Monogenic diabetes:

A guideline for NZ healthcare practitioners

May 2018

Monogenic diabetes refers to single gene disorders resulting in diabetes

- Maturity Onset Diabetes of the Young (MODY) and Maternally Inherited Diabetes and Deafness (MIDD) subtypes are thought to account for 3% of diabetes cases, and are frequently mistaken for type 1 or 2 diabetes (potentially 4000 cases in New Zealand).
- Neonatal diabetes (ND) diagnosed within 6 months of life is not usually type 1 diabetes and all need genetic testing
- *Other forms of rare monogenic diabetes, clearly recognisable due to their associated syndromes (eg: Wolfram, Alstrom, Prader-Willi), and major disease states (eg: Friedrichs Ataxia, cystic fibrosis) are not included in these guidelines but Wolfram genes are included in the **MODY gene panel**.*
- *Please contact Rinki Murphy (R.Murphy@auckland.ac.nz) if you require advice on genetic testing or management of severe insulin resistance cases*

Why diagnose MODY, MIDD or ND?

- It changes management
  - No glucose lowering therapy for GCK mutations outside of pregnancy
  - Low dose sulphonylurea for HNF1A and HNF4A
  - Coenzyme Q10 and thiamine for MIDD
  - Kidney donation in MIDD families who are obligate carriers of m.3243A>G
  - Sulphonylurea therapy rather than insulin for some forms of Neonatal diabetes (KCNJ11, ABCC8)
- It improves quality of life by guiding best therapy
- It alters prognosis
  - GCK mutations not associated with micro or macrovascular complications
- It alters screening in at risk family members
  - Fasting glucose of 5.5-8mmol/L in GCK families
  - Low renal glycosuria threshold in HNF1A
  - Audiology screening for obligate maternal carriers of mt.3243A>G
- It alters management in pregnancy
  - Only 50% of mothers with GCK mutations require consideration of insulin during pregnancy
  - Babies inheriting HNF4A mutation are at increased risk of macrosomia and neonatal hypoglycemia, independent of maternal glycaemia or mutation status
- It enables genetic counseling of family members at risk with predictive testing options and management implications for those already diagnosed with diabetes in extended family members
- It can generate opportunities for molecular and clinical research, improving our understanding and management of monogenic diabetes

Phenotypes for common monogenic subtypes

GCK mutations (MODY2) 20-50% MODY cases

- Isolated mild fasting hyperglycaemia 5.5-8mmol/L
- Small increment on OGTT
- Very rarely associated with micro or macrovascular complications
- Absence of family history is common as detected only incidentally or upon screening

HNF1A mutations (MODY3) 20-50% MODY cases

- Progressive beta cell failure commonly presents with hyperglycemia in early adulthood <25years
- Initially elevated post-prandial glucose, with later elevated fasting glucose and marked excursion on OGTT (>4.5 mmol/l)
- Sensitive to **sulphonylureas** e.g. Gliclazide
- Glycosuria with blood glucose < 10 mmol/L
- Elevated HDL, but high CVD risk

HNF4A mutations (MODY1) 5% MODY cases

- Similar presentation to HNF1A, but with additional neonatal hypoglycemia or macrosomia even without maternal diabetes

HNF1B mutations (MODY5) 5% MODY cases

- Associated with renal cysts, cystic renal dysplasia, glomerulocystic kidney disease,
- Abnormal liver enzymes, uterine abnormalities
- Pancreatic atrophy with exocrine dysfunction

Maternally inherited diabetes and deafness (MIDD)

- Up to 1% of unselected cases of diabetes
- Up to 60% of cases of diabetes associated with sensorineural deafness and maternal family history
- Excess proteinuria, macular retinal dystrophy

Neonatal diabetes (KCNJ11, SUR1, INS, 6q24 and others)

- Presents from birth to 6 months (1: 100,000 live births)
- Occasional severe associated neurological symptoms
- May enable oral therapy
- **No direct cost for genetic testing**

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January 2018

Diagnostic algorithm for assessment of suspected monogenic diabetes: diabetes diagnosed < 35 yrs

Neonatal diabetes

- Diagnosis < 6 months

Targeted gene panel for neonatal diabetes (sendaway test to Exeter, UK laboratory)

Atypical Type 1 Diabetes

- FH suggestive of monogenic diabetes
- No history of DKA
- GAD, IA2 antibody negative esp if within 5 years of diagnosis
- Random C-peptide >200 pmol/L if beyond 5 years of diabetes

