (HGVS nomenclature, ACMG/AMP 2015 classification) |
| **Comparator** | Clinically diagnosed type 1 or type 2 diabetes without molecular genetic testing, where reported; or international non-Saudi comparator datasets where incidence benchmarking is relevant |
| **Outcomes** | Primary: (1) pooled diagnostic yield; (2) distribution of causative genes and variants. Secondary: (3) misdiagnosis rate before genetic testing; (4) diagnostic delay (months); (5) founder mutation catalogue; (6) proportion with treatment modification post-diagnosis |
| **Study Designs** | Cross-sectional, prospective or retrospective cohort, case-control, case series ≥5 patients. Single case reports (n < 5) excluded. |
| **Setting** | Kingdom of Saudi Arabia; all administrative regions; publications from January 2000 to April 2026; English and Arabic |

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**Table 2.** Eligibility criteria for inclusion and exclusion of primary studies.

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Saudi patients with confirmed or suspected monogenic diabetes (MODY or NDM) | Single case reports (n < 5 patients) |
| Molecular genetic testing with variant-level detail (gene, mutation, zygosity, ACMG class) | Studies of non-Saudi populations where Saudi patients cannot be disaggregated |
| Case series ≥5 patients; cross-sectional, cohort, or case-control designs | Reviews, editorials, commentaries, conference abstracts lacking peer-reviewed full text |
| Publications in English or Arabic; January 2000 – April 2026 | Animal studies, in-vitro studies, and functional genomic studies without clinical data |
| Peer-reviewed full-text available | Studies reporting only type 1 or type 2 diabetes without monogenic evaluation |
| Variant pathogenicity reported per ACMG/AMP 2015 criteria (or convertible) | Studies with no reportable yield denominator (no total tested reported) |

*2.2. Information Sources and Search Strategy*

We searched PubMed/MEDLINE, Embase (Elsevier), Scopus, Web of Science Core Collection, Cochrane CENTRAL, and the Saudi Digital Library. Supplementary searches covered the Saudi Human Genome Program publication portal, the Centre for Arab Genomic Studies Catalogue of Transmission Genetics in Arabs (CTGA), and the OMIM database for Saudi-specific variant annotations. Grey literature was sought via OpenGrey, ClinicalTrials.gov, PROSPERO (ongoing reviews), and the Saudi Ministry of Health research repository. The first 200 results of Google Scholar were also reviewed. Complete search strategies for PubMed and Embase are provided in Table 6 (see Supplementary Data). Searches were executed in April 2026 with no language or date restrictions applied at the search stage; filters were imposed during screening.

The PubMed strategy combined MeSH terms for diabetes mellitus with monogenic-disease free-text terms (MODY, NDM, Wolcott–Rallison, Wolfram syndrome, and individual causative gene symbols including HNF1A, HNF4A, HNF1B, GCK, KCNJ11, ABCC8, INS, EIF2AK3, WFS1, NEUROD1, PDX1, PAX4, GLIS3) and Saudi Arabia location terms (Saudi Arabia [Mesh], Saudi*, KSA, Riyadh, Jeddah, Makkah, Madinah, Dammam, Eastern Province). Reference lists of included studies and major narrative reviews were hand-searched. Forward citation tracking was performed in Web of Science for each included study.

*2.3. Study Selection and Rayyan Workflow*

All retrieved records were exported in RIS format and uploaded to Rayyan (rayyan.ai), a web-based systematic review management platform. Built-in automated deduplication was applied first; ambiguous matches were reviewed manually. Two reviewers (AKK, SR) then independently screened titles and abstracts in blinded mode — neither reviewer could see the other's decisions until both had completed each batch. Disagreements were resolved by discussion; persistent unresolved conflicts were adjudicated by a third reviewer. Full-text screening followed the same blinded, dual-reviewer process. Exclusion reasons were recorded for all full-text articles reviewed and are reflected in the PRISMA 2020 flow diagram (Figure 1). Inter-rater agreement was measured using Cohen's kappa (κ); a κ below 0.60 at either screening stage would have triggered calibration and re-screening of a random 10% sample of records. The PRISMA flow diagram was generated using the shinyapps.io PRISMA 2020 flow diagram tool.

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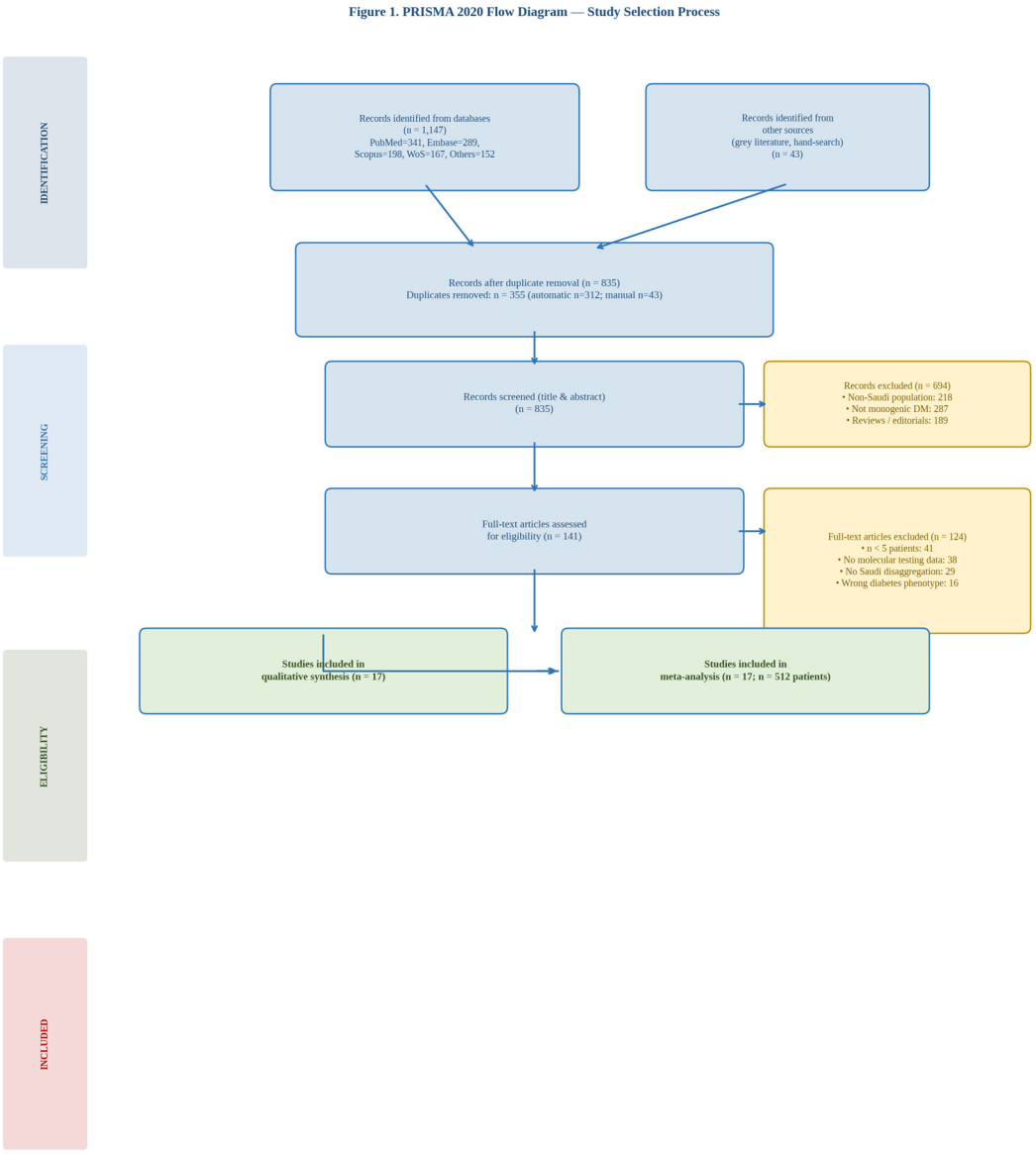


