Australian and New Zealand joint society consensus statement on genetic testing for monogenic diabetes in adults

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Abstract

Introduction: Monogenic diabetes accounts for 2–5% of diabetes. Although its identification has substantial therapeutic implications, more than 80% of affected individuals are undiagnosed or misdiagnosed as having type 1 or 2 diabetes. This consensus statement reviews genetic testing for monogenic diabetes in adults and provides evidence-based recommendations. With representation from the Australian Diabetes Society (ADS), Endocrine Society of Australia (ESA), Human Genetics Society of Australasia (HGSA), New Zealand Society for the Study of Diabetes (NZSSD) and Royal College of Pathologists of Australasia (RCPA), the writing group: (i) defined questions to be addressed, (ii) conducted critical literature reviews, (iii) graded the evidence, and (iv) generated recommendations that were refined until consensus was achieved. All contemporary literature was considered, with a focus on Australian and New Zealand data, where available.

Main recommendations: Indications for genetic testing for monogenic diabetes in adults include: (i) diabetes onset before 12 months of age, (ii) glucokinase (*GCK*)-hyperglycaemia phenotype, (iii) diabetes onset before 30 years of age without markers of type 1 or 2 diabetes, (iv) syndromic monogenic diabetes phenotype, or (v) high probability of monogenic diabetes using validated screening tools. Individuals undergoing genetic testing should be provided with comprehensive pre- and post-test counselling. Genetic testing typically involves next-generation sequencing, and should include classically syndromic genetic variants (eg, m.3243A>G, *HNF1B* variants) even in individuals with isolated diabetes. A molecular diagnosis facilitates gene-specific treatment, surveillance, reproductive planning and cascade testing of relatives. In pregnancies of individuals with *GCK*-hyperglycaemia, maternal treatment can be individualised to known or assumed fetal genotype. Individuals with monogenic diabetes variants of uncertain significance or negative results may be considered for further phenotype or genotype assessment and recruitment into research studies.

Changes in management: This consensus statement aims to raise awareness of monogenic diabetes among clinicians involved in the care of patients with diabetes, and to improve genetic testing rates across Australia and New Zealand.

Monogenic diabetes refers to diabetes resulting from single-gene variants, with or without additional syndromic manifestations.[1] Monogenic diabetes accounts for 2–5% of diabetes and poses substantial clinical implications for treatment, surveillance and reproductive planning; yet, more than 80% of monogenic diabetes is undiagnosed or misdiagnosed as type 1 or 2 diabetes.[2] Monogenic diabetes can present either very early in life (neonatal diabetes) or in childhood or young–mid adulthood (historically termed maturity-onset diabetes of the young or MODY). A recent international systematic review from the Precision Medicine in Diabetes Initiative (PMDI) recommended that laboratory and scientific reports avoid the term MODY and instead use monogenic diabetes for either neonatal or non-neonatal presentations of diabetes together with gene name nomenclature (eg, "*HNF1A*-diabetes" instead of "*HNF1A*-MODY" or "MODY3").[1]

This consensus statement is a joint initiative between the Australian Diabetes Society (ADS), Endocrine Society of Australia (ESA), Human Genetics Society of Australasia (HGSA), New Zealand Society for the Study of Diabetes (NZSSD) and Royal College of Pathologists of Australasia (RCPA), with the aim of providing guidance on monogenic diabetes testing in adults that is tailored to the populations and health care systems of Australia and New Zealand.

Methods

This consensus statement was generated through a collaborative, iterative process involving an appointed writing group of 11 experts in the areas of monogenic diabetes and genetic testing, with representation from seven Australian and New Zealand regions (Auckland, New South Wales, Queensland, South Australia, Victoria, Waikato, Western Australia), and society representation from Australian and New Zealand members of ADS (AA, TD, SD, EE, JG), ESA (SD, EE, JG, RP), HGSA (SD, MG, JH, JT, KW), NZSSD (RM, RP), RCPA (JH) and Royal College of Pathologists United Kingdom (RCPath UK; MG). An initial planning meeting was held in September 2023 to define the scope and questions. Conflicts of interests were declared, although no recommendations pertain to these external interests. The writing group critically reviewed English language, PubMed-indexed articles up to 30 March 2024 using search terms pertaining to the six questions listed below. Each topic was assigned to authors who collated the key data, generated recommendations and created referenced presentations that were reviewed at an evidence meeting in April 2024. Recommendations were refined through consensus, and each was passed by a majority vote. A draft manuscript was created with input from all authors and led by the writing group co-chairs (SD, RM, JG). The draft manuscript was circulated to all authors before review and ultimately endorsement by six Australian and New Zealand

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societies (ADS, ESA, HGSA, NZSSD and RCPA, as well as the Australasian Diabetes in Pregnancy Society).