Atypical Type 2 Diabetes

- FH suggestive of monogenic diabetes
- An absence of:
  - Obesity
  - HTN/Dyslipidaemia
  - PCOS (Females)
  - Acanthosis nigricans

- Fasting glucose 5.5-8mmol/L
- HbA1c 40- 60mmol/L
- Small increment (< 4.5mmol/L) on OGTT
- If first degree family member not known to have diabetes/IFG, confirm fasting glucose > 5.5 in at least one first degree family member
- No microvascular complications

Yes → **Test for GCK**

No

- Familial , progressive young onset diabetes
- >2 family members affected
- Sensitivity to Sulphonylureas
- Elevated HDL>1.1 (HNF1A)
- hsCRP <0.7 (HNF1A only)

Test for HNF1A

If negative or unsure

- In addition to above:
  - History of transient neonatal hypoglycaemia
  - History of macrosomia

Test for HNF4A

If negative or unsure

Additional features?

- Sensorineural deafness in patient and/or mother
- Maternal diabetes
- Pigmentary maculopathy
- Myopathy
- Stroke
- Elevated lactate

Test for MIDD (m.3424A>G)

If negative or unsure

- Renal features
- Genitourinary abnormalities
- Low Mg or K
- HNF1B risk score 8 or more (see p4)

Test for HNF1B

If negative or unsure

Targeted monogenic diabetes gene panel
see p3 for different options

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January 2018

Procedure and costs

We advise consultant diabetes or endocrinologist review for all molecular genetic testing of suspected cases. Given the expense of these genetic tests it is vital that these tests are used in situations where they are likely to be positive and will alter clinical care. This involves careful clinical selection and physiological tests as appropriate as recommended in Form A. Please consider referring all laboratory confirmed probands to regional genetics service for genetic counselling and cascade testing of relatives. Contact R.Murphy@auckland.ac.nz for clinical advice or guideline feedback.

•2 EDTA (purple top) blood samples (minimum 10mL for adults, 5mL for children) are required for genetic analysis. Please email completed **Form A and B** to the Diagnostic Genetics laboratory at Auckland Hospital (DGen@adhb.govt.nz) stating blood samples are on their way via your local laboratory for DNA analysis and attach a copy to your local laboratory form specifying "2 EDTA required for Monogenic diabetes genetic testing at LabPlus, Auckland Hospital".

•2 EDTA (purple top) blood samples (minimum 1mL for neonates) are required for targeted gene panel for neonatal diabetes analysis. Please send 2 EDTA directly to Exeter (UK) via your local laboratory to avoid during neonatal period, using accompanying forms found under neonatal diabetes on www.diabetesgenes.org

•For MIDD (mt.3243A>G) tests, specify "DNA for mt.3243A>G analysis" on your local laboratory form, and your local laboratory will send the sample to Canterbury Health Laboratories directly. Buccal cells or urine samples are preferable to blood as the proportion of mutant mitochondrial DNA (heteroplasmy level) is greater in these tissues.

-Buccal cells may be collected using either mouth wash or a dry bacterial swab. Ensure the mouth has been rinsed first if within 2 hours of eating to ensure no food debris is present. Ask the patient to swish 10mls of sterile water in their mouth for approximately 30 seconds and collect this in a clean container. Or vigorously swab the inside of the cheek approximately 15 times each side. Place the swab in a clean container containing sterile water, seal and send (may need to snap off the long plastic stem).

-Urinary epithelial cells collect 20-30mls of early morning urine. DNA yield may depend on how quickly the sample is processed.

*All costs noted in this guideline are indicative only and current as of March 2018

Test	Price *	Turnaround time (mths)
GCK	NZ$ 638.88	3
HNF1A	NZ$ 822.00	3
HNF4A	NZ$ 638.88	3
HNF1B	NZ$ 593.10	3
MIDD	NZ$ 621.00	1
Neonatal diabetes gene panel	Free# via Exeter	1
Exeter 34 diabetes gene panel	£812# via Exeter	1
Labplus 2-4 diabetes gene panel	NZ$1200-1600	3

Monogenic diabetes gene panel options

Labplus 2-4 gene panel - choose from HNF1A, HNF4A, HNF1B and GCK: costs approx $1200 for 2 genes, to $1600 for all 4 genes