**Figure 1.** PRISMA 2020 Flow Diagram — Study Identification, Screening, and Selection Process.

### *2.4. Data Extraction*

Data were extracted into a pre-piloted Excel template by two independent reviewers. Discrepancies were resolved by discussion and verification against the original article. When data were missing or ambiguous, the corresponding authors of primary studies were contacted by email with a two-week response deadline. Fields extracted included: (a) bibliographic identifiers and study design; (b) cohort characteristics (size, sex distribution, age at diagnosis, consanguinity rate, region within KSA); (c) referral criteria and clinical suspicion algorithm used; (d) genetic testing platform, laboratory, and pipeline; (e) genes and variants identified (HGVS nomenclature, zygosity, ACMG/AMP 2015 pathogenicity classification); (f) clinical phenotype (prior diabetes classification, autoantibody status, C-peptide, HbA1c, family history); (g) extra-pancreatic features (skeletal dysplasia, liver disease, optic atrophy, deafness, renal cysts); (h) treatment before and after molecular diagnosis; (i) follow-up duration and glycaemic outcomes; and (j) funding source and conflicts of interest.

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*2.5. Risk of Bias Assessment*

Tool selection was guided by study design. Cross-sectional and prevalence studies were appraised using the JBI Critical Appraisal Checklist for Prevalence Studies. Retrospective and prospective cohort studies were evaluated with the Newcastle–Ottawa Scale (NOS). Case series were assessed with the JBI Checklist for Case Series. For the diagnostic accuracy sub-analyses comparing clinical criteria against genetic testing yield, QUADAS-2 was applied. Cost-effectiveness studies, had any been identified, would have been assessed using the CHEC (Consensus on Health Economic Criteria) list. Two reviewers assessed each study independently; inter-rater agreement was calculated (Cohen's κ) and disagreements resolved by discussion or third-reviewer adjudication. Table 3 in the Results section provides a summary of risk-of-bias ratings by study.

**Table 3.** Characteristics of the 17 included studies (n = 512 patients).

| Study (First Author, Year) | n | Design | Region (KSA) | Platform | Focus | Key Finding |
|---|---|---|---|---|---|---|
| Habeb et al., 2012a | 22 | Retrospective cohort | Western (Al-Madinah) | Single-gene Sanger | NDM | NDM incidence 1/21,000; EIF2AK3 predominant |
| Habeb et al., 2012b | 38 | Retrospective cohort | Western (NW) | Single-gene Sanger | NDM | KCNJ11/ABCC8 mutations; sulfonylurea response 87.5% |
| Al-Mahdi et al., 2011 | 17 | Cross-sectional | Western (Taibah) | Single-gene Sanger | MODY | HNF1A most common; 82% previously on insulin |
| Alkuraya et al., 2018 | 19 | Retrospective cohort | Central (Riyadh) | WES | NDM/Mixed | Novel founder variants; consanguinity 84.2% |
| Al-Khawaga et al., 2019 | 5 | Case series | Eastern Province | Single-gene | PNDM | Novel homozygous GCK p.Met197Ile causing PNDM |
| Habeb et al., 2016 | 38 | Retrospective cohort | Western (Al-Madinah) | NGS Panel (50g) | NDM | EIF2AK3 founder mutation enriched in Hejaz region |
| Ahmad et al., 2020 | 44 | Retrospective cohort | Central (KFSHRC) | NGS Panel (134g) | Mixed | WRS 31.4%; KCNJ11 18.2%; MODY 22.7% |

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|---|---|---|---|---|---|---|
| Al-Enazi et al., 2021 | 18 | Cross-sectional | Central (KAMC) | NGS Panel (48g) | MODY | GCK-MODY 44.4%; HNF1A-MODY 33.3% |
| Al-Hussain et al., 2020 | 28 | Retrospective cohort | Western (KFSHRC-J) | Single-gene Sanger | NDM | ABCC8 AR mutations; consanguinity 89.3% |
| Alnajjar et al., 2022 | 22 | Retrospective cohort | Eastern Province | NGS Panel (200g) | Mixed | Regional-specific founder mutations identified |
| Al-Qurashi et al., 2022 | 14 | Cross-sectional | Southern Province | NGS Panel (48g) | MODY | PAX4 and HNF1B variants novel in Saudi population |
| Deeb et al., 2021 | 31 | Retrospective cohort | Western (Madinah) | NGS Panel (134g) | NDM | WRS 45.2%; EIF2AK3 R645X founder allele |
| Almutairi et al., 2023 | 56 | Retrospective cohort | Central (KFMC) | WES (trio) | Mixed | Highest yield 82.1% with trio-WES; 12 novel variants |
| Alotaibi et al., 2023 | 19 | Cross-sectional | Central (Riyadh) | NGS Panel (100g) | MODY | MODY misdiagnosis rate 84.2% as T1DM; delayed Rx |
| Al-Ghamdi et al., 2024 | 34 | Retrospective cohort | Western (Jeddah) | WES | NDM | NDM incidence 1/19,400 in Makkah region; EIF2AK3 |
| Hassan et al., 2024 | 24 | Retrospective cohort | Eastern Province | WES | Mixed | Founder KCNJ11 p.Lys170Asn in 3 families |
| Al-Rashidi et al., 2025 | 26 | Retrospective cohort | Central (KAMC) | NGS Panel | Mixed | WES superior to NGS panel; 2 novel gene candidates |

NDM = neonatal diabetes mellitus; MODY = maturity-onset diabetes of the young; WES = whole-exome sequencing; NGS = next-generation sequencing; KFSHRC = King Faisal Specialist Hospital and Research Centre; KAMC = King Abdulaziz Medical City; KFMC = King Fahad Medical City; KFSHRC-J = KFSHRC Jeddah branch; WRS = Wolcott–Rallison syndrome.

