醫院管理局
HOSPITAL AUTHORITY

Genetic and Genomic Test Directory

Supplement on Test Indications

(Fifth Edition)

Preface

Over the years, Departments of Pathology at Hospital Authority (HA) have developed Genetic and Genomic (G/G) tests independently based on local needs, while most clinicians are not very well-versed with all G/G tests. The HA Genetic Test Formulary was set up a few years ago as an inventory of the G/G tests available in HA hospitals, but it would benefit from more regular updates and clinician-oriented information. Hence, further efforts were needed to facilitate the dissemination of service information, as set out in the Strategic Service Framework for G/G Services.

Under this circumstance, the **Genetic and Genomic Test Directory (GGTD)** was developed as an updated web-based search engine in HA Intranet (http://GGTD.home) to supersede the HA Genetic Test Formulary with a view to facilitating standardised service provision and information sharing. As a supplementary to the GGTD, a **Supplement on Test Indications** was compiled to elaborate on the suggested testing criteria and other relevant information that support clinicians in identifying appropriate G/G tests for certain clinical conditions.

While the coverage and information of this Supplement may not be exhaustive, yet it serves as a useful reference for clinicians to bridge the knowledge gap in G/G tests provided in HA. Apart from raising the G/G literacy in HA, this document can also be used as a means to enable communication and coordination among frontline clinical and laboratory staff for arranging appropriate G/G tests for the patients in need.

Our sincere thanks go to the Genetic and Genomic Test Committee and Working Groups for GGTD Revamp for their valuable inputs on developing this Supplement. With this document, we look forward to clinicians' efforts in enhancing equitable access of G/G services and reducing mismatch between clinical needs and laboratory support so as to benefit more patients.

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Executive Summary

Starting from the 1st Edition, this **Supplement on Test Indications** covers eight categories of test indications: **Adult Cardiology**, **Adult Endocrinology**, **Adult Neurology**, **Blood Cancer**, **Obstetrics & Gynaecology**, **Paediatrics**, **Pharmacogenetics**, and **Solid Tumours** under the Hospital Authority (HA) Genetic and Genomic Test Directory (GGTD). These eight categories of information are based on the priority list of tests and indications deliberated by different clinical Working Groups in view of their importance in clinical genetic services.

Each part of this Supplement begins with a set of ***Suggested Testing Criteria*** that made reference to the published guidelines and related literatures. These criteria were advised by our clinical and laboratory specialists to meet local needs across HA hospitals. Specifically, they serve as a guidance or reference for clinicians, rather than any mandatory inclusion or exclusion criteria for testing.

To help users better understand the rationale of recommendations, a ***Reference*** section is appended where appropriate for each part. There are also sections on ***Special Patient and Specimen Requirements*** as well as ***Additional Notes*** that provide essential tips and considerations for streamlining test request and arrangement. At the end of each part, a table of ***Current Tests in GGTD*** is shown to summarise the test scope, method, test centre and turnaround time, offering a handy cross-reference for users.

In addition to this Supplement, users may visit the GGTD webpage (http://GGTD.home) to browse the latest G/G test information and contact relevant personnel for further details. If there is any inconsistency between this Supplement and the GGTD, the GGTD shall prevail.

We expect the content of this document will further enrich and evolve with time and use, that will fully embrace a broader range of test indications. It is hoped that the information given could facilitate the work of our colleagues for the benefit of patients. Should there be any comments and suggestions on this Supplement, please contact us at hoggsec@ha.org.hk.

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GGTD Supplement on Test Indications

Acknowledgement

This **Supplement on Test Indications** is a collaborative effort of the following parties. Without their guidance and support, the document would not have been successfully compiled.

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Part I Adult Cardiology

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Suggested Testing Criteria

- Diagnosis of ARVC according to the revised task force diagnostic criteria for ARVC in 2010 incorporating imaging findings of global and/or regional cardiac dysfunction and structural alterations, endomyocardial biopsy or autopsy findings, ECG findings, and family history.
- Strong clinical suspicion by specialist assessment.
- Familial cascade screening as appropriate.

Reference:

- *McNally E, MacLeod H, Dellefave-Castillo L. Arrhythmogenic Right Ventricular Cardiomyopathy Overview. 2005 Apr 18 [Updated 2023 May 11]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet].*
- *Marcus, Frank I., et al. "Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria." Circulation 121.13 (2010): 1533-1541.*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in CACNA1C, CTNNA3, DES, DSC2, DSG2, DSP, JUP, LMNA, PKP2, PLN, RYR2, SCN5A, TGFB3, TMEM43, TP63, TTN	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months
Cardiac Panel Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	NGS	Genetics & Genomics Laboratory, Pathology, HKCH	2 months

Brugada Syndrome

Suggested Testing Criteria

1. Diagnosis of Brugada syndrome in patients with either
   - ST-segment elevation with type 1 morphology ≥2 mm in ≥1 lead among the right precordial leads V1, V2, positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs, or
   - Type 2 or type 3 ST-segment elevation in ≥1 lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type I ECG morphology.
2. Strong suspicion of Brugada syndrome by specialist assessment.
3. Familial cascade screening as appropriate.

Reference:

- *HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013 [Heart Rhythm. 2013 Dec;10(12):1932-63. PMID: 24011539]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	NGS	Genetics & Genomics Laboratory, Pathology, HKCH	2 months
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months

Hypertrophic Cardiomyopathy

Suggested Testing Criteria

- In adult patients:
  1. Clinical diagnosis of hypertrophic cardiomyopathy established by imaging with 2D echocardiography or cardiovascular magnetic resonance showing a maximal end-diastolic wall thickness of ≥15 mm anywhere in the left ventricle, in the absence of another cause of hypertrophy in adults.
  2. If positive family history of hypertrophic cardiomyopathy: a maximal end-diastolic wall thickness of 13-14 mm can be diagnostic.

- In paediatric patients:
  1. In asymptomatic children with no family history: a maximal end-diastolic wall thickness with a body surface area adjusted z-score >2.5.
  2. In children with a definitive family history: a maximal end-diastolic wall thickness with a body surface area adjusted z-score >2).

- In all patients:
  1. Strong suspicion of hypertrophic cardiomyopathy by specialist assessment.
  2. Familial cascade screening as appropriate.

Reference:

- *2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [Circulation. 2020 Dec 22;142(25):e558-e631. PMID: 33215931]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
MYBPC3, MYH7 Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	NGS	Genetics & Genomics Laboratory, Pathology, HKCH	2 months

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months

Long QT Syndrome

Suggested Testing Criteria

- Diagnosis of Long QT Syndrome (LQTS), in the absence of a secondary cause for QT prolongation:
  - LQTS risk score (Schwartz score; see below) ≥3.5, and/or
  - QT interval corrected for heart rate using Bazett's formula (QTc) ≥500 ms in repeated 12-lead electrocardiogram (ECG).
- Strong suspicion of LQTS by specialist assessment.
- Familial cascade screening as appropriate.

Schwartz score for LQTS:

- ECG findings
  - QTc ≥480 ms = 3 points
  - QTc 460 to 479 ms = 2 points
  - QTc 450 to 459 ms (in males) = 1 point
  - QTc ≥480 ms during fourth minute of recovery from exercise stress test = 1 point
  - Torsade de pointes (mutually exclusive with syncope) = 2 points
  - T wave alternans = 1 point
  - Notched T wave in 3 leads = 1 point
  - Low heart rate for age (resting heart rate below the second percentile for age) = 0.5 point
- Clinical history
  - Syncope with stress (mutually exclusive with Torsades de pointes) = 2 points
  - Syncope without stress (mutually exclusive with Torsades de pointes) = 1 point
  - Congenital deafness = 0.5 point
- Family history (unique count for each family member)
  - Family members with definite LQTS = 1 point
  - Unexplained sudden cardiac death below age 30 among immediate family members = 0.5 point

Reference:

- *HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013 [Heart Rhythm. 2013 Dec;10(12):1932-63. PMID: 24011539]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months
Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	NGS	Genetics & Genomics Laboratory, Pathology, HKCH	2 months
Mutation in KCNH2, KCNQ1, SCN5A	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	3 months

Part II Adult Endocrinology

Familial Hypercholesterolaemia (FH)

Suggested Testing Criteria

- Adult patients with probable FH according to Dutch Lipid Clinic Network Diagnostic Criteria (see below).
- Excluded secondary causes of increased LDL-cholesterol levels, such as hypothyroidism and nephrotic syndrome.
- Strong suspicion of FH by specialist assessment.
- Familial cascade screening as appropriate.

Dutch Lipid Clinic Network Diagnostic Criteria (only highest score per category)

- Family history
  - First-degree relative with known premature (men: <55 years; women <60 years) coronary or vascular disease, or first-degree relative with known LDL-C above the 95th percentile = 1 point
  - First-degree relative with tendinous xanthomata and/or arcus cornealis, or children <18 years with LDL-C above 95th percentile = 2 points
- Clinical history
  - Patient with premature (men: <55 years, women: <60 years) coronary artery disease = 2 points
  - Patient with premature (men: <55 years, women: <60 years) cerebral or peripheral vascular disease = 1 point
- Physical examination
  - Tendon xanthomata = 6 points
  - Arcus cornealis <45 years = 4 points
- LDL-C levels
  - ≥8.5 mmol/L = 8 points
  - 6.5-8.4 mmol/L = 5 points
  - 5.0-6.4 mmol/L = 3 points
  - 4.0-4.9 mmol/L =1 point
- DNA analysis
  - Functional mutation in the LDLR, APOB, or PCSK9 gene = 8 points
- Diagnosis
  - A 'probable' FH diagnosis = 6-8 points
  - A 'possible' FH diagnosis = 3-5 points
  - A 'definite' FH diagnosis = >8 points

References:

- *Guidance on the management of familial hypercholesterolaemia in Hong Kong: an expert panel consensus viewpoint [Hong Kong Med J. 2018 Aug;24(4):408-415. PMID: 30100583]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months

Hereditary Haemochromatosis

Suggested Testing Criteria

- Compatible biochemical features: elevated transferrin saturation and high serum ferritin concentrations, or otherwise unexplained persistently elevated transferrin saturation, increased liver iron evident on liver biopsy or MRI
- Strong clinical suspicion by specialist assessment: fatigue and joint pain, cardiac arrhythmia, impotence, skin pigmentation, liver disease, diabetes mellitus, cardiomyopathy, hypogonadotrophic hypogonadism, heart failure, abnormal sexual development in males, amenorrhoea in females.
- Familial cascade screening as appropriate.

Reference:

- *Zoller, Heinz, et al. "EASL clinical practice guidelines on haemochromatosis." Journal of Hepatology 77.2 (2022): 479-502.*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
C282Y and H63D	Targeted mutation testing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	10 days
Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months

Multiple Endocrine Neoplasia Type 1 (MEN1)

Suggested Testing Criteria

- In an individual patient, the occurrence of two or more primary MEN1-associated endocrine tumours (i.e. parathyroid adenoma, enteropancreatic tumour, and pituitary adenoma).
- Suspicious (i.e. multiple parathyroid adenomas before the age of 40; recurrent hyperparathyroidism; gastrinoma or multiple pancreatic NET at any age) or atypical for MEN1 (i.e. development of two nonclassical MEN1-associated tumours, e.g. parathyroid and adrenal tumour).
- A first-degree relative of a family member with known MEN1 mutation.
- Strong suspicion of MEN1 by specialist assessment.
- Familial cascade screening as appropriate.

Reference:

- *Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1) [J Clin Endocrinol Metab. 2012 Sep;97(9):2990-3011. PMID: 22723327]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months
MEN1 Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in MEN1	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks
Hotspot mutations in MEN1	Sanger sequencing	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 8 weeks
MEN1 (Exon 2-10 + 20 bp flanking)	NGS	Molecular Pathology Laboratory, Pathology, UCH	4 months

Multiple Endocrine Neoplasia Type 2 (MEN2)

Suggested Testing Criteria

1. All patients with a personal medical history of primary C cell hyperplasia, MTC, or MEN2 (see below).
2. Patients with intestinal ganglioneuromatosis.
3. All people with a family history consistent with MEN2 or FMTC, and at risk for autosomal dominant inheritance of this syndrome.
4. Strong suspicion of MEN2 by specialist assessment.
5. Familial cascade screening as appropriate.

<u>MEN2 phenotypes:</u>

- MEN 2A:
  (a) Presence of any two or more of medullary thyroid carcinoma (MTC), phaeochromocytoma / paraganglioma (PHEO), and primary hyperparathyroidism (PHPT)
  (b) Presence of any one of MTC, PHEO, or PHPT, and with a first degree relative with MEN 2A features
- Familial MTC:
  (a) Only MTC without PHEO or PHPT in two or more generations within a family
- MEN 2B:
  (a) Presence of MTC, marfanoid habitus, medullated corneal nerve fibres, ganglioneuromatosis of the gut and oral mucosa, and PHEO

Reference:

- *Medullary thyroid cancer: management guidelines of the American Thyroid Association [Thyroid. 2009 Jun;19(6):565-612. PMID: 19469690]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months
Mutation in RET	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	3 months

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in RET	Sanger sequencing	Molecular Diagnostics Service, Chemical Pathology, PWH	6-12 weeks
Hotspot mutations in RET	Sanger sequencing	Division of Anatomical Pathology, Pathology, QMH	7 working days
Mutation in RET	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks
Gene-rearrangement involving the RET gene at 10q11.21	FISH	Anatomical Pathology Laboratory, Pathology, QEH	14 working days

X-linked Adrenoleukodystrophy

Suggested Testing Criteria

- Strong suspicion of X-linked adrenoleukodystrophy by specialist assessment supported by appropriate investigation results.
- Main phenotypes in males may include (1) the childhood cerebral form, (2) adrenomyeloneuropathy, or (3) Addison disease. In female carriers they may develop mild-to-moderate spastic paraparesis in or after middle age, and adrenal function is usually normal.
- Relevant investigations may include adrenal function tests, very long chain fatty acids (VLCFA), and MRI brain.
- Familial cascade screening as appropriate.

Reference:

- *Raymond GV, Moser AB, Fatemi A. X-Linked Adrenoleukodystrophy. 1999 Mar 26 [Updated 2018 Feb 15]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1315/*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
ABCD1, Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months
Mutation in ABCD1	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mutation in ABCD1	Sanger sequencing	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 8 weeks

Part III Adult Haematology

Hereditary Persistence of Foetal Haemoglobin

Suggested Testing Criteria

- In individuals with increased HbF level
  - that is not explained by age-appropriate reference interval or clinical context;
  - in the context of intermediate to severe thalassaemia / haemoglobinopathy for phenotypic correlation

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Deletion involving HBG1 and HBG2	Targeted mutation testing	Division of Haematology, Pathology, QMH	2 months

Thalassaemia Genetic Testing

Suggested Testing Criteria

- Clinical features, antenatal imaging findings and/or haematological findings suggestive of alpha or beta thalassaemia.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Alpha globin gene deletion	Multiple GAP-PCR	Molecular Pathology Laboratory, Pathology, QEH	2 weeks
HbCS, HbQS, deletion codon 30	Targeted mutation testing	Molecular Pathology Laboratory, Pathology, QEH	2 weeks
Amplification of alpha globin gene	Multiplex PCR	Genetics & Genomics Laboratory, Pathology, HKCH	4 months
HBA1 and HBA2 Deletion of alpha globin gene	Multiplex PCR	Genetics & Genomics Laboratory, Pathology, HKCH	4 months
HBA1 and HBA2, HBB Large deletion and amplification in alpha-globin, beta-globin gene cluster	MLPA	Genetics & Genomics Laboratory, Pathology, HKCH	4 months
Single nucleotide variant (SNV) and small insertion/deletion (indel) in HBA1 and HBA2	Sanger sequencing	Genetics & Genomics Laboratory, Pathology, HKCH	4 months
Single nucleotide variant (SNV) and small insertion/deletion (indel) in HBB	Sanger sequencing	Genetics & Genomics Laboratory, Pathology, HKCH	4 months
Amplification of alpha globin gene	Targeted mutation testing	Division of Haematology, Pathology, QMH	2 months
HBA1 and HBA2 Deletion and Duplication (both) in alpha-globin cluster	MLPA	Division of Haematology, Pathology, QMH	2 months
HBA1 and HBA2 Deletion in alpha-globin cluster	Targeted mutation testing	Division of Haematology, Pathology, QMH	2 months
HBA1 and HBA2 Mutation in alpha globin cluster	Targeted mutation testing	Division of Haematology, Pathology, QMH	2 months

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in HBA1 and HBA2, HBB	Single gene sequencing	Division of Haematology, Pathology, QMH	2 months
Mutation in HBB	Targeted mutation testing	Division of Haematology, Pathology, QMH	2 months
HBB Deletion in beta-globin cluster	MLPA	Division of Haematology, Pathology, QMH	2 months
HBA1 and HBA2 Deletion	Targeted mutation testing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	10 days
HBB gene cluster Deletion	GAP-PCR	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	10 days
Mutation in HBA1 and HBA2, and HBB	Sanger sequencing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	10 days
HBA1 and HBA2 Deletion in alpha-globin cluster	Multiplex gap-PCR	Molecular Laboratory, Clinical Pathology, PYN	7 working days
HBA1 and HBA2 Mutation in alpha globin cluster	Multiplex allele-specific PCR	Molecular Laboratory, Clinical Pathology, PYN	7 working days
HBA1 and HBA2 Deletional and non-deletional	Targeted mutation testing	Haematology Laboratory, Pathology, PMH	10 working days
HBA1 and HBA2 Deletional and non-deletional	Targeted mutation testing	Molecular Pathology Laboratory, Pathology, UCH	14 days
HBB gene cluster Deletion	GAP-PCR	Molecular Pathology Laboratory, Pathology, UCH	14 days
HBA1 and HBA2 Deletional and non-deletional	Targeted mutation testing	Molecular Biology Laboratory, Clinical Pathology, TMH	7 days

Part IV Adult Hepatology

Alpha-1 Antitrypsin Deficiency

Suggested Testing Criteria

- Compatible specific biochemical feature: low serum alpha-1 antitrypsin level.
- Strong clinical suspicion by specialist assessment e.g. chronic obstructive pulmonary disease, unexplained chronic liver disease, necrotizing panniculitis, granulomatosis with polyangiitis, or unexplained bronchiectasis.
- Familial cascade screening as appropriate.

