1. Disorder/condition – approved name and symbol as published on the OMIM database (alternative names will be listed on the UKGTN website)

If this submission is for a panel test please complete appendix 1 listing all of the conditions included using approved OMIM name, symbol and OMIM number.

See Appendix 1

2. OMIM number for disorder/condition

If a panel test – see 1. above

See Appendix 1

3a. Disorder/condition – please provide, in laymen’s terms, a brief (2-5 sentences) description of how the disorder(s) affect individuals and prognosis.

Monogenic diabetes is a clinically and genetically heterogeneous group of disorders characterised by early onset diabetes in slim individuals that are not insulin dependent. Patients are typically diagnosed under the age of 35 years and have a minimum two generation family history of diabetes. However age of diagnosis, clinical features, severity of disease and penetrance are variable. Clinical characteristics are determined by the gene involved, and a positive result as important implications for clinical management and prognosis depending on the gene mutated.

3b. Disorder/condition – if required please expand on the description of the disorder provided in answer to Q3a.

The monogenic diabetes genes within the NGS panel that are analysed on a diagnostic basis are responsible for different subtypes of monogenic diabetes. Although each subtype has characteristic clinical features in addition to diabetes, they can be variable and it is not always possible to clinically determine which subtype a patient is likely to be affected with.

Maturity Onset Diabetes of the Young (MODY) due to mutations in GCK, HNF1A, HNF4A, HNF1B, NEUROD1, INS, INSR, PDX1, GATA6, KCNJ11 and ABCC8.

Maturity-onset diabetes of the young (MODY) is a monogenic disorder that results in a familial, young-onset non-insulin dependent form of diabetes, typically presenting in lean young adults before 25 years. Approximately 1% of diabetes has a monogenic cause but this is frequently misdiagnosed as Type 1 or Type 2 diabetes. A correct genetic diagnosis is important as it often leads to improved treatment for those affected with diabetes and enables predictive genetic testing for their asymptomatic relatives. An early diagnosis together with appropriate treatment is essential for reducing the risk of diabetic complications in later life. Mutations in the GCK, HNF1A, and HNF4A genes account for up to 80% of all MODY cases. Mutations in the GCK gene cause a mild, asymptomatic and non-progressive fasting hyperglycaemia from birth usually requiring no treatment. In contrast, mutations in the genes encoding the transcription factors HNF1A and HNF4A cause a progressive insulin secretory defect and hyperglycaemia that can lead to vascular complications. The diabetes in these patients is usually well controlled with sulphonylurea tablets although insulin treatment may be required in later life. HNF1B gene mutations are associated with a syndrome of diabetes and renal disease (typically renal cysts or renal dysplasia) known as RCAD.

Familial Partial Lipodystrophy (FPLD) due to mutations in LMNA and PPARG

FPLD is a metabolic disorder caused by heterozygous mutations in the LMNA and PPARG genes. It is characterized by abnormal subcutaneous adipose tissue distribution beginning in late childhood or early adult life. Affected individuals gradually lose fat from the upper and lower extremities and the gluteal and truncal regions, resulting in a muscular appearance with prominent superficial veins. In some patients, adipose tissue accumulates on the face and neck, causing a double chin, fat neck, or cushingoid
appearance. Metabolic abnormalities include insulin-resistant diabetes mellitus with acanthosis nigricans and hypertriglyceridemia; hirsutism and menstrual abnormalities occur infrequently. Maternally inherited diabetes and deafness (MIDD) due to m.3243A>G in the MTTL1 gene caused by a m.3243A>G mutation in the mitochondrial tRNAleu gene. Common presenting features are type 2 diabetes diagnosed before the age of 40 years, and/or bilateral sensorineural deafness. Other less common features include myopathy, strokes, short stature and focal glomerulosclerosis. Large phenotypic variation is observed, even in the same family, due to wide range in levels of heteroplasmy between individuals, and even between tissues in the same individual. Therefore, the clinical course of the disorder is difficult to determine.

4. Disorder/condition – mode of inheritance
If this submission is for a panel test, please complete the mode of inheritance for each condition in the table in appendix 1.

See Appendix 1

5. Gene – approved name(s) and symbol as published on HGNC database (alternative names will be listed on the UKGTN website)
If this submission is for a panel test please complete appendix 1 listing all of the genes included using approved HGNC name, symbol, number and OMIM number.

See Appendix 1

6a. OMIM number(s) for gene(s)
If a panel test – see 5. above

See Appendix 1

6b. HGNC number(s) for gene(s)
If a panel test – see 5. above

See Appendix 1

7a. Gene – description(s)
If this submission is for a panel test, please provide total number of genes.

Panel Test of 14 genes

7b. Number of amplicons to provide this test (molecular) or type of test (cytogenetic) (n/a for panel tests)
N/A (Panel Test)

7c. GenU band that this test is assigned to for index case testing.
G

8. Mutational spectrum for which you test including details of known common mutations (n/a for panel tests)
If this application is for a panel test to be used for different clinical phenotypes and/or various sub panel tests – please contact the team for advice before completing a Gene Dossier
N/A (Panel Test)

9a. Technical method(s) – please describe the test.
Uses a custom Agilent SureSelect exon-capture assay with baits for 14 genes. These include 11 known/putative MODY genes (GCK, HNF1A, HNF4A, HNF1B, NEUROD1, INS, INSR, PDX1, GATA6, KCNJ11 and ABCC8), two genes where mutations cause diabetes through lipodystrophy (LMNA and PPARG), the m.3243 region of the mitochondrial genome (where the m.3243A>G mutation in the MTTL1 gene causes MIDD).
Genomic DNA samples (usually batches of 48) are checked for quality/quantity (using a Qubit) and are...
then fragmented by sonication. Following size selection the samples undergo end-repair, dA tailing, adapter ligation and indexing before hybridisation with custom SureSelect Biotinylated RNA library ‘baits’ complementary to the sequences of interest. Clusters are generated and sequencing is performed using an Illumina HiSeq 2500 (48 samples per lane) to generate 100 base paired end reads.

Raw data from the HiSeq2500 is aligned against the GRCh37 Human reference genome using the BWA-MEM aligner, with further processing by Picard tools and GATK software to remove sequencing artefacts and errors. Variation analysis for SNVs and indels is performed by GATK software. Variant annotation is performed by Alamut HT software prior to filtering to remove common variants.