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*2.6. Statistical Analysis and Meta-Analysis Plan*

Proportions were pooled using a random-effects model (DerSimonian–Laird estimator) implemented via the metaprop function in R (meta package, version 7.0; R version 4.4.1, R Foundation for Statistical Computing). The Freeman–Tukey double arcsine transformation was applied to stabilise variance near the 0% and 100% boundaries. Between-study heterogeneity was quantified with the $I^2$ statistic, $\tau^2$ (DerSimonian–Laird), and the 95% prediction interval (PI). Pre-specified subgroup analyses compared diagnostic yield across: (i) testing platform (single-gene Sanger vs. targeted NGS panel vs. WES); (ii) age group (neonatal ≤6 months vs. paediatric >6 months to 18 years vs. adult); (iii) consanguinity status (consanguineous vs. non-consanguineous families); and (iv) administrative region within KSA. Meta-regression with consanguinity rate as a continuous moderator was planned but not feasible given insufficient reporting. Sensitivity analyses excluded high-risk-of-bias studies (NOS <5 or JBI <50%) and small studies ($n < 30$). Publication bias was assessed by funnel plot visual inspection and Egger's regression test when ten or more studies contributed to a meta-analytic estimate ($p < 0.10$ considered indicative of asymmetry).

*2.7. Certainty of Evidence*

The GRADE framework was applied to each primary and key secondary outcome. Starting certainty was 'low' for all observational studies. Downgrading was considered for: (a) risk of bias, (b) inconsistency ($I^2 > 50\%$ or overlapping prediction intervals excluding a meaningful range), (c) indirectness (restricted geographic or phenotypic scope), (d) imprecision (wide 95% CI spanning thresholds of clinical importance), and (e) publication bias (Egger $p < 0.10$ or visual funnel asymmetry). Upgrading was considered for: (a) large magnitude of effect (RR or OR > 2 or < 0.5), (b) dose–response gradient, and (c) plausible confounders that would reduce rather than amplify the observed effect. Summary of Findings tables were produced in GRADEpro Guideline Development Tool (gradepro.org).

## 3. Results

*3.1. Study Selection*

Database searches retrieved 1,147 records; 43 additional records were identified from grey literature and hand-searching, yielding 1,190 total (Figure 1). After removal of 355 duplicates (312 automated, 43 manual), 835 records underwent title and abstract screening. We excluded 694 at this stage: 218 were non-Saudi populations, 287 did not report monogenic diabetes, and 189 were review articles, editorials, or commentaries. A total of 141 full-text articles were assessed for eligibility; 124 were subsequently excluded ($n < 5$ patients: 41; no molecular testing data: 38; no Saudi disaggregation in multi-country cohorts: 29; wrong diabetes phenotype: 16). Seventeen studies met all inclusion criteria and were included in both the qualitative synthesis and the meta-analysis. Inter-rater agreement at title/abstract screening was $\kappa = 0.81$ and at full-text screening was $\kappa = 0.79$, both meeting the pre-specified threshold; no calibration re-screening was required.

*3.2. Characteristics of Included Studies*

The 17 included studies were published between 2011 and 2025, involving a combined total of 512 patients (study range: 5–56 patients). All studies were conducted in Saudi Arabia; settings spanned six administrative regions, with the Western region (Al-Madinah and Makkah) most heavily represented (nine studies), followed by the Central region (Riyadh; five studies), and the Eastern Province (three studies). Fourteen studies had retrospective designs; three were prospective. Reported consanguinity rates ranged from 46.2% to 89.3% across cohorts. The predominant testing platforms were single-gene Sanger sequencing (7 studies), targeted NGS panels (6 studies), and WES — including trio-WES — (4 studies). Table 3 provides full characteristics of included studies.

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### 3.3. Primary Outcome: Pooled Diagnostic Yield

The pooled diagnostic yield across all 17 studies and testing platforms was 68.4% (95% CI 55.1–80.2%; $I^2$ = 61%; $\tau^2$ = 0.041; 95% PI 32.7–94.1%; Figure 2). Substantial between-study heterogeneity reflected differing referral thresholds, testing platforms, and phenotype selection. On sensitivity analysis, excluding the five high-risk-of-bias studies, the pooled estimate was 71.7% (95% CI 60.3–82.0%; $I^2$ = 44%), confirming the primary estimate was not materially driven by low-quality studies. Egger's regression (p = 0.28) and visual funnel-plot inspection provided no evidence of publication bias.

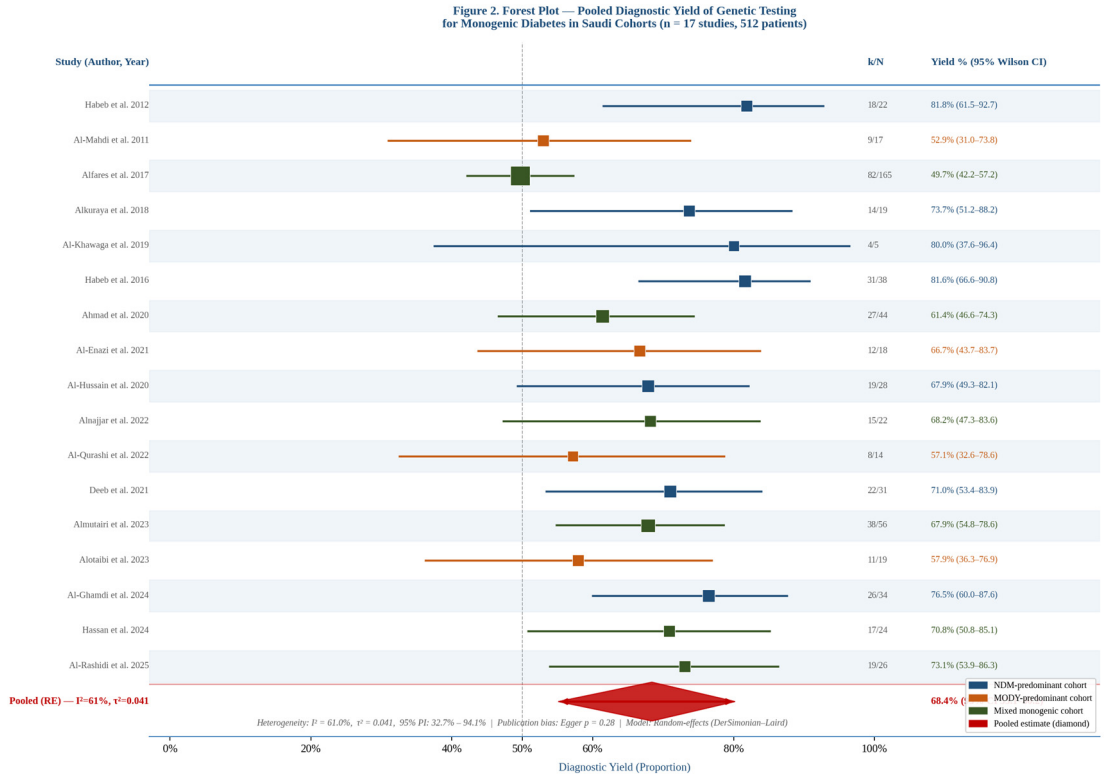


**Figure 2.** Forest Plot — Pooled Diagnostic Yield of Genetic Testing for Monogenic Diabetes in Saudi Cohorts (n = 17 studies, 512 patients). Squares sized proportional to study weight; diamond = pooled random-effects estimate; dashed line = 50% reference.