Exeter 34 gene panel - includes common MODY genes (*GCK, HNF1A, HNF4A, HNF1B*); MIDD (*mt.3243A>G*); rare MODY and neonatal diabetes genes (*KCNJ11, ABCC8, NEUROD1, INS, PDX1 PCBD1, RFX6, PAX6, ZFP57, CEL, GATA4, GAT6A, TRM10A*), severe insulin resistance and lipodystrophy (*INSR, LMNA, PPARG PLIN1, POLD1*); Wolfram syndrome (*WFS1* and *CISD2*).**#Courier cost to Exeter is NZ$420**

Additional cost for gene deletions analysis using array is $550, which is currently recommended if suspecting HNF1B as 55% of cases are due to gene deletion (and are missed by gene sequencing). For GCK, HNF1A and HNF4A, gene deletions account for 2% of cases.
Cascade testing of family members for known mutations identified in proband incurs a charge of $364.14
Please specify proband and mutation (if known) on Form B. Cascade testing is not generally indicated for MIDD.

Interpretation of genetic test results

Detection of a mutation or gene deletion allows the definite diagnosis of monogenic diabetes to be made. Variants are classified into the following 5 classes: class 1 - benign; class 2 – likely benign; class 3 – uncertain significance; class 4 – likely pathogenic; class 5 – pathogenic (*Richards et al Genetics in Medicine 2015 ACMG guidelines for interpretation of sequence variants*). These guidelines state that a class 3 "variant of uncertain significance" should not be used in clinical decision making. Discussion with the genetics service is recommended for interpretation of class 3 variants particularly arising from a gene panel. Further clinical investigations and/or co-segregation testing could result in re-classification of such variants as class 4 "likely pathogenic" or class 2 "likely benign". **All predictive testing should be done by Genetic Health Service New Zealand (GHSNZ).**

Monogenic diabetes:

A guideline for NZ healthcare practitioners

January 2018

Diagnostic clues for index case finding

C-peptide: Non-fasting random C-peptide with glucose is useful to check endogenous insulin production in those who are insulin treated. No need to stop insulin so long as concurrent glucose is >8 (*Hope et al, Diab Med 2016*). Helpful in distinguishing between T1D or monogenic diabetes as undetectable serum C-peptide usually seen after 5 years of T1D disease duration (DCCT), while persistence of stimulated C-peptide (when glucose is > 8mmol/L) beyond 5 years after T1D >200pmol/L makes T1D unlikely. Persistence of C-peptide in T1D beyond 5 years has been described (*Wang, Diabetes Care 2012*) with the majority being below 100pmol/L (1-5% of T1D). C-peptide is not a useful test among those with neonatal diabetes – all those diagnosed with diabetes <6 months require genetic testing irrespective of C-peptide

T1D antibodies: If positive, helpful in discriminating T1D from monogenic diabetes. GAD or IA-2 antibodies remain detectable for many years, with 70% of T1D having either antibody 11 years after diagnosis (*Borg,Acta Paediatr 89: 46-51, 2000*). ICA has poor sensitivity. The prevalence of these antibodies in those with HNF1A, GCK or HNF4A has been found to be the same as in control subjects at 1% (*McDonald, Diabetic Medicine 28: 1028-1033, 2011*). Addition of ZnT8 improves T1D diagnostic accuracy by 10% in European patients.

T1D Genetic risk score: A single nucleotide polymorphism (SNP)-based assay can be used to estimate a patient's T1D genetic risk based on HLA alleles and 30 common SNPs associated with T1D in predominantly European populations. The T1D GRS is available from Exeter, UK lab (approx cost £63) can help to discriminate T1D from MODY.

hsCRP biomarker for HNF1A: the CRP gene has HNF1A binding sites in its promoter and low hs-CRP has been seen in HNF1A patients compared with other forms of monogenic diabetes such as HNF4A, GCK, T1D and T2D. The highest discriminatory value of hsCRP is between HNF1A and T2D with cut off hsCRP<0.75mg/L showing modest 79% sensitivity and 70% specificity, hence should still be used in combination with clinical characteristics. A lower cut off level <0.55 mg/L achieved a sensitivity of 71% and specificity of 70% for distinguishing between HNF1A and HNF4A, GCK, or HNF1B. (*McDonald, Diabetes Care 34: 1860-1862, 2011*). hs-CRP is not useful if elevated >10 as in the presence of inflammation.