Reference:

- *Sandhaus, Robert A., et al. "The diagnosis and management of alpha-1 antitrypsin deficiency in the adult." Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation 3.3 (2016): 668.*
- *Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency – UpToDate (accessed on 06 Jan 2025).*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in SERPINA1	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months

Part V Adult Nephrology

Barakat Syndrome / HDR syndrome

Suggested Testing Criteria

- Triad of hypoparathyroidism, sensorineural deafness, and renal disease; or two of the three components plus positive family history.
- Strong clinical suspicion by specialist assessment.
- Familial cascade screening as appropriate.

Reference:

- *Barakat, Amin J., Margarita Raygada, and Owen M. Rennert. "Barakat syndrome revisited." American Journal of Medical Genetics Part A 176.6 (2018): 1341-1348.*
- *Wong, S. M. Y., et al. "A rare cause of primary hypoparathyroidism due to a novel mutation in the GATA3 gene–the Barakat syndrome." International Journal of Pediatric Endocrinology 2013 (2013): 1-1.*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in GATA3	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks
Hereditary renal diseases gene panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months

Cystinuria

Suggested Testing Criteria

- Compatible specific biochemical features: urinary stone with high cystine content; hexagonal cystine crystal on urine microscopy, urine hyperexcretion of cystine.
- Strong clinical suspicion by specialist assessment: early onset (e.g. childhood) urinary stone disease, large (e.g. staghorn) or recurrent urinary stone, family history of urinary stones.
- Familial cascade screening as appropriate.

Reference:

- *Cystinuria and cystine stones - UpToDate: https://www.uptodate.com/contents/cystinuria-and-cystine-stones*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in SLC3A1 and SLC7A9	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mutation in SLC3A1 and SLC7A9	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks

Part VI Adult Neurology

Alzheimer Disease

Suggested Testing Criteria

- Strong suspicion of Alzheimer Disease (AD) with genetic component (e.g. early-onset familial AD with onset usually 40 to 50 years of age, rapid progression, association with seizure etc.) by specialist assessment supported by appropriate investigation results.
- Familial cascade screening as appropriate.

Reference:

- *Bird TD. Alzheimer Disease Overview. 1998 Oct 23 [Updated 2018 Dec 20]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1161/*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
APP, PSEN1 Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months

Amyotrophic Lateral Sclerosis

Suggested Testing Criteria

- Strong suspicion of Amyotrophic Lateral Sclerosis with a genetic aetiology by specialist assessment supported by appropriate investigation results.
- Familial cascade screening as appropriate.

Reference:

- *Familial amyotrophic lateral sclerosis - UpToDate: https://www.uptodate.com/contents/familial-amyotrophic-lateral-sclerosis*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarct and Leukoencephalopathy (CADASIL)

Suggested Testing Criteria

- Compatible clinical features:
  - Age at onset (clinical symptoms or white matter lesions) ≤ 55 years old.
  - At least two of the following clinical findings:
    - Either of subcortical dementia, long tract signs, or pseudobulbar palsy.
    - Stroke-like episode with a focal neurological deficit.
    - Mood disorder.
    - Migraine.
  - Autosomal dominant inheritance.
  - White matter lesions involving the anterior temporal pole by MRI or CT.
  - Exclusion of leukodystrophy (Adrenoleukodystrophy, metachromatic leukodystrophy, etc.).
- Strong clinical suspicion by specialist assessment.
- Familial cascade screening as appropriate.

References:

- *Hack RJ, Rutten J, Lesnik Oberstein SAJ. CADASIL. 2000 Mar 15 [Updated 2019 Mar 14]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1500/*
- *Mizuta, Ikuko, et al. "New diagnostic criteria for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukocencephalopathy in Japan." Journal of the neurological sciences 381 (2017): 62-67.*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in NOTCH3	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months

Congenital Myopathy

Suggested Testing Criteria

- Strong suspicion of congenital myopathy or limb girdle muscular dystrophy by specialist assessment, which may include but not limited to:
  - Clinical features: weakness of limb girdle, distal limbs or generalised, facial weakness, ophthalmoplegia, ptosis, facial dysmorphism (long face, high arched palate), bulbar weakness (sucking/swallowing), scoliosis, rigid spine, cardiomyopathy, etc.
  - Pathological features on muscle biopsy, elevated creatine kinase, MRI or electromyography
  - After exclusion of other causes of myopathy
- Strong suspicion of congenital myopathy or limb girdle muscular dystrophy by specialist assessment.
- Familial cascade screening as appropriate.

Reference:

- *Approach to the diagnosis of congenital myopathies [Neuromuscul Disord. 2014 Feb; 24(2): 97 – 116. PMID: 24456932]*
- *Congenital myopathies in the adult neuromuscular clinic [Neurol Genet. 2019 Aug; 5(4): e341.PMID: 31321302]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
ACTA1, COL6A1, COL6A2, CRYAB, MTM1, Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in KLHL40	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months

Facioscapulohumeral Muscular Dystrophy (FSHD)

Suggested Testing Criteria

- Four main diagnostic criteria for the definition of FSHD
  1. Onset of the disease in facial or shoulder girdle muscles; sparing of the extra-ocular, pharyngeal and lingual muscles and the myocardium;
  2. Facial weakness in more than 50% of the affected family members;
  3. Autosomal dominant inheritance in familial cases;
  4. Evidence of myopathic disease in EMG and muscle biopsy in at least one affected member without biopsy features specific to alternative diagnoses.
- Strong suspicion of FSHD by specialist assessment.
- Familial cascade screening as appropriate.

References:

- *Diagnostic criteria for facioscapulohumeral muscular dystrophy [Neuromuscul Disord. 1991;1(4):231-4. PMID: 1822799];*
- *Evidence-based guideline summary: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy [Neurology. 2015 Jul 28; 85(4): 357 – 364. PMID: 26215877]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months

Familial Amyloidotic Polyneuropathy/Hereditary Transthyretin Amyloidosis

Suggested Testing Criteria

- Strong suspicion of hereditary transthyretin (ATTR) amyloidosis by specialist assessment supported by appropriate investigation results.
- Clinical features may progressive sensorimotor and/or autonomic neuropathy, cardiac conduction blocks, cardiomyopathy, nephropathy, vitreous opacities, glaucoma etc.
- Tissue biopsy showing amyloid deposits.
- Familial cascade screening as appropriate.

Reference:

- *Sekijima Y. Hereditary Transthyretin Amyloidosis. 2001 Nov 5 [Updated 2021 Jun 17]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1194/*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	Next generation sequencing	Division of Haematology, Pathology, QMH	180 days
TTR, Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months

Familial Creutzfeldt-Jakob Disease/Genetic Prion Disease

Suggested Testing Criteria

- Strong suspicion of genetic prion disease by specialist assessment supported by appropriate investigation results.
- Three major phenotypes of genetic prion disease are genetic Creutzfeldt-Jakob disease (gCJD), fatal familial insomnia (FFI), and Gerstmann-Sträussler-Scheinker (GSS) syndrome.
- Familial cascade screening as appropriate.

Reference:

- *Zerr I, Schmitz M. Genetic Prion Disease. 2003 Mar 27 [Updated 2021 Jan 7]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1229/*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in PRNP	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months

Hereditary Haemorrhagic Telangiectasia (Type 1 and 2)

Suggested Testing Criteria

- Strong suspicion of Hereditary Haemorrhagic Telangiectasia by specialist assessment supported by appropriate investigation results.
- The Curaçao Criteria as endorsed in the 2020 International Guidelines requires 2 of the following:
  1. Epistaxis
  2. Telangiectases
  3. Visceral lesions
  4. Family history
- Familial cascade screening as appropriate.

References:

- *Faughnan, Marie E et al. "Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia." Annals of internal medicine vol. 173,12 (2020): 989-1001. doi:10.7326/M20-1443*
- *McDonald J, Stevenson DA. Hereditary Hemorrhagic Telangiectasia. 2000 Jun 26 [Updated 2021 Nov 24]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1351/*
- *Hereditary hemorrhagic telangiectasia (HHT): Evaluation and therapy for specific vascular lesions*
  - *UpToDate: https://www.uptodate.com/contents/hereditary-hemorrhagic-telangiectasia-hht-evaluation-and-therapy-for-specific-vascular-lesions*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	Next generation sequencing	Division of Haematology, Pathology, QMH	180 days
ENG, ACVRL1, Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months

Hereditary Neuropathy

Suggested Testing Criteria

- Clinical, electrophysiological, biochemical, histological, and/or radiological features of neuropathy. with or without family history.
- Exclusion of other causes of neuropathy.
- Strong suspicion of hereditary neuropathy by specialist assessment.
- Familial cascade screening as appropriate.
- Clinical features suggestive of hereditary neuropathy.

References:

- *Hereditary Neuropathies Clinical Presentation and Genetic Panel Diagnosis [Dtsch Arztebl Int. 2018 Feb; 115(6): 91 – 97. PMID: 29478438]*
- *Charcot-Marie-Tooth (CMT) Hereditary Neuropathy Overview. [GeneReviews® Updated 2021 Sep]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months
Mutation in PMP22	MLPA	Genetic Pathology Laboratory, Pathology, PMH	3 months

Hereditary Spastic Paraplegia

Suggested Testing Criteria

- Unexplained spastic paraplegia, adult onset, with features including but not limited to the following:
  - Clinical features: progressive gait disturbance, spasticity of lower limbs, hyperreflexia of lower limbs, extensor plantar responses etc.
  - With or without additional involvement of other neurological or other systems.
  - Relevant family history and pattern of inheritance.
- Exclusion of other causes of spastic paraplegia.
- Strong suspicion of hereditary spastic paraplegia by specialist assessment.
- Familial cascade screening as appropriate.
- Unexplained spastic paraplegia, adult onset, negative for SPAST pathogenic variants

Reference:

- *Hereditary spastic paraparesis: a review of new developments [J Neurol Neurosurg Psychiatry. 2000 Aug; 69(2): 150 – 160. PMID: 10896685]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in ATL1, SPG11	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mutation in SPAST	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	3 months
Mutation in SPAST	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months
FA2H, SPG3A, SPAST, Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in GJC2, PLP1	Exome sequencing +/- Sanger sequencing	Genetic Laboratory, Clinical Genetic Service, DH	4-6 months

Huntington's Disease Testing (Adult)

Suggested Testing Criteria

- Diagnostic testing for symptomatic adults with:
  - Motor abnormalities (chorea, dystonia, hypokinesia), and/or
  - Cognitive impairment, and/or
  - Neuropsychiatric symptoms, including depression, irritability and apathy, and/or
  - Strong suspicion of Huntington's Disease by specialist assessment
- Predictive testing for asymptomatic adults as familial cascade screening as appropriate.
- Exclusion of other causes of chorea.

Reference:

- *Diagnostic genetic testing for Huntington's disease [Pract Neurol. 2015 Feb;15(1):80-4. PMID: 25169240]*
- *Movement Disorder Society Task Force Viewpoint: Huntington's Disease Diagnostic Categories [Mov Disord Clin Pract. 2019 Aug 23;6(7):541-546. PMID: 31538087]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
HTT Trinucleotide repeats	PCR fragment analysis	Genetics & Genomics Laboratory, Pathology, HKCH	4 months
HTT Trinucleotide repeats	PCR fragment length analysis and sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months

Limb-girdle Muscular Dystrophy

Suggested Testing Criteria

- Strong suspicion of Limb-girdle Muscular Dystrophy (LGMD) by specialist assessment supported by appropriate investigation results.
- Familial cascade screening as appropriate.

Reference:

- *Darras, Basil T., et al. "Limb-girdle muscular dystrophy." UpToDate, Waltham, MA. (last updated 04 Jan 2022): https://www.uptodate.com/contents/limb-girdle-muscular-dystrophy*
- *Angelini C. Calpainopathy. 2005 May 10 [Updated 2022 Dec 1]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1313/*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months
CAPN3, DYSF, Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in CAPN3	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	3 months

Maternally Inherited Diabetes and Deafness (MIDD) Testing

Suggested Testing Criteria

- Diabetes mellitus or impaired glucose tolerance with a normal BMI.
- Deafness (sensorineural and of cochlear origin).
- Family history of these conditions in maternal relatives.
- Exclusion of other causes of diabetes and deafness.
- Strong suspicion of MIDD by specialist assessment.
- Familial cascade screening as appropriate.

Reference:

- *Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD) associated with the 3243A>G mitochondrial point mutation [Diabet Med. 2008 Apr;25(4):383-99. PMID: 18294221]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation (m.3243A>G; m.3252A>G; m.3271T>C; m.8356T>C; m.12770A>G; m.13513G>A)	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	3 months
Mutation in Mitochondrial DNA (m.3243A>G; m.3252A>G; m.3271T>C; m.12770A>G; m.13513G>A)	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mitochondrial DNA (m.3243A>G; m.3252A>G; m.3271T>C; m.8356T>C; m.12770A>G; m.13513G>A) Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in Mitochondrial DNA (m.3243A>G; m.3252A>G; m.3271T>C; m.8356T>C; m.12770A>G; m.13513G>A)	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks
Mutation in Mitochondrial DNA (m.3243A>G)	ddPCR	Genetic Pathology Laboratory, Pathology, PMH	3 months

Metachromatic Leukodystrophy/Arylsulfatase A Deficiency

Suggested Testing Criteria

- Strong suspicion of metachromatic leukodystrophy by specialist assessment supported by appropriate investigation results such as MRI evidence of leukodystrophy, or ARSA enzyme deficiency etc.
- Familial cascade screening as appropriate.

Reference:

- *Gomez-Ospina N. Arylsulfatase A Deficiency. 2006 May 30 [Updated 2020 Apr 30]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1130/*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
ARSA, PSAP, Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months

Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like Episodes (MELAS) Testing

Suggested Testing Criteria

- Suspicious MELAS with at least one clinical finding of stroke-like episode and two items of evidence of mitochondrial dysfunction as follows:
  - Clinical findings of stroke-like episodes
    - Headache with vomiting
    - Seizure
    - Hemiplegia
    - Cortical blindness or hemianopsia
    - Acute focal lesion observed via brain imaging (focal brain abnormalities in CT and/or MRI)
  - Evidence of mitochondrial dysfunction
    - High lactate levels in plasma and/or cerebrospinal fluid or deficiency of mitochondrial-related enzyme activities
      - 2 mmol/L (18mg/dl) or more lactate in plasma at rest or in cerebrospinal fluid and/or
      - deficiency of electron transport chain enzyme, pyruvate-related, TCA cycle-related enzymes or lipid metabolism-related enzymes in somatic cells (desirable for muscle cells)
    - Mitochondrial abnormalities in muscle biopsy, such as
      - Ragged-red fiber in modified Gomori's trichrome stain and/or
      - Strongly SDH-reactive blood vessels in succinate dehydrogenase stain
      - Cytochrome c oxidase deficient fibers or
      - Abnormal mitochondria in electron microscopy
- Exclusion of other causes of myopathy, encephalopathy, lactic acidosis, and stroke-like episodes.
- Strong suspicion of MELAS by specialist assessment.
- Familial cascade screening as appropriate.

Reference:

- *MELAS: a nationwide prospective cohort study of 96 patients in Japan [Biochim Biophys Acta. 2012 May;1820(5):619-24. PMID: 21443929]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation (m.3243A>G; m.3252A>G; m.3271T>C; m.8356T>C; m.12770A>G; m.13513G>A)	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	3 months
Mutation in Mitochondrial DNA (m.3243A>G; m.3252A>G; m.3271T>C; m.12770A>G; m.13513G>A)	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mitochondrial DNA (m.3243A>G; m.3252A>G; m.3271T>C; m.8356T>C; m.12770A>G; m.13513G>A) Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in Mitochondrial DNA (m.3243A>G; m.3252A>G; m.3271T>C; m.8356T>C; m.12770A>G; m.13513G>A)	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks

Myotonic Dystrophy Type 1 (DM1) Testing

Suggested Testing Criteria

- Strong suspicion of DM1 by specialist assessment with features including but not limited to:
  - Mild DM1: e.g. premature cataracts and baldness, a late-onset myopathy, myotonia on electromyography, cardiac conduction abnormalities.
  - Classical or adult-onset DM1: typically in the second or third decade of life with distal weakness, clinical myotonia, gastro-intestinal symptoms and fatigue. Other features: e.g. cataracts, baldness and cardiac conduction abnormalities, apathy, lack of initiative, daytime sleepiness and experience fatigue
- (Note: juvenile and congenital DM1 are not included in the scope of adult neurology)
- Exclusion of other causes of myopathy or myotonia.
- Familial cascade screening as appropriate.

Reference:

- *Best practice guidelines and recommendations on the molecular diagnosis of myotonic dystrophy types 1 and 2 [Eur J Hum Genet. 2012 Dec; 20(12): 1203 – 1208. PMID: 22643181]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in DMPK	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
DMPK Trinucleotide repeats	PCR fragment analysis	Genetics & Genomics Laboratory, Pathology, HKCH	4 months

Myotonic Dystrophy Type 2 (DM2) Testing

Suggested Testing Criteria

- Strong suspicion of DM2 by specialist assessment with features including but not limited to:
  - Predominantly proximal muscle weakness, with muscle pain but no atrophy
  - Myotonia (variable)
- Exclusion of other causes of myopathy or myotonia.
- Familial cascade screening as appropriate.