Based on principles of evidence grading for guidelines,[3,4] and recent high impact endocrinology guidelines,[5] consensus recommendations were graded according to quality and strength of evidence. Recommendations were graded as "weak" if based on low quality data comprising expert opinion or small uncontrolled studies, and "strong" if based on data of moderate quality (at least one large uncontrolled study or meta-analysis) or high quality (controlled studies or large series of large uncontrolled studies).

1. Purpose: what is the purpose of genetic testing for monogenic diabetes?

1A. Clinical value of genetic testing

Recommendation: Diagnosis of monogenic diabetes can alter therapy *[Strong]*, provide predictive testing options to relatives *[Strong]*, and may improve quality of life *[Weak]*.

The identification of a pathogenic variant in patients with monogenic diabetes can substantially change management of hyperglycaemia. The exquisite sensitivity of KATP-neonatal diabetes and *HNF1A*- and *HNF4A*-diabetes to sulfonylureas often allows cessation of insulin treatment and improvement in quality of life.[1,6] Identification of glucokinase (*GCK*)–hyperglycaemia typically permits cessation of diabetes treatment, as mild hyperglycaemia is due to a higher glucose homeostat.[1,6] In pregnancies of mothers with *GCK*–hyperglycaemia, maternal treatment can be tailored to known or assumed fetal genotype. The therapeutic and reproductive implications for a proband, discussed in Sections 5 and 6, generally extend to affected relatives.

1B. Current approaches in Australia and New Zealand

In Australia, patients with suspected monogenic diabetes are typically referred by their treating clinician, usually an endocrinologist, for assessment by a specialist genetics service. The patient receives genetic counselling and undergoes detailed phenotyping before being offered genetic testing, if appropriate, typically via a next-generation sequencing (NGS) panel through an Australian, New Zealand or overseas laboratory with concurrent testing of more than 50 monogenic diabetes genes.[7] Genetic test results are returned to patients via letter, telehealth or in-person appointments with the genetics service according to clinical need, with comprehensive correspondence written to treating clinicians so treatment changes can be instituted where appropriate. As there is currently no Medicare rebate for monogenic diabetes genetic testing, test costs (typically > $1000) are incurred by the requesting genetics service or patient.[8]

In New Zealand, genetic testing for monogenic diabetes is publicly funded. Test costs are paid by Health New Zealand Te Whatu Ora and charged to the requesting hospital service; there is no cost to patients. Diagnostic genetic tests may be requested by an endocrinologist or through genetic services, whereas cascade predictive genetic testing is conducted through genetic services.[9]

If Australia were to follow New Zealand's lead and provide publicly funded monogenic diabetes testing via treating endocrinologists or genetic services, this would ensure equitable access to testing and increase diagnostic rates. There is significant heterogeneity in access to specific expertise in monogenic diabetes across Australia and New Zealand, with access often limited in rural and remote areas. This may improve with more clinician training and telehealth-based services.[10]

2. Selecting patients: which patients should be selected for genetic testing?

2A. International consensus recommendations

Recommendation: Adapting international recommendations regarding monogenic diabetes genetic testing in adults to the Australian and New Zealand landscape:

- Large gene panel testing for monogenic diabetes is recommended in all individuals who were diagnosed with diabetes before the age of 12 months.
- Large gene panel testing for monogenic diabetes is recommended in non-obese individuals with diabetes diagnosed before the age of 30 years with negative pancreatic autoantibodies and/or a retained serum C-peptide response to hyperglycaemia.
- *GCK* variant testing is recommended in non-obese individuals with persistent mild hyperglycaemia at any age, and should be considered in non-obese women with gestational diabetes and fasting glucose > 5.5 mmol/L, especially if there is a compelling family history.

[Strong]

The PMDI reached consensus on indications for monogenic diabetes testing in 2023;[1] these differ slightly from the 2022 International Society for Pediatric and Adolescent Diabetes (ISPAD) recommendations.[11] The PMDI recommendations were based on the systematic review of current evidence and opinion of experts (including from Australasia) to achieve the greatest cost-effective yield. We have accordingly adopted the same patient groups as the PMDI Grade A/B recommendations, although we advise that *GCK* testing should be considered — rather than being recommended — in the gestational diabetes group as explained below.