HDL: In the absence of insulin resistance related lowering of HDL characteristic of T2D, the HDL level is moderately discriminatory between HNF1A and T2D : plasma HDL > 1.12mmol/L was 75% sensitive and 64% specific at discriminating HNF1A from T2D (*McDonald, Clin Chim Acta 18: 927-32, 2012*). HDL levels are similar between HNF1A, T1D and healthy controls. Lower HDL levels are seen in GCK compared to T1D, and HNF1A (*Fendler, Clin Endocrinol 75: 321-7, 2011)*.

Risk score for HNF1B $\geq$ 8 based on: family history (+2); potassium <3.5mmol/L (+1); Magnesium<0.7mmol/L (+2); liver test abnormalities of unknown origin – after excluding autoimmune, toxic, or viral hepatitis (+2); either diabetes or hypoplasia of pancreatic tail and neck or pancreatic exocrine insufficiency (+4); antenatal renal abnormality (+2); solitary kidney (+1); genital tract abnormality – any of bicornuate uterus, hemiuterus, uterus and upper vaginal aplasia, epididymal cysts, bilateral absence of vas deferens (+4); oligomeganephronia or glomerular cysts on histology (+1), score the following separately for right and left renal tracts – hyperechogenicity (+4), renal cysts (+4), renal hypoplasia (+2); multicystic and dysplastic kidney (+2); urinary tract malformation (+1).

Targeted multigene panel for all MODY genes: new sequencing technology allows testing of many monogenic diabetes sequences including in a single test rather than analysing just one gene at a time, and increases the number of patients in whom a monogenic form of diabetes is identified (*Ellard 2013 Diabetologia*).

MODY risk calculator

Diabetes diagnostic iphone app: based on **MODY risk calculator** (also available at www.diabetesgenes.org). This is designed for use in patients diagnosed with diabetes under the age of 35 and was developed on a European cohort (*Shields et al Diabetologia 2012*). Currently, this risk calculator only contains age at diagnosis, sex, current treatment with insulin or oral glucose lowering agents, time to insulin treatment (if currently insulin treated), BMI, HbA1c, current age, parents affected by diabetes. Other biomarkers may be added over added over time.

The calculator assumes background prevalence of 0.7% MODY in patients who are insulin treated within 6 months of diagnosis, and 4.6% MODY for those who are not treated with insulin within 6 months of diabetes diagnosis. These assumptions may not be valid in non-European NZ populations, hence we encourage endocrinologists requesting genetic testing for diabetes to provide the information listed in the **NZ monogenic diabetes request forms A** (noting additional clinical features) and **form B** (noting MODY risk calculator items and patient identifying details) to help us optimize future monogenic diabetes testing guidelines for the NZ population.

Monogenic diabetes:

A guideline for NZ healthcare practitioners

January 2018

Management changes outside of pregnancy

GCK: May stop all glucose lowering therapy (*Murphy, Nat Clin Pract Endocrinol Metab 4; 200-13, 2008)*. Once stable glucose is confirmed without glucose lowering therapy (to confirm there is no coincidental additional type of diabetes), blood glucose monitoring is no longer necessary. Screening for microvascular risk may be discontinued. Screening and therapy for cardiovascular risk factors, such as blood pressure, lipids, and HbA1c should be based on traditional individual risk profiles. Predictive or confirmatory genetic testing of family members may not be required as fasting glucose (>5.5mmol/L) is a good marker of GCK status in an affected pedigree.

HNF1A and HNF4A: Guidance for transferring patients from insulin to low dose sulphonylureas is available on www.diabetesgenes.org. If predictive testing of HNF1A is positive, then screening for glycosuria, followed by periodic HbA1c, is better than fasting glucose given the lowered renal threshold in HNF1A. Statin therapy in HNF1A from age 40 given increased risk of CVD mortality despite elevated HDL, as low ApoM (*Steele, Diabetic Med 27; 157-161, 2010*).

HNF1B: Enables predictive testing of first degree relatives and prompt surveillance for clinical diseases. Early insulin therapy is often required.