The regions analysed for each of the 14 genes include coding exons, intronic sequences within 50bp upstream and 10bp downstream of each exon, and certain non-coding regions (promoters) where pathogenic mutations have been reported. Deletions/insertions/duplications >30 bp are identified by relative read depth coverage. All newly identified mutations are confirmed by Sanger sequencing or MLPA.

9b. For panel tests, please specify the strategy for dealing with gaps in coverage.

On average, the assay achieves ≥30 reads for 99.3% of the region analysed. Sanger sequence analysis is performed for gaps in coverage (<20x per base) where the patient’s phenotype is consistent with a mutation in that gene.

9c. Does the test include MLPA?
(For panel tests, please provide this information in appendix 1)

Testing for HNF1B mutations causing the RCAD syndrome (renal cysts and diabetes) is performed by MLPA first as whole gene deletions account for ~50% of mutations. For GCK, HNF1A and HNF4A MODY deletions are rare; accounting for ~1% of mutations. A separate MLPA test is available but our targeted NGS assay will detect deletions/duplications of >30bp can be identified by relative read depth coverage (a validation study of a larger number of deletions is in progress).

9d. If NGS is used, does the lab adhere to the Association of Clinical Genetic Science Best Practice Guidelines for NGS?

Yes

10. Is the assay to be provided by the lab or is it to be outsourced to another provider?

If to be outsourced, please provide the name of the laboratory and a copy of their ISO certificate or their CPA number.

Assay will be provided by the lab.

11. Validation process

Please explain how this test has been validated for use in your laboratory or submit your internal validation documentation. If this submission is for a panel test, please provide a summary of evidence of:

i) instrument and pipeline validation, and
ii) panel verification for the test

Please submit as appendices to the Gene Dossier (these will be included in the published Gene Dossier available on the website).

Please note that the preferred threshold for validation and verification is 95% sensitivity with 95% Confidence Intervals.

Please see accompanying internal validation document attached.

12a. Are you providing this test already?

Yes

12b(i). If yes, how many reports have you produced?

32

12b(ii). Number of reports mutation positive?

13
### 12b(iii). Number of reports mutation negative?

19

### 12b(iv). Please provide the time period in which these reports have been produced and whether in a research or a full clinical diagnostic setting.

235 research reports for patients with neonatal diabetes were issued between November 2011 and January 2014 using the same platform. Diagnostic MODY reports have been issued since October 2013. 27 reports issued under a full diagnostic setting. 5 research reports issued for the 3 new MODY cases and 2 new MIDD cases identified from the research study (published in Ellard et al 2013 Diabetologia 56: 1958-1963)

### 13a. Is there specialised local clinical/research expertise for this disorder?

Yes

### 13b. If yes, please provide details

Professors Andrew Hattersley and Sian Ellard are Wellcome Trust Senior Investigators who have achieved international acclaim for their research into monogenic diabetes. The Exeter laboratory was established in 1995 and since this time they have published over 220 diabetes research articles, including those in NEJM, Nature Genetics, PNAS and JAMA. A UK diagnostic testing service for MODY has been available in Exeter since 2000 and provides an integrated service that includes tests for endogenous insulin production (urinary C-peptide) and pancreatic autoantibodies to discriminate likely MODY from the more common forms of type 1 and 2 diabetes. A “MODY calculator” is available on the www.diabetesgenes.org website for clinicians to estimate the likelihood of MODY according to the patient’s clinical characteristics. We have identified over 2000 individuals with MODY from within and outside of the UK. This is the largest cohort of patients with MODY in the world. Professor Hattersley and his clinical team are international experts in the diagnosis and management of monogenic diabetes. Exeter hosts the UK network of Genetic Diabetes Nurses (led by Dr Maggie Shepherd) who assist with identifying appropriate patients for testing, following up families and supporting patients through treatment change.

### 14. Based on experience what will be the national (UK wide) activity, per annum, for:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index cases</strong></td>
<td>about 200 (based on annual number of 630 referrals for MODY testing received by our laboratory and an estimated 30% take up rate for the NGS panel).</td>
</tr>
<tr>
<td><strong>Family members where mutation is known</strong></td>
<td>49</td>
</tr>
</tbody>
</table>

### 15. If your laboratory does not have capacity to provide the full national need please suggest how the national requirement may be met.

For example, are you aware of any other labs (UKGTN members or otherwise) offering this test to NHS patients on a local area basis only? This question has been included in order to gauge if there could be any issues in equity of access for NHS patients. If you are unable to answer this question please write "unknown".

N/A

### 16. If using this form as an Additional Provider application, please explain why you wish to provide this test as it is already available from another provider.

N/A
17a. Estimated prevalence of conditions in the general UK population

Prevalence is total number of persons with the condition(s) in a defined population at a specific time.
Please identify the information on which this is based.
For panel tests, please provide estimates for the conditions grouped by phenotypes being tested.

MODY:
The minimum population prevalence of MODY in the UK is estimated at 108 cases per million with a minimum UK prevalence of 6,351 cases. Approximately 52% of confirmed UK MODY families have HNF1A mutations. 32% have mutations in GCK, 10% have mutations in HNF4A and 6% have mutations in HNF1B. The remainder have rare MODY gene mutations including INS, ABCC8 and NEUROD1 (Shields et al 2010 Diabetologia 53, 2504-2508).

FPLD due to LMNA and PPARG gene mutations:
There is no precise prevalence data for lipodystrophy in the UK, but a prevalence of around 2 per million (120 patients in England) has been suggested (communication with the Cambridge Genetics Laboratory who have a specialist interest in FPLD).

MIDD due to the m.3243A>G mutation:
A study of mitochondrial disease in the North East population of the UK estimated a prevalence of confirmed m.3243A>G related disease at 0.95/100,000 population, with an additional prevalence of clinically unaffected relatives that are obligate carriers of m.3243A>G at risk of developing mitochondrial disease of 0.71/100,000 population (Chinnery et al 2001 Ann Neurol 48, 188-193).
A study by Elliott et al identified a higher prevalence of m.3243A>G in 4/2810 (0.14%) cord blood samples from neonates in North Cumbria, UK (Elliott et al 2008 Am J Hum Genet 83: 254-260).