We recommend screening with a large gene panel (≥ 6 genes tested per PMDI definition) for monogenic forms of neonatal diabetes in all individuals diagnosed with diabetes before 12 months of age, given the low prevalence of non-genetic types of diabetes.[1] Although the yield of genetic testing is higher with diabetes onset before 6 versus 12 months of age (up to 82% *v* 0–28%), the potential yield is sufficiently high to warrant genetic testing in all individuals with diabetes diagnosed within the first year of life.[1]

We also recommend large gene panel testing for monogenic diabetes in all non-obese people diagnosed with diabetes before 30 years of age (lower probability of type 2 diabetes), who have negative autoantibody titres and/or retained serum C-peptide response to hyperglycaemia (lower probability of type 1 diabetes). Interpretation of autoantibody results should consider time since diabetes diagnosis and the possibility of false-positive results (eg, single mildly elevated titres).

With regards to the specific phenotype of *GCK*–hyperglycaemia, we recommend *GCK* testing in non-obese individuals with a typical phenotype of persistent (eg, over years) mild hyperglycaemia with HbA_{1c} levels of 5.6–7.8% (38–62 mmol/mol) or fasting glucose concentrations of 5.5–7.8 mmol/L outside of pregnancy. We also advise that *GCK* testing be considered in non-obese women with gestational diabetes and untreated

fasting glucose levels of more than 5.5 mmol/L (ie, including the diagnostic oral glucose tolerance test), as recently reviewed in detail by the PMDI.1 Up to 22% of such women will be found to have *GCK*–hyperglycaemia,[12] with significant pregnancy implications (see Section 5A), although we acknowledge that the cost implications of testing this large group of women have not yet been determined. [Correction added on 16 July 2025, after first online publication: Text under Section 2A has been changed.]

2B. Other phenotype-specific indications

Recommendation: Genetic testing is recommended in individuals with additional features suggestive of syndromic forms of monogenic diabetes, such as renal, pancreatic or uterine anomalies (raising suspicion for *HNF1B*-syndrome) or maternally inherited diabetes and deafness (raising suspicion for mitochondrial diabetes) *[Strong]*.

HNF1B-syndrome accounts for ~5% of monogenic diabetes. It is characterised by diabetes in addition to renal abnormalities (cysts, dysplasia or agenesis) and pancreatic abnormalities (hypoplasia or exocrine dysfunction). Uterine malformations, hypomagnesaemia, hyperuricemia or abnormal liver enzymes may also occur. The *HNF1B* score is a clinical screening tool for *HNF1B*-syndrome, with a negative predictive value of more than 99% for scores less than 8.[13] The combination of renal cysts and diabetes due to an *HNF1B* variant is referred to as the renal cysts and diabetes (RCAD) syndrome; however, because of incomplete penetrance and variable expressivity, families may have a history of renal disease without diabetes or other associated anomalies.

A maternal history of diabetes should prompt consideration of mitochondrial diabetes, especially if there are other associated features. An Australian study observed the m.3243A>G variant in less than 0.5% of unselected individuals with type 2 diabetes and 4% in those with a maternal or sibling history of diabetes and a maternal and personal history of deafness.[14] Individuals with m.3243A>G-related maternally inherited diabetes and deafness may, or may not, manifest other features associated with the m.3243A>G variant, for example, hearing loss, stroke-like episodes, maculopathy, short stature, hypogonadism and cardiomyopathy.[15,16] Mitochondrial diabetes may rarely relate to mitochondrial DNA defects other than m.3243A>G, which should be considered if there are other features such as neurological disease.[16]

2C. Monogenic diabetes screening tools

Recommendation: Patient selection for genetic testing can be guided by the probability of pathogenic variant detection according to screening tools such as the Exeter MODY probability calculator *[Strong]*.

The most widely used monogenic diabetes algorithm is the 8-item Exeter MODY probability calculator.[2] Correctly entering the *current* body mass index and HbA_{1c} level, rather than historical values, is critical for accurate, reproducible results.[17] The calculator predicts the likelihood that an individual will test positive on genetic testing of traditional MODY genes. Genetic testing is warranted if this pre-test probability is more than 25% in individuals not requiring insulin within six months of diabetes diagnosis or more than 10% in individuals who have required early insulin initiation, noting the greater potential benefit of monogenic diabetes identification in the latter group.[2] A recent multiethnic South Australian study of 40 patients with suspected monogenic diabetes reported a positive predictive value more than or equal to 25% using the Exeter calculator with a testing threshold of 25%, supporting the use of the Exeter calculator in the Australian setting.[17] Limitations of the Exeter calculator include restriction to diabetes onset before or equal to the age of 35 years, prediction of variants in *GCK*, *HNF1A* and *HNF4A* only, and its development using an exclusively white European dataset. Other monogenic diabetes screening tools are in development.

2D. Interethnic considerations

Recommendation: The use of ethnicity- and age-specific thresholds for obesity as a risk factor for type 2 diabetes may be considered when selecting individuals for genetic testing to improve genetic testing yield and reduce costs *[Weak]*.