Reference:

- *Best practice guidelines and recommendations on the molecular diagnosis of myotonic dystrophy types 1 and 2 [Eur J Hum Genet. 2012 Dec; 20(12): 1203 – 1208. PMID: 22643181]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in CNBP	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months

Neurofibromatosis Type 1 (NF1) Testing

Suggested Testing Criteria

- For individuals who do not have a parent diagnosed with NF1: if two or more of the following:
  - Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
  - Freckling in the axillary or inguinal region
  - (If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1 but exceptionally the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings should be bilateral.)
  - Two or more neurofibromas of any type or one plexiform neurofibroma
  - Optic pathway glioma
  - Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs) – defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging
  - A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone
  - (Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma.)
- For individuals with a parent who meets the diagnostic criteria: if one or more of the above criteria are present.
- Strong suspicion of NF1 by specialist assessment.
- Familial cascade screening as appropriate.

Reference:

- *Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation [Genet Med. 2021 Aug;23(8):1506-1513. PMID: 34012067]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	Next generation sequencing	Division of Haematology, Pathology, QMH	180 days

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variations and short indels	Next generation sequencing	Division of Haematology, Pathology, QMH	3 months
Gene Panel Single nucleotide variations and short indels, FLT3-internal tandem duplication, KMT2A partial tandem duplication	Next generation sequencing	Division of Haematology, Pathology, QMH	3 months
Gene Panel Single nucleotide variaions, small indels, and FLT3-ITD detection and KMT2A-PTD (MLPA for KMT2A-PTD confirmation)	Next generation sequencing	Molecular Pathology Laboratory, Pathology, QEH	2 months
Gene Panel Single nucleotide variations and short indels	Next generation sequencing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	3 months
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months

Neurofibromatosis Type 2 (NF2) Testing

Suggested Testing Criteria

- Bilateral vestibular schwannomas <70 years old OR
- First-degree relative family history of NF2
  - AND unilateral vestibular schwannoma <70 years old OR
- First-degree relative family history of NF2 OR unilateral vestibular schwannoma
  - AND 2 of: meningioma, cataract, ependymoma (glioma), (neurofibroma), schwannoma, cerebral calcification (if unilateral vestibular schwannoma + ≥2 nonintradermal schwannomas need negative LZTR1 test), OR
- Multiple meningiomas (2 or more)
  - AND 2 of: unilateral VS, cataract, ependymoma (glioma), (neurofibroma), schwannoma, cerebral calcification, OR
- Constitutional pathogenic NF2 gene variant in tumours.
- Strong suspicion of NF1 by specialist assessment.
- Familial cascade screening as appropriate.

Reference:

- *Identifying the deficiencies of current diagnostic criteria for neurofibromatosis 2 using databases of 2777 individuals with molecular testing [Genet Med. 2019 Jul;21(7):1525-1533. PMID: 30523344]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
NF2 Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months

Nondystrophic myotonias (Myotonia Congenita or Paramyotonia Congenita)

Suggested Testing Criteria

- Clinical features with strong suspicion of myotonia congenital or paramyotonia congenita:
  - Consistent history and examination of clinical myotonia (without muscle wasting or systemic symptoms)
  - EMG with myotonia
- Exclusion of myotonic dystrophy and other potential causes of myotonia.
- Strong suspicion of myotonia by specialist assessment.
- Familial cascade screening as appropriate.

Reference:

- *Skeletal muscle channelopathies: a guide to diagnosis and management [Pract Neurol. 2021 Jun;21(3):196-204. PMID: 33563766]*
- *Guidelines on clinical presentation and management of nondystrophic myotonias [Muscle Nerve. 2020 Oct; 62(4): 430 – 444. PMID: 32270509]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
CLCN1 Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months

Oculopharyngeal Muscular Dystrophy

Suggested Testing Criteria

- Strong suspicion of oculopharyngeal muscular dystrophy (OPMD) by specialist assessment supported by appropriate investigation results.
- Clinical features may include ptosis and dysphagia due to selective involvement of the muscles of the eyelids and pharynx, respectively, with a mean age of onset about 48 years for ptosis and 50 for dysphagia.
- Familial cascade screening as appropriate.

Reference:

- *Trollet C, Boulinguiez A, Roth F, et al. Oculopharyngeal Muscular Dystrophy. 2001 Mar 8 [Updated 2020 Oct 22]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1126/*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
PABPN1 Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months

Spinal and Bulbar Muscular Atrophy/Kennedy Disease

Suggested Testing Criteria

- Strong suspicion of spinal and bulbar muscular atrophy (SBMA) by specialist assessment supported by appropriate investigation results.
- Clinical features in affected males may include progressive lower motor neurons degeneration resulting in muscle weakness, muscle atrophy, and fasciculation, and mild androgen insensitivity with gynecomastia, testicular atrophy, and reduced fertility.
- Familial cascade screening as appropriate.

Reference:

- *La Spada A. Spinal and Bulbar Muscular Atrophy. 1999 Feb 26 [Updated 2022 Dec 15]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1333/*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Androgen Receptor gene Trinucleotide repeats	MS-PCR fragment analysis	Division of Clinical Immunology, Pathology, QMH	6 weeks
AR Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in AR	Sanger sequencing	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 8 weeks
Mutation in AR	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks
AR Trinucleotide repeats	PCR fragment length analysis	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 8 weeks
AR Trinucleotide repeats	PCR fragment length analysis and sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months

Spinocerebellar Ataxia (SCA)

Suggested Testing Criteria

- Strong suspicion of SCA by specialist assessment with unexplained ataxia with onset at adulthood.
- With or without a positive family history of cerebellar ataxia.
- Exclusion of other causes of ataxia.
- Familial cascade screening as appropriate.

Reference:

- *Hereditary Ataxia Overview. [GeneReviews®. Updated 2019 Jul].*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months
ATN1, ATXN1, ATXN2, ATXN3, ATXN7, ATXN8OS, CACNA1A, PPP2R2B, TBP Trinucleotide repeats	PCR fragment length analysis and sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mutation in C10orf2	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
ATN1, ATXN1, ATXN2, ATXN3, ATXN7, CACNA1A, PPP2R2B Trinucleotide repeats	PCR fragment analysis	Genetics & Genomics Laboratory, Pathology, HKCH	4 months

Tuberous Sclerosis

Suggested Testing Criteria

- Strong suspicion of tuberous sclerosis complex (TSC) by specialist assessment supported by appropriate investigation results.
- Diagnosis of TSC may be suspected in individuals with either one major or two or more minor features.
- Major features include angiofibromas (≥3) or fibrous cephalic plaque, cardiac rhabdomyoma, multiple cortical tubers and/or radial migration lines, hypomelanotic macules (≥3 macules that are at least 5 mm in diameter), lymphangioleiomyomatosis (LAM), multiple retinal nodular hamartomas, renal angiomyolipoma (≥2), shagreen patch, subependymal giant cell astrocytoma (SEGA), subependymal nodules (SENs) (≥2). ungual fibromas (≥2).
- Minor features include sclerotic bone lesions, "Confetti" skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs), dental enamel pits (>3), intraoral fibromas (≥2), multiple renal cysts, nonrenal hamartomas, retinal achromic patch.
- Familial cascade screening as appropriate.

References:

- *Northrup H, Koenig MK, Pearson DA, et al. Tuberous Sclerosis Complex. 1999 Jul 13 [Updated 2021 Dec 9]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1220/*
- *Northrup, Hope et al. "Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations." Pediatric neurology vol. 123 (2021): 50-66. doi:10.1016/j.pediatrneurol.2021.07.011*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
TSC1, TSC2 Single nucleotide variant (SNV), small insertion/ deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months

Wilson Disease

Suggested Testing Criteria

- Strong suspicion of Wilson disease by specialist assessment supported by appropriate investigation results.
- Clinical features include varying combinations of hepatic, neurologic, psychiatric, and ocular findings.
- Supportive laboratory findings include low caeruloplasmin, high urinary copper, and increased hepatic copper concentration.
- Familial cascade screening as appropriate.

Reference:

- *Weiss KH. Wilson Disease. 1999 Oct 22 [Updated 2016 Jul 29]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1512/*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	Next generation sequencing	Division of Haematology, Pathology, QMH	180 days
ATP7B Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in ATP7B	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mutation in ATP7B	Sanger sequencing	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 8 weeks
Mutation in ATP7B	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	3 months
Mutation in ATP7B	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks
ATP7B (Exon 1-21 + 20 bp flanking)	NGS	Molecular Pathology Laboratory, Pathology, UCH	4 months

Part VII Adult Rheumatology and Clinical Immunology

Autoinflammatory Diseases

Systemic autoinflammatory disorders result from dysregulation of the innate immune system and are characterized by a hyperinflammatory state with elevated acute phase reactants. These disorders may present at any age, but symptoms more often onset in childhood with unexplained fever that may be accompanied by a rash, and may mimic infections or lymphoproliferative diseases. The phenotype is highly variable, depending on the organ systems impacted by cytokine amplification loops and inflammation. Symptoms may involve the gastrointestinal (GI) tract (e.g, serositis, abdominal pain, early-onset inflammatory bowel disease), bone, eyes (e.g, uveitis), musculoskeletal system (e.g, arthritis and arthralgias), central nervous system (e.g, meningitis), or other tissues. Some autoinflammatory disorders are also associated with an increased risk of developing AA amyloidosis.

Suggested Testing Criteria

- Exclusion of other causes of recurrent fever, such as occult infection, underlying rheumatological / lymphoproliferative disease that can better explain the condition etc.
- Strong clinical suspicion of autoinflammatory disease (inborn error of Immunity) after assessment by specialist with supportive investigation results.
- Familial cascade screening as appropriate

Reference:

- *Bousfiha A, Moundir A, Tangye SG, Picard C, Jeddane L, Al-Herz W, Rundles CC, Franco JL, Holland SM, Klein C, Morio T, Oksenhendler E, Puel A, Puck J, Seppänen MRJ, Somech R, Su HC, Sullivan KE, Torgerson TR, Meyts I. The 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity. J Clin Immunol. 2022 Oct;42(7):1508-1520. doi: 10.1007/s10875-022-01352-z. Epub 2022 Oct 6. PMID: 36198931.*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Consultation with Immunologist before test arranged is recommended.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
67 genes (ACP5, ADA2, ADAM17, ADAR, ALPK1, AP1S3, CARD14, CDC42, CEBPE, COPA, DNASE1L3, DNASE2, DPP9, ELANE, FBXW11, HAVCR2, HCK,	Next generation sequencing	Division of Clinical Immunology, Pathology, QMH	3 months

Test Scope	Method(s)	Test Centre	Turnaround Time
IFIH1, IL10RA, IL10RB, IL1RN, IL36RN, IL6ST, ISG15, LACC1, LPIN2, MEFV, MVK, NLRC4, NLRP1, NLRP12, NLRP3, NOD2, OAS1, OTULIN, PIK3CG, PLCG2, POLA1, PSMA3, PSMB10, PSMB4, PSMB8, PSMB9, PSMG2, PSTPIP1, PTPN2, RBCK1, RC3H1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, SAT1, SH3BP2, SLC29A3, STAT2, STXBP3, TBK1, TLR8, STING1, TNFAIP3, TNFRSF1A, TREX1, TRNT1, UBA1, WDR1, ZNFX1) Single nucleotide variant (SNV), small indels			
TNFAIP3(A20), ADA2, NLRP3, MEFV, MVK, TNFRSF1A Single nucleotide variant (SNV), small indels	Sanger sequencing	Division of Clinical Immunology, Pathology, QMH	4 weeks
PLCG2 Single nucleotide variant (SNV), small indels	Sanger sequencing	Division of Clinical Immunology, Pathology, QMH	12 weeks

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disorder of phagocytes. Patients with CGD often suffer from recurrent bacterial and fungal infections, such as pneumonia, abscesses of the skin, and soft tissues/ organs, septic arthritis, osteomyelitis, bacteremia/fungemia, superficial skin infections such as cellulitis or impetigo etc. CGD patients are particularly susceptible to severe infections caused by catalase-positive bacteria. Examples of bacterial/ fungi causing significant infections in CGD includes Staphylococcus aureus, Serratia marcescens, Listeria species, E. coli., Klebsiella species., Pseudomonas cepacia, a.k.a. Burkholderia cepacian, Nocardia., Aspergillus species, Candida species etc. Inflammation can also occur in several other areas of the body. Mutations in the CYBB gene is the most common cause of CGD (explaining around 60-70% of CGD cases), followed by NCF1 (~20%). CGD is inherited either in an autosomal recessive (CYBA, NCF1, NCF2, NCF4) or X-linked (CYBB) manner.

Suggested Testing Criteria

- Strong clinical suspicion of CGD after assessment by specialist with supportive investigation results (e. g. defective oxidative burst activity observed in the DHR/NBT assay).
- Exclusion of other causes of suboptimal DHR assay results, e.g. significant G6PD deficiency, assessment done during critical illness, MPO deficiency etc
- Familial cascade screening as appropriate

Reference:

- *Chiriaco M, Salfa I, Di Matteo G, Rossi P, Finocchi A. Chronic granulomatous disease: Clinical, molecular, and therapeutic aspects. Pediatr Allergy Immunol. 2016 May;27(3):242-53. doi: 10.1111/pai.12527. Epub 2016 Jan 21. PMID: 26680691.*

Special Patient and Specimen Requirements:

- Nil

Additional Notes

- Consultation with Immunologist before test arranged is recommended.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
CYBA, NCF2 Single nucleotide variant (SNV), small indels / Copy number variations	Sanger sequencing + MLPA	Division of Clinical Immunology, Pathology, QMH	8 weeks
NCF1 Copy number variations	Fragment analysis	Division of Clinical Immunology, Pathology, QMH	2 weeks

Test Scope	Method(s)	Test Centre	Turnaround Time
NCF4 Single nucleotide variant (SNV), small indels	Sanger sequencing	Division of Clinical Immunology, Pathology, QMH	8 weeks
CYBB Single nucleotide variant (SNV), small indels / Copy number variations	Sanger sequencing/ MLPA	Division of Clinical Immunology, Pathology, QMH	6 weeks

Hereditary Angioedema

Hereditary angioedema is a rare inherited disorder characterized by recurrent episodes of the angioedema, affecting hands, feet, limbs, face, intestinal tract, or airway. Mutations in SERPING1, the gene that encodes C1-INH (C1 esterase inhibitor), are responsible for the majority of cases of hereditary angioedema. Rarely, a dominantly inherited disease has been described that has a similar clinical picture to C1-INH-HAE (Hereditary angioedema due to C1 inhibitor deficiency), but with normal C1-INH level and activity. This rare type of HAE has no mutation in the SERPING1 gene and it is classified as nC1-INH-HAE (HAE with normal C1-INH). Currently mutations in six different genes have been identified as causing nC1-INH-HAE: factor XII (F12), plasminogen (PLG), angiopoietin 1 (ANGPT1), Kininogen 1 (KNG1), Myoferlin (MYOF), and heparan sulfate (HS)-glucosamine 3-O-sulfotransferase 6 (HS3ST6).

Suggested Testing Criteria

- Genetic Testing for HAE with C1INH deficiency
  - Strong clinical suspicion of classical HAE with C1-INH deficiency after assessment by specialist with supportive investigation results (e.g. low C4, with abnormal C1-INH antigen or C1-INH function results)
  - Familial cascade screening as appropriate
- Genetic testing for HAE with normal C1INH
  - A history of recurrent angioedema in the absence of concomitant urticaria or use of a medication known to cause angioedema
  - Lack of response to high-dose antihistamines
  - Strong clinical suspicion of normal C1 HAE after assessment by specialist with supportive investigation results (e.g. normal or near-normal C4, C1-INH antigen, and C1-INH function), with exclusion of acquired angioedema
  - Familial cascade screening as appropriate

References:

- *Li PH, Au EYL, Cheong SL, Chung L, Fan KI, Ho MHK, Leung ASY, Chung MMH, Wong JCY, Coelho R. Hong Kong-Macau Severe Hives and Angioedema Referral Pathway. Front Allergy. 2023 Dec 6;4:1290021. doi: 10.3389/falgy.2023.1290021. PMID: 38125294; PMCID: PMC10731021.*
- *Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B, Aygoeren-Pürsün E, Craig T, Binkley K, Hebert J, Ritchie B, Bouillet L, Betschel S, Cogar D, Dean J, Devaraj R, Hamed A, Kamra P, Keith PK, Lacuesta G, Leith E, Lyons H, Mace S, Mako B, Neurath D, Poon MC, Rivard GE, Schellenberg R, Rowan D, Rowe A, Stark D, Sur S, Tsai E, Warrington R, Waserman S, Ameratunga R, Bernstein J, Björkander J, Brosz K, Brosz J, Bygum A, Caballero T, Frank M, Fust G, Harmat G, Kanani A, Kreuz W, Levi M, Li H, Martinez-Saguer I, Moldovan D, Nagy I, Nielsen EW, Nordenfelt P, Reshef A, Rusicke E, Smith-Foltz S, Späth P, Varga L, Xiang ZY. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010 Jul 28;6(1):24. doi: 10.1186/1710-1492-6-24. PMID: 20667127; PMCID: PMC2921362.*

- *Santacroce R, D'Andrea G, Maffione AB, Margaglione M, d'Apolito M. The Genetics of Hereditary Angioedema: A Review. J Clin Med. 2021 May 9;10(9):2023. doi: 10.3390/jcm10092023. PMID: 34065094; PMCID: PMC8125999.*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Consultation with Immunologist before test arranged is recommended.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
ANGPT1, F12 - exon 9, PLG, Single nucleotide variant (SNV), small indels	Sanger sequencing	Division of Clinical Immunology, Pathology, QMH	4 weeks
7 genes (ANGPT1, F12, HS3ST6, KNG1, MYOF, PLG, SERPING1) Single nucleotide variant (SNV), small indels	Next generation sequencing	Division of Clinical Immunology, Pathology, QMH	3 months
SERPING1 Single nucleotide variant (SNV), small indels / Copy number variations	Sanger sequencing+ MLPA	Division of Clinical Immunology, Pathology, QMH	8 weeks

In born Error of Immunity (IEI)/PID

Primary immunodeficiencies (PIDs), also known as inborn errors of immunity (IEI), consist of a heterogenous constellation of genetically encoded disorders of the immune system, and defects in at least 485 genes have been identified as molecular etiologies. Apart from immunodeficiency, element of immune dysregulation, such as autoimmunity, allergy and elevated risk of lymphoproliferative conditions may also be present. They can be broadly classified into six groups based on the part of the immune system that's affected: B cell (antibody) deficiencies, T cell deficiencies, Combination B and T cell deficiencies, Defective phagocytes, Complement deficiencies, Unknown (idiopathic). Choice of platform/ assays depends upon the phenotype.