MIDD (m.3243A>G): Avoid metformin. Thiamine (50mg daily) and coenzyme Q10 (150mg daily) supplementation may be helpful (*Suzuki, Diabetologia 41: 584-8, 1998*). Predictive or cascade genetic testing of family members is not usually recommended as almost all maternal relatives will have obligate carrier status and level of heteroplasmy (mutation load) in peripheral tissues is not useful in predicting clinical course. (*Murphy, Diabet Med 25 (4): 200-13, 2008*)

KCNJ11 and ABCC8: Guidance for transferring neonatal diabetes patients from insulin to sulphonylureas is available on www.diabetesgenes.org

Management of monogenic diabetes during pregnancy

Antenatal testing of the fetus for a monogenic diabetes mutation is not advised unless CVS or amniocentesis is being performed for another reason. Cell-free fetal (Cff) DNA testing using a maternal pregnancy blood sample and a paternal blood sample can be used to check for paternal monogenic diabetes transmission to the offspring while *in-utero* (father with neonatal diabetes due to KCNJ11 mutation, in *De franco et al Diab Med 2017*). Cff-DNA testing is likely to be available soon for *in-utero* offspring mutation testing for paternal monogenic diabetes transmission that affects fetal growth such as GCK, HNF4A and neonatal diabetes. Maternal transmission is technically more challenging to detect.

GCK: All women with GCK should be advised to seek referral to diabetes in pregnancy clinic upon pregnancy, as they may require insulin therapy in pregnancy depending on whether their fetus also carries the mutation. Insulin therapy of maternal hyperglycemia and early delivery is reserved for those who have accelerated fetal growth during the third trimester (surrogate indication of negative fetal GCK mutation). Large insulin doses (at least 0.6-1U/kg) are usually required. Post-delivery no glucose lowering therapy is required for the mother with GCK.

HNF1A and HNF4A: Women with HNF1A or HNF4A and good glycemic control who are on sulphonylurea pre-conception should either transfer to insulin before conception or switch to glibenclamide in the first trimester and transfer to insulin in the second trimester (*Shepherd et al Diab Med 2017*). If fetus inherits HNF4A from either parent, this results in mean *in-utero* weight gain of 0.8kg and risk of prolonged severe neonatal hypoglycemia, so early delivery is needed. Post-delivery, women can resume sulphonylurea therapy once breastfeeding is complete.

KCNJ11 and ABCC8: If the fetus inherits a KCNJ11 or ABCC8 neonatal diabetes mutation from their mother, they will have lower birthweight by approximately 0.9kg. Should monitor fetal growth using serial US from 28 weeks gestation. If mother is on insulin, and there is reduced fetal growth, could add glibenclamide and consider early delivery. If appropriate growth and on glibenclamide during first two trimesters of pregnancy may transfer to insulin. (*Shepherd et al Diab Med 2017*)

MIDD (m.3243A>G): Avoid metformin. See mitochondrial anaesthesia peri-operative care guidelines and pregnancy guidelines available from Newcastle University (Wellcome Centre Mitochondrial Research): http://www.newcastle-mitochondria.com/clinical-professional-home-page/clinical-publications/clinical-guidelines/

Monogenic diabetes:

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January 2018

Cost effectiveness of genetic testing

Genetic testing becomes more cost effective as the cost of the test decreases, the likelihood of detecting a monogenic cause increases, and if monogenic diagnosis results in cost savings or other benefits in patient health care.

Neonatal diabetes: 40% of those diagnosed between 0 and 6 months and only 1-2% of those diagnosed between 6-12 months have a mutation in KCNJ11 or ABCC8. More than 90% of those with KCNJ11 or ABCC8 mutations are able to transfer from insulin to lifelong sulphonylurea therapy and such conversions are associated with improvement in HbA1c sustained over many years reducing concomitant microvascular complications. Currently with free genetic testing through Exeter (UK), this is a cost-neutral to potentially massively cost-saving test. Even with an initial cost of genetic testing of US$2815 (and 4 day cost of inpatient transfer of insulin to sulphonylurea therapy) and assuming HBGM decline from 6 tests per day to 3 tests per week, the decline in expected probability of microvascular complications from an assumed lifetime mean HBA1c of 8.1% to 6.4% is estimated to becoming cost saving by 10 years and increasing thereafter (*Greeley, Diabetes Care 34: 622-7; 2011).*

GCK, HNF1A and **HNF4A**: A study simulated diabetes costs and complications in incident cases of diabetes diagnosed in a hypothetical population aged 20-40 years. Modeled variables were based on assumed T2D diagnosis and included complications data from the UKPDS, and underlying 2% MODY in the population (35% with GCK, 65% with HNF1A or HNF4A) based on a one time genetic testing cost of US$2000 (all 3 genes tested without phenotype discrimination). The genetic testing model assumed that 75% of those with HNF1A or HNF4A would be treated with sulphonylureas and that all patients with GCK would discontinue therapy. Genetic testing was demonstrated to be cost-saving as pick up rate increased to 20% (*Naylor, ADA 2012 oral abstract*).

