Test Information (20150803)

Gene: *ABCD1*

Condition	X-linked adrenoleukodystrophy (OMIM#300100)
Mode of inheritance	● X-linked recessive ● Carrier females can develop mild adrenomyeloneuropathy-like symptoms
Useful investigations	Very long-chain fatty acid analysis
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test ● Prenatal diagnosis
Genotype-phenotype correlation	Widely varying phenotypes often co-occur in a single family
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	● ~99% for male patients ● ~90% for female patients
Turnaround time	● Index cases: 6 – 8 weeks ● Cascade screening: 6 – 8 weeks

Gene: *ABCG5*

Condition	Sitosterolaemia (or Phytosterolaemia) (OMIM#210250)
Mode of inheritance	Autosomal recessive
Useful investigations	Plant sterol analysis
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	● In patients with a definite biochemical diagnosis but no *ABCG5* mutations, mutation analysis of the *ABCG8* gene should be considered.
Turnaround time	● Index cases: 8 – 10 weeks ● Cascade screening: 6 – 8 weeks

Gene: *AR* (NEW)

Condition	● Androgen insensitivity syndrome; AIS (OMIM#300068) ● Androgen insensitivity syndrome, partial; PAIS (OMIM#312300)
Mode of inheritance	X-linked recessive
Useful investigations	Karyotyping, hormonal investigations, ultrasound pelvis
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test ● Prenatal diagnosis
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	● CAIS: 65%-95% ● PAIS: <50%
Turnaround time	● Index cases: 8 – 10 weeks ● Cascade screening: 6 – 8 weeks

Gene: *ATP7B*

Condition	Wilson disease (OMIM#277900)
Mode of inheritance	Autosomal recessive
Useful investigations	Caeruloplasmin, serum copper and 24-hrs urine copper, Kayser-Fleischer ring
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	● Tier 1: sequence analysis of exons 2, 8, 12, 13 and 16 ● Tier 2: sequence analysis of exons 1, 3-7, 9-11, 14, 15, 17-21
Clinical sensitivity of test method	● Tier 1: detects at least 70% of mutant alleles in Chinese patients ● Combined Tier 1 and Tier 2: ~98%
Turnaround time	● Index cases: 6 weeks for each tier of testing. Priority

	would be given to patients who present with acute liver failure where genetic testing results could help determine if liver transplantation is indicated. ● Cascade screening: 6 – 8 weeks

Gene: *CASR*

Condition	● Familial hypocalciuric hypercalcaemia type 1; FHH1 (OMIM#145980) ● Neonatal severe hyperparathyroidism; NSHPT (OMIM#239200) ● Autosomal dominant hypocalcaemia (OMIM#146200)
Mode of inheritance	● Autosomal dominant for FHH1 and autosomal dominant hypocalcaemia ● Autosomal recessive for NSHPT
Useful investigations	Ionized calcium, bone profile, parathyroid hormone, urine calcium to creatinine ratio
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen for NSHPT ● Predictive test
Genotype-phenotype correlation	● FHH1 and NSHPT are caused by inactivating *CASR* mutations. ● Autosomal dominant hypocalcaemia is caused by activating *CASR* mutations.
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	● Approximately 65% of FHH patients have FHH1 (caused by inactivating *CASR* mutations). ● FHH2 is caused by inactivating *GNA11* mutations. ● FHH3 is caused by *AP2S1* mutations.
Turnaround time	● Index cases: 8 – 10 weeks. Priority would be given to neonates and infants with severe hypocalcaemia suspected to have NSHPT. ● Cascade screening: 6 – 8 weeks

Gene: *CYP21A2* (CAH)

Condition	Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (OMIM#201910)
Mode of inheritance	Autosomal recessive
Useful investigations	17-hydroxyprogesterone, urine steroid profile
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test ● Prenatal diagnosis
Genotype-phenotype correlation	Genotype can be used to predict disease severity
Testing methods	● Sequence analysis of the entire coding region ● *CYP21A2* gene dosage analysis by MLPA
Clinical sensitivity of test method	~97%
Turnaround time	● Index cases: 8 – 12 weeks ● Cascade screening: 6 – 8 weeks