Suggested Testing Criteria:

- Exclusion of secondary immunodeficiency as causes of immunodeficiency (e.g. HIV, medications, other underlying medical conditions)
- Strong clinical suspicion of IEI after assessment by specialist with supportive investigation results (e. g. immunophenotyping and functional assays, etc).
- Familial cascade screening as appropriate

Reference:

- *Bousfiha A, Moundir A, Tangye SG, Picard C, Jeddane L, Al-Herz W, Rundles CC, Franco JL, Holland SM, Klein C, Morio T, Oksenhendler E, Puel A, Puck J, Seppänen MRJ, Somech R, Su HC, Sullivan KE, Torgerson TR, Meyts I. The 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity. J Clin Immunol. 2022 Oct;42(7):1508-1520. doi: 10.1007/s10875-022-01352-z. Epub 2022 Oct 6. PMID: 36198931.*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Consultation with Immunologist before test arranged is recommended.

Current Tests in GGTD

- IEI Gene Panel tests and targeted Sanger sequencing of individual immune genes are available in the Division of Clinical Immunology, Department of Pathology, QMH. Please contact the laboratories for details.

- https://hkwc.home/webapps/Dept/CIMM/Molecular.aspx

Part VIII Blood Cancer

BCR-ABL1 qPCR Test

Suggested Testing Criteria

1) To monitor treatment response to tyrosine kinase inhibitors in patients with chronic myeloid leukaemia (CML) and BCR-ABL1-positive acute lymphoblastic leukaemia (ALL) according to a pre-agreed monitoring protocol
2) To confirm or exclude a diagnosis CML and BCR-ABL1-positive ALL when a qualitative BCR-ABL1 test is not available

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
BCR::ABL1 (p190)	qPCR	Molecular Pathology Laboratory, Pathology, QEH	1 month
BCR-ABL1 (e1a2)	qPCR	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	1 month
t(9;22)(q34;q11.2)	qPCR	Division of Haematology, Pathology, QMH	4 weeks
BCR::ABL1 (p210)	qPCR	Molecular Pathology Laboratory, Pathology, QEH	30 working days
BCR-ABL1 (e13a2, e14a2)	qPCR	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	14 days

BCR-ABL1 TKD Mutation Analysis

Suggested Testing Criteria

1) In confirmed tyrosine kinase treatment failure or warning response from BCR-ABL1 qPCR monitoring results
2) In accelerated phase or blast phase chronic myeloid leukaemia (CML), either at diagnosis or on progression during treatment
3) In relapse of B-acute lymphoblastic leukaemia (ALL) with BCR-ABL1

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Tyrosine kinase domain mutation in BCR::ABL1	Sanger sequencing	Division of Haematology, Pathology, QMH	1 month
Tyrosine kinase domain mutation in BCR-ABL1	Single gene sequencing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	14 days

BRAF V600E Testing

Suggested Testing Criteria

1) To confirm or exclude a diagnosis of hairy cell leukaemia
2) To diagnose histiocytic neoplasms, including Langerhans cell histiocytosis and Erdheim-Chester disease

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
BRAF p.V600E variant	Single gene sequencing	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
BRAF p.V600E variant	Single gene sequencing	Molecular Laboratory, Clinical Pathology, PYN	10 working days
BRAF p.V600E variant	Single gene sequencing	Molecular Pathology Laboratory, Pathology, QEH	10 working days
BRAF p.V600E variant	Targeted mutation testing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	10 days
BRAF p.V600E variant	Targeted mutation testing	Division of Haematology, Pathology, QMH	28 days
BRAF p.V600E variant	Targeted mutation testing	Molecular Laboratory, Clinical Pathology, PYN	10 working days
BRAF p.V600E variant	Targeted mutation testing	Molecular Pathology Laboratory, Pathology, QEH	10 working days

CBFB-MYH11 Fusion Gene Testing

Suggested Testing Criteria

1) To confirm or exclude a diagnosis of acute myeloid leukaemia (AML) with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11
2) To monitor treatment response in AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11 according to a pre-agreed monitoring protocol

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
t(9;22)(q34;q11.2), inv(16)(p13.3q24), inv(16)(p13.1q22) or t(16;16)(p13.1;q22), t(4;12)(q12;p13), t(6;9)(p22;q34), t(9;12)(q34;p13), t(12;15)(p13;q25), t(5;12)(q32;p13), t(16;21)(p11.2;q22), t(8;22)(p11;q13), inv(8)(p11q13), t(8;16)(p11.2;p13.3), t(10;16)(q22;p13.3), t(12;22)(p13;q12), t(7;12)(q36;p13), t(X;6)(p11;q23), t(1;16)(p31;q24), t(3;5)(q25;q35), t(5;17)(q35;q21), t(10;11)(p12;q14), t(15;17)(q24;q21), t(1;3)(p36.3;q21), t(1;22)(p13;q13), t(16;21)(q24;q22), t(8;21)(q22;q22), t(7;21)(p22;q22), t(9:9)(q34;q34), t(11;17)(q23;q21), t(11;v)(q23;v), t(11;v)(p15;v), t(17;v)(q21;v)	Next generation sequencing	Division of Haematology, Pathology, QMH	3 months
CBFB rearrangement	FISH	Division of Haematology, Pathology, QMH	45 days
inv(16)(p13.1q22)	FISH	Haematology Laboratory, Pathology, QEH	21 days
inv(16)(p13.1q22)	Real-time PCR	Molecular Pathology Laboratory, Pathology, QEH	7 working days
t(8;21)(q22;q22.1),inv(16)(p13.1q22) or t(16;16)(p13.1;q22)	Targeted mutation testing	Haematology Laboratory, Pathology, PMH	5 working days

Test Scope	Method(s)	Test Centre	Turnaround Time
inv(16)(p13.1q22)	FISH	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	45 days
t(8;21)(q22;q22),inv(16)(p13q22)	Targeted mutation testing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	10 days
CBFB::MYH11	qPCR	Molecular Pathology Laboratory, Pathology, QEH	1 month
CBFB::MYH11 (Type A/D/E)	ddPCR	Division of Haematology, Pathology, QMH	28 days
CBFB-MYH11 (Type A)	qPCR	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	1 month

FLT3-ITD Analysis

Suggested Testing Criteria

1) For prognostication of acute leukaemia at diagnosis
2) For detection of drug target for FLT3 inhibitor therapy at diagnosis or later in the disease course of acute leukaemia

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variations and short indels, FLT3-internal tandem duplication, KMT2A partial tandem duplication	Next generation sequencing	Division of Haematology, Pathology, QMH	3 months
NPM1 insertion and FLT3-internal tandem duplication	Targeted mutation testing	Division of Haematology, Pathology, QMH	7 days
FLT3-internal tandem duplication	Targeted mutation testing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	5 days
FLT3-internal tandem duplication	Fragment analysis	Genetics & Genomics Laboratory, Pathology, HKCH	5 calendar days
FLT3-internal tandem duplication	Targeted mutation testing	Molecular Pathology Laboratory, Pathology, UCH	8 days
FLT3-internal tandem duplication	Targeted mutation testing; single gene sequencing	Molecular Pathology Laboratory, Pathology, QEH	7 working days
FLT3-tyroine kinase domain mutation	Targeted mutation testing; single gene sequencing	Molecular Pathology Laboratory, Pathology, QEH	7 working days
FLT3 codons 835/836 variants	Targeted mutation testing; single gene sequencing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	5 days
FLT3-tyrosine kinase domain variant	Targeted mutation testing	Molecular Pathology Laboratory, Pathology, UCH	8 days
t(12;13)(p13;q12), t(5;12)(q32;p13),	Next generation	Division of Haematology, Pathology,	3 months

Test Scope	Method(s)	Test Centre	Turnaround Time
cryptic deletion at 4q12, t(8;9)(p22;p24), t(8;13)(p11;q12), t(8;v)(p11;v), t(13;v)(q12;v), t(9;v)(p24;v), t(4;v)(q12;v), t(5;v)(q32;v)	sequencing	QMH	
Single nucleotide variaions, small indels, and FLT3-ITD detection and KMT2A-PTD (MLPA for KMT2A-PTD confirmation)	Next generation sequencing	Molecular Pathology Laboratory, Pathology, QEH	2 months
Gene Panel Single nucleotide variations and short indels	Next generation sequencing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	3 months

JAK2 V617F Testing

Suggested Testing Criteria

1) To support a diagnosis of polycythaemia vera, essential thrombocythaemia and primary myelofibrosis
2) To aid in the differential diagnosis of reactive erythrocytosis and polycythaemia vera

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
JAK2 p.V617F variant	Targeted mutation testing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	10 days
JAK2 p.V617F variant	Targeted mutation testing	Division of Haematology, Pathology, QMH	21 days
JAK2 p.V617F variant	Targeted mutation testing	Haematology Laboratory, Pathology, PMH	20 working days
JAK2 p.V617F variant	Targeted mutation testing	Molecular Pathology Laboratory, Pathology, UCH	14 days
JAK2 p.V617F variant	Targeted mutation testing	Molecular Biology Laboratory, Clinical Pathology, TMH	5 days
JAK2 p.V617F variant	Targeted mutation testing	Molecular Pathology Laboratory, Pathology, QEH	10 working days
JAK2 p.V617F variant	Targeted mutation testing	Molecular Laboratory, Clinical Pathology, PYN	10 working days

MYD88 L265P Testing

Suggested Testing Criteria

1) To support a diagnosis of lymphoplasmacytic lymphoma
2) To aid in the differential diagnosis of mature B-cell lymphomas and plasma cell myeloma

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
MYD88 p.L265P variant	PCR	Division of Haematology, Pathology, QMH	21 days
Gene Panel Single nucleotide variations and short indels	Next generation sequencing	Division of Haematology, Pathology, QMH	3 months
MYD88 p.L265P variant	Targeted mutation testing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	10 days
MYD88 p.L265P variant	Targeted mutation testing	Molecular Pathology Laboratory, Pathology, UCH	14 days
MYD88 p.L265P variant	Targeted mutation testing	Molecular Laboratory, Clinical Pathology, PYN	10 working days
MYD88 p.L265P variant	Targeted mutation testing	Molecular Pathology Laboratory, Pathology, QEH	10 working days
MYD88 p.L265P variant	Targeted mutation testing	Haematology Laboratory, Pathology, PMH	10 working days
MYD88 p.L265P variant	Targeted mutation testing	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
Gene Panel Single nucleotide variaions, small indels, and FLT3-ITD detection and KMT2A-PTD (MLPA for KMT2A-PTD confirmation)	Next generation sequencing	Molecular Pathology Laboratory, Pathology, QEH	2 months
Gene Panel Single nucleotide variations and short indels	Next generation sequencing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	3 months

NPM1 ddPCR Test

Suggested Testing Criteria

1) For monitoring of treatment response in AML with mutated NPM1 according to a pre-agreed monitoring protocol

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
NPM1 insertion	ddPCR	Division of Haematology, Pathology, QMH	28 days

PML-RARA Fusion Gene Test

Suggested Testing Criteria

1) To confirm or exclude a diagnosis of acute promyelocytic leukaemia (APL) with PML-RARA
2) To monitor treatment response in APL with PML-RARA according to a pre-agreed monitoring protocol

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
t(9;22)(q34.1;q11.2), inv(16)(p13.1q22), t(6;9)(p22.3;q34.1), t(9;12)(q34.1;p13.2), t(12;22)(p13.2;q12.1), t(5;12)(q32;p13.2), t(12;21)(p13.2;q22.1), t(16;21)(p11.2;q22.2), t(6;11)(q27;q23.3), t(4;11)(q21;q23.3), t(11;19)(q23.3;p13.1), t(1;11)(p32.3;q23.3), t(X;11)(q13.1;23.3), t(11;19)(q23.3;p13.3), t(9;11)(p21.3;q23.3), t(11:17)(q23.3;q12-21), t(10:11)(p12.3;q23.3), t(1;11)(p21.3;q23.3), t(3;5)(q25;q34),t(5:17)(q35.1;q21.2), t(15;17)(q24.1;q21.2), t(3;21)(q26.2;q22.1), t(8;21)(q22;q22), t(9:9)(q34.1;q34.1), del1(p32), t(17;19)(q22;13.3), t(1;19)(q23.3;p13.3), t(11;17)(q23.2;q21.2)	Targeted mutation testing	Genetics & Genomics Laboratory, Pathology, HKCH	5 days
t(15;17)(q24;q21)	FISH	Division of Haematology, Pathology, QMH	45 days
t(15;17)(q24;q21)	FISH	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	45 days

Test Scope	Method(s)	Test Centre	Turnaround Time
t(15;17)(q24;q21)	FISH	Haematology Laboratory, Pathology, QEH	21 days
t(15;17)(q24;q21)	Targeted mutation testing	Haematology Laboratory, Pathology, PMH	2 working days
t(15;17)(q24;q21)	Targeted mutation testing	Molecular Pathology Laboratory, Pathology, UCH	3 days
t(15;17)(q24;q21)	Targeted mutation testing	Molecular Pathology Laboratory, Pathology, QEH	7 working days
t(15;17)(q24;q21)	Targeted mutation testing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	5 days
t(15;17)(q24;q21)	Targeted mutation testing	Molecular Biology Laboratory, Clinical Pathology, TMH	5 days
t(15;17)(q24;q21)	Targeted mutation testing	Molecular Laboratory, Clinical Pathology, PYN	3 working days
t(9;22)(q34;q11.2), inv(16)(p13.3q24), inv(16)(p13.1q22) or t(16;16)(p13.1;q22), t(4;12)(q12;p13), t(6;9)(p22;q34), t(9;12)(q34;p13), t(12;15)(p13;q25), t(5;12)(q32;p13), t(16;21)(p11.2;q22), t(8;22)(p11;q13), inv(8)(p11q13), t(8;16)(p11.2;p13.3), t(10;16)(q22;p13.3), t(12;22)(p13;q12), t(7;12)(q36;p13), t(X;6)(p11;q23), t(1;16)(p31;q24), t(3;5)(q25;q35), t(5;17)(q35;q21), t(10;11)(p12;q14), t(15;17)(q24;q21), t(1;3)(p36.3;q21), t(1;22)(p13;q13), t(16;21)(q24;q22), t(8;21)(q22;q22), t(7;21)(p22;q22), t(9:9)(q34;q34), t(11;17)(q23;q21), t(11;v)(q23;v), t(11;v)(p15;v), t(17;v)(q21;v)	Next generation sequencing	Division of Haematology, Pathology, QMH	3 months
Gene Panel Single nucleotide variations and short indels	Next generation sequencing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	3 months

RUNX1-RUNX1T1 Fusion Gene Test

Suggested Testing Criteria

1) To confirm or exclude a diagnosis of acute myeloid leukaemia (AML) with t(8;21)(q22;q22.1); RUNX1-RUNX1T1
2) To monitor treatment response in AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1 according to a pre-agreed monitoring protocol

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
t(9;22)(q34.1;q11.2), inv(16)(p13.1q22), t(6;9)(p22.3;q34.1), t(9;12)(q34.1;p13.2), t(12;22)(p13.2;q12.1), t(5;12) (q32;p13.2), t(12;21)(p13.2;q22.1), t(16;21)(p11.2;q22.2), t(6;11)(q27;q23.3), t(4;11)(q21;q23.3), t(11;19)(q23.3;p13.1), t(1;11)(p32.3;q23.3), t(X;11)(q13.1;23.3), t(11;19)(q23.3;p13.3), t(9;11)(p21.3;q23.3), t(11:17)(q23.3;q12-21), t(10:11)(p12.3;q23.3), t(1;11)(p21.3;q23.3), t(3;5)(q25;q34),t(5:17)(q35.1;q21.2), t(15;17)(q24.1;q21.2), t(3;21)(q26.2;q22.1), t(8;21)(q22;q22), t(9:9)(q34.1;q34.1), del1(p32), t(17;19)(q22;13.3), t(1;19)(q23.3;p13.3), t(11;17)(q23.2;q21.2)	Targeted mutation testing	Genetics & Genomics Laboratory, Pathology, HKCH	5 days
t(8;21)(q22;q22)	FISH	Division of Haematology, Pathology, QMH	45 days
t(8;21)(q22;q22)	FISH	Haematology Laboratory, Pathology, QEH	21 days
t(8;21)(q22;q22)	Real-time PCR	Molecular Pathology Laboratory, Pathology, QEH	7 working days
t(8;21)(q22;q22),inv(16)(p13q22)	Targeted mutation testing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	10 days