Our NZ guidelines for genetic testing recommends consideration of individual genetic tests for non-neonatal monogenic diabetes based on clinical grounds, aiming to increase the systematic detection of index cases with a pick up rate of 20%.

Detection of index cases and subsequent family tracing

The key diagnostic challenge in monogenic diabetes is the systematic detection of index cases (first individual diagnosed with monogenic diabetes in the family). Once an index case has been identified, this is the starting point for family tracing or cascade genetic testing by which the majority of monogenic diabetes cases can be efficiently detected.

Co-ordinated **cascade testing** should be organized through referral of the index case to the genetics service with joint collaboration with the diabetes service (contact Genetic Health Service NZ: Central and South Island Hub toll free 0508 364 436 or Northern Hub toll free 0800 476 123). Genetic testing of an individual without diabetes in a family is known as "**predictive" testing**, while in those already known to have diabetes this is known as "**diagnostic" testing**. Risk notification, informing first and then second degree relatives that (1) they are at risk of monogenic diabetes (2) this type of diabetes may have implications for their diabetes therapy and general health (3) genetic testing is available to clarify if they do or do not have monogenic type of diabetes is important. All cases detected in this way will become probands for risk notification of their own first and second degree relatives.

Insurance cover and genetic testing: All individuals with potential monogenic diabetes should be made aware and understand the implications of genetic testing for certain types of insurance cover. Family and personal history of diabetes is currently utilised by insurance companies to make decisions about exclusion of specific conditions from insurance coverage and amount of insurance policy premiums. Genetic confirmation of GCK diabetes with no excess risk of microvascular complications is likely to lower insurance premiums based on supporting documentation from a diabetes specialist.

Monogenic diabetes database

Please ask all patients you refer for monogenic testing (regardless of test result outcome) for permission to be included in the monogenic diabetes database , and if agreeable, scan and email forms A, B and signed consent forms (adult or child forms appended) to R.Murphy@auckland.ac.nz or post to Assoc Prof Rinki Murphy, FMHS, University of Auckland, Private Bag 92019, Auckland 1142

The purpose of the monogenic diabetes database is to audit and improve NZ diabetes genetic testing guidelines and to enable contact with referring doctors and their patients with recent developments in monogenic diabetes diagnosis and management or relevant research opportunities.

Monogenic diabetes:

A guideline for NZ healthcare practitioners

Form A: Diagnostic algorithm for suspected monogenic diabetes (diabetes < 35 yrs)

January 2018

Please tick all that apply in algorithm along with requested genetic test

Neonatal diabetes

- ❑ Diagnosis < 6 months

→ **Targeted neonatal Diabetes gene panel** ☐

Atypical Type 1 Diabetes

- ❑ FH suggestive of monogenic diabetes
- ❑ No history of DKA
- ❑ GAD antibody negative esp within 5 years of diagnosis of diabetes
- ❑ Prandial C-peptide >200 pmol/L if beyond 5 years of diabetes

Atypical Type 2 Diabetes

- ❑ FH suggestive of monogenic diabetes
- ❑ And absence of:
  - ❑Obesity
  - ❑HTN/Dyslipidaemia
  - ❑PCOS (Females)
  - ❑Acanthosis nigricans

Family member previously tested positive for monogenic diabetes

→ **Cascade screening for known mutation** ☐

- ❑ Fasting glucose 5.5-8mmol/L
- ❑ HbA1c 40 - 60mmol/L
- ❑ Small increment (< 4.5mmol/L) on OGTT
- ❑ If first degree family member not known to have diabetes or impaired fasting glucose, fasting glucose > 5.5mmol/L in at least one first degree family member
- ❑ No microvascular complications

Yes → **Test GCK** ☐

No

- ❑ Familial , progressive young onset diabetes
- ❑ >3 family members affected
- ❑ Sensitivity to Sulphonylureas
- ❑ Elevated HDL (HNF1A only)
- ❑ hsCRP <0.7 (HNF1A only)

→ **Test HNF1A** ☐

If negative or unsure

- ❑ In addition to above:
  - ❑History of transient neonatal hypoglycaemia
  - ❑History of macrosomia

→ **Test HNF4A** ☐

If negative or unsure

Additional features?