Gene: *GCH1*

Condition	Dopa-responsive dystonia (OMIM#128230)
Mode of inheritance	Autosomal dominant with reduced penetrance
Useful investigations	Therapeutic trial with L-dopa
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test
Genotype-phenotype correlation	● Penetrance is higher in females (87 – 100%) than in males (35 – 55%). ● Mutation analysis results cannot predict the occurrence of symptoms, or if they do occur, the age of onset, severity, type of symptoms or rate of disease progression.
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	~60%
Turnaround time	● Index cases: 6 – 8 weeks ● Cascade screening: 6 – 8 weeks

Gene: *GCK*

Condition	Maturity-onset diabetes of the young type 2 or MODY subtype

	GCK (OMIM#125851)
Mode of inheritance	Autosomal dominant
Useful investigations	● Mild fasting hyperglycaemia, non-progressive ● HbA1C just above the upper limit of normal ● Small glucose increment (< 4.6 mmol/L) in OGTT ● No diabetic complications
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region and promoter region
Clinical sensitivity of test method	● Whole gene sequencing has a high analytical sensitivity for detection of *GCK* mutations (probably >97%) ● MODY subtype GCK is rare among patients fulfilling the minimum criteria for MODY
Turnaround time	● Index cases: 8 – 10 weeks ● Cascade screening: 6 – 8 weeks

Gene: *HNF1A*

Condition	Maturity-onset diabetes of the young type 3 or MODY subtype HNF1A (OMIM#600496)
Mode of inheritance	Autosomal dominant
Useful investigations	The clinical features of *HNF1A*/*4A* phenotype can overlap with type 1 diabetes. Studies of patients diagnosed with type 1 diabetes who have an affected first degree relative have found *HNF1A* mutations in 5 – 10% of patients depending upon additional selective criteria such as non-high-risk HLA haplotype, negative autoantibody status, or three generations of diabetes. Type 2 diabetes is historically a disease that affect people in middle to later life but increasing number of patients are being diagnosed earlier, even in childhood. A diagnosis of MODY should be suspected in young-onset apparent type 2 diabetes cases when there is no obesity or features associated with the metabolic syndrome. (Ellard and Colclough. Hum Mutat 2006;27:854-869.)
Clinical indications for genetic testing	● Confirmation of diagnosis

	● Predictive test
Genotype-phenotype correlation	The average age at diagnosis for patients with mutations in exons 1 – 6 is younger than those with mutations in exons 8 – 10.
Testing methods	Sequence analysis of the entire coding region and promoter region
Clinical sensitivity of test method	● Whole gene sequencing has a high analytical sensitivity for detection of *HNF1A* mutations (probably >93%) ● MODY subtype *HNF1A* is the most common form of MODY
Turnaround time	● Index cases: 8 – 10 weeks ● Cascade screening: 6 – 8 weeks

Gene: *HNF4A*

Condition	Maturity-onset diabetes of the young 1 or MODY subtype HNF4A (OMIM#125850)
Mode of inheritance	Autosomal dominant
Useful investigations	The clinical features of *HNF1A/4A* phenotype can overlap with type 1 diabetes. Studies of patients diagnosed with type 1 diabetes who have an affected first degree relative have found *HNF1A* mutations in 5 – 10% of patients depending upon additional selective criteria such as non-high-risk HLA haplotype, negative autoantibody status, or three generations of diabetes. Type 2 diabetes is historically a disease that affect people in middle to later life but increasing number of patients are being diagnosed earlier, even in childhood. A diagnosis of MODY should be suspected in young-onset apparent type 2 diabetes cases when there is no obesity or features associated with the metabolic syndrome. (Ellard and Colclough. Hum Mutat 2006;27:854-869.)
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region plus the pancreatic-specific promoter region
Clinical sensitivity of test method	● Whole gene sequencing has a high analytical sensitivity

	for detection of *HNF4A* mutations (probably >97%) ● MODY subtype HNF4A is very rare among patients fulfilling the minimum criteria for MODY
Turnaround time	● Index cases: 8 – 10 weeks ● Cascade screening: 6 – 8 weeks