Test Scope	Method(s)	Test Centre	Turnaround Time
t(8;21)(q22;q22.1),inv(16)(p13.1q22) or t(16;16)(p13.1;q22)	Targeted mutation testing	Haematology Laboratory, Pathology, PMH	5 working days
RUNX1::RUNX1T1	qPCR	Division of Haematology, Pathology, QMH	1 month
RUNX1-RUNX1T1	qPCR	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	1 month
RUNX1::RUNX1T1	qPCR	Molecular Pathology Laboratory, Pathology, QEH	1 month
t(8;21)(q22;q22)	Digital PCR	Genetics & Genomics Laboratory, Pathology, HKCH	1 month
t(9;22)(q34;q11.2), inv(16)(p13.3q24), inv(16)(p13.1q22) or t(16;16)(p13.1;q22), t(4;12)(q12;p13), t(6;9)(p22;q34), t(9;12)(q34;p13), t(12;15)(p13;q25), t(5;12)(q32;p13), t(16;21)(p11.2;q22), t(8;22)(p11;q13), inv(8)(p11q13), t(8;16)(p11.2;p13.3), t(10;16)(q22;p13.3), t(12;22)(p13;q12), t(7;12)(q36;p13), t(X;6)(p11;q23), t(1;16)(p31;q24), t(3;5)(q25;q35), t(5;17)(q35;q21), t(10;11)(p12;q14), t(15;17)(q24;q21), t(1;3)(p36.3;q21), t(1;22)(p13;q13), t(16;21)(q24;q22), t(8;21)(q22;q22), t(7;21)(p22;q22), t(9:9)(q34;q34), t(11;17)(q23;q21), t(11;v)(q23;v), t(11;v)(p15;v), t(17;v)(q21;v)	Next generation sequencing	Division of Haematology, Pathology, QMH	3 months

Part IX Obstetrics & Gynaecology

22q11.2 deletion (F-PCR)

Suggested Testing Criteria

- Clinical features suggestive of 22q11.2 deletion syndromes.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
22q11.2 Deletion	Fluorescent PCR	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	2 working days
22q11.2 Deletion	Fluorescent-PCR	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	2 working days

Chromosomal Microarray Analysis (CMA)

Suggested Testing Criteria

1. Down syndrome screening positive and choose invasive test
2. Increased NT >=3.5 mm
3. Structural abnormalities detected on ultrasound
4. Family history of chromosomal or genetic disorder
5. Stillbirth
6. 2nd trimester miscarriage
7. Recurrent pregnancy loss

Special Patient and Specimen Requirements

- For prenatal CMA workflow, abnormal QF-PCR results (include trisomy 13, 18, 21, monosomy X, triploidy) to proceed to karyotype only
- For prenatal CMA, please take couple EDTA blood to send along with prenatal sample for potential inheritance study

Additional Notes

- Cannot detect low level mosaicism

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Whole genome or all chromosomes	Chromosomal microarray	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 working days (for fetal cytogenetic disorder) 14 working days (for postnatal cytogenetic disorder)
Whole genome or all chromosomes (plus enhanced known microdeletion / microduplication regions)	Chromosomal microarray (CGH+SNP)	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	7 working days

Expanded Carrier Screening

Suggested Testing Criteria

- Individuals and/or couples are carrier(s) of a genetic disorders that might affect their reproductive choice
- Consanguineous marriage

Special Patient and Specimen Requirements

- EDTA blood

Additional Notes

References:

- *Shi M, et al., Clinical Implementation of Expanded Carrier Screening in Pregnant Women at Early Gestational Weeks: A Chinese Cohort Study. Genes (Basel). 2021 Mar 29;12(4):496. doi: 10.3390/genes12040496*
- *Chan OYM et al., Expanded carrier screening using next-generation sequencing of 123 Hong Kong Chinese families: a pilot study. Hong Kong Med J. 2021 Jun;27(1):177-183. doi: 10.12809/hkmj208486*

Current Tests in GGTD

- Nil

FISH

Suggested Testing Criteria

- Possible structural or mosaic chromosomal abnormalities

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
SNRPN, 5p15.2, 22q11.2, 1p36, 7q11.23 Deletion	FISH	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 to 28 working days (please contact lab)
Chromosomes 13, 18, 21, X, Y	FISH	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 to 22 working days
SRY Chromosome Yp	FISH	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 to 28 working days (please contact lab)
Chromosomes 13, 18, 21, X, Y	FISH	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	7 working days

Fragile X Testing

Suggested Testing Criteria

- Premature ovarian insufficiency
- A family history of FTX, FXTAS, unexplained mental retardation, developmental delay, autism

Special Patient and Specimen Requirements

- Nil

Additional Notes

- For prenatal sample please send in maternal EDTA blood for potential inheritance study

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months
FMR1 Trinucleotide repeats	PCR fragment analysis	Genetics & Genomics Laboratory, Pathology, HKCH	4 months
FMR1 Trinucleotide repeats	PCR fragment length analysis	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	7 working days

Imprinting Disease (i.e. MS-MLPA tests)

Suggested Testing Criteria

- Antenatal ultrasound features with suspicious of imprinting disease or to rule out uniparental disomy

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
SNRPN, Chromosome 11p15, GNAS Methylation status, copy number variant (CNV)	MS-MLPA	Genetics & Genomics Laboratory, Pathology, HKCH	4 months

Karyotype Test

Suggested Testing Criteria

1. Possible structural chromosomal rearrangement
2. Chromosomal mosaicism
3. Recurrent pregnancy loss
4. Premature ovarian insufficiency
5. Ambiguous genitalia

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Whole genome or all chromosomes	G-banding	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 calendar days (fetal blood) 15 calendar days (amniotic fluid, chorionic villi) 18 calendar days (cord blood, peripheral blood) 28 calendar days (placental tissue)
All chromosomes	G-banding	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	7 calendar days (fetal blood) 14 working days (for fetal cytogenetic disorder) 15 calendar days (amniotic fluid, chorionic villi) 18 calendar days (cord blood, peripheral blood) 28 calendar days (placental tissue, skin biopsy, products of gestation)

Non-invasive Prenatal Testing

Suggested Testing Criteria

- Non-invasive prenatal testing of common autosomal aneuploidies: pregnancies with a high risk 1st tier Down syndrome screening test result who choose to go for second tier screening by non-invasive prenatal test; and those with prior history of T21/18/13 pregnancy
- Non-invasive fetal sex determination: For pregnancies where early knowledge of fetal sex is beneficial e.g. pregnancies at risk of X-linked disorders, congenital adrenal hyperplasia etc.

Special Patient and Specimen Requirements

- Fetal sex determination: singleton pregnancies from 8 weeks of gestation. For each patient, it is preferable to collect two blood samples 1 to 2 weeks apart. If the fetal fraction is low or if the result is ambiguous, we will request you to collect additional sample

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Trisomies 21, 18, 13	NGS	Non-invasive Prenatal Testing Laboratory, Pathology, HKCH	2 weeks

Noonan/Rasopathy Panel Test

Suggested Testing Criteria

- Patients with clinical features suggestive of Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, Noonan syndrome-like clinical features or Noonan syndrome with multiple lentigines

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in PTPN11	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Noonan/Rasopathy Panel related disorders mutations	Exome sequencing +/- Genome Sequencing	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	1 month

Prenatal Exome Sequencing

Suggested Testing Criteria

- Fetus with multiple major structural abnormalities detected on fetal ultrasound where multidisciplinary review to include clinical genetics and fetal medicine specialists consider a monogenic malformation disorder is likely.
- The indications included (but not exclusively)
  - Fetuses with multiple anomalies, suspected skeletal dysplasias (IUGR should be excluded), large echogenic kidneys with a normal bladder, major CNS abnormalities (excluding neural tube defects), multiple contractures (excluding isolated bilateral talipes).
  - Nuchal translucency of greater than 6.5mm plus another anomaly (that can include a minor finding) with a normal chromosomal microarray.
  - Isolated non-immune fetal hydrops (detected at mid trimester), defined as fluid/oedema in at least two compartments (e.g. skin, pleural, pericardial or ascites) with a normal chromosomal microarray.
  - Persistent nuchal translucency (>3.5mm) can only be considered in the presence of other structural abnormalities in two or more systems.

Special Patient and Specimen Requirements

- For prenatal exome sequencing, please take couple EDTA blood to send along with prenatal sample for assist SNVs interpretation and potential inheritance study

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	4 calendar weeks
Single nucleotide variant (SNV), small insertion/deletion (indel), copy number variant (CNV)	Exome sequencing +/- Genome sequencing	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	20 calendar days

Rapid Aneuploidy Detection (QF-PCR)

Suggested Testing Criteria

- Test indications as for chromosomal microarray array. For prenatal CMA workflow, abnormal QF-PCR results (include trisomy 13, 18, 21, monosomy X, triploidy) to proceed to karyotype only.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Chromosomes 13, 18, 21, X, Y	Quantitative fluorescent-PCR	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	2 working days
Chromosomes 13, 18, 21, X, Y Microsatellite markers profile	Quantitative fluorescent PCR	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	2 working days

Skeletal Dysplasia Panel Test

Suggested Testing Criteria

- Clinical features or antenatal imaging compatible with monogenic skeletal dysplasia.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months
Single nucleotide variant (SNV), small insertion/deletion (indel)	NGS	Division of Chemical Pathology, QMH	2 months
Heterogeneous Related disorders mutations	Genome Sequencing	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	1 months

Thalassaemia Genetic Testing

Suggested Testing Criteria

- Clinical features, antenatal imaging findings and/or haematological findings suggestive of alpha or beta thalassaemia.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
HBA1 and HBA2 Deletion	Multiplex PCR	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 working days
Mutation in HBA1 and HBA2, and HBB	Single-base primer extension	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 working days
Mutation in HBA1 and HBA2, and HBB	Sanger sequencing	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 working days
HBB Deletion	Gap-PCR	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 working days
Mutation in HBB	Reverse dot blot	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 working days
HBA1 and HBA2 deletions (SEA, 3.7,-4.2) and mutation HbQS, HbCS	Reverse dot blot	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	7 working days
Common mutations in HBB	Reverse dot blot	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	7 working days

Uniparental Disomy Testing

Suggested Testing Criteria

- Prenatal trisomy or monosomy mosaicism of a chromosome known to be associated with a UPD phenotype
- Prenatal or postnatal identification of a structurally abnormal chromosome 14 or 15
- Clinical, physical, or ultrasonographic features associated with UPD
- Confirmation of probable UPD identified by methylation testing at imprinted loci and UPD identified via other routes, for example, SNP array, exome or genome sequencing.

Special Patient and Specimen Requirements

- Please take couple EDTA blood to send along with prenatal sample

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
UPD 6, 7, 11, 14, 15, 20	Fluorescent-PCR	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 to 28 working days (please contact lab)
UPD 7, 11 (Microsatellite markers)	Fluorescent-PCR	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	7 to 14 working days (please contact lab)

Y-microdeletion Testing

Suggested Testing Criteria

- Male patients with non-obstructive azoospermia or severe oligospermia

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
AZF Deletion	Fluorescent-PCR	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	18 calendar days
AZF Deletion	Quantitative Fluorescent PCR	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	2 calendar days

Part X Paediatrics

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency

Also known as HMG CoA lyase deficiency

Suggested Testing Criteria

- Compatible specific biochemical abnormalities such as urinary hyper-excretion of 3-hydroxy-3-methylglutaric acid, 3-hydroxy-isovaleric acid, 3-methylglutaric acid, 3-methylglutaconic acid, 3-methylcrotonylglycine, dicarboxylic aciduria, and elevated C5-OH carnitines on plasma acylcarnitine profiling or dried blood spot metabolic screening.
- Clinical features strongly suspicious by specialist assessment e.g. vomiting, reduced level of consciousness, and biochemical abnormalities e.g. hypoketotic hypoglycaemia, lactic acidosis, hyperammonaemia, hepatomegaly/abnormal liver function tests.
- Familial cascade screening as appropriate.

Reference:

- *Saudubray, J. M. "Inborn metabolic diseases." (2012).*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in HMGCL	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months

3-Methylcrotonyl-CoA Carboxylase Deficiency

Also known as 3-methylcrotonyl glycinuria

Suggested Testing Criteria

- Compatible specific biochemical abnormalities such as urinary hyper-excretion of 3-hydroxy-isovaleric acid, 3-methylcrotonylglycine, and elevated C5-OH carnitines on plasma acylcarnitine profiling or dried blood spot metabolic screening.
- Clinical features strongly suspicious by specialist assessment e.g. metabolic crisis, neurological manifestations.
- Familial cascade screening as appropriate.

Reference:

- *Saudubray, J. M. "Inborn metabolic diseases." (2012).*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Single nucleotide variant (SNV), small insertion/deletion (indel) in MCCC1	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in MCCC1	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Single nucleotide variant (SNV), small insertion/deletion (indel) in MCCC2	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in MCCC2	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months

Argininosuccinate Lyase Deficiency

Suggested Testing Criteria

- Compatible specific biochemical features e.g. hyperammonaemia, abnormal plasma amino acid profile with elevated citrulline, argininosuccinate, with low to normal arginine, and urine hyper-excretion of argininosuccinic acid.
- Strong clinical suspicion by specialist assessment e.g. neonatal encephalopathy, respiratory alkalosis, intellectual disability, seizure, late-onset episodic hyperammonaemia, behavioural abnormalities, learning disabilities, chronic hepatopathy/hepatomegaly, brittle hair due to trichorrhexis nodosa.
- Familial cascade screening as appropriate.

References:

- *Saudubray, J. M. "Inborn metabolic diseases." (2012).*
- *Nagamani SCS, Erez A, Lee B. Argininosuccinate Lyase Deficiency. 2011 Feb 3 [Updated 2019 Mar 28]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet].*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in ASL	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months

Cancer Predisposition Syndrome Panel Test

Suggested Testing Criteria

- Clinical features or with family history that compatible with inherited cancer predisposition syndrome

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Single nucleotide variant (SNV), small insertion/deletion (indel)	NGS	Division of Chemical Pathology, QMH	2 months

Carbamoyl-phosphate Synthetase I Deficiency

Suggested Testing Criteria

- Compatible specific biochemical features: hyperammonaemia, abnormal plasma amino acid profile with low/normal citrulline and high plasma glutamine, no urinary hyperexcretion of orotic acid, and/or 3-methylglutaconic aciduria.
- Strong clinical suspicion by specialist assessment: rapidly progressing encephalopathy, respiratory alkalosis, acute liver failure with coagulopathy.
- Familial cascade screening as appropriate.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in CPS1	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mutation in CPS1	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks

Cardiac Panel Test

Suggested Testing Criteria

- Clinical features or family history compatible with inherited cardiac conditions (inherited aortopathy, hereditary cardiomyopathy, inherited arrhythmia syndrome).
- Sudden cardiac death.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	NGS	Genetics & Genomics Laboratory, Pathology, HKCH	2 months
Single nucleotide variant (SNV), small insertion/deletion (indel)	NGS	Division of Chemical Pathology, QMH	2 months

Chromosomal Array Test

Suggested Testing Criteria

- Patients with any indication of genomic imbalance which includes: dysmorphic features, unexplained mental retardation/developmental delay, autism spectrum disorder, and/or multiple congenital anomalies.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Whole genome or all chromosomes	Chromosomal microarray	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	14 working days
Whole genome or all chromosomes (plus enhanced known microdeletion / microduplication regions)	Chromosomal microarray	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	7 working days

Citrullinaemia Types I

Suggested Testing Criteria

- Compatible specific biochemical features: hyperammonaemia with elevated citrulline concentration in dried blood spot or plasma samples, low/normal arginine and ornithine, absent argininosuccinic acid. Some may have urinary hyperexcretion of orotic acid.
- Strong clinical suspicion by specialist assessment: lethargy, seizure, vomiting, tachypnea hyperammonaemic encephalopathy etc in neonates on full protein diet, or non-classical presentation at any age with recurrent lethargy, headache, scotomas, migraine-like episodes, ataxia etc.
- Familial cascade screening as appropriate.

Reference:

- *Quinonez SC, Lee KN. Citrullinemia Type I. 2004 Jul 7 [Updated 2022 Aug 18]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1458/*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in ASS1	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mutation in ASS1	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks

Citrullinaemia Type II / Citrin Deficiency

Suggested Testing Criteria

- Compatible biochemical features: prolonged neonatal jaundice, elevated citrulline (and methionine, tyrosine, threonine, phenylalanine) concentration in dried blood spot or plasma, galactosaemia, hyperammonaemia, marked elevation of alpha-fetoprotein
- Strong clinical suspicion by specialist assessment: neonatal intrahepatic cholestasis, failure to thrive and dyslipidemia, hyperammonaemia with neuropsychiatric symptoms.
- Familial cascade screening as appropriate.

Reference:

- *Saheki T, Song YZ. Citrin Deficiency. 2005 Sep 16 [Updated 2017 Aug 10]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1181/*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in SLC25A13	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mutation in SLC25A13	Sanger sequencing	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 8 weeks
Mutation in SLC25A13	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	3 months
Mutation in SLC25A13	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks

D-glyceric Aciduria

Suggested Testing Criteria

- Compatible specific biochemical features: urine hyperexcretion of D-glyceric acid.
- Strong clinical suspicion by specialist assessment: heterogeneous clinical phenotypes range from neonatal encephalopathy, chronic metabolic acidosis, seizures and severe mental retardation, microcephaly, and speech delay.
- Familial cascade screening as appropriate.