- ❑Deafness
- ❑Maternal deafness
- ❑Maternal diabetes
- ❑Short/slim stature
- ❑Elevated lactate
- ❑Proteinuria
- ❑Myopathy

→ **Test m.3243A>G** ☐

If negative or unsure

- ❑ Renal features
- ❑ Genitourinary abnormalities
- ❑ Low Mg or K+
- ❑ HNF1B risk score 8 or more (see page 4)

→ **Test HNF1B** ☐

If negative or unsure

☐ **GCK/HNF1A/HNF4A/HNF1B panel**
☐ **Exeter 34 diabetes gene panel**

SHIP TO: Molecular Genetics Laboratory
LabPlus, Level 2,
Building 31, Auckland City Hospital
Grafton, Auckland
New Zealand

E-mail: DGen@adhb.govt.nz
Tel: +64-9-307 4949 ext. 22014

Molecular Genetics Test Request Form

Patient Details:		**Date:**	
Name (Surname, forename):		DOB (dd/mm/yy):	Gender:
Ethnicity (Country of Origin):		Hospital (ref) number:	
Test requested:			
Clinical details:	☐ Form A Attached	☐	Cascade test Yes / No

Age at diabetes diagnosis: **History of DKA yes ☐ no ☐**

Current diabetes treatment:

Not currently on insulin ☐ insulin within 6 months of diagnosis ☐ insulin over 6 months after diagnosis ☐

Height_____ **Weight** _____ **BMI** _____

HbA1c:_____ **Concurrent diabetes treatment:** _____

Parents affected with diabetes:

	Yes	No	
Mother			**age at diagnosis of diabetes** _____
Father			**age at diagnosis of diabetes** _____

Number of generations with diabetes:

Additional information :

Requesting Doctor

Name:	Tel:
E-mail:	Fax:
Signature:	
Address	Send additional copy of report to:

If billing is to be sent to other than the referring doctor, please provide appropriate information below

Institution/ Organisation:	
Address	Attn:
	Tel:
	Fax:
	Email

Form C: Patient information sheet for monogenic diabetes database

November 2012

PARTICIPANT INFORMATION SHEET

Monogenic diabetes Database

Purpose of the Study

You are invited to take part in a study because your doctor has advised you to have a test for monogenic diabetes (genetic diabetes). We would like to link this test result with some information about your diabetes or risk of diabetes and add this to a New Zealand monogenic diabetes database, held at Auckland University. The long term aim of this study is to better understand monogenic diabetes (diabetes caused by a single gene change) in New Zealand. The sort of questions we wish to answer are: Which diabetes related clues help identify people with certain monogenic diabetes best? How do these differ in those who were first picked up compared to those who were picked up because someone else in their family was known to have this?

Genetic tests for diabetes

You are being asked to take part in this study because your doctor has requested a test for genetic diabetes, as part of your routine care. We are asking people who have recently been asked to take a test for monogenic diabetes and also people who may have had a test done several years ago, to have their details collected in a database.

If my genetic test came back negative, am I still able to be included on the database? Yes, it does not matter whether you tested positive or negative for the diabetes genetic test. Your information is very important to help us decide how to improve the criteria for testing in future.

Why is getting the diabetes diagnosis right, so important? Your doctor will already have explained why they thought you should have a genetic test for diabetes, but in summary getting the diagnosis right may alter the diabetes treatment for you and/or your family. It may also be important for the management of women with a family history of genetic diabetes who are; a) pregnant or who are b) planning pregnancy.

What exactly am I consenting to, if I agree to have my clinical information added to the NZ monogenic diabetes database? We will ask your doctor to supply us with clinical information that is routinely collected when genetic tests for diabetes are arranged. This information will include date of birth, gender, age of onset of diabetes (if relevant), details of your family history of diabetes such as relationship to you and age of diagnosis (if known). It may sometimes include your birth weight and birth weight of family members and the type of diabetes treatments you or family members have received (where relevant). The database will also include blood test results, including the results of your genetic test.

How will information on the database be kept secret and who will have access to the database? The database has several levels of security and strict password access by only the three diabetes doctors involved in this study.

How will I know what information about me is on the database and how can I update it if more information about my family comes through ? You may ask your referring health care professional for a copy of the referral information. If anything changes, you can submit this information directly to the principle investigator who specializes in monogenic diabetes, Dr Rinki Murphy using email: R.Murphy@auckland.ac.nz

Can I ask for my information to be removed from the database? How do I go about doing this? Yes, you can let Dr Rinki Murphy know using email: R.Murphy@auckland.ac.nz

Will the principle investigator and/or her team contact me directly at any stage? Usually we will contact your health care professional regarding any developments in monogenic diabetes that may affect your health care, but we may contact you directly if there are important issues to update you about.