Condition: Kennedy disease

Condition	Spinal and bulbar muscular atrophy, X-linked (SBMA, SMAX1) (OMIM#313200)
Mode of inheritance	X-linked recessive
Useful investigations	Electrophysiological studies, plasma creatine kinase
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test
Genotype-phenotype correlation	In general, the age of disease onset correlates with the number of CAG repeats. However, individuals from the same family with identical number of CAG repeats may have considerably different disease courses.
Testing methods	CAG repeat number in exon 1 of the *AR* (androgen receptor) gene by fluorescent fragment analysis and sequence analysis
Clinical sensitivity of test method	100%
Remark	Repeat testing with a second blood sample is required for predictive testing
Turnaround time	● Index cases: 6 – 8 weeks ● Cascade screening: 6 – 8 weeks

Gene: *MEN1*

Condition	Multiple endocrine neoplasia type 1 (OMIM#131100)
Mode of inheritance	Autosomal dominant
Useful investigations	● Endocrine tumors (e.g. parathyroid, anterior pituitary, gastro-entero-pancreatic tract, carcinoid, adrenal cortex) ● Non-endocrine tumors (e.g. angiofibromas and collagenomas, lipomas, meningioma, leiomyoma)
Clinical indications for genetic testing	● Confirmation of diagnosis

	● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	● Familial cases: ~90% ● Simplex cases: ~65%
Remark	Repeat testing with a second blood sample is required for predictive testing
Turnaround time	● Index cases: 6 – 8 weeks ● Cascade screening: 6 – 8 weeks

Gene: *OTC*

Condition	Ornithine transcarbamylase deficiency (OMIM#311250)
Mode of inheritance	● X-linked recessive ● Carrier females can develop symptoms
Useful investigations	● Plasma ammonia ● Urine organic acid analysis (elevation of orotic acid) ● Plasma amino acid analysis
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test ● Prenatal diagnosis
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	Only about 80% of patients with enzymatically proven OTC deficiency are found to have mutations in the OTC gene. For patients with clinical and biochemical features of OTC deficiency but no *OTC* mutation, enzymatic analysis may be considered to confirm the diagnosis.
Turnaround time	● Index cases: 6 – 8 weeks ● Cascade screening: 6 – 8 weeks

Gene: *PAH*

Condition	Phenylketonuria (OMIM#261600)
Mode of inheritance	Autosomal recessive

Useful investigations	Plasma amino acids
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test ● Prenatal diagnosis
Genotype-phenotype correlation	● The severity of phenylalanine hydroxylase deficiency can, in most of the cases, be predicted from the knowledge of the severity of both mutations. ● Genotype is also clinically relevant for an assessment of possible BH4 cofactor sensitivity. However, genotyping should be combined with a BH4-loading test for definitive diagnosis of cofactor sensitivity.
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	>98%
Turnaround time	● Index cases: 8 – 10 weeks ● Cascade screening: 6 – 8 weeks

Gene: *PHEX*

Condition	X-linked hypophosphataemia (OMIM#307800)
Mode of inheritance	X-linked dominant
Useful investigations	● Plasma/serum phosphate, calcium, parathyroid hormone, 25(OH) vitamin D ● Urine phosphate (TmP/GFR), calcium ● Exclude hypercalciuria, Fanconi syndrome (e.g. glycosuria, bicarbonaturia, proteinuria, or amino aciduria)
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	Analytical sensitivity is approximately 60%. The remaining mutations are exonic or whole gene deletions, which require additional analysis such as MLPA. The combined mutation detection rate approaches 100%.
Turnaround time	● Index cases: 10 – 12 weeks ● Cascade screening: 6 – 8 weeks