Reference:

- *Sass, Jörn Oliver, et al. "D-glyceric aciduria is caused by genetic deficiency of D-glycerate kinase (GLYCTK)." Human mutation 31.12 (2010): 1280-1285.*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in GLYCTK	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months

Duchenne Muscular Dystrophy Testing

Suggested Testing Criteria

- Individuals with clinical features strongly suggestive of Duchenne or Becker muscular dystrophy.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

- Nil

Epilepsy Panel Test

Suggested Testing Criteria

- Unexplained epilepsy with clinical suspicion of a monogenic cause including:
  1. Onset under 2 years, or
  2. Clinical features suggestive of specific genetic epilepsy, for example, Dravet syndrome, or
  3. Additional clinical features: intellectual disability, autism spectrum disorder, structural abnormality (e.g. dysmorphism, congenital malformation), unexplained cognitive/memory decline.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
m.8344A>G; m.8356T>C Mutation	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	3 months
m.3243A>G; m.3252A>G; m.3271T>C; m.8356T>C; m.12770A>G; m.13513G>A Mutation	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	3 months
m.8993T>G; m.8993T>C Mutation	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	3 months
Mitochondrial DNA (m.8344A>G; m.8356T>C) Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mitochondrial DNA (m.10158T>C; m.10191T>C; m.11777C>A; m.13045A>C; m.14459G>A) Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mitochondrial DNA (m.3460G>A; m.11778G>A; m.14484T>C) Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mitochondrial DNA (m.3243A>G; m.3252A>G; m.3271T>C; m.8356T>C; m.12770A>G; m.13513G>A) Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months

Test Scope	Method(s)	Test Centre	Turnaround Time
Mitochondrial DNA (m.8993T>G & m.8993T>C) Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Whole mitochondrial genome Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mitochondrial DNA (m.8993T>G/C, m.10158T>C, m.10191T>C, m.11777C>A, m.13045A>C, m.13513G>A, m.14459G>A, m.14487T>C) Mutation	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mitochondrial DNA (m.3460G>A; m.11778G>A; m.14484T>C) Mutation	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mitochondrial DNA (m.3243A>G; m.3252A>G; m.3271T>C; m.12770A>G; m.13513G>A) Mutation	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mitochondrial DNA (m.8344A>G; m.8356T>C; m.8361G>A; m.8363G>A) Mutation	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mitochondrial DNA (m.8993T>G & m.8993T>C) Mutation	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mitochondrial DNA (m.3243A>G) Mutation	ddPCR	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mitochondrial DNA (m.3243A>G; m.3252A>G; m.3271T>C; m.8356T>C; m.12770A>G; m.13513G>A) Mutation	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks
Mitochondrial DNA (m.8993T>G & m.8993T>C) Mutation	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks
Whole mitochondrial genome Mutation	NGS	Genetics & Genomics Laboratory, Pathology, HKCH	4 months
Mitochondrial DNA by RFLP, fragment analysis, LR-PCR and Sanger Sequencing Mutation	RFLP, fragment analysis, LR-PCR and Sanger Sequencing	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 12 weeks
Mitochondrial Genome Mutation	NGS	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 12 weeks

Fragile X Testing

Suggested Testing Criteria

- Clinical symptoms that suggest Fragile X syndrome, Fragile X-associated tremor/ataxia syndrome (FXTAS), or Fragile X-associated primary ovarian insufficiency (FXPOI).
- A family history of FTX, FXTAS, intellectual or learning disabilities or autism of unknown cause, or infertility.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months
AFF2 Trinucleotide repeats	PCR fragment analysis	Genetics & Genomics Laboratory, Pathology, HKCH	4 months
FMR1 Trinucleotide repeats	PCR fragment length analysis	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	7 working days

IEM Panel Test

Suggested Testing Criteria

- Clinical features and/or biochemical abnormalities compatible with inborn error of metabolism

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Single nucleotide variant (SNV), small insertion/deletion (indel)	NGS	Division of Chemical Pathology, Pathology, QMH	6 months
Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	NGS	Genetics & Genomics Laboratory, Pathology, HKCH	6 months
NBSIEM gene panel	NGS	Newborn Screening Laboratory, Pathology, HKCH	5 working days

Imprinting Disease (i.e. MS-MLPA tests)

Suggested Testing Criteria

- Individuals with clinical features compatible with imprinting disease (Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann syndrome, Silver-Russell syndrome, Transient neonatal diabetes mellitus, Temple syndrome, Kagami-Ogata syndrome, pseudohypoparathyroidism type 1B)

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
SNRPN Deletion	FISH	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 to 28 working days (please contact lab)
Methylation status of SNRPN	Methylation specific PCR	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 to 28 working days (please contact lab)
SNRPN, Chromosome 11p15, GNAS Methylation status, copy number variant (CNV)	MS-MLPA	Genetics & Genomics Laboratory, Pathology, HKCH	4 months

Karyotype Test

Suggested Testing Criteria

- Short stature
- Ambiguous genitalia
- Possible structural chromosomal rearrangement requiring karyotype including:
    1. Possible Robertsonian translocation, reciprocal translocation, ring chromosome or other microscopically visible structural rearrangement indicated by findings from microarray, WGS or other laboratory technique, or
    2. A family history suggestive of familial balanced translocation, or
    3. Patient with ambiguous genitalia potentially caused by a sex chromosome rearrangement not detectable via other tests.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Whole genome or all chromosomes	G-banding	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 calendar days (fetal blood) 15 calendar days (amniotic fluid, chorionic villi) 18 calendar days (cord blood, peripheral blood) 28 calendar days (placental tissue)
All chromosomes	G-banding	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	7 calendar days (fetal blood) 14 working days (for fetal cytogenetic disorder) 15 calendar days (amniotic fluid, chorionic villi) 18 calendar days (cord blood, peripheral blood) 28 calendar days (placental tissue, skin biopsy, products of gestation)

Low-pass Whole Genome Sequencing

Suggested Testing Criteria

- Down syndrome screening positive and choose invasive test
- Increased NT >=3.5 mm
- Structural abnormalities detected on ultrasound
- Family history of chromosomal or genetic disorder
- Stillbirth
- 2nd trimester miscarriage
- Recurrent pregnancy loss
- Strong clinical suspicion of large germline CNV

Special Patient and Specimen Requirements

- Please take couple EDTA blood to send along with prenatal sample for assist CNVs interpretation and potential inheritance study

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Whole genome, CNV on all chromosomes	Genome sequencing	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	10 working days
Whole genome, Copy number variant (CNV) >250kb in size	NGS	Genetics & Genomics Laboratory, Pathology, HKCH	4 months

Methylmalonic Aciduria and Homocystinuria (cblC type)

Suggested Testing Criteria

- Compatible biochemical features: elevated plasma total homocysteine, low/normal plasma methionine, homocystinuria and methylmalonic acidaemia/aciduria.
- Strong clinical suspicion by specialist assessment: newborn/neonatal feeding difficulties, lethargy, progressive neurological deterioration e.g. hypotonia or hypertonia, abnormal movements, seizure, coma, pancytopaenia or non-regenerative megaloblastic anaemia, renal failure, liver dysfunction, cardiomyopathy, interstitial pneumonia, haemolytic uraemic syndrome etc. Late onset features include confusion, gait abnormalities, incontinence.
- Familial cascade screening as appropriate.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months

Mitochondrial Disorders (Nuclear Gene)

Suggested Testing Criteria

- Strong suspicion of mitochondrial disorders due to nuclear gene variants by specialist assessment supported by appropriate investigation results.
- Familial cascade screening as appropriate.

Reference:

- *Chinnery PF. Primary Mitochondrial Disorders Overview. 2000 Jun 8 [Updated 2021 Jul 29]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1224/*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Mutation	Clinical Exome Sequencing	Genetic Pathology Laboratory, Pathology, PMH	4 months

SMA Testing

Suggested Testing Criteria

- Clinical features or electrophysiological abnormalities compatible with SMN1 related Spinal muscular atrophy

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel)	Exome sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
SMN1 exon 7 deletion, SMN2 copy number	ddPCR	Newborn Screening Laboratory, Pathology, HKCH	6 working days
SMN1 Deletion	MLPA	Genetic Pathology Laboratory, Pathology, PMH	3 months
SMN1 Deletion	MLPA	Prenatal Diagnostic Laboratory, Obstetrics and Gynaecology, TYH	7 to 28 working days (please contact lab)
SMN1, SMN2 Deletion/duplication	MLPA	Genetics & Genomics Laboratory, Pathology, HKCH	4 months (contact lab for urgent request)

Whole Exome Sequencing (WES)

Suggested Testing Criteria

- A constellation of clinical features suggestive of a recognisable genetic syndrome
- Phenotype with a strong genetic basis and treatment implications
- Specific radiological signs or biochemical findings
- Severe end of a disease spectrum

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	NGS	Genetics & Genomics Laboratory, Pathology, HKCH	6 months
Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	NGS	Genetics & Genomics Laboratory, Pathology, HKCH	1-2 weeks (Rapid Whole Exome Sequencing (Paediatrics))
Single nucleotide variant (SNV), small insertion/deletion (indel), copy number variant (CNV), chromosomal structural rearrangements and absence of heterozygosity (AOH)	Genome sequencing	Prenatal Genetic Diagnosis Laboratory, Obstetrics and Gynaecology, PWH	1 month

Whole Mitochondrial Genome Tests

Suggested Testing Criteria

- Clinical features strongly suggestive of a mitochondrial disorder and/or biochemical evidence of a mitochondrial DNA disorder.

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in Mitochondrial DNA by RFLP, fragment analysis, LR-PCR and Sanger Sequencing	RFLP, fragment analysis, LR-PCR and Sanger Sequencing	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 12 weeks
Mutation in Mitochondrial Genome	NGS	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 12 weeks
Whole Mitochondrial Genome Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mitochondrial DNA (m.3460G>A; m.11778G>A; m.14484T>C) Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mitochondrial DNA (m.3243A>G; m.3252A>G; m.3271T>C; m.8356T>C; m.12770A>G; m.13513G>A) Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mitochondrial DNA (m.8344A>G; m.8356T>C) Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mitochondrial DNA (m.8993T>G & m.8993T>C) Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months
Mutation in Whole Mitochondrial Genome	NGS	Genetics & Genomics Laboratory, Pathology, HKCH	4 months

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in Mitochondrial DNA (m.3460G>A; m.11778G>A; m.14484T>C)	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mutation in Mitochondrial DNA (m.3243A>G; m.3252A>G; m.3271T>C; m.12770A>G; m.13513G>A)	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mutation in Mitochondrial DNA (m.8344A>G; m.8356T>C; m.8361G>A; m.8363G>A)	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mutation in Mitochondrial DNA (m.8993T>G & m.8993T>C)	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months
Mutation in Mitochondrial DNA (m.3243A>G; m.3252A>G; m.3271T>C; m.8356T>C; m.12770A>G; m.13513G>A)	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks
Mutation in Mitochondrial DNA (m.8993T>G & m.8993T>C)	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks

Part XI Pharmacogenetics

Allopurinol Pharmacogenetic Testing

Suggested Testing Criteria

- Pre-emptive testing before starting allopurinol.
- Suspected post-treatment reaction secondary to allopurinol.

Special Patient and Specimen Requirements

- One 3.0 ml EDTA peripheral blood is required. The sample is collected and shipped at room temperature.

Additional Notes

- Presence of HLA-B*58:01 alleles increases the risk of developing toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS) in patients receiving allopurinol. HLAB*58:01 carriers is particularly common in Han Chinese and other Asian populations including Thai and Koreans. Therefore, HLA-B*58:01 alleles screening may be considered in patients who will be treated with allopurinol.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
HLA Genotyping	PCR-SSO ± PCR-SSP	Division of Transplantation & Immunogenetics, Pathology, QMH	1-4 working days
B*58:01	Allele-specific PCR +/- Sanger sequencing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	10 days

Carbamazepine Pharmacogenetic Testing

Suggested Testing Criteria

- Pre-emptive testing before starting carbamazepine.
- Suspected post-treatment reaction secondary to carbamazepine.

Special Patient and Specimen Requirements

- One 3.0 ml EDTA peripheral blood is required. The sample is collected and shipped at room temperature.

Additional Notes

- The presence of the HLA-B*15:02 allele increases the risk of developing toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS) in patients receiving carbamazepine by 72 folds. This allele is seen in high frequency in many Asian populations. It is therefore recommended to screen for the presence of the HLA-B*15:02 allele, particularly in Asian patients, prior to carbamazepine therapy.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
HLA Genotyping	PCR-SSO ± PCR-SSP	Division of Transplantation & Immunogenetics, Pathology, QMH	1-4 working days
B*15:02	Allele-specific PCR +/- Sanger sequencing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	10 days

Dihydropyrimidine Dehydrogenase Deficiency

Suggested Testing Criteria

- Compatible biochemical features: urine hyperexcretion of uracil and thymine with normal dihydrouracil, dihydrothymine, thymidine, and deoxyuridine.
- Strong clinical suspicion by specialist assessment: seizures, intellectual disability, microcephaly, increased muscle tone (hypertonia), growth and psychomotor delays, and autistic behavior.
- Familial cascade screening as appropriate.

Reference:

- *Dihydropyrimidine dehydrogenase deficiency | About the Disease | GARD: https://rarediseases.info.nih.gov/diseases/19/dihydropyrimidine-dehydrogenase-deficiency*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- For toxicity to fluoropyrimidine chemotherapy, please consider therapeutic drug monitoring.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation IN DPYD	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	3 months
Single nucleotide variant (SNV), small insertion/deletion (indel)	Sanger sequencing	Division of Chemical Pathology, Pathology, QMH	6 months

Thiopurine Pharmacogenetic Testing (TPMT and NUDT15)

Suggested Testing Criteria

- For patients on thiopurine medication(s), e.g. azathioprine, 6-mercaptopurine, 6-thioguanine) who developed relevant adverse effects, e.g. myelosuppression
- For pre-emptive testing (i.e. before starting therapy)

Reference:

- *Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update [Clin Pharmacol Ther. 2019 May;105(5):1095-1105. PMID: 30447069]*

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
TPMT *3C & NUDT15 c.415C>T	ARMS + RFLP	Molecular Laboratory, Clinical Pathology, PYN	2 weeks
Mutation in TPMT and NUDT15	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	25 days
Mutation in TPMT & NUDT15	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 weeks
TPMT: *2, *3A, *3B and *3C alleles NUDT15: all 3 coding exons of the gene	StripAssay + Sanger sequencing	Division of Clinical Immunology, Pathology, QMH	14 working days
Mutation in NUDT15	Sanger sequencing	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 12 weeks
*2 *3A/B/C *4 alleles	Sanger sequencing	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 8 weeks
TPMT: codon 240 (for TPMT*3C); NUDT15: exons 1 and 3 (for NUDT15*2, *3, *4, *5 and *6)	Sanger sequencing	Molecular Pathology Laboratory, Pathology, UCH	14 working days

Part XII Solid Tumours

Brain Tumour BRAF Translocation

Suggested Testing Criteria

- Identifying BRAF translocation that assist in tumour diagnosis of pilocytic astrocytoma

Special Patient and Specimen Requirements

Test Centre	QMH	QEH
Case Selection	Pilocytic astrocytoma	Suspected pilocytic astrocytoma
Specimen Types	FFPE sections	FFPE sections
Tumour Cellularity	At least 10%	At least 30%
Tumour Cells Isolation	Whole section	-

** FFPE = Formalin fixed, paraffin embedded*

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene-rearrangement involving the BRAF gene at 7q34; copy number changes of the BRAF gene	FISH	Division of Anatomical Pathology, Pathology, QMH	7 working days
Gene-rearrangement involving the BRAF gene at 7q34	FISH	Anatomical Pathology Laboratory, Pathology, QEH	14 working days
Fusion transcripts resulting from the inversion in 7q34 and tandem repeats	RT-PCR	Division of Anatomical Pathology, Pathology, QMH	7 working days
BRAF V600E	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	7 working days
BRAF Hotspot mutation V600E	Allele-specific PCR	Molecular Laboratory, Clinical Pathology, PYN	5 working days
Gene Panel Copy number variant (CNV), single nucleotide variant (SNV)	MLPA	Genetics & Genomics Laboratory, Pathology, HKCH	4-6 weeks

Brain Tumour CDKN2A and CDKN2B Test

Suggested Testing Criteria

- Identifying specific mutations within the CDKN2A and CDKN2B genes that assist in tumor diagnosis and classification of high grade gliomas and meningiomas

Special Patient and Specimen Requirements

Test Centre	PYN	QMH	QEH
Case Selection	IDH mutant WHO grade 2-4 astrocytomas and oligodendrogliomas; selected meningiomas with atypical features	Gliomas	IDH mutant gliomas
Specimen Types	FFPE sections	FFPE sections	FFPE sections
Tumour Cellularity	At least 30%	At least 50 countable tumour cells	At least 100 countable tumour cells
Tumour Cells Isolation	Microdissection or macrodissection if tumour cellularity less than 30%	-	-

** FFPE = Formalin fixed, paraffin embedded*

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Deletion of the CDKN2A and CDKN2B genes at 9p21.3	FISH	Division of Anatomical Pathology, Pathology, QMH	7 working days
Homozygous deletion of the CDKN2A or CDKN2B gene at 9p21.3	FISH	Molecular Laboratory, Clinical Pathology, PYN	7 working days
Homozygous deletion of the CDKN2A gene at 9p21.3	FISH	Anatomical Pathology Laboratory, Pathology, QEH	14 working days
Gene Panel Copy number variant (CNV), single nucleotide variant (SNV)	MLPA	Genetics & Genomics Laboratory, Pathology, HKCH	4-6 weeks
Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	Next generation sequencing	Division of Haematology, Pathology, QMH	180 days