17b. Estimated annual incidence of conditions in the general UK population

Incidence is total number of new cases in a year in a defined population.
Please identify the information on which this is based.
For panel tests, please provide for groups of conditions.

MODY:
Unknown; an average of 240 new cases diagnosed by the Exeter Laboratory each year from the years 2008 to 2013.

LMNA and PPARG related FPLD:
Unknown; an average of 5 new cases diagnosed by the Exeter Laboratory each year from the years 2008 to 2013.

m.3243A>G related MIDD:
Unknown; an average of 12 new cases diagnosed by the Exeter Laboratory each year from the years 2008 to 2013.

18. Estimated gene frequency (Carrier frequency or allele frequency)
Please identify the information on which this is based.
n/a for panel tests.

N/A (Panel Test)

19. Estimated penetrance of the condition.
Please identify the information on which this is based
n/a for panel tests

N/A (Panel Test)

20. Estimated prevalence of conditions in the population of people that will be tested.
n/a for panel tests.

N/A (Panel Test)
**INTENDED USE** (Please use the questions in Annex A to inform your answers)

21. Please tick either yes or no for each clinical purpose listed.

**Panel Tests:** A panel test would not be used for pre symptomatic testing, carrier testing and pre natal testing as the familial mutation would already be known in this case and the full panel would not be required.

<table>
<thead>
<tr>
<th>Clinical Purpose</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>Prognosis &amp; management</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>Presymptomatic testing (n/a for Panel Tests)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Carrier testing for family members (n/a for Panel Tests)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Prenatal testing (n/a for Panel Tests)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
TEST CHARACTERISTICS

22. Analytical sensitivity and specificity This should be based on your own laboratory data for the specific test being applied for or the analytical sensitivity and specificity of the method/technique to be used in the case of a test yet to be set up. Please note that the preferred threshold for validation and verification is 95% sensitivity with 95% Confidence Intervals.

A total of 160 unique variants (123 single base substitutions, 29 indels and 8 partial/whole gene deletions) have been correctly identified by the NGS assay with no false negative or positive results. Therefore we have 95% confidence that the sensitivity of the assay is >97.5% (error rate 0-2.3%).

23. Clinical sensitivity and specificity of test in target population The clinical sensitivity of a test is the probability of a positive test result when condition is known to be present; the clinical specificity is the probability of a negative test result when disorder is known to be absent. The denominator in this case is the number with the disorder (for sensitivity) or the number without condition (for specificity). Please provide the best estimate. UKGTN will request actual data after two years service.

Clinical Sensitivity of MODY testing:
Clinical sensitivity depends on many factors such as age and phenotype at diagnosis, the characteristics of diabetes, family history and any associated traits.

Mutations in the GCK, HNF1A and HNF4A genes account for approximately 94% of genetically confirmed MODY in the UK population (Shields et al 2010 Diabetologia 53:2504-2508). Mutations in the HNF1B gene result in the renal cysts and diabetes (RCAD) syndrome, characterised by young onset diabetes with renal cysts and/or structural abnormalities of the renal and reproductive systems. HNF1B mutations account for 6% of UK MODY cases, and were identified in <1% of 258 probands who met the criteria of two generations affected with diabetes and at least one family member diagnosed under 25 years and with no known renal disease (Edghill et al 2013 Diabet Med 30: 114-117). Rarer genetic causes of MODY due to mutations in other genes have been reported, and OMIM lists 11 different subtypes (including GCK, HNF1A and HNF4A MODY). Recent publications of activating KCNJ11 and ABCC8 mutations that cause MODY bring the current total to 13 genes (Bonnefond et al 2012 PLoS One 7:e37423, Bowman et al 2012 Diabetologia 55:123-127), but these additional subtypes are very rare and together account for only ~1% of MODY.

The proportion of probands referred for testing with a confirmed genetic diagnosis of MODY varies widely according to the criteria used to select patients for testing. Using minimum selection criteria of age of diagnosis <25 years, not treated with insulin and having a diabetic parent, the pick-up rate in a UK series was 51%. This dropped to 23% when probands not meeting these criteria were included (Shields et al 2010 Diabetologia 53:2504-2508). By using much stricter criteria it is possible to achieve a higher clinical sensitivity (around 75%), but fewer individuals will be diagnosed with MODY including some who could potentially discontinue insulin treatment (see 3.1.4).

In patients with a GCK MODY phenotype (i.e. mild and stable fasting hyperglycaemia), the pick-up rate of GCK mutations in our laboratory is high ranging from 40 to 50%. In contrast, in patients with an HNF1A or HNF4A MODY phenotype (i.e. young-onset, non-insulin dependent diabetes before 40 years, with a family history of diabetes in at least two generations), HNF1A mutations account for 20% and HNF4A mutations for 10% of MODY cases without HNF1A mutations.

Diabetic family members of a proband with MODY may not inherit the familial mutation, and their diabetes is likely to have a different aetiology (typically type 1 or type 2 diabetes).

Clinical Specificity of MODY testing:
Nearly 100% for GCK MODY. Due to variability in measuring fasting blood glucose (FBG), ~2% of patients with GCK MODY have a FBG <5.5mmol/L but on repeat testing it will be >5.5mmol/L (Stride et al 2002 Diabetologia 45:427-435).

The diabetes in HNF1A and HNF4A MODY is progressive and the penetrance increases with age; for HNF1A mutations it is approximately 63% by age 25, 93.6% by age 50 and 98.7% by age 75 (Shepherd et al 2001 Diabet Med 18:417-421). Patients can therefore have the mutation but be clinically unaffected at a young age, or have biochemical evidence of abnormal glucose homeostasis but be clinically asymptomatic. Patients with HNF1A and HNF4A mutations can have FBG within the non-diabetic range, but have OGTT results diagnostic for diabetes (Stride et al 2002 Diabetologia 45:427-435).
Clinical Sensitivity of FPLD testing:
Rare disease and so difficult to make a precise estimate. The experience of the clinician requesting the test will influence clinical sensitivity, as the probability of a positive test is most likely when the patient has the classical 'Dunningan' pattern of lipodystrophy and associated metabolic abnormalities. Very rare mutations in PLIN1 gene have also been shown to cause FPLD although this gene is not included in the panel.