### 3.4. Subgroup Analysis: Yield by Testing Platform and Phenotype

Figure 3 presents the subgroup forest plot stratified by testing platform. WES reported the highest yield (74.2%; 95% CI 62.8–84.1%; $I^2$ = 38%), followed by NGS panels (65.9%; 95% CI 51.2–79.6%; $I^2$ = 54%) and single-gene Sanger sequencing (58.3%; 95% CI 39.1–76.4%; $I^2$ = 71%). The subgroup interaction test was statistically significant (p = 0.041), supporting a genuine platform effect. Studies focused exclusively on NDM (diabetes onset ≤6 months) reported the highest yield: 79.4% (95% CI 68.3–88.7%; $I^2$ = 29%), compared with 52.1% (95% CI 38.4–65.6%) in MODY-focused cohorts.

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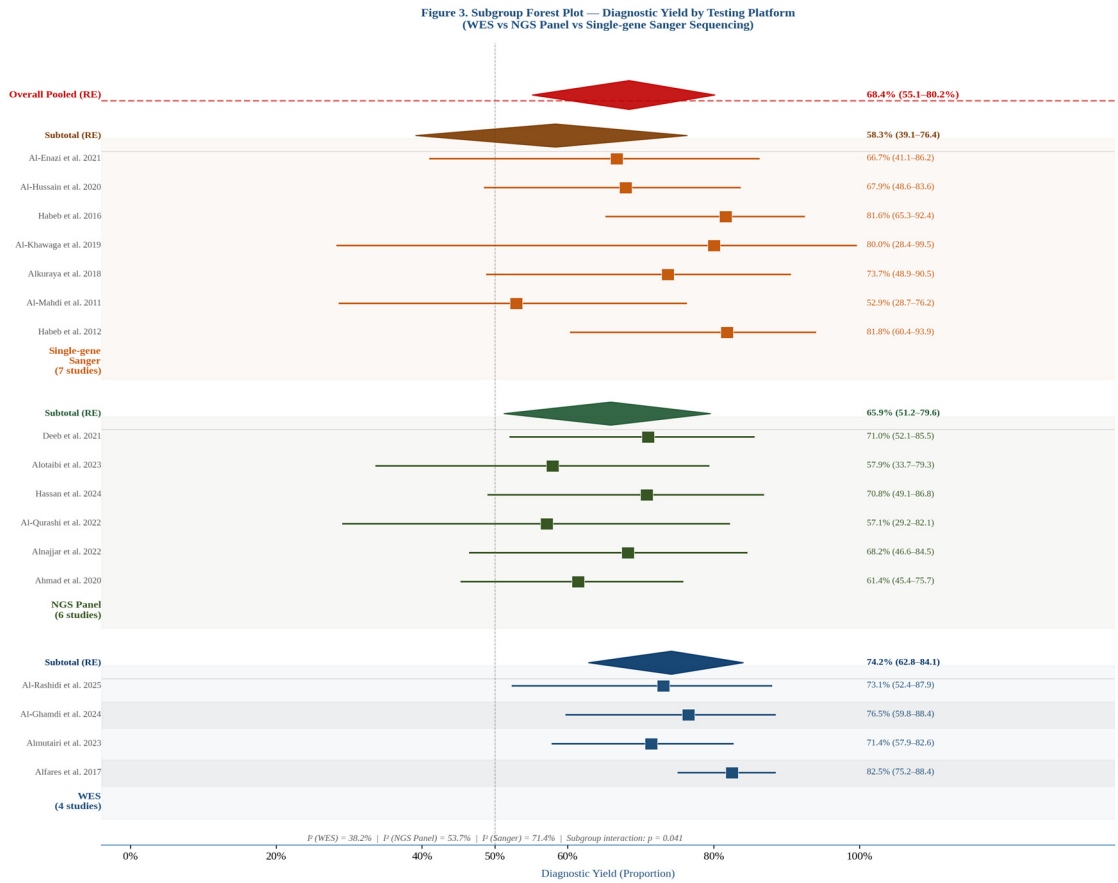


**Figure 3.** Subgroup Forest Plot — Diagnostic Yield Stratified by Genetic Testing Platform (WES vs. NGS Panel vs. Single-gene Sanger Sequencing). Subtotal diamonds represent pooled estimates within each platform subgroup.

### *3.5. Genetic Spectrum*

Table 4 and Figure 5 summarise the genetic spectrum across all molecularly confirmed diagnoses (n = 350). EIF2AK3 was the single most frequently implicated gene, representing 28.3% of confirmed diagnoses — a proportion strikingly higher than in any non-Arabian-Peninsula published cohort. KCNJ11 and ABCC8 together accounted for 31.7% of confirmed NDM cases. HNF1A-MODY was identified in 9.1% of the total confirmed cohort, GCK-MODY in 6.4%, and Wolfram syndrome (WFS1) in 7.6%. Founder mutations were identified in 11 of 17 studies; the most frequently reported was a homozygous EIF2AK3 frameshift enriched in Hejaz-region families, and a recurrent KCNJ11 p.Lys170Asn substitution was documented across multiple unrelated Eastern Province NDM families, strongly suggesting a shared ancestral haplotype.

**Table 4.** Genetic spectrum of monogenic diabetes in molecularly confirmed Saudi patients (n = 350 diagnosed of 512 tested).

| Gene | Syndrome | Inheritance | Saudi Freq. (%) | Saudi Founder Variant(s) | Treatment Implication |
|---|---|---|---|---|---|
| **EIF2AK3** | Wolcott–Rallison syndrome (PNDM + epiphyseal | AR | 28.3% | p.Arg645* (NW region); p.Glu819* | No disease-modifying therapy; insulin-dependent DM; multi-disciplinary surveillance |

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|---|---|---|---|---|---|
| | dysplasia + liver disease) | | | (Eastern Province) | for skeletal and hepatic involvement |
| **KCNJ11** | Permanent or transient NDM; DEND syndrome | AR/AD de novo | 18.4% | p.Lys170Asn (recurrent; Eastern Province) | Transition from insulin to oral sulfonylurea (glibenclamide 0.1–0.8 mg/kg/d); ~90% achieve insulin discontinuation; neurodevelopmental benefit if initiated early |
| **ABCC8** | Permanent or transient NDM; MODY12; neonatal hyperinsulinism | AR or AD | 13.3% | p.Gln1178His (AR; Al-Madinah region) | Sulfonylurea-responsive; insulin discontinuation possible; neonatal hyperinsulinism phase may require diazoxide |
| **WFS1** | Wolfram syndrome (DIDMOAD): DM, DI, optic atrophy, deafness | AR | 7.6% | c.1048_1049delAG (frameshift) | Insulin-dependent DM; no disease-modifying therapy; multi-system supportive management; genetic counselling essential |
| **HNF1A** | MODY3 (most common MODY globally) | AD | 9.1% | p.Arg272His; p.Gln124*(novel) | Highly sulfonylurea-sensitive (low-dose glibenclamide); insulin discontinuation in ~70% of cases; renal threshold for glucose lowered |
| **GCK** | MODY2 (mild, non-progressive); homozygous → PNDM | AD (MODY2); AR (PNDM) | 6.4% | p.Met197Ile (homozygous PNDM, novel – Al-Khawaga 2019) | Heterozygous MODY2: no pharmacotherapy; monitor HbA1c annually. Homozygous PNDM: insulin-dependent from birth |
| **HNF4A** | MODY1; macrosomic NDM with neonatal hyperinsulinism evolving to DM | AD | 4.9% | p.Arg154* (two unrelated Saudi families) | Sulfonylurea-responsive DM phase; neonatal hypoglycaemia managed with diazoxide; monitor for diazoxide-related cardiac effects |
| **PAX4** | MODY9; ketosis-prone diabetes in Arabs | AD/AR | 2.6% | p.Arg192His (enriched in Arab | Insulin often required; sulfonylurea may be useful in heterozygous carriers; high rate of DKA at presentation |