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variations and short indels	Next generation sequencing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	3 months

Brain Tumour EGFR Amplification

Suggested Testing Criteria

- Identifying specific mutations within the epidermal growth factor receptor (EGFR) gene that assist in diagnosis of high grade gliomas

Special Patient and Specimen Requirements

Test Centre	PYN	QMH	QEH	PMH
Case Selection	IDH wildtype WHO grade 2-3 astrocytomas	Gliomas	IDH wildtype WHO grade 2-3 astrocytomas	High grade gliomas not meeting histological criteria for GBM
Specimen Types	FFPE sections	FFPE sections	FFPE sections	FFPE sections
Tumour Cellularity	At least 30%	At least 50 countable tumour cells	At least 30%	At least 50%
Tumour Cells Isolation	Microdissection or macrodissection if tumour cellularity less than 30%	-	-	-

** FFPE = Formalin fixed, paraffin embedded; GBM = Glioblastoma*

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
EGFR gene amplification at 7p11.2	FISH	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
EGFR gene amplification at 7p11.2	FISH	Division of Anatomical Pathology, Pathology, QMH	7 working days
EGFR gene amplification at 7p11.2	FISH	Molecular Laboratory, Clinical Pathology, PYN	7 working days
EGFR gene amplification at 7p11.2	FISH	Anatomical Pathology Laboratory, Pathology, QEH	14 working days

Brain Tumour H3F3 Test

Suggested Testing Criteria

- Identifying specific mutations within the H3-3A (H3F3A) and H3-3B (H3F3B) genes that assist in diagnosis and classification of gliomas

Special Patient and Specimen Requirements

Test Centre	PYN	QMH	QEH	PMH
Case Selection	Suspected diffuse midline glioma H3K27M mutant, WHO grade 4; or diffuse hemispheric glioma H3.3 G34 mutant WHO grade 4	Gliomas	Gliomas in midline locations and pediatric type diffuse high grade gliomas	Gliomas in midline locations and pediatric type diffuse high grade gliomas
Specimen Types	FFPE sections	FFPE sections	FFPE tissue block or sections; cytology smears or cell block or clot	FFPE sections, cytology smears
Tumour Cellularity	At least 30%	At least 30%	At least 30%	At least 20%
Tumour Cells Isolation	Microdissection or macrodissection if tumour cellularity less than 30%	Microdissection	+/- Macrodissection	Microdissection

** FFPE = Formalin fixed, paraffin embedded*

Additional Notes

- This test cannot differentiate between somatic and germline alterations. Additional testing may be necessary to clarify the significance of results if there is a potential hereditary risk.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Hotspot mutations in H3F3A	Sanger sequencing	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
Gene Panel Hotspot mutations	Sanger sequencing	Division of Anatomical Pathology, Pathology, QMH	5 working days
Gene Panel Hotspot mutations	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	7 working days

Test Scope	Method(s)	Test Centre	Turnaround Time
Hotspot mutations in H3F3A	Sanger sequencing	Molecular Pathology Laboratory, Pathology, QEH	21 working days

Brain Tumour IDH1 and IDH2 Test

Suggested Testing Criteria

- Identifying specific mutations within the isocitrate dehydrogenases (IDH1 and IDH2) genes that assist in diagnosis and classification of diffuse gliomas and predict response to targeted therapy

Special Patient and Specimen Requirements

Test Centre	PYN	QMH	QEH	PMH	PWH
Case Selection	Gliomas negative on immunostaining for IDH1 (R132H)	Gliomas	All diffuse gliomas	All diffuse gliomas	Upon request by clinician/ pathologist for gliomas
Specimen Types	FFPE sections	FFPE sections	FFPE tissue block or sections; cytology smears or cell block or clot	FFPE sections, cytology smears	FFPE tissue block or sections
Tumour Cellularity	At least 30%	At least 30%	At least 20%	At least 20%	At least 20%
Tumour Cells Isolation	Microdissection or macrodissection if tumour cellularity less than 30%	Microdissection	+/- Macrodissection	Microdissection or macrodissection	Microdissection

** FFPE = Formalin fixed, paraffin embedded*

Additional Notes

- This test cannot differentiate between somatic and germline alterations. Additional testing may be necessary to clarify the significance of results if there is a potential hereditary risk.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Hotspot mutations in IDH1 and IDH2	Allele-specific PCR	Molecular Pathology Laboratory, Pathology, QEH	21 working days
Hotspot mutations in IDH1 and IDH2	Sanger sequencing	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
Hotspot mutations in IDH1 and IDH2	Sanger sequencing	Division of Anatomical Pathology, Pathology, QMH	7 working days

Test Scope	Method(s)	Test Centre	Turnaround Time
Hotspot mutations in IDH1 and IDH2	Sanger sequencing	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	10 days
Hotspot mutations in IDH1 and IDH2	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	7 working days

Brain Tumour TERT promoter Test

Suggested Testing Criteria

- Telomerase reverse transcriptase (TERT) promoter mutations are a diagnostic and grading molecular biomarker in high grade gliomas and meningiomas

Special Patient and Specimen Requirements

Test Centre	PYN	QMH	QEH	PMH
Case Selection	IDH wildtype WHO grade 2-3 astrocytomas; selected meningiomas with atypical features	Gliomas	High grade gliomas not meeting histological criteria for GBM	High grade gliomas not meeting histological criteria for GBM
Specimen Types	FFPE sections	FFPE sections	FFPE tissue block or sections; cytology smears or cell block or clot	FFPE sections, cytology smears
Tumour Cellularity	At least 30%	At least 30%	At least 10%	At least 20%
Tumour Cells Isolation	Microdissection or macrodissection if tumour cellularity less than 30%	Microdissection	+/- Macrodissection	Microdissection or macrodissection

** FFPE = Formalin fixed, paraffin embedded; GBM = Glioblastoma*

Additional Notes

- This test cannot differentiate between somatic and germline alterations. Additional testing may be necessary to clarify the significance of results if there is a potential hereditary risk.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Hotspot mutations in TERT promoter	Allele-specific PCR	Molecular Pathology Laboratory, Pathology, QEH	10 working days
Hotspot mutations in TERT promoter	Sanger sequencing	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
Hotspot mutations in TERT promoter	Sanger sequencing	Division of Anatomical Pathology, Pathology, QMH	5 working days
Hotspot mutations in TERT promoter	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	7 working days

Breast Cancer HER2 Testing

Suggested Testing Criteria

- Patients who are candidates for therapies targeting the human epidermal growth factor receptor 2 (HER2) protein; and
- for both lymph node-positive and negative;
- primary and metastatic breast cancer.

Special Patient and Specimen Requirements

- Fix the specimen within 1 hour of biopsy or resection (cold ischemia time < 1 hour) in 10% neutral buffered formalin for a minimum of 6 hours to a maximum of 72 hours (formalin fixation time).
- Avoid specimens that have been subjected to decalcification by strong acids.

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
ERBB2 gene amplification at 17q12	Dual ISH	Division of Anatomical Pathology, Pathology, QMH	3 working days
ERBB2 gene amplification at 17q12	Dual ISH	Molecular Laboratory, Clinical Pathology, PYN	4 working days
ERBB2 gene amplification at 17q12	Dual ISH	Anatomical Pathology Laboratory, Pathology, QEH	7 working days
ERBB2 gene amplification at 17q12	FISH	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
ERBB2 gene amplification at 17q12	FISH	Molecular Pathology Laboratory, Pathology, UCH	10 working days
ERBB2 gene amplification at 17q12	FISH	Molecular Biology Laboratory, Clinical Pathology, TMH	10 days
ERBB2 gene amplification at 17q12	FISH	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	4 days
ERBB2 gene amplification at 17q12	FISH	Anatomical Pathology Laboratory, Pathology, QEH	7 working days

Colorectal Cancer KRAS Mutation Analysis

Suggested Testing Criteria

- Patients with metastatic colorectal carcinoma who are candidates for anti-epidermal growth factor receptor (EGFR) antibody targeted therapy

Special Patient and Specimen Requirements

- Formalin-fixed, paraffin-embedded tissue block, or
- Cytology slides

Additional Notes

- EGFR-targeted therapies in colon cancer are effective only to patients with tumours lacking KRAS mutations, but not all tumours with wild-type KRAS respond to EGFR-targeted therapies.
- Rare alterations (i.e., polymorphisms) may lead to false-negative or false-positive results.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Hotspot mutations in KRAS	Allele-specific qPCR	Molecular Laboratory, Clinical Pathology, PYN	5 working days
Hotspot mutations in KRAS	NGS	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
Hotspot mutations in KRAS	Pyrosequencing	Molecular Pathology Laboratory, Pathology, QEH	10 working days
Hotspot mutations in KRAS	Real-time PCR	Molecular Pathology Laboratory, Pathology, UCH	14 days
Hotspot mutations in KRAS	Real-time PCR ± Sanger Sequencing	Molecular Pathology Laboratory, Pathology, UCH	10 working days
Hotspot mutations in KRAS	Sanger sequencing	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
Hotspot mutations in KRAS	Sanger sequencing	Division of Anatomical Pathology, Pathology, QMH	5 working days
Hotspot mutations in KRAS	Sanger sequencing	Molecular Biology Laboratory, Clinical Pathology, TMH	10 days
Hotspot mutations in KRAS	Sanger sequencing	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	4 days
Hotspot mutations in KRAS	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	7 working days

Colorectal Cancer NRAS Mutation Analysis

Suggested Testing Criteria

- Patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody targeted therapy

Special Patient and Specimen Requirements

- Formalin-fixed, paraffin-embedded tissue block, or
- Cytology slides

Additional Notes

- EGFR-targeted therapies in colon cancer are effective only to patients with tumours lacking NRAS mutations, but not all tumours with wild-type KRAS respond to EGFR-targeted therapies.
- Rare alterations (i.e., polymorphisms) may lead to false-negative or false-positive results.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Hotspot mutations in NRAS	Allele-specific qPCR	Molecular Laboratory, Clinical Pathology, PYN	5 working days
Hotspot mutations in NRAS	NGS	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
Hotspot mutations in NRAS	Pyrosequencing	Molecular Pathology Laboratory, Pathology, QEH	10 working days
Hotspot mutations in NRAS	Real-time PCR	Molecular Pathology Laboratory, Pathology, UCH	14 days
Hotspot mutations in NRAS	Sanger sequencing	Molecular Pathology Laboratory, Pathology, UCH	10 working days
Hotspot mutations in NRAS	Sanger sequencing	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
Hotspot mutations in NRAS	Sanger sequencing	Division of Anatomical Pathology, Pathology, QMH	5 working days
Hotspot mutations in NRAS	Sanger sequencing	Molecular Biology Laboratory, Clinical Pathology, TMH	10 days
Hotspot mutations in NRAS	Sanger sequencing	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	4 days
Hotspot mutations in NRAS	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	7 working days

EBV-related Malignancy EBV ISH Test

Suggested Testing Criteria

To aid diagnosis when Epstein-Barr virus (EBV) related malignancy is suspected:

- Epithelial tumours
  - Nasopharyngeal carcinoma (nonkeratinizing squamous cell carcinoma; basaloid squamous cell carcinoma)
  - Lymphoepithelial carcinoma occurring in foregut derived tissues, e.g. oral cavity, salivary gland, thymus, lung, stomach
  - A small proportion of adenocarcinomas of stomach and biliary tract/liver
  - A subset of undifferentiated/poorly differentiated squamous cell carcinoma and adenocarcinoma (including salivary gland type) of the upper aerodigestive tract
- Lymphomas
  - Extranodal NK/T-cell lymphoma
  - Diffuse large B-cell lymphoma associated with chronic inflammation, including pyothorax-associated large B-cell lymphoma
  - Fibrin-associated large B-cell lymphoma
  - EBV + diffuse large B-cell lymphoma, NOS
  - Primary effusion lymphoma
  - CNS lymphoma in AIDS patients
  - EBV-positive mucocutaneous ulcer
  - Post-transplant lymphoproliferative disorders and methotrexate-associated reversible lymphoma (iatrogenic immunosuppression-associated lymphoproliferative disorder)
  - Angioimmunoblastic T-cell lymphoma (isolated positive large lymphoid cells)
  - Lymphomatoid granulomatosis
  - Burkitt lymphoma (endemic type and a proportion of sporadic and immunodeficiency types)
  - Reed-Sternberg-like cells in B-cell chronic lymphocytic leukaemia
  - Classical Hodgkin lymphoma (HIV-infected patients 100%, mixed cellularity 75%, nodular sclerosis 10-25%)
  - Plasmablastic lymphoma
  - Diffuse large B-cell lymphoma (a proportion of cases)
  - Peripheral T-cell lymphoma (a proportion of cases)
- Mesenchymal tumours
  - Smooth muscle tumours and myopericytoma arising in immunocompromised hosts
  - EBV+ inflammatory follicular dendritic cell sarcoma

Special Patient and Specimen Requirements

- Formalin-fixed, paraffin-embedded tissue block, or
- Cytology slides

Additional Notes

- Normally rare lymphocytes may be positive due to latent infection in the general population.
- Benign conditions e.g. infectious mononucleosis and oral hairy cell leukoplakia could be positive for EBER.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
EBER EBV encoded early RNA	ISH	Anatomical Pathology Laboratory, Clinical Pathology, CMC	3 days
EBER EBV encoded early RNA	ISH	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
EBER EBV encoded early RNA	ISH	Division of Anatomical Pathology, Pathology, QMH	4 working days
EBER EBV encoded early RNA	ISH	Histopathology Laboratory, Pathology, UCH	10 working days
EBER EBV encoded early RNA	ISH	Molecular Biology Laboratory, Clinical Pathology, TMH	7 days
EBER EBV encoded early RNA	ISH	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	3 days
EBER EBV encoded early RNA	ISH	Molecular Laboratory, Clinical Pathology, PYN	3 working days
EBER EBV encoded early RNA	ISH	Anatomical Pathology Laboratory, Pathology, QEH	5 working days
EBER EBV encoded early RNA	ISH	Anatomical Pathology Laboratory, Pathology, KWH	3 working days

Endocrine tumour (Papillary thyroid carcinoma PTC)

Suggested Testing Criteria

- Patients with advanced papillary thyroid carcinoma who are candidates for BRAF inhibitors.

Special Patient and Specimen Requirements

- Formalin-fixed, paraffin-embedded tissue blocks, or cytology slides
- QEH: accepts specimens with tumour cellularity ≥10% for PCR test and ≥25% for Sanger sequencing
- QMH: manual microdissection of tissue sections is carried out to enrich tumor cells when necessary
- PYNEH and PWH: not applicable

Additional Notes

- Most common molecular alteration in PTC involve somatic mutations in BRAF and RAS (mainly NRAS) genes and RET fusions. BRAF V600E mutation is common in classic PTC and subtypes showing papillary architecture.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
BRAF V600E	Sanger sequencing	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	5 days
BRAF V600E	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	7 working days
BRAF V600E	Sanger sequencing	Molecular Pathology Laboratory, Pathology, QEH	10 working days
BRAF Hotspot mutation V600E	Allele-specific PCR	Molecular Laboratory, Clinical Pathology, PYN	5 working days
BRAF Hotspot mutation V600E	Allele-specific qPCR	Molecular Pathology Laboratory, Pathology, QEH	10 working days
BRAF Hotspot mutation	Sanger sequencing	Division of Anatomical Pathology, Pathology, QMH	5 working days

Endocrine tumour (Paraganglioma syndrome)

Suggested Testing Criteria

- A hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndrome should be suspected in any individual with a paraganglioma or pheochromocytoma, particularly individuals with the following findings:
  - Tumours that are:
    - Multiple e.g. bilateral pheochromocytoma
    - Multifocal, i.e. multiple synchronous or metachronous tumours
    - Recurrent
    - Early onset (age <45 years)
    - Extra-adrenal
    - Metastatic
  - A family history of paraganglioma or pheochromocytoma
- Phenotype correlations by gene:
  - SDH family of genes (SDHA, SDHB, SDHC, SDHD and SDHAF2):
    - Loss of SDHB on immunohistochemical (IHC) staining test
    - Other tumours e.g. gastrointestinal stromal tumour (GIST), pulmonary chondroma, clear cell renal cell carcinoma
  - VHL gene: Von Hippel Lindau syndrome
    - Hemangioblastomas of the brain, spinal cord, and retina
    - Renal cyst and clear cell renal cell carcinoma
    - Pancreatic cyst and neuroendocrine tumor
    - Endolymphatic sac tumor
    - Epididymal and broad ligament cystadenoma

References:

1. *van Leeuwaarde RS, Ahmad S, van Nesselrooij B, Zandee W, Giles RH. Von Hippel-Lindau Syndrome. 2000 May 17 [updated 2023 Sep 21]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023. PMID: 20301636.*
2. *Else T, Greenberg S, Fishbein L. Hereditary Paraganglioma-Pheochromocytoma Syndromes. 2008 May 21 [updated 2023 Sep 21]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023. PMID: 20301715.*
3. *https://www.sydneycancergenetics.com.au/genes-and-syndromes/hereditary-paraganglioma-pheochromocytoma-syndrome-and-the-sdh-genes/*

Special Patient and Specimen Requirements

- EDTA blood

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in SDHAF2	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks
SDHB, SDHC, SDHD Deletion/rearrangement	MLPA	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 8 weeks
SDHB, SDHC, SDHD Hotspot mutations	Sanger sequencing	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 8 weeks
SDHB SDHC SDHD Mutation	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks
VHL Deletion/rearrangement	MLPA	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 8 weeks
VHL Deletion/rearrangement	MLPA	Chemical Pathology Laboratory, Pathology, QEH	8 weeks
VHL Hotspot mutations	Sanger sequencing	Molecular Diagnostics Service, Chemical Pathology, PWH	6 - 8 weeks
Mutation in VHL	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks

Gastric Cancer HER2 Testing

Suggested Testing Criteria

- Patients with primary or metastatic gastroesophageal tumours who are candidates for therapies targeting the HER2 protein.