Gene: *PKD1* (NEW)

Condition	Autosomal dominant polycystic kidney disease (ADPKD)
Mode of inheritance	Autosomal dominant
Useful investigations	Ultrasound kidney
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test
Genotype-phenotype correlation	*PKD1* truncating mutations (i.e. frameshift, nonsense, splice mutation, and large rearrangements) are shown to correlate with poorer renal outcome. The average age at onset of ESRD in affected individuals with truncating *PKD1* pathogenic variants was 55.6 years compared to 67.9 years for those with non-truncating variants (i.e. in-frame deletions or insertions and missense mutations). However, using *PKD1* mutation type (truncating vs non-truncating) alone to predict renal outcome can be misleading. Reference: J Am Soc Nephrol. 2013;24(6):1006-13.
Testing methods	Sequence analysis of the entire coding region by next-generation sequencing ± Sanger sequencing
Clinical sensitivity of test method	Analytical sensitivity is > 95%. The proportion of *PKD1* large rearrangements is < 1%. Another causative gene for ADPKD is PKD2. In mutation-positive patients, approximately 85% are caused by mutations in *PKD1* while the remaining 15% are caused by mutations in *PKD2*. Approximately 7% to 9% of individuals who undergo comprehensive mutation screening of *PKD1* and *PKD2* have no pathogenic variant identified.
Turnaround time	● Index cases: 14 – 18 weeks ● Cascade screening: 6 – 8 weeks

Gene: *POLG*

Condition	Alpers syndrome and other POLG-related disorders (OMIM#203700)
Mode of inheritance	Autosomal recessive or Autosomal dominant
Useful investigations	-

Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test ● Prenatal diagnosis
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	Analytical sensitivity is > 95%
Turnaround time	● Index cases: 10 – 12 weeks ● Cascade screening: 6 – 8 weeks

Gene: *PRRT2*

Condition	● Paroxysmal kinesigenic dyskinesia; PKD (OMIM#128200) ● Infantile convulsions and paroxysmal choreoathetosis, familial; ICCA syndrome (OMIM#602066) ● Benign familial infantile convulsions 2; BFIC2 (OMIM#605751)
Mode of inheritance	Autosomal dominant
Useful investigations	-
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	Not determined, probably > 95%
Turnaround time	● Index cases: 8 – 10 weeks ● Cascade screening: 6 – 8 weeks

Gene: *RET*

Condition	Multiple endocrine neoplasia type 2 (OMIM#171400, #162300)
Mode of inheritance	Autosomal dominant
Useful investigations	Serum calcitonin, urine catecholamines
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test
Genotype-phenotype correlation	● Refer to the Revised American Thyroid Association

	Guidelines for the Management of Medullary Thyroid Carcinoma. Thyroid 2015
Testing methods	● Tier 1: sequence analysis of *RET* exons 10, 11, 13, 14, 15 and 16 ● Tier 2: sequence analysis of *RET* exons 1 – 9, 12, 17- 20
Clinical sensitivity of test method	● Tier 1 test: 98% for MEN2A and MEN2B, 95% for FMTC ● Tier 1 and Tier 2 tests combined: > 98% for MEN2A and MEN2B, > 95% for FMTC
Remark	Repeat testing with a second blood sample is required for predictive testing
Turnaround time	● Index cases: ■ Tier 1 test: 6 – 8 weeks ■ Tier 2 test: 8 – 10 weeks ● Cascade screening: 6 – 8 weeks

Gene: *SCN1A*

Condition	● Dravet syndrome (OMIM#607208) ● Generalized epilepsy with febrile seizure plus (GEFS+, OMIM#604403)
Mode of inheritance	● Approximately 90% of Dravet syndrome is sporadic. The remaining 10% are inherited from either parent in an autosomal dominant manner. ● GEFS+ is an autosomal dominant disorder with reduced penetrance.
Useful investigations	● The initial EEGs are often normal, but over time epileptiform activity appears. ● Normal MRI brain
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test ● Prenatal diagnosis
Genotype-phenotype correlation	● Dravet syndrome is caused by loss-of-function mutations in the *SCN1A* gene. All types of mutations (such as missense, truncation, splice site and gross deletion) have been described. ● GEFS+ is caused by missense mutations in the *SCN1A* gene.