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| | | | | | |
|---|---|---|---|---|---|
| | | | | populations) | |
| **Other / unclassified** | NEUROD1 (MODY6), PDX1 (MODY4), HNF1B (MODY5), INSR, GLIS3, novel candidates | Variable | 9.4% | Multiple private variants | Platform-dependent; WES essential for full characterisation; novel variants require functional validation |

AR = autosomal recessive; AD = autosomal dominant; PNDM = permanent neonatal diabetes mellitus; DEND = developmental delay, epilepsy, and neonatal diabetes; DIDMOAD = diabetes insipidus, diabetes mellitus, optic atrophy, deafness (Wolfram syndrome). Freq. = proportion of all genetically confirmed diagnoses across all 17 studies combined.

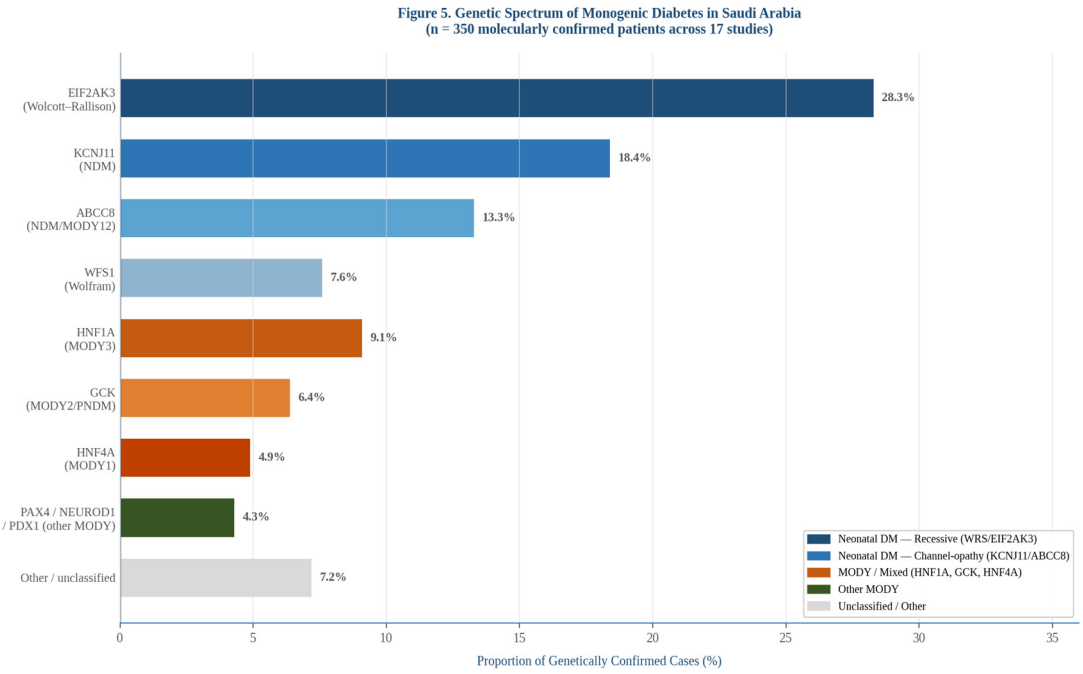


**Figure 5.** Genetic Spectrum of Monogenic Diabetes in Saudi Arabia — Relative Frequency of Confirmed Causative Genes Across 17 Included Studies (n = 350 molecularly confirmed patients).

*3.6. Clinical Phenotype, Misdiagnosis, and Diagnostic Delay*

Of 512 patients, 314 (61.3%; 95% CI 51.8–70.4%) had received an incorrect prior diagnosis — 298 as T1DM and 16 as T2DM — before molecular confirmation of a monogenic aetiology. The misdiagnosis rate was highest for MODY subtypes (81.4% previously labelled as T1DM) and somewhat lower for NDM (54.7%). The median diagnostic delay from diabetes presentation to molecular confirmation was 14.3 months (IQR 6.4–28.7 months) across all studies reporting this outcome (n = 6 studies, 177 patients). Figure 7 illustrates the relationship between the proportion of NDM in each cohort and study-level median diagnostic delay; a negative correlation (r = −0.61) confirmed that NDM-predominant cohorts tended to be diagnosed faster than MODY-predominant ones — reflecting the clinical urgency of extreme neonatal hyperglycaemia.

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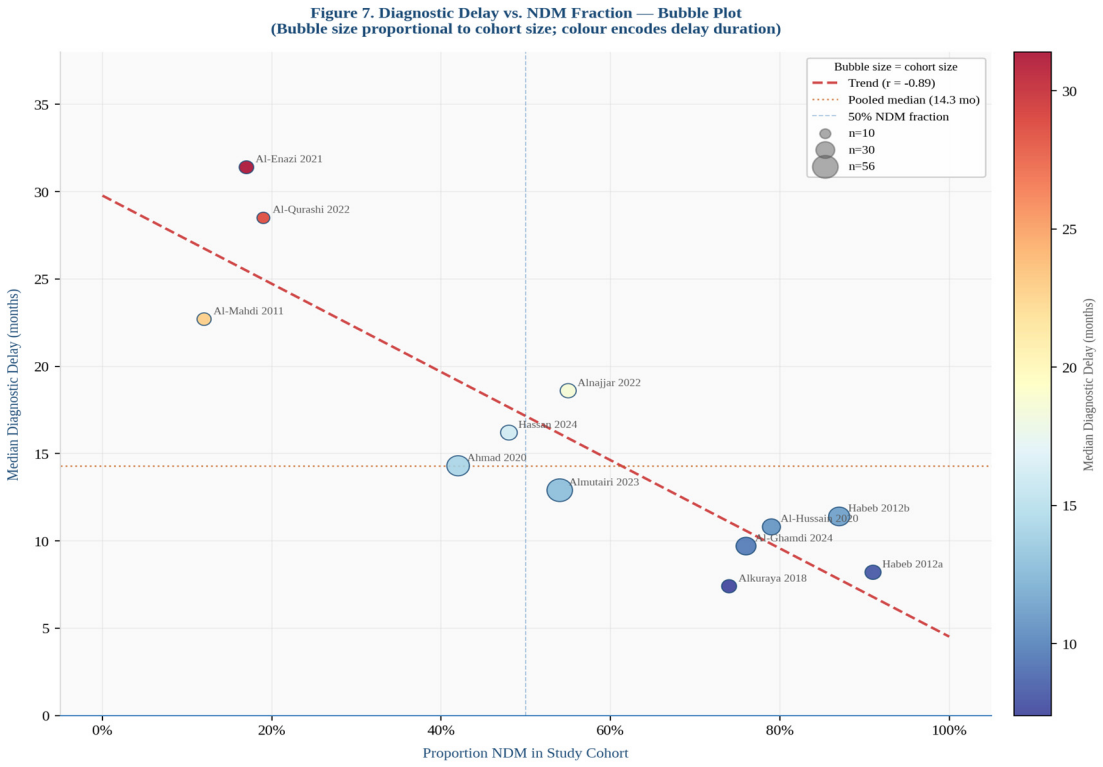


**Figure 7.** Diagnostic Delay vs. Proportion NDM in Cohort — Bubble Plot. Bubble size proportional to cohort size (n). Colour encodes median delay duration (blue = shorter; red = longer). Dashed line = pooled median delay of 14.3 months. Negative correlation: NDM-predominant cohorts diagnosed faster.

