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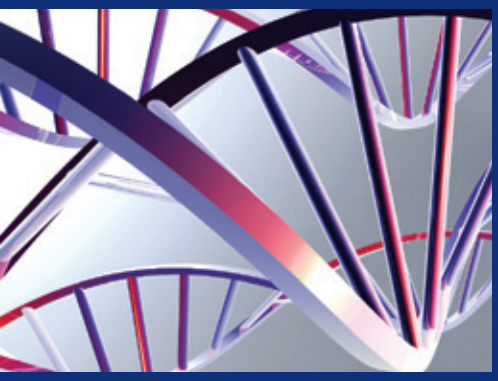

Targeted Gene Panels

Endocrine and Multisystem Disorders

- Maturity Onset Diabetes of the Young (MODY)
- Permanent Neonatal Diabetes (PND)
- Familial Hyperinsulinism (FHI)
- RASopathy Syndromes
- Disorders of Sex Development (DSD)

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Identifying the causative gene mutation can provide a definitive diagnosis and may inform the best course of patient treatment or management. It can also allow for screening of family members for identification and management of disease risk, as well as facilitate reproductive options (only available through a clinical genetic service).

Gene panels include:

Maturity Onset Diabetes of the Young (MODY)

MODY accounts for about 1-2% of people with diabetes.[1] MODY is characterised by early onset (usually before 25 years), negative islet cell antibody testing and pancreatic B-cell dysfunction with impaired insulin secretion.[1]

MODY is an autosomal dominant condition, meaning each child of an affected parent has a 50% chance of inheriting the disease. To date, at least 10 genes, which collectively contain over 800 mutations, have been identified to cause MODY.

MODY can often be treated with oral medication or diet alone. Without genetic testing to detect the specific mutation, MODY is often not recognised. As a result, affected individuals may be assumed to have Type 1 or Type 2 diabetes, and therefore receive unnecessary or inappropriate therapy.[2] Determining the MODY subtype can also provide information about likely disease course and decrease the risk of diabetic complications through improved treatment.[2]

Permanent Neonatal Diabetes (PND)

Neonatal diabetes is a rare monogenic form of diabetes mellitus diagnosed within the first 6 months of life. The condition is caused by reduced amounts of the hormone insulin, resulting in an excess of glucose in the bloodstream (hyperglycaemia). About half of neonatal diabetes cases lead to a lifelong permanent form of the disease. The most common causes are mutations in the genes KCNJ11 or ABCC8, that code for proteins involved in the control of insulin production.[3] Another 20% of cases are due to mutations in the insulin gene itself, INS.[3] In addition, several other genes have been implicated as causative factors, though these are much rarer. The Permanent Neonatal Diabetes gene panel test can help verify what form of neonatal diabetes a patient has, enabling targeted clinical management and preparing parents for long term treatment of the disorder if necessary. Substituting insulin for doses of sulfonylureas in certain forms of permanent neonatal diabetes has been shown to significantly improve diabetes control3, so an accurate early diagnosis can have a large impact on the child's quality of life.[3]

Familial Hyperinsulinism (FHI)

FHI is characterised by low blood glucose levels (hypoglycaemia), caused by genetic mutations leading to inappropriate regulation of the release of insulin from the pancreas. Accurate identification of the causative mutation is important as it provides an indication of potential responsiveness to diazoxide treatment and the requirement for surgery[4].

The majority of cases of FHI are due to mutations in the ABCC8 or KCNJ11 genes, though several other genes may also cause the condition. FHI can present within hours of birth, or may take months or years to emerge. Early genetic diagnosis can guide appropriate management to prevent serious complications[4].

RASopathy Syndromes

'RASopathies' are a range of genetic syndromes caused by mutations in the genes involved in the Ras/mitogen activated protein kinase (MAPK) pathway, that is critical for normal development. The most common RASopathy is Noonan syndrome. Others include LEOPARD syndrome, Cardiofaciocutaneous syndrome, Costello syndrome, Noonan-like syndrome with loose anagen hair and Neurofibromatosis type 1.