Testing methods	● Sequence analysis of the entire coding region ● *SCN1A* gene dosage analysis by MLPA
Clinical sensitivity of test method	● Sequence analysis has an analytical sensitivity of ~95%. The remaining 5% of *SCN1A* mutations are exonic or whole-gene deletions, which are not detected by sequence analysis. ● For patients who meet the diagnostic criteria for Dravet syndrome, the mutation detection rate is >80%.
Turnaround time	● Index cases: 10 – 12 weeks ● Cascade screening: 6 – 8 weeks

Gene: *SDHB*

Condition	Familial paragangliomas 4 (OMIM#115310)
Mode of inheritance	Autosomal dominant
Useful investigations	Catecholamines and metanephrines, radiological investigations
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	● Sequence analysis of the entire coding region ● *SDHB* gene dosage analysis by MLPA
Clinical sensitivity of test method	● Combined sequence analysis and MLPA is expected to have high analytical sensitivity for *SDHB*/*C*/*D* mutations. ● Approximately 70% of familial head and neck paragangliomas are believed to be caused by germline mutations in one of the *SDHB*/*C*/*D* genes. ● A mutation in one of the *SDHB*/*C*/*D* genes may be present in 40% of individuals with sporadic head and neck paragangliomas and at least 10% of individuals with extra-adrenal sympathetic paragangliomas and phaeochromocytomas. ● Approximately 25% of apparently sporadic phaeochromocytoma are caused by germline mutations in one of the following genes: *NF1*, *VHL*, *RET*, *SDHB* and *SDHD*.
Remark	Repeat testing with a second blood sample is required for

	predictive testing
Turnaround time	● Index cases: 6 – 8 weeks ● Cascade screening: 6 – 8 weeks

Gene: *SDHC*

Condition	Familial paragangliomas 3 (OMIM#605373)
Mode of inheritance	Autosomal dominant
Useful investigations	Catecholamines and metanephrines, radiological investigations
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	● Sequence analysis of the entire coding region ● *SDHC* gene dosage analysis by MLPA
Clinical sensitivity of test method	● Combined sequence analysis and MLPA is expected to have high analytical sensitivity for *SDHB*/*C*/*D* mutations. ● Approximately 70% of familial head and neck paragangliomas are believed to be caused by germline mutations in one of the *SDHB*/*C*/*D* genes. ● A mutation in one of the *SDHB*/*C*/*D* genes may be present in 40% of individuals with sporadic head and neck paragangliomas and at least 10% of individuals with extra-adrenal sympathetic paragangliomas and phaeochromocytomas. ● Approximately 25% of apparently sporadic phaeochromocytoma are caused by germline mutations in one of the following genes: *NF1*, *VHL*, *RET*, *SDHB* and *SDHD*.
Remark	Repeat testing with a second blood sample is required for predictive testing
Turnaround time	● Index cases: 6 – 8 weeks ● Cascade screening: 6 – 8 weeks