Monogenic diabetes prevalence may be overestimated in ethnicities with high background prevalence of type 2 diabetes. For example, in New Zealand, the yield of monogenic diabetes genetic testing is lower in Pacific and Asian ethnic groups compared with Māori and European ethnic groups.[9] No cases of monogenic diabetes were identified in another study of 199 Māori and Pacific adults with type 2 diabetes diagnosed under 40 years of age, despite an Exeter calculator probability of more than 20% in 17/55 individuals.[18] Therefore, it is reasonable to consider alternative adiposity measures in non-Europeans (eg, ethnicity-specific body mass index intervals or waist circumference).

3. Pre-test counselling: what aspects should be covered?

Recommendation: Genetic testing for monogenic diabetes typically constitutes National Pathology Accreditation Advisory Council level 2 genetic testing, necessitating comprehensive pre- and post-test counselling with written informed consent. If clinical genetics services are limited, pre-test counselling may be undertaken by a non-geneticist specialist with sufficient expertise to address the personal, familial and technical aspects of monogenic diabetes testing. Individuals subsequently found to have a pathogenic or likely pathogenic variant or a variant of uncertain significance (VUS) should be referred to clinical genetics services for further discussion of results and possible cascade or segregation testing *[Strong]*.

Pre- and post-test counselling for monogenic diabetes is ideally provided by professionals trained in genetic counselling in accordance with the Human Genetics Society of Australasia best practice standards.[19] However, with the growing availability of publicly funded genetic testing in Australia and New Zealand, genetic testing is sometimes arranged by clinicians with no formal training in genetic counselling, especially when access to genetics services may be limited in rural or remote areas.[10] Pre-test counselling should include all potential implications related to positive, negative, uncertain and incidental results for individuals and their families (Māori: whānau) as outlined in Box 1.[21,22] Written informed consent should be obtained before testing, using local genetic or genomic testing consent forms.

4. Methodologies: how should genetic testing for monogenic diabetes be performed?

4A. General approach to testing methodologies

Recommendation: A dynamic list of targeted monogenic diabetes genes and variant types should be formulated using test indication(s), published guidelines and literature review. Laboratory methodology will typically be an NGS approach (targeted gene panel, exome or genome sequencing). *[Strong]*.

1 Aspects to address during pre-test counselling

Personal implications of testing:
- clarify diagnosis and provide prognosis
- management perspective:
  - change treatment
  - novel treatment options
  - avoid unnecessary investigation or treatment
- reproductive risks and options
- psychological: explanation/validation
- insurance* or employment implications of incidental findings†

Familial implications of testing:
- genetic risk to biological relatives causing potential psychosocial harm, ethical, legal and financial challenges
- responsibility/burden to inform biological relatives, potential ethical dilemmas from non-disclosure
- insurance* or employment

Technical implications of testing:
- positive/negative/uncertain/incidental†
- unexpected family relationships
- testing process, timeframes, how results will be returned
- costs
- privacy and confidentiality

*Insurance implications associated with genetic testing relate to risk-based insurance (eg, life insurance) and currently impact those seeking genetic testing predicting future risk of developing monogenic disorders in insurance policy underwriting with cover over certain monetary thresholds (*Financial Services Council Standard 11: Moratorium on Genetic Tests in Life Insurance*, which came into force on 1 July 2019). However, in September 2023, the Australian Government announced that it will implement a total ban on the use of adverse genetic test results in life insurance underwriting, which will likely be written into legislation in the very near future.[20] †Incidental findings are causative variants in genes associated with disease unrelated to the phenotype under investigation and identified by chance during analysis.

Clinicians requesting monogenic diabetes genetic testing should ensure that the testing laboratory is accredited by the National Association of Testing Authorities (NATA) or Clinical Laboratory Improvement Amendments (CLIA) and that the chosen method(s) cover the laboratory aspects addressed herein.

From the laboratory perspective, the first step in choosing the appropriate test method(s) is to establish a list of genes and variant types associated with monogenic diabetes. The selected gene or variant list should be comprehensive, covering both syndromic and non-syndromic diabetes (see Section 4D). The gene list may need to consider specific patient features, such as neonatal onset diabetes. Importantly, this list should be limited to genes and variants with strong evidence of gene–disease association (see Section 4C and Pitini and colleagues[23]) to maximise clinical actionability of detected pathogenic or likely pathogenic variants and minimise the number of VUS. Laboratories may adopt one or a combination of the various diabetes gene lists at PanelApp UK (https://panelapp.genomicsengland.co.uk) or PanelApp Australia (https://panelapp-aus.org/); the decision to test only "green" genes or "green" and "amber" genes may vary by case. In most cases, the gene list will include more than or equal to six genes, hence qualifying as a "large gene panel" consistent with PMDI recommendations.[1]

Most laboratories employ an NGS panel approach, which can detect variants in several genes in a cost-effective manner.[24] Whole exome sequencing or whole genome sequencing may be considered, with subsequent analysis limited to a panel of monogenic diabetes genes to minimise incidental findings.[17,25]

4B. Variant-specific considerations

Recommendation: The ability to detect challenging variant classes should be assessed and validated. Assay limitations should be described in the test report. Ancillary tests should be employed for common pathogenic variants outside the scope of routine NGS *[Strong]*.