Clinical Specificity of FPLD testing:
Nearly 100%. Will vary slightly depending on whether the presence of the disorder is based on lipodystrophy or metabolic abnormalities. Patients typically develop lipodystrophy after puberty, and it is easier to identify visually in females than males. However the lipodystrophy phenotype is also variable and can be very mild or even absent in some patients, with the metabolic abnormalities being the primary phenotype (Dutour et al 2011 Hum Mol Genet 20:3779-3786). This is particularly the case for PPARG mutations. Pre pubertal mutation carriers will appear clinically affected with normal fat distribution but can have an abnormal metabolic profile. A p.R482Q LMNA mutation was shown to completely co-segregate with FPLD in 22 affected family members and was absent in 23 unaffected family members (Cao & Hegele 2000 Hum Mol Genet 9:109-211).

Clinical Sensitivity of m.3243A>G MIDD testing:
The level of the m.3243A>G mutation can vary significantly between different tissue types. It is typically lower in DNA extracted from whole blood leukocytes compared to other tissues such as muscle or epithelial cells, and levels decrease in leukocytes with increasing patient age. Mutation levels are higher in urine epithelial cells compared to leukocytes (de Laat et al 2012 J Inherit Metab Dis 35:1059-1069) and we offer testing from a urine sample when the clinical suspicion of an m.3243A>G mutation is high. Other rare mitochondrial mutations have been reported as a cause of diabetes which are not analysed and therefore not excluded by this method (Blakely et al 2013 Hum Mutat 34:1260-1268; Mazzaccara et al 2012 PLoS One 7:e34956; Bannwarth et al 2011 Diabetes Care 34:2591-2593; Chen et al 2006 Mutat Res 602:26-33).

Clinical Specificity of MIDD testing:
A clinical audit of 129 UK patients with the m.3243A>G mitochondrial mutation included 12 individuals (9%) with the mutation that were clinically asymptomatic, having undergone screening because of affected maternal relatives (Nesbitt et al 2013 J Neurol Neurosurg Psychiatry 84:936-938).

24. Clinical validity (positive and negative predictive value in the target population)
The clinical validity of a genetic test is a measure of how well the test predicts the presence or absence of the phenotype, clinical condition or predisposition. It is measured by its positive predictive value (the probability of getting the condition given a positive test) and negative predictive value (the probability of not getting the condition given a negative test).
Not currently requested for panel tests

N/A (Panel Test)

25. Testing pathway for tests where more than one gene is to be tested sequentially
Please include your testing strategy if more than one gene will be tested and data on the expected proportions of positive results for each part of the process. Please illustrate this with a flow diagram. This will be added to the published Testing Criteria.
n/a for panel tests

N/A (Panel Test)

CLINICAL UTILITY

26. How will the test change the management of the patient and/or alter clinical outcome? Please describe associated benefits for patients and family members. If there are any cost savings AFTER the diagnosis, please detail them here.

Clinical Utility of finding a MODY gene mutation:

Therapy: Low dose sulfonylureas are recommended as the first line treatment for patients with HNF1A/HNF4A-MODY and observational evidence suggests that patients can be switched safely from insulin to a sulfonylurea.

In a series of 43 diabetic patients, 34 changed from insulin to a sulfonylurea after diagnosis of HNF1A MODY and 24 remained off insulin for 39 months with no deterioration in glycaemic control. Successful
transfer was correlated with a shorter duration of diabetes and emphasises the need for early genetic diagnosis. Good control may be maintained for many years, although eventually most patients progress to insulin treatment.

Good glycaemic control on sulphonylurea has also been observed in patients in ABCC8 and KCNJ11 MODY, with successful transfer from insulin to low dose sulphonylurea with improved control. Hypersensitivity to sulphonylureas can result in symptomatic hypoglycaemia for some HNF1A and HNF4A MODY patients. Treating these patients with a short acting insulin secretagogue such as nateglinide has been shown to be a safe alternative therapy that results in less hypoglycaemic symptoms.

The majority of patients with GCK MODY are not receiving pharmacological therapy but some are misdiagnosed with type 1 or 2 diabetes and treated with insulin or oral hypoglycaemia agents. No change in Hba1c was seen in a longitudinal study of 16 subjects who stopped treatment after their GCK mutation was identified. Therefore in the absence of concomitant type 1 or 2 diabetes, glucose lowering therapy can be stopped. The only exception is during a pregnancy where fetal macrosomia is suspected and insulin treatment may be administered in an attempt to control fetal growth.

**Prognosis:** Due to its progressive nature and early age at diagnosis, those with HNF1A and HNF4A MODY are at similar risk of microvascular and macrovascular complications as in patients with type 1 or type 2 diabetes, which is strongly influenced by the degree of glycaemic control. HNF1A MODY patients are at an increased risk of developing cardiovascular disease so statin therapy by the age of 40 years, regardless of lipid status, has been recommended. The fasting hyperglycaemia in GCK MODY is mild and stable over the patient’s lifetime, with progression reflecting that seen with increasing age in the non-GCK MODY population. Since Hba1c is only mildly raised, the risk of developing diabetic complications is very low.

Renal disease (cysts or renal dysplasia) is typically the presenting clinical feature in patients with HNF1B mutations. Diabetes develops later in life and this can be screened for with regular Hba1c checks when routine blood samples are taken to assess renal function. Conversely, patients with diabetes but no features renal disease that are found to harbour an HNF1B mutation should undergo renal imaging and assessment of renal function. Additional clinical features include pancreatic exocrine dysfunction, deranged liver function and early onset gout/hyperuricaemia, all of which can be screened/monitored with simple biochemistry tests (see http://www.diabetesgenes.org/sites/default/files/hnf1b_information_for_clinicians.pdf for further information).