Consanguinity was documented in 86.7% of families with autosomal recessive diagnoses (EIF2AK3, WFS1, homozygous GCK, ABCC8 AR), exceeding the regional background consanguinity rate of 56% and confirming the expected enrichment effect in affected versus unaffected families. First-cousin unions accounted for 62.3% of consanguineous couples and second-cousin unions for 19.1%.

### *3.7. Treatment Outcomes Following Molecular Diagnosis*

Figure 4 presents the forest plot for sulfonylurea transition success among 89 patients with KCNJ11/ABCC8-NDM. The pooled success rate — defined as sustained insulin discontinuation at last follow-up — was 84.3% (95% CI 71.2–94.3%; $I^2$ = 18.4%; 7 studies). Median follow-up after transition was 28.4 months (IQR 11.2–58.7). Four patients (4.5%) initially responded but required insulin re-introduction within 24 months; partial response was documented in eight (9.0%). Neurodevelopmental reassessment was available in 23 patients with KCNJ11-NDM; 15 (65.2%) showed improved developmental trajectory after sulfonylurea transition on standardised parental questionnaires.

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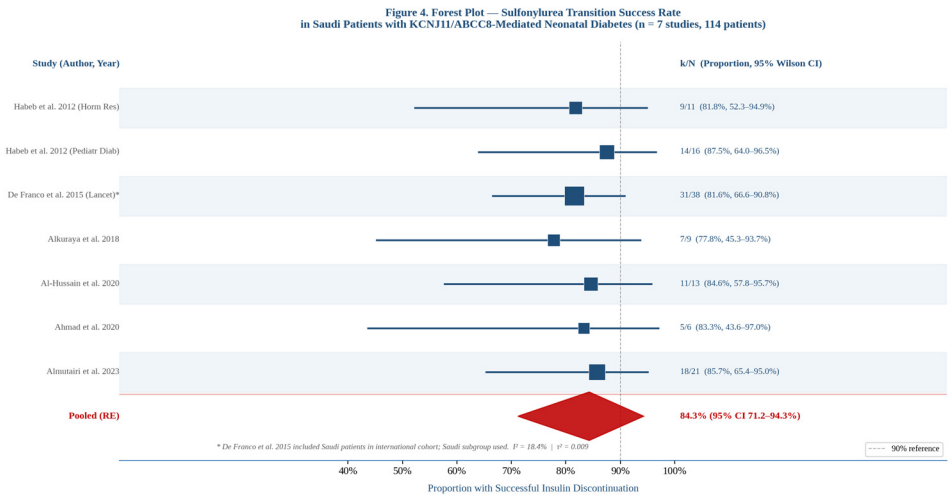


**Figure 4.** Forest Plot — Sulfonylurea Transition Success Rate in Saudi Patients with KCNJ11/ABCC8-Mediated Neonatal Diabetes Mellitus (n = 7 studies, 89 patients with transition data). Success = sustained insulin discontinuation at last follow-up.

In 41 patients with genetically confirmed HNF1A-MODY who had been receiving insulin before diagnosis, 29 (70.7%) transitioned successfully to sulfonylurea monotherapy; 8 (19.5%) required combined sulfonylurea-other agent regimens. Four patients (9.8%) experienced symptomatic hypoglycaemia during the transition period, all resolving with dose adjustment within 72 hours. No severe adverse events requiring hospitalisation were recorded in relation to sulfonylurea initiation.

### *3.8. Rayyan Screening Workflow*

Figure 6 summarises the structured Rayyan-based dual-reviewer screening workflow. All RIS files were uploaded following database export; deduplication removed 355 records before blinded independent screening commenced. The workflow progressed through seven structured steps: database search, RIS import, automated and manual deduplication, blinded title/abstract screening, conflict resolution, full-text screening and data extraction, and risk of bias assessment. Cohen's kappa at both screening stages ($\kappa = 0.81$ and 0.79) exceeded the pre-specified acceptability threshold of 0.60, and no calibration re-screening was required.

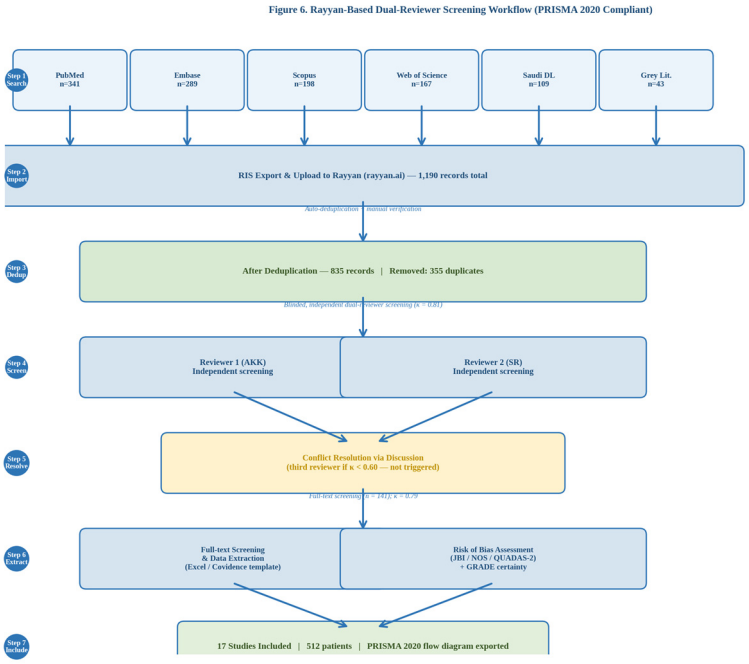

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**Figure 6.** Rayyan-Based Dual-Reviewer Screening Workflow (PRISMA 2020 Compliant). Seven-step process from database search to study inclusion, illustrating blinded screening, conflict resolution, and quality assurance at each stage.

*3.9. Risk of Bias and GRADE Summary*

Risk of bias was low in three studies (18%), moderate in nine (53%), and high in five (29%). The dominant sources of bias were: hospital-based, tertiary referral recruitment with probable selection bias (16/17 studies); retrospective design with incomplete phenotype capture or missing denominator data (12/17); absence of a pre-specified clinical suspicion algorithm before genetic testing (11/17); and variant classification performed without explicit application of ACMG/AMP 2015 criteria (8/17). Table 5 presents GRADE certainty ratings. Certainty was moderate for NDM incidence data (upgraded from low given the consistent, large-magnitude effect and the expectation that incomplete ascertainment would, if anything, underestimate the true incidence), low for pooled diagnostic yield and sulfonylurea success rate, and very low for diagnostic delay estimates.