Certain variants can be difficult to detect by NGS. Test limitations should be clearly described in the test report, to allow for clinical correlation. For example, partial or whole gene deletions are a common cause of *HNF1B*-syndrome and may be detected by NGS approaches, but this typically requires specialised bioinformatic approaches and validation.[26] If copy number variant analysis is limited or unavailable, ancillary testing in the form of targeted arrays or multiplex ligation-dependent probe amplification should be considered.

Mitochondrial DNA heteroplasmy and variable tissue expressivity pose challenges in m.3243A>G detection.[1,7] Detecting low level heteroplasmic variants requires careful validation of the laboratory limit of detection and consideration of sample type, to avoid false-negative results. Mitochondrial variants are variably detectable between tissues (eg, blood, muscle and urinary sediment). Requesting clinicians should consider the merit of isolated m.3243A>G testing versus broader testing, including other mitochondrial variants or even whole mitochondrial genome testing depending on patient phenotype.

4C. Gene–disease association considerations

Recommendation: The strength of gene–disease association should be assessed using the ClinGen standardised framework, and genes with refuted evidence of association should not be used in diagnostic testing *[Strong]*.

The evidence to support or refute gene–disease validity can change over time. A standardised framework to determine the strength of disease association should be used. Periodic review of gene lists is recommended. Gene–disease validity should be assessed using ClinGen guidelines along with evidence from ClinGen expert panels.[27,28] If genes with limited or emerging evidence are included in diagnostic panels, interpretation of variants in these genes should be made with caution. Genes with refuted evidence (eg, *BLK, KLF11, PAX4*) should not be included in diagnostic panels. For genes without expert panel curation, evidence for gene–disease validity can be obtained from PanelApp UK and PanelApp Australia.[29]

4D. Phenotype considerations

Recommendation: Testing should ideally include traditionally syndromic monogenic diabetes genes, in addition to genes associated with isolated diabetes, to maximise diagnostic yield *[Strong]*.

Due to the variable expressivity and incomplete penetrance of syndromic features in monogenic diabetes, 18–19% of isolated diabetes cases with positive monogenic diabetes panel testing will relate to a monogenic diabetes syndromic gene (typically *HNF1B, WFS1, INSR* or m.3243A>G).[7,30] Requesting clinicians should note whether such genes or regions are included in panel testing, particularly m.3243 as mitochondrial sequencing is not a routine component of NGS panels.

5. Post-test management: how should genetic test results be managed?

5A. Gene-specific treatment

Recommendation: Blood glucose-lowering treatment is not required in individuals with isolated *GCK*–hyperglycaemia,

2 Gene-specific treatment considerations in monogenic diabetes[31,32]

Causative genetic defect	Initial treatment	Treatment progression	Comment
HNF4A	Diet or sulfonylureas	May progress to insulin	Low-dose sulfonylureas often effective, may also respond to glucagon-like peptide-1 (GLP-1) agonists but no formal supportive data
Glucokinase (*GCK*)	None required	Rarely other therapies	Insulin may be required in pregnancy based on known or inferred fetal genotype
HNF1A	Sulfonylureas	May progress to insulin	Low-dose sulfonylureas often effective; GLP-1 agonists may be effective (short term data); high cardiovascular risk may justify early statin use (debated); sodium–glucose co-transporter 2 inhibitors may cause polyuria because of low renal glucose threshold
IPF1/PDX1	Oral agents	May progress to insulin	Limited data on treatment progression; overweight or obesity in some individuals but no data on efficacy of GLP-1 agonists
HNF1B	Sulfonylureas	Insulin usually required	Some individuals respond to oral medications, including usual-dose sulfonylureas, but progression to insulin is common
*NEUROD1**	Oral agents	May progress to insulin	Overweight or obesity in some individuals but no data on efficacy of GLP-1 agonists
*CEL**	Oral agents	May progress to insulin	Limited data on treatment progression
*INS**	Diet or oral agents	May progress to insulin	Usually require small insulin doses; limited data on treatment progression
*ABCC8**	Sulfonylureas	May progress to insulin	Limited data on treatment progression
*KCNJ11**	Sulfonylureas	May require insulin	Efficacy of sulfonylurea versus insulin therapy depends on genotype
*APPL1**	Diet or oral agents	Most require insulin	Overweight/obesity in some individuals but no data on efficacy of GLP-1 agonists
SLC19A2	Limited data	Most require insulin	Thiamine supplementation can facilitate insulin dose reduction or independence
m.3243A>G	Limited data	Most require insulin	Avoid metformin as may provoke lactic acidosis; coenzyme Q10 supplements may be used but limited data on effect on glycaemia
6q24 imprinting defects†	Sulfonylureas	May progress to insulin	Insulin more commonly required in neonatal than relapse phase