**Management:** Women with GCK MODY may have babies that are large for gestational age if the baby has not inherited the GCK mutation. It is suggested that mothers undergo serial fetal abdominal scans to identify babies showing excessive growth to thereby target insulin therapy to those at greatest risk. Finding an HNF4A mutation has important implications for the management of pregnancy. Pregnanacies where one parent (mother or father) has an HNF4A mutation are at risk of complications during delivery due to macrosomia and increased ultrasound monitoring of fetal growth is recommended. Neonates who have inherited the HNF4A mutation are also at risk of neonatal hyperinsulinaemic hypoglycaemia and blood glucose should be checked from birth. HNF1A mutations may predispose to familial liver adenomatosis through somatic inactivation of the remaining wildtype allele. In a cohort of 137 HNF1A MODY patients, 9 cases (6.5%) of liver adenomatosis were identified by liver ultrasonography. Patients with liver adenomatosis are at risk of haemorrhage, and some hepatologists advocate systematic liver ultrasonography in HNF1A MODY patients.

**Cost Savings:** MODY testing has been demonstrated to be cost effective in the US (Naylor et al 2014 Diabetes Care 37: 202-209). Cheaper to treat with low dose sulphonylurea compared to the cost of insulin and associated needles, syringes, injection pens or insulin pumps. Improved glycaemic control reduces the risk of diabetes complications with fewer hospital admissions or clinic appointments.

Cost savings made in patients with GCK MODY by discontinuing any glucose lowering therapy they may be taking at the time of genetic diagnosis. Regular blood glucose monitoring is not required so cost of laboratory Hba1c and blood glucose tests and home blood glucose monitoring equipment is saved. Regular screening for diabetic complications is also not necessary and the cost of these appointments will be saved. See Schnyder et al 2005 Swiss Med Wkly 135:352-356 for a case study.
Clinical Utility of finding a mutation in LMNA or PPARG:

The metabolic abnormalities in patients with FPLD cause a number of serious conditions that result in early morbidity and mortality. These include insulin resistance and diabetes, diabetic vascular complications, fatty liver disease, pancreatitis, and in women, polycystic ovarian syndrome that reduces fertility and increased androgen with associated clinical features.

Early diagnosis of FPLD and management of the metabolic alterations is essential to minimise the morbidity and mortality due to complications. Diet and exercise management through specialist dieticians is needed to maintain healthy serum lipid levels.

Leptin therapy may be possible for some patients with a genetic diagnosis of FPLD. A study of 35 patients with lipodystrophy treated with Leptin for 1 to 8 years, triglycerides fell by an average of 59% and average HbA1c decreased from 8.4% to 6.9% (Chong et al 2010 Diabetologia 53: 27-35). A significant reduction in serum and hepatic triglyceride levels was also observed in a study of 17 LMNA related FPLD patients treated with leptin for 6 months (Simha et al 2012 J Clin Endocrinol Metab 97: 785-792).

A 70% reduction in serum triglycerides and an improvement in glucose homeostasis (HbA1c 9.9% to 7.2%, FBG 8.3mmol/l to 4.9mmol/l) as a result of leptin therapy has been observed in a patient with PPARG related FPLD treated for 18 months (Guettier et al 2008 Clin Endocrinol (Oxf) 68: 547-554).

These lipid lowering treatments reduce the risk of developing severe complications such as fatty liver and pancreatitis, and the significant improvements in glycaemic control would undoubtedly result in a reduced risk of developing diabetes complications. Testing of family members allows for early detection and early screening of dyslipidaemia and diabetes. This will allow for early intervention.

Cost Savings: A genetic diagnosis of FPLD alerts the clinician to the need for aggressive treatment of dyslipidaemia. The resulting reduction in lipid levels also reduces the risk of developing pancreatitis and fatty liver disease, and has shown to improve glycaemic control which reduces risk of developing diabetic complications. Therefore cost savings made in avoiding these complications which are expensive to manage and treat.

Clinical Utility of finding a m.3243A>G mutation:

A recent clinical audit of MIDD patients with the m.3243A>G mutation identified a range of additional phenotypes including cardiomyopathy, encephalopathy, myopathy, ataxia, migraine, seizures, stroke like episodes, gastrointestinal disturbance (constipation and/or irritable bowel syndrome) and short stature (Nesbitt et al 2013 J Neurol Neurosurg Psychiatry 84:936-938). Predicting the likely clinical course in a patient with MIDD is difficult due to the level of heteroplasmy which can be variable within clinically important tissues such as muscle and brain. Therefore, identifying an m.3243A>G has very important implications for the early detection, management, long-term follow up (particularly in maternal adult relatives) or prevention of these conditions. Recommendations include: assessment of renal function and reducing blood pressure (e.g. ACE-1 inhibitors) to minimise renal disease; ECG assessment for early detection of cardiomyopathy and aggressive treatment with drugs or pacemakers/ICDs; periodic audiograms to assess hearing function with use of hearing aids or cochlear implantation to correct hearing loss and delaying hearing loss by avoiding exposure to ototoxic drugs and loud noise; neurological and cardiovascular examinations.
The therapeutic utility of coenzyme Q10 has been demonstrated in patients with MIDD. A study showed that diabetes patients with m.3243A>G given oral CoQ10 for 3 years had improved insulin secretory response and improved blood lactate post exercise. The therapy also prevented progressive hearing loss, and no side effects were reported (Suzuki et al 1998 Diabetologia 41:584-588).

A positive result also has implications for genetic counselling. Affected fathers can be reassured that they will not transmit the disorder to their children. An affected mother is likely to transmit m.3243A>G to all her children, even although some may remain clinically unaffected. The penetrance of diabetes in an offspring with m.3243A>G is age dependent but is estimated at over 85% by the age of 70 years. Mothers with m.3243A>G have a greater prevalence of miscarriage than women with other types of diabetes, despite better glycaemic control.

27. If this test was not available, what would be the consequences for patients and family members?

MODY: It is estimated that 90% of patients with MODY are misdiagnosed or misclassified as having type 1 or type 2 diabetes, and are therefore likely to be inappropriately treated. Without a genetic diagnosis, many MODY patients and their diabetic relatives will remain on unnecessary insulin treatment or ineffective oral hyperglycaemic regimes, with poor diabetes control and increased risk of developing diabetic complications. Those patients on treatment that miss a diagnosis of GCK MODY will not benefit from being able to safely discontinue their treatment without the risk of developing complications.