The RASopathy syndromes arise from distinct gene mutations and have some phenotypic differences, though many features overlap, including cardiac defects, characteristic facial features, and neurocognitive delay, among others.[5] Early definitive diagnosis with genetic testing allows for surveillance and early intervention for these clinical problems, assisting with specific treatment of disease manifestations and prevention of some complications.[6]

Disorders of Sex Development (DSD)

DSD are variable medical conditions involving development of the reproductive system – either sex determination, or sex differentiation. DSD can present with ambiguous genitalia in early infancy. Up to 1 in 300 infants may require assessment of external genitalia with a risk of DSD, for which genetic testing is recognised as one of the key elements of clinical diagnosis.[7] DSD cases can also present later in life, with delayed puberty in adolescence. Genetic testing can clarify the diagnosis and the aetiology, inform recurrence risks and assist with management of the disorder. Testing also delivers information on adrenal health, germ-line tumour risks, and long-term fertility of the patient.[8]

The genes included for each condition have been selected on the basis of clinical significance by an expert team of genetic pathologists and scientists at Mater Pathology. Our pathologists provide comprehensive interpretation, reporting and advice to referring clinicians utilising the service. The test is performed under strict quality standards within our molecular genetics laboratory and has been accredited for compliance with the international standard for medical testing (ISO:15189), by the National Association of Testing Authorities (NATA).

Accredited for compliance with NPAAC Standards and ISO 15189

Targeted Gene Panels	% of clinical cases in which a mutation is identified*
Maturity Onset Diabetes of the Young (MODY)	
HNF4A (MODY 1), GCK (MODY 2), HNF1A (MODY 3), PDX1 (MODY 4), HNF1B (MODY 5), NEUROD1 (MODY 6), PAX4 (MODY 9), INS (MODY 10), ABCC8 (MODY12), KCNJ11 (MODY13) Note: MLPA testing to detect large deletions/duplications is included for genes HNF4A, GCK, HNF1A andHNF1B.	80-90% of cases
Permanent Neonatal Diabetes (PND)	
ABCC8, EIF2AK3, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, NEUROD1, PDX1	~75% of cases
Familial Hyperinsulinism (FHI)	
ABCC8, GCK, GLUD1, HADH, HNF4A, KCNJ11, SLC16A1, UCP2	60-65% of cases
RASopathy Syndromes	
BRAF, CBL, HRAS, KAT6B, KRAS, MAP2K1, MAP2K2, NF1, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1, SPRED1	75-85% of Noonan syndrome 90-95% of LEOPARD syndrome 98% of Cardiofaciocutaneous syndrome 80-90% of Costello syndrome >60% of Neurofibromatosis 1 >85% Legius syndrome
Disorders of Sex Development (DSD)	
46, XY DSD *Sex Determination: CBX2, DHH, DMRT1, NR5A1 (SF1), SOX9, WT1* *Sex Differentiation: AMH, AMHR2, AR, ARX, CYP11A1, CYP17A1, DHCR7, HSD17B3, HSD3B2, LHCGR, MAMLD1, POR, SRD5A2, STAR, TSPYL1* ***46, XX DSD*** *Sex Determination: RSPO1, SOX9, WNT4* *Sex Differentiation: CYP11B1, CYP19A1, HSD11B1, LHCGR, NR3C1, POR*	50-60% of cases

*Frequencies are estimated from data published in GeneReviews®, Pagon et al (1993-2016)

Note: At Mater Pathology, we are constantly reviewing the most current published clinical journals and updating our panels to ensure the most significant and relevant genes are used. Please see our website – http://pathology.mater.org.au/genepanels for the most up to date information and lists of genes included in our panels.

Limitations of the test

This assay will only assess sequence variants in the coding regions of the genes in the appropriate subpanel, with >99% of targeted bases sequenced at >25X read depth. Copy number variations, large deletions or duplications, triplet repeat expansions, structural rearrangements and mosaic states cannot be assessed by this testing methodology. Deletion /duplication analysis using multiplex ligation-dependant probe amplification (MLPA) is routinely performed for four genes in the MODY panel (see table above).

Important Service Details:

Request/Payment/Consent Form:	Please download current forms from our website (pathology.mater.org.au/genepanels) or contact us at Phone: +61 7 3163 8500. All forms must be completed and accompany the sample being sent to the laboratory. There is currently no Medicare rebate for this test in Australia.
Sample required:	2ml EDTA—whole blood OR 2µg genomic DNA
Turnaround time:	8-10 weeks
Shipping:	Room Temperature (please contact the laboratory +61 7 3163 8500 for instructions on shipping samples from outside of Australia).
Address:	Mater Pathology, Level 6, Mater Hospital Brisbane, Raymond Terrace, South Brisbane, QLD 4101, Australia.
Further Information:	For more details about this test please refer to our website (pathology.mater.org.au/genepanels).

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