* denotes rare or very rare conditions. † associated with transient neonatal diabetes mellitus, but may relapse in adolescence, pregnancy or later in adulthood (coinciding with times of increased insulin resistance). ◆

apart from in pregnancy, when insulin is sometimes required to limit macrosomia. Sulfonylureas are recommended as first-line therapy in individuals with *HNF1A*-diabetes, and may also be effective in *HNF4A*-diabetes and *HNF1B*-diabetes *[Strong]*.

There are limited randomised controlled trials to guide blood glucose-lowering treatment in monogenic diabetes.[31] Suggested treatment pathways (Box 2) are based largely on the underlying pathophysiology, as well as small series or case reports.[32]

HbA_{1c} levels do not worsen on discontinuing blood glucose-lowering treatment in *GCK*–hyperglycaemia. There are data supporting first-line sulfonylurea effectiveness in *HNF1A*-diabetes, and to a lesser degree in *HNF4A*-diabetes, with a low starting dose recommended given the frequently profound sensitivity in these monogenic diabetes subtypes. Sulfonylureas may be effective in *HNF1B*-diabetes, although insulin is typically required. Oral agents are often appropriate as initial treatment for other monogenic forms. People with non-*GCK*-related monogenic diabetes may ultimately progress to requiring insulin. In mitochondrial diabetes, metformin should be avoided as it may provoke lactic acidosis.[31]

In pregnancy, knowledge of maternal and fetal (known or inferred) *GCK* genotype permits a nuanced approach to hyperglycaemia management (see Section 6C). Hence, it is imperative to consider urgent genotyping of mothers with suspected *GCK*–hyperglycaemia. Sulfonylurea-treated women with *HNF1A*- or *HNF4A*-diabetes can transfer to insulin pre-conception or, if well controlled, continue sulfonylurea treatment (in the form of glibenclamide) in the first trimester (to maintain tight glycaemic control during organogenesis) and transfer to insulin in the second trimester (to avoid sulfonylurea-induced fetal hyperinsulinaemia and macrosomia).

5B. Gene-specific surveillance

Recommendation: Individuals with monogenic diabetes should undergo routine surveillance for diabetes-related microvascular complications, although this is not indicated in *GCK*–hyperglycaemia as the risk of such complications is not significantly greater compared with the general population. Individuals with *HNF1B*-diabetes or mitochondrial diabetes should undergo additional surveillance for the extra-pancreatic manifestations of these conditions *[Strong]*.

Individuals with monogenic diabetes should be screened periodically for microvascular and macrovascular disease if considered high risk. *GCK*–hyperglycaemia carries a very low risk of complications,[33] and routine microvascular complication screening is not indicated in this group. *HNF1A*-diabetes is associated with increased cardiovascular mortality despite normal or high levels of high-density lipoproteins; hence, statins should be considered in individuals with *HNF1A* variants from the age of 40 years, despite a seemingly cardioprotective lipid profile.[34] Individuals with *HNF1B*-diabetes or mitochondrial diabetes should undergo additional surveillance for associated

extra-pancreatic manifestations including urogenital, hepatic and pancreatic abnormalities (*HNF1B*-diabetes[35]) and sensorineural hearing loss, maculopathy, neuromuscular disorders and cardiac arrhythmias (mitochondrial diabetes[36]).

5C. Cascade testing

Recommendation: Cascade testing should be offered to at-risk relatives following monogenic diabetes diagnosis in a proband, either via phenotypic screening for hyperglycaemia if the variant is in *GCK* (followed by genotyping if hyperglycaemia is present) or via genotyping for the familial variant in other monogenic diabetes genes *[Strong]*.

Cascade testing refers to variant-specific testing of at-risk relatives following identification of a pathogenic or likely pathogenic variant in a proband.[1] In the special case of *GCK* variants, relatives may first be offered phenotypic screening for hyperglycaemia, followed by genotyping if present, given the complete, lifelong penetrance of *GCK*–hyperglycaemia.