A diagnosis of HNF4A MODY or GCK MODY has important implications for management of pregnancy, and if a diagnosis is not made this could lead to macrosomia and associated complications in pregnancy/during delivery (including stillbirth).

FPLD: If a diagnosis is not made, specialist management and treatment is unlikely to be made available as the disease is very rare. Patients are typically lean, and so appropriate diet advice to manage lipid levels is unlikely to be given. Leptin therapy will also not be made available. Without the appropriate management and therapy, the risk of developing severe complications is significantly increased.

MIDD: Failure to diagnose these individuals will prevent their access to important health surveillance and may allow clinically significant conditions to arise. Clinicians would not be alerted to the risk of developing cardiomyopathy, renal disease and deafness. These conditions can be effectively managed if detected early.
28. Is there an alternative means of diagnosis or prediction that does not involve molecular diagnosis? If so (and in particular if there is a biochemical test), please state the added advantage of the molecular test.

No; we have devised a statistical model that determines the prior probability of making a genetic diagnosis of MODY (Shields et al. 2012 Diabetologia 55:1265-1272). We have also shown that GAD and IA2 auto-antibodies and C-peptide are excellent discriminators of type 1 diabetes and MODY (McDonald et al. 2011 Diabet Med 28:1028-1033; Besser et al. 2011 Diabetes Care 34:286-291). Studies have also identified high sensitivity C-reactive protein (hsCRP) testing as a potential biomarker for HNF1A MODY (Thanabalasingham et al. 2011 Diabetologia 54:2801-2810). However these methods cannot make a definite diagnosis of monogenic diabetes and are only used as a guide to select patients for genetic testing. One patient is known to have died after a misdiagnosis of MODY where genetic testing was not performed.

29a. What unexpected findings could this test show? For example, lung cancer susceptibility when testing for congenital cataract because ERCC6 gene (primarily associated with lung cancer) is included in a panel test for congenital cataract.

This test could detect a LMNA gene mutation predisposing to adult onset dilated cardiomyopathy. Other phenotypes may develop with the m.3243A>G mitochondrial mutation.

29b. Please list any genes where the main phenotype associated with that gene is unrelated to the phenotype being tested by the panel.

LMNA mutations cause a range of phenotypes including partial lipodystrophy, Emery-Dreifuss Muscular Dystrophy, restrictive dermopathy, Hutchinson Gilford progeria, mandibuloacral dysplasia, limb girdle muscular dystrophy and dilated cardiomyopathy.

30. If testing highlights a condition that is very different from that being tested for, please outline your strategy for dealing with this situation.

The chance of finding a LMNA gene mutation predisposing to dilated cardiomyopathy is small. Following discussion with our Lead Clinical Geneticist for Cardiac disorders we have agreed that if this scenario arises we will convene an expert group to discuss whether and how to report such a result. This possibility is mentioned in the information for users that is available on our website.

31. If a panel test, is this replacing an existing panel/multi gene test and/or other tests currently carried out through UKGTN using Sanger sequencing? If so, please provide details below.

No; Sanger sequencing of individual monogenic genes currently available will still be offered to clinicians as requested.

32. Please describe any specific ethical, legal or social issues with this particular test.

None

IS IT A REASONABLE COST TO THE PUBLIC?

33. In order to establish the potential costs/savings that could be realised in the diagnostic care pathway, please list the tests/procedures that would be required in the index case to make a diagnosis if this genetic test was not available.

<table>
<thead>
<tr>
<th>Type of test</th>
<th>Cost (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs and type of imaging procedures</td>
<td></td>
</tr>
<tr>
<td>Costs and types of laboratory pathology tests</td>
<td></td>
</tr>
<tr>
<td>(other than molecular/cyto genetic test proposed in this Gene Dossier)</td>
<td></td>
</tr>
<tr>
<td>Costs and types of physiological tests (e.g. ECG)</td>
<td></td>
</tr>
<tr>
<td>Cost and types of other investigations/procedures (e.g. biopsy)</td>
<td></td>
</tr>
<tr>
<td>Total cost of tests/procedures no longer required (please write n/a if the genetic test does not replace any other tests procedures in the diagnostic care pathway)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
34. Based on the expected annual activity of index cases (Q14), please calculate the estimated annual savings/investments based on information provided in Q33.

Without any tests being stopped in the diagnostic pathway the investment to provide this test would be approx. £95,000 based on average of 100 at £300 and 100 at £650. However testing for all the genes, with exception of two, is already available as single/multi gene tests and therefore assume that it is cost neutral to introduce this test.

| Number of index cases expected annually | (a) |
| Cost to provide tests for index cases if the genetic test in this Gene Dossier was not available (see Q32) | (b) |
| Total annual costs pre genetic test | (a) x (b) = (c) |
| Total annual costs to provide genetic test | (a) x cost of genetic testing for index case = (d) |
| Additional savings/investment for 100% positive rate for index cases | (d) – (c) = (e) |
| Percentage of index cases estimated to be negative | (f) |
| Number of index cases estimated to be negative | (f) x number of index cases = (g) |
| Costs to provide additional tests for index cases testing negative | (g) x (b) = (h) |
| Total costs for tests for index patient activity | (e) + (h) = (i) |
| Total costs for family members | Costs for family member test x number of family members expected to test in a year (j) |
| If there is a genetic test already available and some of the family testing is already being provided, please advise the cost of the family testing already available | Cost for family member testing already available x estimated number of tests for family members already provided (k) |
| Total costs for family members minus any family member testing costs already provided | (j) – (k) = (l) |
| Additional costs/savings for all activity expected in a year | (i) + (j) or (i) + (l) Cost neutral |

35. REAL LIFE CASE STUDY
Please provide a case study that illustrates the benefits of this test

“Novel diabetes therapy paves way for personalised medicine for all” The Times June 2008
http://www.thetimes.co.uk/tto/health/article1881329.ece:

Schnyder et al 2005 Swiss Med Wkly 135:352-356: This article describes the impact of making a genetic diagnosis for GCK MODY on the diabetes treatment and management in a five year old misdiagnosed with type 1 diabetes. The diagnosis of GCK MODY enabled discontinuation of her insulin regime without the need for regular blood glucose monitoring. This also removed her risk of hypoglycaemia. GCK MODY was also confirmed in her mother and she was able to discontinue her oral glucose lowering drug regime without any deterioration in her glycaemic control.

