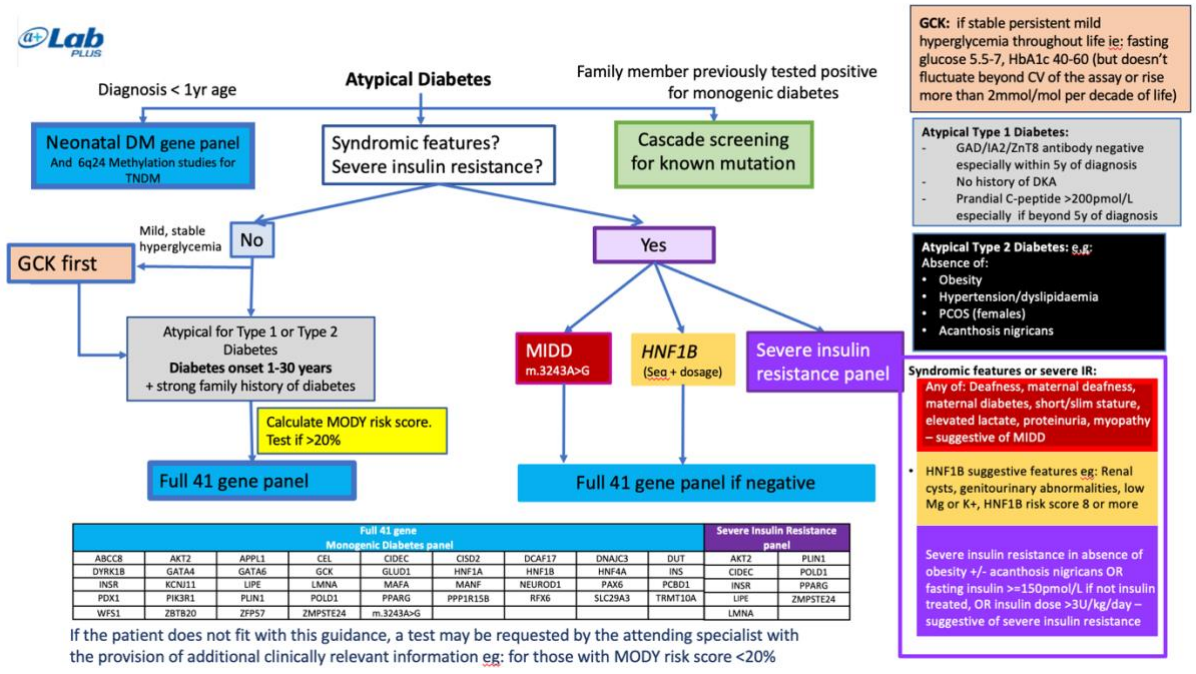
Monogenic diabetes testing guidelines for NZ healthcare practitioners 2024

What is the importance of making a genetic diagnosis?
The correct monogenic classification of diabetes has implications for treatment, clinical prognosis and cascade genetic counselling of family members and future offspring.

Key updates of this guideline

- **Neonatal diabetes gene panel** is recommended for all those with diabetes diagnosed in the first 1 year of life (the highest yield is expected in those with diabetes less than 6 months or 9 months of life)
- **The Monogenic diabetes gene panel** (currently 41 genes) is indicated for all other tests.
    - The "glucokinase (GCK) first" option may be indicated for those in whom a GCK phenotype is most likely
    - Similarly test "HNF1B first", "mt.3243A>G first", OR "severe insulin resistance genes first", may be indicated depending on the phenotype
    - If only a subset of genes are required for the initial request then only those genes will be reported on with a comment that the analysis may be expanded to the full panel upon email request to do so
- **Both panel tests cost $688**

Who to test:



Full 41 gene Monogenic Diabetes panel									Severe Insulin Resistance panel	
ABCC8	AKT2	APPL1	CEL	CIDEC	CISD2	DCAF17	DNAJC3	DUT	AKT2	PLIN1
DYRK1B	GATA4	GATA6	GCK	GLUD1	HNF1A	HNF1B	HNF4A	INS	CIDEC	POLD1
INSR	KCNJ11	LIPE	LMNA	MAFA	MANF	NEUROD1	PAX6	PCBD1	INSR	PPARG
PDX1	PIK3R1	PLIN1	POLD1	PPARG	PPP1R15B	RFX6	SLC29A3	TRMT10A	LIPE	ZMPSTE24
WFS1	ZBTB20	ZFP57	ZMPSTE24	m.3243A>G					LMNA	