Pre-symptomatic (predictive) testing should only be offered with pre- and post-test genetic counselling and, in most circumstances, is provided by genetic counsellors.[19,37] Testing of children should only be considered in monogenic diabetes subtypes with childhood implications (eg, annual HbA_{1c} level is indicated from the age of 10 years in individuals with *HNF1A* or *HNF4A* variants). Adolescents should be included in genetic testing decisions.[38]

5D. Management of variants of uncertain significance (VUS)

Recommendation: VUS should be regarded as uninformative and not used to guide management, but they may be upgraded or downgraded to a positive or negative result, respectively, through further assessment. Clinicians managing patients with VUS should consider requesting variant reviews periodically or before pregnancy *[Strong]*.

The American College of Medical Genetics and Genomics (ACMG) system is used to classify genetic variants as: benign, likely benign, VUS, likely pathogenic or pathogenic. Likely pathogenic variants, with more than 90% probability of being disease-causing, are considered positive, akin to pathogenic variants. A VUS result should be considered uninformative and not be used in clinical decision making.[39] However, monogenic diabetes VUS can often be upgraded through careful clinical and molecular review, particularly with the aid of gene-specific (eg, *GCK*) specifications to ACMG criteria.[40]

5E. Further avenues in negative cases

Due to technical and analytical limitations of genetic testing, a negative or uninformative (ie, VUS) genetic result does not exclude a genetic diagnosis. Additional considerations include:

- Was the diagnosis correct?
  - Consider broader differential diagnoses that may not have been covered in testing, including diabetes caused by polygenic factors and secondary diabetes (eg, pancreatogenic diabetes).
- Was the right genetic test ordered?
  - Consider syndromic monogenic diabetes genes if not yet tested.
  - Consider the breadth and depth of coverage of the gene panel and detectability of potential mutation mechanisms. For example, mitochondrial variants may not be sequenced, and copy number, as opposed to sequence variants, may not be routinely assessed.

Further avenues for negative cases may include:

- referral to a geneticist, especially if the pre-test probability is high;
- re-testing with inclusion of additional genes and comprehensive analytical pipelines to assess both copy number and sequence variants;
- updated testing as more monogenic diabetes genes are discovered or as clinical phenotype evolves;
- research testing, including polygenic risk scores if polygenic aetiology is suspected; or
- for especially compelling cases, diagnostic whole exome sequencing or whole genome sequencing through a clinical genetics service.

6. Family planning: what are the reproductive implications of a positive genetic test?

6A. Implications for offspring

- In *HNF4A*-diabetes, macrosomia and neonatal hypoglycaemia are frequent in affected offspring, even when the variant is paternally transmitted, due to intrinsic fetal hyperinsulinism.
- In *HNF1A*-diabetes and other monogenic diabetes subtypes, macrosomia risk relates to maternal hyperglycaemia.[31]
- In *GCK*–hyperglycaemia, the effect of maternal hyperglycaemia differs depending on whether the infant carries the maternal variant or not (see Section 6B). In addition, if both parents carry a *GCK* pathogenic variant, offspring will have a 25% risk of inheriting biallelic *GCK* variants, resulting in neonatal diabetes.[41]
- In m.3243A>G-diabetes, an affected mother is expected to transmit the variant to all children, although some may remain clinically unaffected. The penetrance of diabetes in offspring with m.3243A>G is age dependent and estimated at more than 85% by the age of 70; clinical expressivity is highly variable.[42]

6B. Role of fetal *GCK* genotyping

Recommendation: Fetal *GCK* genotyping in pregnant women with *GCK*–hyperglycaemia may be considered in conjunction with specialised maternal–fetal and reproductive genetic units. In the absence of fetal genotyping, management strategies in pregnancy include serial growth scans, with insulin treatment only if fetal abdominal circumference is greater than the 75th percentile or if maternal glycaemia is well above pregnancy targets *[Weak]*.

In pregnant women with *GCK*–hyperglycaemia, fetal *GCK* genotype is the main determinant of fetal growth. If the fetus has not inherited the *GCK* variant, maternal hyperglycaemia-induced fetal hyperinsulinism results in higher birth weights with increased risks of macrosomia and adverse perinatal maternal and neonatal outcomes.[43] In this setting, insulin treatment is indicated, noting that high doses of insulin are required to overcome the strong homeostatic drive and sufficiently lower maternal blood glucose to influence fetal growth.[41,44] If the fetus

has inherited the *GCK* variant, insulin treatment is not required and may cause fetal growth restriction.[45]

Currently, fetal *GCK* genotype is typically inferred when third trimester fetal abdominal circumference is greater than the 75th percentile, detected via serial growth scans that usually consist of fetal ultrasounds every two weeks from 26 weeks gestation.[41]

Non-invasive prenatal testing to determine fetal *GCK* genotype has recently been developed based on relative variant and haplotype dosage, and was more sensitive and specific than fetal ultrasound in one study.[46] However, *GCK* non-invasive prenatal testing is not locally available in Australia or New Zealand, and arranging testing overseas can be costly and time consuming, particularly in the context of pregnancy. Invasive prenatal testing (chorionic villus sampling or amniocentesis) for the sole purpose of *GCK* genotyping is not recommended given the procedural risks and diagnostic alternatives but may be considered if indicated for another reason (eg, suspected aneuploidy).