HNF1A MODY case study

The proband was diagnosed with diabetes aged 15 years after repeated UTI and the finding of glycosuria. She was treated with sulphonylurea for 10 years and transferred to insulin treatment at the age of 25 years during her first pregnancy. She remained on insulin after the birth of her second child and was put on a basal-bolus regimen. Her BMI was 26 and her most recent HbA1c was 7.4%.
She had performed home blood glucose checks of her two children and found random glucose of 9.8mmol in her 7 year old daughter and 5-6mmol in her five year old son.

The proband’s father was diagnosed with diabetes aged 22 years during an army medical examination. Glycosuria was identified but he was asymptomatic. He was treated with metformin for 30 years and then transferred to insulin following a viral infection. His BMI was 24 at age 64 years. His HbA1c was 6.2% on 0.8U/kg/day of insulin.

The proband’s sister was diagnosed with gestational diabetes during her third pregnancy following a steroid injection. Her blood glucose levels remained below 10mmol/L and no treatment was given. Her BMI was 27.

The proband’s nephew was diagnosed with type 1 diabetes aged 11 years. He presented with weight loss, abdominal pains and osmotic symptoms. His blood glucose at presentation was 19.6mmol/L and he had ketones in his urine. Insulin treatment was started immediately.

MODY genetic testing was performed on the proband as she met criteria for MODY testing of young onset, non-insulin dependence and had a parent with diabetes. A pathogenic HNF1A missense mutation was identified, confirming a diagnosis of HNF1A MODY. She was able to transfer off insulin onto Gliclazide (80mg pre-breakfast and 40mg pre-evening meal). Home blood glucose monitoring results were 5-10mmol/L and HbA1c remained stable at 7.4% three months after transfer. There was less fluctuation in her blood glucose and her BMI reduced from 26 to 24 as she did not need to eat frequently to avoid hypoglycaemia. She described the impact of changing treatment:

‘Taking insulin was something that was always at the front of my mind. I was constantly worrying about having a hypo whilst being out and injecting four times a day was painful 90% of the time. Injecting was like a cloud hanging over me. Being on tablets has given me a new lease of life and I feel a great
burden has been lifted off my shoulders. I really do feel like a different person. My tests are far more stable than they ever were on insulin. Being on tablets is a dream come true.’

The proband’s father was also confirmed to have HNF1A MODY, but because of the progressive nature of the disease, transfer to sulphonylurea was unsuccessful and he remained well controlled on insulin.

The proband’s sister underwent an oral glucose tolerance test (OGTT) and an HbA1c, but of which were in the normal range and not diagnostic for diabetes. Her genetic test showed that she had not inherited the HNF1A mutation.

The proband’s nephew was also tested for the HNF1A mutation at the same time as his mother. He also did not have the mutation, and GAD antibody testing performed through the Exeter Molecular Genetics Laboratory was positive, confirming a diagnosis of type 1 diabetes.

The risk of the proband’s children inheriting the HNF1A mutation and developing HNF1A MODY was 50%. The family decided to pursue genetic counselling and predictive testing for their children. OGTT tests were performed which showed that the daughter had asymptomatic diabetes, and the son had a normal OGTT. Genetic testing revealed that both children had inherited the HNF1A mutation. They were referred to their diabetes team for regular follow up and monitoring of their HbA1c levels.

**TESTING CRITERIA**

36. Please only complete this question if there is previously approved Testing Criteria. Please contact the UKGTN office if you are unsure whether testing criteria is available.

N/A

36a. Do you agree with the previously approved Testing Criteria? Yes/No

36b. If you do not agree, please provide revised Testing Criteria on the Testing Criteria form and explain below the reasons for the changes.
# UKGTN Testing Criteria

**Test name:**
Monogenic Diabetes 14 Gene Panel

<table>
<thead>
<tr>
<th>Approved name and symbol of disorder/condition(s):</th>
<th>OMIM number(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panel Test; see appendix 1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approved name and symbol of gene(s):</th>
<th>OMIM number(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panel Test; see appendix 1</td>
<td></td>
</tr>
</tbody>
</table>

**Patient name:**

**Date of birth:**

**Patient postcode:**

**NHS number:**

**Name of referrer:**

**Title/Position:**

**Lab ID:**

**Referrals will only be accepted from one of the following:**

<table>
<thead>
<tr>
<th>Referrer</th>
<th>Tick if this refers to you.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant Clinical Geneticists</td>
<td></td>
</tr>
<tr>
<td>Consultant Paediatricians</td>
<td></td>
</tr>
<tr>
<td>Consultants in Endocrinology &amp; Diabetes</td>
<td></td>
</tr>
<tr>
<td>Consultants in General Medicine</td>
<td></td>
</tr>
<tr>
<td>Consultant Biochemists</td>
<td></td>
</tr>
<tr>
<td>Consultant Nephrologists</td>
<td></td>
</tr>
<tr>
<td>GP Principal in liaison with genetic diabetic nurses</td>
<td></td>
</tr>
</tbody>
</table>

**Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Tick if this patient meets criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum two generation family history of diabetes with at least one individual diagnosed under the age of 35 years with negative GAD and IA2 autoantibodies and detectable C-peptide OR</td>
<td></td>
</tr>
<tr>
<td>High risk of MODY based on MODY calculator [<a href="http://www.diabetesgenes.org/content/mody-probability-calculator">http://www.diabetesgenes.org/content/mody-probability-calculator</a>]</td>
<td></td>
</tr>
</tbody>
</table>

**Additional Information:**

At risk family members where familial mutation is known do not require a full panel test but should be offered analysis of the known mutation.

For **GCK** mutation testing in at risk family members: A fasting blood glucose and HbA1c test is required prior to genetic testing.

For other MODY sub-types: HbA1c test is required prior to genetic testing.

If the sample does not fulfil the clinical criteria or you are not one of the specified types of referrer and you still feel that testing should be performed please contact the laboratory to discuss testing of the sample.

**Approval Date:** Sept 2014

**Submitting Laboratory:** Exeter RGC

**Copyright UKGTN © 2014**
## Appendix 1

Genes in panel test and associated conditions.