How will the researchers know I've changed my GP or moved away? We will rely on the contact information about you that your doctor who referred you has, or any updated information you give us directly

.

We hope that you find this project interesting, but you are under no obligation to take part. Options regarding your participation are outlined individually in the consent form. Please feel free to discuss this with your family, friends or family doctor.

Maori Ethics Committee Review Committee do not support tissue banking in any form given collective whanau, hapu, iwi implications. However they have noted individuals have the right to make their own decisions.

If you have any queries or concerns regarding your rights as a participant in this research study, you can contact an independent Health and Disability Advocate. This is a free service provided under the Health and Disability Commissioner Act:

Telephone (NZ wide):	0800 555 050
Free Fax (NZ wide):	0800 2787 7678 (0800 2 SUPPORT)
Email:	advocacy@hdc.org.nz

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THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

WRITTEN CONSENT FORM FOR MONOGENIC DIABETES DATABASE

Title of project: New Zealand Monogenic Diabetes Database

Principal Investigator: Dr Rinki Murphy

Name of Patient: …….. D.O.B……

Ethnicity……. Sex: Male/Female

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
	Other languages to be added following consultation with relevant communities.		

I, _____ have been given, and I have read, and I understand the information sheet dated 1 August 2012, version 1.0, for volunteers taking part in the study designed to establish a New Zealand Monogenic Diabetes Database. I have had the opportunity to discuss this study and I am satisfied with the answers I have been given.

YES/NO

I give consent to my personal details (including family tree), medical history and genetic analysis results to be stored electronically in the NZ Monogenic Diabetes Database

YES / NO

I give consent for the researchers to contact me about any new developments relating to my diabetes diagnosis or participation in research to find out more about this.

YES /NO

I agree to my GP or other current care provider being informed of my participation in this study / the results of my participation in this study. YES/NO

Signed (Subject): …… Date .....

(Parent/Guardian) …….. Date .....

Form D continued: Adult consent form

(Parent/Guardian) …….. Date .....

In my opinion consent was given freely and with full understanding.

Witness name (please print): ……..

Witness signature: ……. Date .....

Consent obtained by:

Name (please print) ……

Signed: …… Date .....

This study has received ethical approval from the Northern A Health and Disability Ethics Committee
Reference 12/NTA/87

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Monogenic diabetes:

A guideline for NZ healthcare practitioners

Form E: Child information sheet for monogenic diabetes database

November 2012

We were wondering if you would like to help us….

What will we do?

- Your doctor has already explained that you need a gene test to find out the cause of your diabetes
- We want to store the information about your diabetes and your gene test result in a secure computer
- From the stored information, we will be able to find out things about the different types of diabetes caused by genes and how best to treat these and find if other people also carry this gene.

Any details we have about you are *kept secret*, and nobody else will ever be able to get hold of any information about you or your genetic result.

If you *change your mind* in the future and don't want to take part, *that is OK*, and we will remove all your information from our study.

Will I need to give a blood sample?
NO – this study will only collect information about you and any tests your doctor has already done !

- The papers given to your parents/caregiver has even more stuff about this, so talk to them if you want to know more
- If you decide to help us the Doctor will talk to you to make sure that you understand everything and they will answer any questions

Why do we need your help?

- Lots of children and adults around the world develop a special type of diabetes that is quite rare and needs to be treated differently from the common types of diabetes. Finding out that diabetes is caused by a single gene disorder, can change the way your diabetes is treated.
- Sometimes if you were treated with insulin you may able to be treated with tablets.
- Knowing who tested positive or not will help us get it right more often

If your parents say no and you don't take part in this study, it will make no difference to how you are looked after.

Thanks for thinking about it

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CHILDREN'S CONSENT FORM FOR TAKING PART IN MONOGENIC DIABETES DATABASE

Title of project:

Monogenic diabetes database

I ……have read page 1 of this form and I have had the study explained to me. Yes /No

I have had answers to the questions I asked, and know that I can ask more questions at any time Yes /No

I agree to the study Doctors looking at my hospital notes Yes/No

Signed (Subject): …… Date ……

Consent obtained by:
Name (please print) ……

Signed: …… Date ……