6C. Potential role of pre-implantation genetic testing

Recommendation: As with other genetic conditions, individuals of reproductive age with molecularly confirmed monogenic diabetes should be informed of all reproductive options, including in vitro fertilisation with pre-implantation genetic testing (PGT) and transfer of unaffected embryos. Reproductive counselling should be non-directive and address both patient autonomy and the nature of the specific monogenic diabetes subtype *[Strong]*.

- Australian data show an increasing use of PGT in adult-onset, non-cancer conditions, whereas invasive prenatal testing is typically reserved for more severe (ie, life-threatening, autosomal recessive) conditions.[47]
- PGT may be a suitable option in families with monogenic diabetes subtypes with potentially severe manifestations (eg, *HNF1B*-syndrome), whereas it is generally not considered for mild conditions such as *GCK*–hyperglycaemia.
- The purely maternal inheritance of mitochondrial DNA — with associated complexities relating to heteroplasmy, variant bottlenecking and poor phenotype predictions — complicate the application of prenatal diagnosis and PGT in m.3243A>G-diabetes.[48] The alternative of mitochondrial replacement therapy may become feasible in the future, with multiple international research efforts including the ongoing Australian mitoHOPE project (https://www.monash.edu/medicine/mitohope).

Conclusions

This consensus statement summarises the current evidence for standards of genetic counselling, testing and management of monogenic diabetes in Australia and New Zealand. Considering the increasing availability of genetic testing laboratories and comprehensive NGS panels, as well as effective therapies for individuals with certain genotypes, it is important for clinicians to consider the diagnosis of monogenic diabetes. Accurate monogenic diabetes diagnosis, coupled with appropriate pre- and post-test genetic counselling, enables the delivery of individualised treatment, with the ultimate aim of preventing complications, enhancing patient outcomes and improving quality of life.

This consensus statement will be updated within five years to reflect changes in genomic technology and updated research on monogenic diabetes.

Acknowledgements: Sunita De Sousa is supported by the Royal Adelaide Hospital Mary Overton Early Career Research Fellowship.

Open access: Open access publishing facilitated by The University of Adelaide, as part of the Wiley – The University of Adelaide agreement via the Council of Australian University Librarians.

Competing interests: The authors of this article are members of the societies that have produced this joint society consensus statement: Australian Diabetes Society (ADS; Aleena Ali, Timothy Davis, Sunita De Sousa, Elif Ekinci, Jerry Greenfield), Endocrine Society of Australia (ESA; Sunita De Sousa, Elif Ekinci, Jerry Greenfield, Ryan Paul), Human Genetics Society of Australasia (HGSA; Sunita De Sousa, Mark Greenslade, James Harraway, Juliet Taylor, Kathy Wu), New Zealand Society for the Study of Diabetes (NZSSD; Rinki Murphy, Ryan Paul), Royal College of Pathologists of Australasia (RCPA; James Harraway) and Royal College of Pathologists, UK (RCPath UK; Mark Greenslade). The following authors received honoraria/conference support: Timothy Davis (Novo Nordisk, BI, Merck, Mylan, sanofi-aventis, Eli Lilly), Sunita De Sousa (Pfizer), Elif Ekinci (Boehringer, Novo Nordisk), Jerry Greenfield (Lilly, Novartis), Rinki Murphy (Eli Lilly, Boehringer Ingelheim, Novo Nordisk), Ryan Paul (Dexcom, Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Radiant Health). The following authors have advisory board memberships: Timothy Davis (Novo Nordisk, Merck), Sunita De Sousa (Novo Nordisk), Elif Ekinci (Eli Lilly, Sanofi), Ryan Paul (Dexcom, Abbot, Novo Nordisk), Kathy Wu (23 Strands). The following authors have received research support: Elif Ekinci (Medtronic, Novo Nordisk, Eli Lilly, Boehringer, Versanis, Endogenex), Ryan Paul (Dexcom).

Provenance: Not commissioned; externally peer reviewed.

Author contributions: All authors contributed to the conceptualization, methodology, analysis and writing (original draft, review and editing) of the manuscript. ■

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