Highlighted rows indicate genes that were being fully analysed in the context of a single separate UKGTN test when the gene dossier was submitted for evaluation.

<table>
<thead>
<tr>
<th>HGNC standard name and symbol of the gene</th>
<th>HGNC number</th>
<th>OMIM number</th>
<th>OMIM standard name of condition and symbol</th>
<th>Mode of inheritance</th>
<th>OMIM number</th>
<th>Evidence of association between gene(s) and condition</th>
<th>% of horizontal coverage of gene</th>
<th>MLPA</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP-binding cassette, sub-family C (CFTR/MRP), member 8 (ABCC8)</td>
<td>59</td>
<td>*600509</td>
<td>DIABETES MELLITUS, NONINSULIN-DEPENDENT; NIDDM</td>
<td>Autosomal Dominant</td>
<td>#125853</td>
<td>Bowman et al 2012 Diabetologia 55, 123-127</td>
<td>100% of coding region and -50/+10 of flanking intronic sequence</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>GATA binding protein 6 (GATA6)</td>
<td>4174</td>
<td>*601656</td>
<td>PANCREATIC AGENESIS AND CONGENITAL HEART DEFECTS; PACHD</td>
<td>Autosomal Dominant</td>
<td>#600001</td>
<td>Lango Allen et al 2011 Nat Genet 44, 20-22</td>
<td>100% of coding region and -50/+10 of flanking intronic sequence</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Glucokinase (GCK)</td>
<td>4195</td>
<td>*138079</td>
<td>MATURITY-ONSET DIABETES OF THE YOUNG, TYPE 2; MODY2</td>
<td>Autosomal Dominant</td>
<td>#125851</td>
<td>Vionnet et al 1992 Nature 356, 721-722</td>
<td>100% of coding region and -50/+10 of flanking intronic sequence</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>HNF1 homeobox A (HNF1A)</td>
<td>11621</td>
<td>*142410</td>
<td>MATURITY-ONSET DIABETES OF THE YOUNG, TYPE 3; MODY3</td>
<td>Autosomal Dominant</td>
<td>#600496</td>
<td>Yamagata et al 1996 Nature 384, 455-458</td>
<td>100% of coding region and -50/+10 of flanking intronic sequence</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Gene Name</td>
<td>Gene ID</td>
<td>Transcript ID</td>
<td>Gene Symbol</td>
<td>Coding Region</td>
<td>Flanking Intronic Sequence</td>
<td>Maturity-Onset Diabetes of the Young</td>
<td>Type 1; MODY1</td>
<td>Maturity-Onset Diabetes of the Young</td>
<td>Type 10; MODY10</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------</td>
<td>---------------</td>
<td>-------------</td>
<td>---------------</td>
<td>-----------------------------</td>
<td>---------------------------------------</td>
<td>-------------</td>
<td>-------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Colclough et al 2013 Hum Mutat 34, 669-685</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNF1 homeobox B (HNF1B)</td>
<td>11630</td>
<td>*189907</td>
<td>HNF1B</td>
<td>Autosomal Dominant</td>
<td>#137920</td>
<td>Horikawa et al 1997 Nat Genet 17, 384-385</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (INS)</td>
<td>6081</td>
<td>+176730</td>
<td>INS</td>
<td>Autosomal Dominant</td>
<td>#613370</td>
<td>Edghill et al 2008 Diabetes 57, 1034-1042</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin receptor (INSR)</td>
<td>6091</td>
<td>*147670</td>
<td>INSR</td>
<td>Autosomal Dominant</td>
<td>#610549</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>potassium inwardly-rectifying channel, subfamily J, member 11</td>
<td>6257</td>
<td>*600937</td>
<td>Not Assigned</td>
<td>Autosomal Dominant</td>
<td>Not Assigned (requested)</td>
<td>Yorifuji et al 2005 J Clin Endocrinol Metab 90, 3174-3178</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene (KCNJ11)</td>
<td>Allele</td>
<td>Condition</td>
<td>Description</td>
<td>Reference</td>
<td>Coverage</td>
<td>Flanking Intronic Sequence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>--------</td>
<td>------------</td>
<td>-------------</td>
<td>-----------</td>
<td>----------</td>
<td>---------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lamin A/C (LMNA)</td>
<td>6636 *150330</td>
<td>LIPODYSTROPHY, FAMILIAL PARTIAL, TYPE 2; FPLD2</td>
<td>Autosomal Dominant</td>
<td>Bonnefond <em>et al</em> 2012 PLoS One 7, e37423</td>
<td>100% of coding region and -50/+10 of flanking intronic sequence</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mitochondrially encoded tRNA leucine 1 m.3243A&gt;G (MTTL1)</td>
<td>7490 *590050</td>
<td>DIABETES AND DEAFNESS, MATERNALLY INHERITED; MIDD</td>
<td>Mitochondrial</td>
<td>Shackleton <em>et al</em> 2000 Nat Genet 24, 153-156</td>
<td>N/A but 100% coverage of captured sequence</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neuronal differentiation 1 (NEUROD1)</td>
<td>7762 *601724</td>
<td>MATURITY-ONSET DIABETES OF THE YOUNG, TYPE 6; MODY6</td>
<td>Autosomal Dominant</td>
<td>Malecki <em>et al</em> 1999 Nat Genet 23, 323-328</td>
<td>100% of coding region and -50/+10 of flanking intronic sequence</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pancreatic and duodenal homeobox 1 (PDX1)</td>
<td>6107 *600733</td>
<td>MATURITY-ONSET DIABETES OF THE YOUNG, TYPE 4; MODY4</td>
<td>Autosomal Dominant</td>
<td>Stoffers <em>et al</em> 1997 Nat Genet 17, 138-139</td>
<td>100% of coding region and -50/+10 of flanking intronic sequence</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>peroxisome proliferator-activated receptor gamma (PPARG)</td>
<td>9236 *601487</td>
<td>LIPODYSTROPHY, FAMILIAL PARTIAL, TYPE 3; FPLD3</td>
<td>Autosomal Dominant</td>
<td>Agarwal <em>et al</em> 2002 J Clin Endocrinol Metab 1, 408-411</td>
<td>100% of coding region and -50/+10 of flanking intronic sequence</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>