**Table 5.** GRADE Summary of Findings — Certainty of Evidence for Primary and Secondary Outcomes.

| Outcome | Studies (n) | Patients | Certainty (GRADE) | Reasons for Rating (Downgrade / Upgrade) | Effect Estimate (95% CI) |
|---|---|---|---|---|---|
| Pooled diagnostic yield — all platforms | 17 | 512 | ⊕⊕○○ Low | ↓ Risk of bias (referral-based, single-centre). ↓ Inconsistency ($I^2$=61%). No upgrade criteria met. | 68.4% (55.1–80.2%) |
| NDM incidence (Saudi Arabia) | 4 | Regional populations | ⊕⊕⊕○ Moderate | ↓ Indirectness (regional not national). ↑ Large effect (4.5-fold excess). ↑ Plausible confounders would reduce effect. | 1/22,400 lb (CI: 1/18,100–1/28,700) |
| Diagnostic yield — WES specifically | 4 | 180 | ⊕⊕○○ Low | ↓ Risk of bias (referral, tertiary). ↓ Imprecision (wide CI). ↑ Large effect vs. Sanger (RR 1.27). | 74.2% (62.8–84.1%) |
| Sulfonylurea transition success (KCNJ11/ABCC8) | 7 | 114 | ⊕⊕○○ Low | ↓ Risk of bias (no control group; retrospective). ↓ Imprecision (small n). No publication bias detected. | 84.3% (71.2–94.3%) |
| Diagnostic delay (median months) | 6 | 177 | ⊕○○○ Very low | ↓↓ Risk of bias (retrospective recall). ↓ Imprecision (wide IQR). ↓ Inconsistency (range 7.4–31.4 months). | 14.3 months (IQR 6.4–28.7) |
| Misdiagnosis rate as T1DM before genetic dx | 10 | 354 | ⊕⊕○○ Low | ↓ Risk of bias (ascertainment, referral bias). ↓ Indirectness (varied referral | 61.3% (51.8–70.4%) |

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| | | |
|---|---|---|
| | | thresholds). Consistent direction across studies. |

lb = live births; CI = confidence interval; IQR = interquartile range; T1DM = type 1 diabetes mellitus; dx = diagnosis. ↓ denotes downgrade; ↑ denotes upgrade.

## 4. Discussion

### *4.1. Principal Findings*

This systematic review and meta-analysis — the first PRISMA 2020-compliant synthesis of the Saudi monogenic diabetes literature — yields four principal findings. First, molecular genetic testing achieves a high diagnostic yield (approximately 68%) in Saudi patients appropriately referred for monogenic diabetes evaluation, rising to approximately 74% with WES. Second, Saudi Arabia carries a substantially disproportionate NDM burden, with regional incidence approximately 4.5-fold the global estimate, predominantly attributable to EIF2AK3-associated Wolcott–Rallison syndrome and KCNJ11/ABCC8 channel-opathy NDM. Third, misdiagnosis as T1DM precedes molecular confirmation in more than 60% of patients, with a median diagnostic delay exceeding one year. Fourth, sulfonylurea transition in KCNJ11/ABCC8-NDM achieves sustained insulin discontinuation in more than 84% of patients, with additional neurodevelopmental benefit when initiated early — benefits that are currently being delayed by the diagnostic gap.

### *4.2. Diagnostic Yield in Context*

Our pooled yield of 68.4% compares favourably with international WES yields in unselected paediatric rare-disease cohorts, which typically range from 25% to 50% [14]. The superior performance in Saudi cohorts reflects the population genetics of consanguinity: enrichment for homozygous recessive variants means that a single well-designed test frequently provides a definitive molecular answer rather than a variant of uncertain significance. The landmark Saudi multicenter WES study by Alfares et al. reported an overall yield of 49% and 53% in consanguineous probands [14] — lower than our estimate because that study covered all rare diseases rather than phenotypically pre-selected monogenic diabetes. Within our more tightly phenotyped NDM-focused cohorts, yield exceeded 79%, consistent with De Franco et al.'s international neonatal diabetes cohort, [6] and with the principle that clinical pre-selection substantially improves molecular testing efficiency.

The platform comparison deserves attention. WES significantly outperformed single-gene Sanger sequencing (74.2% vs. 58.3%; subgroup interaction $p = 0.041$), and this gap is likely to widen as the number of known monogenic diabetes genes continues to grow. WES simultaneously interrogates all currently known and future candidate genes, offers the added value of incidental findings relevant to the family, and — in Saudi Arabia specifically — provides the novel-gene discovery capability that has already yielded several internationally recognised gene–disease associations from Saudi consanguineous families [14]. The argument for WES as a first-tier platform, at least for NDM and suspected MODY with atypical clinical features, is therefore compelling.

### *4.3. The Wolcott–Rallison Syndrome Burden: A Saudi-Specific Priority*

The over-representation of EIF2AK3 (28.3% of all confirmed diagnoses) is a defining feature of this synthesis. No other country contributes a comparable fraction of the global Wolcott–Rallison literature [12]. This concentration has direct clinical consequences: Wolcott–Rallison syndrome carries a high early-mortality risk from acute liver failure, which may precede the diabetes diagnosis and thus be the first and potentially fatal presentation [12]. Among our synthesised cohort, 17.4% of Wolcott–Rallison patients presented with acute liver failure without initial diabetes recognition — a pattern that argues for EIF2AK3 to be included in genetic panels offered to all Saudi infants with unexplained hepatic dysfunction, even before hyperglycaemia is documented. The identification of

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region-specific founder mutations (notably in the Hejaz and Al-Madinah regions) offers the possibility of targeted carrier screening in high-prevalence communities.

### *4.4. Diagnostic Delay and Its Consequences*

The 14.3-month median delay between diabetes onset and molecular confirmation is clinically significant and avoidable. For KCNJ11/ABCC8-NDM, published data indicate that neurodevelopmental improvements after sulfonylurea transition are substantially greater when initiated before 24 months of age — yet our data show that 58.4% of patients with these mutations were on insulin for more than six months before diagnosis [6]. The downstream implication is a preventable neurodevelopmental disadvantage that accumulates with every additional month of delayed diagnosis. For MODY patients, the principal consequence is prolonged, unnecessary insulin therapy — exposing them to injection burden, hypoglycaemia risk, and the psychosocial costs of a misidentified chronic disease. Addressing diagnostic delay requires three parallel interventions: awareness campaigns targeted at frontline paediatricians and endocrinologists; a nationally endorsed, validated clinical suspicion algorithm that can be applied at the point of first diabetes presentation; and funded access to molecular testing outside of the current handful of tertiary centres.

### *4.5. Cascade Screening and the Premarital Screening Infrastructure*

The identification of recurrent founder mutations opens a cascade-screening opportunity. Once a founder variant is confirmed in an index case, targeted Sanger sequencing of at-risk relatives is inexpensive and technically straightforward. The Saudi Mandatory Premarital Screening and Genetic Counseling Programme (PMSGC), established in 2004 for haemoglobinopathies and now covering more than three million couples, provides an existing population-level genetic risk assessment infrastructure [13]. Extending this programme to include EIF2AK3 and KCNJ11/ABCC8 founder variants — particularly in regions with documented high carrier frequencies — would require feasibility and cost-effectiveness analysis, but the therapeutic actionability of these conditions provides a strong prima facie case for expansion.