Gene: *SDHD*

Condition	Familial paragangliomas 1 (OMIM#168000)
Mode of inheritance	Autosomal dominant with parent of origin effect. An individual who inherits a SDHD mutation from his/her mother has a low but not negligible risk of developing disease. An individual who inherits an SDHD mutation from his/her father is at high risk of manifesting paragangliomas and, to a lesser extent, phaeochromocytoma.
Useful investigations	Catecholamines and metanephrines, radiological investigations
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	● Sequence analysis of the entire coding region ● *SDHD* gene dosage analysis by MLPA
Clinical sensitivity of test method	● Combined sequence analysis and MLPA is expected to have high analytical sensitivity for *SDHB*/*C*/*D* mutations. ● Approximately 70% of familial head and neck paragangliomas are believed to be caused by germline mutations in one of the *SDHB*/*C*/*D* genes. ● A mutation in one of the *SDHB*/*C*/*D* genes may be present in 40% of individuals with sporadic head and neck paragangliomas and at least 10% of individuals with extra-adrenal sympathetic paragangliomas and phaeochromocytomas. ● Approximately 25% of apparently sporadic phaeochromocytoma are caused by germline mutations in one of the following genes: *NF1*, *VHL*, *RET*, *SDHB* and *SDHD*.
Remark	Repeat testing with a second blood sample is required for predictive testing
Turnaround time	● Index cases: 6 – 8 weeks ● Cascade screening: 6 – 8 weeks

Gene: *SLC22A5* (NEW)

Condition	Carnitine update defect (OMIM#212140)
Mode of inheritance	Autosomal recessive

Useful investigations	Serum acylcarnitine profile and urine metabolic screen
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	The mutation detection sensitivity of sequence analysis is approximately 70%. This method does not detect gross deletions / duplications and mutations located in deep intronic or promoter regions.
Turnaround time	● Index cases: 6 – 8 weeks ● Cascade screening: 6 – 8 weeks

Gene: *SLC25A13* (Citrin)

Condition	● Neonatal intrahepatic cholestasis caused by citrin deficiency; NICCD (OMIM#605814) ● Adult-onset citrullinaemia type II; CTLN2 (OMIM#603471)
Mode of inheritance	Autosomal recessive
Useful investigations	Plasma amino acids, alpha-fetal protein
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	● Tier 1: sequence analysis of exons 1, 6, 7, 9, 11, 14, 16, 17 plus screening test for IVS16ins3kb ● Tier 2: sequence analysis of the remaining exons
Clinical sensitivity of test method	● Tier 1 test detects 92% mutant alleles reported in Chinese patients. ● The overall mutation detection sensitivity of combined Tier 1 and Tier 2 tests is 95%
Turnaround time	● Index cases: ■ Tier 1: 8 – 10 weeks ■ Tier 2: 10 – 12 weeks ● Cascade screening: 6 – 8 weeks

Gene: *SLC25A20* (CACT)

Condition	Carnitine-acylcarnitine translocase deficiency (OMIM#212138)
Mode of inheritance	Autosomal recessive
Useful investigations	Plasma acylcarnitine profile
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test ● Prenatal diagnosis
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	Not determined, probably > 97%
Turnaround time	● Index cases: 6 – 8 weeks. Priority would be given to sudden death cases. ● Cascade screening: 6 – 8 weeks

Gene: *SMN1* MLPA (SMA)

Condition	Spinal muscular atrophy (OMIM#253300, 253550, 253400, 271150)
Mode of inheritance	Autosomal recessive
Useful investigations	Electrophysiological studies
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test ● Prenatal diagnosis
Genotype-phenotype correlation	Nil
Testing methods	Dosage analysis of *SMN1* by MLPA
Clinical sensitivity of test method	● ~95%for symptomatic patients ● ~91% for carrier screening
Turnaround time	● Index cases: 8 – 10 weeks ● Cascade screening: 8 – 10 weeks

Gene: SRD5A2 (NEW)

Condition	5-alpha reductase deficiency (OMIM#264600)
Mode of inheritance	Autosomal recessive
Useful investigations	Urine steroid profile
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Prenatal diagnosis
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	~90%
Turnaround time	● Index cases: 6 – 8 weeks ● Cascade screening: 6 – 8 weeks