If the patient does not fit with this guidance, a test may be requested by the attending specialist with the provision of additional clinically relevant information eg: for those with MODY risk score <20%

Updated April 2024

How to test:

- A new streamlined process of completing one electronic form as below is available by searching "monogenic diabetes" on the website below:
  https://testguide.adhb.govt.nz/EGuide/
  No monogenic database or other forms are required.
  Please include as many clinical details as possible, as this information is important for optimal gene variant curation
    - MODY risk calculator score is available on www.diabetesgenes.org
    - HNF1B risk score is listed below (appendix A)
  - Endocrinologists and nurse practitioners within specialist diabetes services may request diabetes genetic testing

- **Cascade testing:** of family (whānau) members is important after identifying a proband with monogenic diabetes to ensure as many people benefit from the correct diagnosis as possible. Our last audit showed that only 1 in 6 probands diagnosed, generated a cascade test, when we would expect a much higher number.
  - Please ask the proband to inform their whānau about their genetic diagnosis so other related members can be referred to Genetic Health Service NZ (GHSNZ) based on the diagnosis in the whānau AND
    - Refer the proband to GHSNZ and include as much detailed information on family structure and relatedness (e.g. parents, how many children, siblings, family planning), ages of 1st degree relatives where they are located in NZ and where proband testing was done (especially if in an external lab). Generally test parents first to determine who else needs testing.
    - It may be possible for the proband's whānau to attend the GHSNZ appointment if the proband is comfortable with this and an appointment may be offered virtually to make such attendance easier. This can be discussed with the scheduler at the time the appointment with GHSNZ is offered.
  - For GCK, family members may be triaged by a fasting glucose or HbA1c given the mild hyperglycemia is highly penetrant from birth.
  - For other monogenic diabetes subtypes
    - if a family member has diabetes, then a **diagnostic cascade genetic test** may be requested by the endocrinologist. Include the proband's NHI and the familial variant on the request so that the laboratory can link the family members together
    - If a family member *does not have diabetes* (or other syndromic features), then a **predictive cascade genetic test** requires a referral to genetic health service for genetic counselling and such tests should only be requested by the genetic health service

- **Other referrals to Genetic Health Service NZ**
  - Genetic counselling for reproductive implications
  - Further assessment of those identified with Class 3 variants of uncertain significance which will usually require additional genetic testing and phenotyping of affected and unaffected family members in order to upgrade

the genetic testing result to a positive (likely pathogenic) or negative (likely benign) result

Further information:

- The use of precision diagnostics for monogenic diabetes: a systematic review and expert opinion. *Communications Medicine* 136 (2023) https://www.nature.com/articles/s43856-023-00369-8
- Genotype-stratified treatment for monogenic insulin resistance: a systematic review *Communications Medicine* 134 (2023)
- https://www.nature.com/articles/s43856-023-00368-9
- Systematic review of treatment of beta-cell monogenic diabetes
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10197799/
- Information for patients and health professionals on clinical care in monogenic diabetes https://www.diabetesgenes.org

Appendix A: HNF1B risk score, consider testing if score ≥8

Characteristics	Item	Value
Family history		+2
Antenatal renal abnormalities	Uni/bilateral abnormality by renal echography	+2
Kidneys and urinary tract		
Left kidney	Hyperechogenicity	+4
	Renal cysts	+4
	Hypoplasia	+2
	Multicystic and dysplastic kidney	+2
	Urinary tract malformation	+1
	Solitary kidney	+1
Right kidney	Hyperechogenicity	+4
	Renal cysts	+4
	Hypoplasia	+2
	Multicystic and dysplastic kidney	+2
	Urinary tract malformation	+1
	Solitary kidney	+1
Electrolyte or uric acid disorders	Low serum Mg^{2+} (<0.7 mmol/l)	+2
	Low serum K^{+} (<3.5 mmol/l)	+1
	Early-onset gout (>30 years of age)	+2
Pathological findings	Oligomeganephronia or glomerular cysts	+1
Pancreas[a]	MODY or hypoplasia of tail and neck of the pancreas or pancreatic exocrine insufficiency	+4
Genital tract	Genital tract abnormality[b]	+4
Liver	Live test abnormalities of unknown origin[c]	+2