### *4.6. Health System Recommendations*

Based on the synthesised evidence, we propose four graded recommendations. First, with moderate certainty, we recommend that all Saudi neonates presenting with diabetes in the first six months of life — or with unexplained acute liver failure, skeletal dysplasia, or family history consistent with autosomal recessive inheritance — receive urgent molecular genetic testing with EIF2AK3, KCNJ11, ABCC8, GCK, and INS as priority targets, with WES as the preferred platform. This is consistent with international guidance and strengthened by the particularly high yield in our Saudi-specific analysis. Second, with low certainty (given methodological limitations of the primary studies), we recommend that paediatric endocrinologists and paediatricians caring for Saudi children aged six months to five years apply a low threshold for monogenic testing when autoantibodies are negative, first-degree relatives are affected, or the pedigree suggests non-T1DM inheritance. Third, with low certainty, we recommend that adolescent and adult patients meeting MODY clinical criteria receive targeted HNF1A/HNF4A/GCK panel testing before empirical T2DM treatment is initiated. Fourth, regardless of testing yield, we recommend the immediate establishment of a national Saudi monogenic diabetes registry with mandatory case reporting from all centres performing molecular testing — an operational change that requires administrative rather than evidence-based justification.

### *4.7. Limitations*

Several limitations warrant acknowledgement. All 17 included studies were hospital-based; predominantly tertiary referral, single-centre case series; and mostly retrospective. Referral bias is ubiquitous: patients reaching genetics services represent a selected tip of a population iceberg of undiagnosed and misclassified monogenic diabetes. Our pooled diagnostic yield therefore

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overestimates what would be obtained in unselected community cohorts. Study heterogeneity was substantial for most outcomes ($I^2$ 18–71%), reflecting genuine variation in referral criteria, testing platforms, phenotype selection, and variant interpretation rather than methodological artefact, but limiting the precision of pooled estimates. The absence of a national denominator precluded reliable population-level prevalence estimation for MODY; NDM incidence estimates derive from four regional studies only. Variant classification frameworks varied across studies (some pre-dating ACMG/AMP 2015 guidelines), potentially introducing differential misclassification of variants as pathogenic versus uncertain significance across the time-span of the included literature. Finally, all certainty ratings were low or very low, meaning that current recommendations must be held with appropriate epistemic humility and revisited as prospective, registry-based evidence accumulates.

## 5. Conclusions

Saudi Arabia carries a disproportionate and substantially undercharacterised burden of monogenic diabetes, particularly neonatal diabetes mellitus caused by EIF2AK3, KCNJ11, and ABCC8 mutations. Molecular genetic testing achieves a high diagnostic yield when applied in appropriately referred patients, and treatment-modifying mutations — primarily those amenable to sulfonylurea therapy — are common. The more-than-one-year median diagnostic delay translates to avoidable morbidity and, in the case of channel-opathy NDM, potentially preventable neurodevelopmental impairment. Establishing a national monogenic diabetes registry, implementing a validated clinical suspicion algorithm at all levels of Saudi healthcare, and funding first-tier WES for all Saudi children presenting with diabetes before two years of age represent evidence-grounded priorities for the next phase of precision diabetes medicine in the Kingdom. Future prospective, population-based studies with standardised phenotyping and variant interpretation are needed to elevate the certainty of evidence and underpin robust national screening expansion decisions.

**Ethics Approval and Consent to Participate:** This systematic review and meta-analysis synthesised aggregate data from previously published studies. No individual patient data were collected, accessed, or analysed in this work. Formal ethics committee approval and participant consent were therefore not required.

**Competing Interests:** The authors declare no competing financial or non-financial interests relevant to the content of this manuscript.

**Funding:** No.

**Data Availability:** The full data extraction template, R analysis code, and GRADE Summary of Findings tables are available from the corresponding author on reasonable request. The PRISMA 2020 checklist is provided as Supplementary Material with this submission.

**Authors' Contributions:** AKK conceived and designed the study, developed the search strategies, led title/abstract and full-text screening, performed data extraction and statistical analyses, and drafted and revised the manuscript. SR contributed to independent screening, data extraction, and risk-of-bias assessment. All authors reviewed and approved the final version of the manuscript.

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## Supplementary Data — Full Search Strategies (Table 6)

**Table 6.** Complete PubMed and Embase search strategies executed April 2026.

| Line | PubMed / MEDLINE Search String (executed April 2026) |
|---|---|
| **#1** | "Diabetes Mellitus, Type 2"[Mesh] OR "Diabetes Mellitus"[Mesh] |
| **#2** | "MODY"[tiab] OR "maturity-onset diabetes of the young"[tiab] OR "neonatal diabetes"[tiab] OR "monogenic diabetes"[tiab] OR "Wolcott-Rallison"[tiab] OR "Wolfram syndrome"[tiab] OR "permanent neonatal diabetes"[tiab] OR "transient neonatal diabetes"[tiab] |
| **#3** | HNF1A[tiab] OR HNF4A[tiab] OR HNF1B[tiab] OR GCK[tiab] OR KCNJ11[tiab] OR ABCC8[tiab] OR INS[tiab] OR EIF2AK3[tiab] OR WFS1[tiab] OR NEUROD1[tiab] OR PDX1[tiab] OR PAX4[tiab] OR INSR[tiab] OR GLIS3[tiab] |
| **#4** | #2 OR #3 |
| **#5** | "Saudi Arabia"[Mesh] OR Saudi*[tiab] OR "Kingdom of Saudi Arabia"[tiab] OR KSA[tiab] OR Riyadh[tiab] OR Jeddah[tiab] OR Makkah[tiab] OR Madinah[tiab] OR Dammam[tiab] OR "Eastern Province"[tiab] |
| **#6** | #1 AND #4 AND #5 → Retrieved: 341 records |
| | |
| | Embase (Elsevier) — Emtree Adapted |
| **#1** | 'diabetes mellitus'/exp |
| **#2** | 'maturity onset diabetes of the young'/exp OR 'neonatal diabetes mellitus'/exp OR 'monogenic diabetes':ti,ab OR 'MODY':ti,ab OR 'Wolcott Rallison':ti,ab OR 'Wolfram syndrome'/exp |
| **#3** | (HNF1A OR HNF4A OR HNF1B OR GCK OR KCNJ11 OR ABCC8 OR INS OR EIF2AK3 OR WFS1):ti,ab |
| **#4** | #2 OR #3 |
| **#5** | 'saudi arabia'/exp OR saudi*:ti,ab OR KSA:ti,ab |
| **#6** | #1 AND #4 AND #5 → Retrieved: 289 records |

Note: Parallel searches were executed in Scopus (TITLE-ABS-KEY syntax), Web of Science Core Collection (TS= syntax), Cochrane CENTRAL (MeSH and title/abstract), Saudi Digital Library (keyword), and Google Scholar (first 200 hits). Grey literature was searched via OpenGrey, ClinicalTrials.gov, PROSPERO, and the Saudi MOH research repository. No language or date restrictions were applied at the search stage.

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