Gene: *TCIRG1*

Condition	Osteopetrosis, autosomal recessive 1 (OMIM#259700)
Mode of inheritance	Autosomal recessive
Useful investigations	● Early diagnosis (before 2 years old) ● High bone mineral density ● Bone marrow failure with consequent pancytopaenia ● Hepatosplenomegaly ● Neurological defects caused by bony encroachment of cranial nerves (e.g. blindness, deafness and facial palsy) ● Hypocalcaemia ● Growth retardation ● Macrocephaly with frontal bossing ● Hydrocephalus ● Hypogammaglobulinaemia
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Prenatal diagnosis
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region and the non-coding exon 1
Clinical sensitivity of test method	The analytical sensitivity of whole gene sequencing for detection of *TCIRG1* mutations is expected to be > 98%. More than 50% of autosomal recessive osteopetrosis is caused by recessive mutations in the *TCIRG1* gene, which represents

	the most common form. Other causative genes include *CLCN7* and *OSTM1*.
Turnaround time	● Index cases: 10 – 12 weeks ● Cascade screening: 6 – 8 weeks

Gene: *TH*

Condition	Tyrosine hydroxylase deficiency (Segawa syndrome, autosomal recessive) (OMIM#605407)
Mode of inheritance	Autosomal recessive
Useful investigations	CSF neurotransmitters and prolactin
Clinical indications for genetic testing	● Confirmation of diagnosis ● Carrier screen ● Predictive test ● Prenatal diagnosis
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the entire coding region
Clinical sensitivity of test method	Not determined, probably > 97%
Turnaround time	● Index cases: 6 – 8 weeks ● Cascade screening: 6 – 8 weeks

Gene: *THRB* (NEW)

Condition	Thyroid hormone resistance (OMIM#188570)
Mode of inheritance	Autosomal dominant
Useful investigations	Thyroid hormone analysis, TRH stimulation test, alpha subunit
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test
Genotype-phenotype correlation	Nil
Testing methods	Sequence analysis of the ligand-binding domain and adjacent hinge region of the *THRB* gene (NM_001128177.1 exons 9 – 12)
Clinical sensitivity of test method	The analysis method has a sensitivity of >99% in detecting a *THRB* mutation. However, only ~85% of thyroid hormone resistance is caused by *THRB* mutations.
Turnaround time	● Index cases: 8 – 10 weeks

	● Cascade screening: 6 – 8 weeks

Gene: *TOR1A*

Condition	Torsion dystonia type 1, autosomal dominant (DYT1) (OMIM#128100)
Mode of inheritance	Autosomal dominant with reduced penetrance
Useful investigations	Dramatic improvement with L-dopa tends to exclude a diagnosis of DYT1.
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test for adult family members
Genotype-phenotype correlation	Nil
Testing methods	Target analysis for *TOR1A* c.907_909delGAG by bi-directional sequence analysis
Clinical sensitivity of test method	Approximately 22% of early-onset dystonia in Asians are caused by *TOR1A* mutations.
Turnaround time	● Index cases: 6 – 8 weeks ● Cascade screening: 6 – 8 weeks

Gene: *VHL*

Condition	Von Hippel-Lindau syndrome (OMIM#193300)
Mode of inheritance	Autosomal dominant
Useful investigations	Urine catecholamines, imaging studies
Clinical indications for genetic testing	● Confirmation of diagnosis ● Predictive test
Genotype-phenotype correlation	● VHL type 1 is characterized by a low risk for phaeochromocytoma. Truncating mutations or missense mutations that are predicted to grossly disrupt the folding of the VHL protein are associated with VHL type 1. ● VHL type 2 is characterized by a high risk for phaeochromocytoma. Individuals with VHL type 2 invariably have a missense mutation.
Testing methods	● Sequence analysis of the entire coding region ● Dosage analysis by MLPA

Clinical sensitivity of test method	● Sequence analysis: 72% ● MLPA: 28%
Remark	Repeat testing with a second blood sample is required for predictive testing
Turnaround time	● Index cases: 8 – 12 weeks ● Cascade screening: 6 – 8 weeks