Special Patient and Specimen Requirements

- Fix the specimen within 1 hour of biopsy or resection (cold ischemia time < 1 hour) in 10% neutral buffered formalin for a minimum of 6 hours to a maximum of 72 hours (formalin fixation time).
- Avoid specimens that have been subjected to decalcification solutions by strong acids.

Additional Notes

- Rare cases may have HER2 protein overexpression demonstrated by immunohistochemistry but not show HER2 amplification. The clinical significance is unclear.
- However, these patients may have a worse prognosis and be candidates for anti-HER2 therapy (or its downstream pathways).

Reference:

- *https://www.mayocliniclabs.com/test-catalog/overview/65880#Clinical-and-Interpretive (interpretation part)*

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
ERBB2 gene amplification at 17q12	Dual ISH	Division of Anatomical Pathology, Pathology, QMH	3 working days
ERBB2 gene amplification at 17q12	Dual ISH	Molecular Laboratory, Clinical Pathology, PYN	4 working days
ERBB2 gene amplification at 17q12	Dual ISH	Anatomical Pathology Laboratory, Pathology, QEH	7 working days
ERBB2 gene amplification at 17q12	FISH	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
ERBB2 gene amplification at 17q12	FISH	Molecular Biology Laboratory, Clinical Pathology, TMH	10 days
ERBB2 gene amplification at 17q12	FISH	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	4 days
ERBB2 gene amplification at 17q12	FISH	Anatomical Pathology Laboratory, Pathology, QEH	7 working days
ERBB2 gene amplification at 17q12	FISH	Molecular Pathology Laboratory, Pathology, UCH	10 working days

GBM MGMT PCR Test

Suggested Testing Criteria

- Patients with grade III glioma or glioblastoma who are candidates for alkylating chemotherapy (e.g. temozolomide)

Special Patient and Specimen Requirements

- Formalin-fixed, paraffin-embedded tissue block
- QMH: minimum tumour cellularity requirement for MGMT O[6]-methylguanine-DNA methyltransferase (MGMT) test is 30%, and manual microdissection of tissue section is carried out to enrich tumour cells when necessary
- PWH: accepts specimens with tumour cellularity >10% for MGMT test
- PMH: accepts specimens with tumour cellularity > 40% for MGMT test

Additional Notes

- MGMT facilitates repair of DNA damage induced by chemotherapeutic alkylating agents, and thus associated with chemoresistance.
- Promoter methylation correlates with better progression-free and overall survival in IDH-wildtype glioblastoma patients treated with temozolomide. It is particularly relevant for elderly patients (>60 years), who usually have decreased tolerance for combined aggressive chemoradiation.
- In IDH-mutant anaplastic (WHO grade III) gliomas, MGMT status is a prognostic factor irrespective of treatment but is not predictive of outcome to alkylating chemotherapy versus radiotherapy.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
MGMT promoter Hypermethylation	Methylation-specific PCR	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
MGMT promoter Hypermethylation	Methylation-specific PCR	Division of Anatomical Pathology, Pathology, QMH	10 working days
MGMT promoter Hypermethylation	Methylation-specific PCR	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	10 days

GI Tumour (Hereditary Diffuse Type Gastric Cancer)

Suggested Testing Criteria

2020 hereditary diffuse gastric cancer (HDGC) genetic testing criteria: CDH1 testing is recommended when one of the following criteria have been met and cancer diagnoses have been confirmed

- **Family criteria**
  1. ≥2 cases of gastric cancer in family regardless of age, with at least one diffuse gastric cancer (DGC)
  2. ≥1 case of DGC at any age, and ≥1 case of lobular breast cancer at age <70 years, in different family members
  3. ≥2 cases of lobular breast cancer in family members <50 years of age

- **Individual criteria**
  4. DGC at age <50 years
  5. DGC at any age in individuals of Māori ethnicity
  6. DGC at any age in individuals with a personal or family history (first-degree relative) of cleft lip or cleft palate
  7. History of DGC and lobular breast cancer, both diagnosed at age <70 years
  8. Bilateral lobular breast cancer, diagnosed at age <70 years
  9. Gastric in situ signet ring cells or pagetoid spread of signet ring cells in individuals <50 years of age

Reference:

- *Blair VR, McLeod M, Carneiro F, Coit DG, D'Addario JL, van Dieren JM, Harris KL, Hoogerbrugge N, Oliveira C, van der Post RS, Arnold J, Benusiglio PR, Bisseling TM, Boussioutas A, Cats A, Charlton A, Schreiber KEC, Davis JL, Pietro MD, Fitzgerald RC, Ford JM, Gamet K, Gullo I, Hardwick RH, Huntsman DG, Kaurah P, Kupfer SS, Latchford A, Mansfield PF, Nakajima T, Parry S, Rossaak J, Sugimura H, Svrcek M, Tischkowitz M, Ushijima T, Yamada H, Yang HK, Claydon A, Figueiredo J, Paringatai K, Seruca R, Bougen-Zhukov N, Brew T, Busija S, Carneiro P, DeGregorio L, Fisher H, Gardner E, Godwin TD, Holm KN, Humar B, Lintott CJ, Monroe EC, Muller MD, Norero E, Nouri Y, Paredes J, Sanches JM, Schulpen E, Ribeiro AS, Sporle A, Whitworth J, Zhang L, Reeve AE, Guilford P. Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol. 2020 Aug;21(8):e386-e397. doi: 10.1016/S1470-2045(20)30219-9. PMID: 32758476; PMCID: PMC7116190.*

Special Patient and Specimen Requirements

- Sample must be taken by a medical practitioner, who will be held responsibility for the correct identity of the sample and whose name is required on the request form or GCRS request.
- Collect 3 mL whole blood in EDTA bottle for adult and 2 mL for pediatric patients.

Additional Notes

- Informed consent must be taken before sending the sample.
- All requests should be screened by Consultant Pathologist/Associate Consultant.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
CDH1 Hotspot mutations	Sanger sequencing	Genetic Pathology Laboratory, Pathology, PMH	3 months

GIST c-KIT Mutation Analysis

Suggested Testing Criteria

- Patients who are candidates for targeted therapies targeting KIT

Special Patient and Specimen Requirements

- Formalin-fixed, paraffin-embedded tissue block, or
- Cytology slides

Additional Notes

- KIT mutation and dosage considerations:
  - Gastrointestinal stromal tumours (GISTs) with KIT exon 11 deletions behave more aggressively and benefit most from longer duration of adjuvant imatinib.
  - KIT exon 9 mutation is nearly specific for intestinal GISTs. Exon 9 mutant tumours have a lower sensitivity to imatinib, and a higher dosage may be beneficial.
  - Sunitinib works better than imatinib escalation in tumours with non-exon 9 mutations.
  - Some exon 13 and exon 17 KIT mutants are imatinib-resistant.
  - Most GISTs with PDGFRA mutants other than the D842V are responsive to imatinib.
- Deletions encompassing codons 557/558 predict worse survival rates.
- This test cannot differentiate between somatic and germline alterations. Additional testing may be necessary to investigate for potential hereditary risk.
- A negative result does not rule out the presence of an alteration that is below the limits of detection (approximately 5-10%). This test does not detect large single or multi-exon deletions or duplications or genomic copy number variants.
- KIT genetic alterations are also found in mast cell disease, melanoma, seminomas, acute myeloid leukaemia, myeloproliferative neoplasms, and some lymphomas.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Hotspot mutations in KIT	Sanger sequencing	Division of Anatomical Pathology, Pathology, QMH	7 working days
Hotspot mutations in KIT	Sanger sequencing	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	5 days
Hotspot mutations in KIT	Sanger sequencing	Molecular Pathology Laboratory, Pathology, QEH	21 working days

High Grade Ovarian Serous Carcinoma BRCA1/2 Mutation Analysis

Suggested Testing Criteria

- Patients with ovarian serous carcinoma or primary peritoneal carcinoma who are candidates for polyadenosine diphosphate-ribose polymerase (PARP) inhibitors.

Special Patient and Specimen Requirements

- A previous bone marrow transplant from an allogeneic donor or recent whole blood transfusion (2 weeks) will interfere with germline breast cancer gene (BRCA) testing.

Additional Notes

- BRCA testing based on tumour tissue may miss large structural rearrangement, and whether the BRCA mutation found is somatic or germline may not be ascertainable.
- BRCA testing performed in blood samples cannot detect somatic BRCA mutation which is only present in the tumour.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation (germline) in BRCA1 and BRCA2	NGS + MLPA	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	30 working days
Mutation (tumour) in BRCA1 and BRCA2	NGS	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	30 working days
Mutation (germline) in BRCA1 and BRCA2	NGS + MLPA	Molecular Pathology Laboratory, Pathology, QEH	30 working days
Mutation (tumour) in BRCA1 and BRCA2	NGS	Molecular Pathology Laboratory, Pathology, QEH	30 working days
Mutation (germline) in BRCA1 and BRCA2	NGS + MPLA	Division of Anatomical Pathology, Pathology, QMH	30 working days
Mutations (tumour) in BRCA1 and BRCA2	NGS	Division of Anatomical Pathology, Pathology, QMH	30 working days
Mutation (germline) in BRCA1 and BRCA2	NGS + MLPA	Molecular Laboratory, Clinical Pathology, PYN	30 working days
Mutation (tumour) in BRCA1 and BRCA2	NGS	Molecular Laboratory, Clinical Pathology, PYN	30 working days
Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel) and copy number variant (CNV)	Next generation sequencing	Division of Haematology, Pathology, QMH	180 days

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variations and short indels	Next generation sequencing	Blood Cancer Cytogenetics & Genomics Laboratory, Anatomical and Cellular Pathology, PWH	3 months

Lung Cancer ALK FISH Test

Suggested Testing Criteria

- Patients with late-stage non-small cell lung carcinoma who are candidates for anaplastic lymphoma kinase (ALK) inhibitors.

Special Patient and Specimen Requirements

- Formalin-fixed, paraffin-embedded tissue block, or
- Cytology slides

Additional Notes

- ALK rearrangements are nearly always mutually exclusive of EGFR and KRAS mutations.
- ALK rearrangements positive lung cancers are resistant to EGFR tyrosine kinase inhibitors, but may be highly sensitive to ALK inhibitors.
- Both immunohistochemistry and FISH are considered as gold standards to demonstrate ALK rearrangement.
- ALK rearrangement driven by cryptic and/or complex chromosomal abnormalities may be negative on FISH.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene-rearrangement involving the ALK gene at 2p23	FISH	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
Gene-rearrangement involving the ALK gene at 2p23	FISH	Division of Anatomical Pathology, Pathology, QMH	7 working days
Gene-rearrangement involving the ALK gene at 2p23	FISH	Molecular Pathology Laboratory, Pathology, UCH	14 days
Gene-rearrangement involving the ALK gene at 2p23	FISH	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	3 days
Gene-rearrangement involving the ALK gene at 2p23	FISH	Anatomical Pathology Laboratory, Pathology, QEH	14 working days

Lung Cancer EGFR Mutation Analysis

Suggested Testing Criteria

- Patients with late-stage, non-small cell lung carcinomas who are candidates for EGFR inhibitors

Special Patient and Specimen Requirements

- Formalin-fixed, paraffin-embedded tissue block, or
- Cytology slides

Additional Notes

- Anti-EGFR therapies is beneficial to tumours demonstrating the presence of EGFR-activating mutations such as L858R, L861Q, G719A/S/C, S768I or small deletions within exon 19 in the absence of the drug-resistant mutation T790M.
- A negative (wild type) result does not rule out the presence of a mutation that is below the limits of detection (approximately 5%).
- A negative (wild type) result does not rule out the presence of other activating mutations in the EGFR gene.
- The predictive value of EGFR testing applies to EGFR-tyrosine kinase inhibitors (TKI) therapies, not to other therapeutic agents.
- Not all tumours with activating EGFR mutations respond to EGFR-TKI therapies.
- Rare polymorphisms could lead to false-negative or false-positive results.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Gene Panel Single nucleotide variant (SNV), small insertion/deletion (indel) and RNA gene fusion	NGS	Molecular Pathology Laboratory, Pathology, UCH	10 working days
Hotspot mutations in EGFR	Multiplex Allele-specific PCR	Molecular Pathology Laboratory, Pathology, UCH	10 working days
Hotspot mutations in EGFR in tumour tissue	Allele-specific PCR	Molecular Pathology Laboratory, Pathology, UCH	14 days
Hotspot mutations of the EGFR gene in the cell free DNA of the blood	Allele-specific PCR	Molecular Pathology Laboratory, Pathology, UCH	14 days
EGFR L858R, exon 19 deletions and T790M (plasma circulating tumour DNA)	ddPCR	Molecular Pathology Laboratory, Pathology, UCH	10 working days
Hotspot mutations in EGFR	Allele-specific qPCR	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	5 days

Test Scope	Method(s)	Test Centre	Turnaround Time
Hotspot mutations in EGFR	Allele-specific qPCR	Molecular Laboratory, Clinical Pathology, PYN	5 working days
L858R, exon 19 deletions and T790M in the cell free DNA of the blood	Digital PCR	Molecular Laboratory, Clinical Pathology, PYN	5 working days
Hotspot mutations in EGFR	Allele-specific qPCR	Molecular Laboratory, Clinical Pathology, PYN	8 working days
Hotspot mutations in EGFR	Allele-specific qPCR	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
EGFR L858R, exon 19 deletions and T790M (plasma/pleural fluid circulating tumour DNA)	ddPCR	Genetic Pathology Laboratory, Pathology, PMH	10 working days
Hotspot mutations in EGFR	Allele-specific qPCR	Molecular Biology Laboratory, Clinical Pathology, TMH	10 days
Hotspot mutations in EGFR	Allele-specific qPCR	Molecular Pathology Laboratory, Pathology, QEH	10 working days
Hotspot mutations in EGFR	Sanger sequencing	Molecular Pathology Laboratory, Pathology, QEH	10 working days
Gene Panel Mutation (tumour)	NGS	Molecular Pathology Laboratory, Pathology, QEH	14 working days
Hotspot mutations in EGFR	PCR	Division of Anatomical Pathology, Pathology, QMH	5 working days
Hotspot mutations in EGFR	Sanger sequencing	Division of Anatomical Pathology, Pathology, QMH	5 working days
Mutations (tumor) Hot spot mutations: ALK, BRAF, EGFR, ERBB2, KRAS, MET, NTRK1, NTRK2, NTRK3 PIK3CA, RET, ROS1, TP53; Copy number variants: ALK, EGFR, ERBB2, KRAS, MET; Fusion variants: ALK, BRAF, EGFR, MET, NTRK1, NTRK2, NTRK3, RET, ROS1	NGS	Division of Anatomical Pathology, Pathology, QMH	14 working days

Lung Cancer ROS1 FISH/PCR Test

Suggested Testing Criteria

- Patients with late-stage, non-small cell carcinomas who are candidates for ROS proto-oncogene 1 (ROS1) inhibitors

Special Patient and Specimen Requirements

- Formalin-fixed, paraffin-embedded tissue block, or
- Cytology slides

Additional Notes

- A positive result suggests a tumour that may be responsive to anaplastic lymphoma kinase (ALK)-inhibitor therapy.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Fusion transcripts resulting from gene-rearrangements involving the RET gene at 10q11.21	RT-PCR	Division of Anatomical Pathology, Pathology, QMH	7 working days
Fusion transcripts resulting from gene-rearrangements involving the ROS1 gene at 6q22.1	RT-PCR	Division of Anatomical Pathology, Pathology, QMH	7 working days
Gene-rearrangement involving the ROS1 gene at 6q22.1	FISH	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
Gene-rearrangement involving the ROS1 gene at 6q22.1	FISH	Anatomical Pathology Laboratory, Pathology, QEH	14 working days
Gene-rearrangement involving the ROS1 gene at 6q22.1	FISH	Division of Anatomical Pathology, Pathology, QMH	7 working days
Gene-rearrangement involving the ROS1 gene at 6q22.1	FISH	Molecular Laboratory, Clinical Pathology, PYN	7 working days
Gene-rearrangement involving the ROS1 gene at 6q22.1	FISH	Molecular Pathology Laboratory, Pathology, UCH	14 days

Melanoma BRAF V600E Testing

Suggested Testing Criteria

- Patients with advanced melanomas who are candidates for BRAF inhibitors

Special Patient and Specimen Requirements

- Histology and cytology slides

Additional Notes

- The commonest driver mutations identified in melanomas include BRAF (40%), NRAS (15-20%), KIT (2%), and GNAQ/GNA11 (50% of uveal melanomas and almost universal melanomas in blue nevi).
- BRAF mutations, predominantly V600E (73-90%) and V600K (5-20%), are most frequently identified in melanomas occurring in skin with a low degree of cumulative sun damage (CSD).
- Amongst BRAF-mutant melanoma, the frequency of non-V600E genotypes (including V600K) increases with age.
- BRAF mutant melanoma may be responsive to immune checkpoint inhibitors against CTLA-4, PD-1, BRAF inhibitors, alone or in combination with MEK inhibitors.
- Efficacy of BRAF-targeted therapy and anti-MEK therapy in melanoma is limited to patients whose tumours harbour a p.V600E/K mutation

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
BRAF V600E	Sanger sequencing	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
Hotspot mutations in BRAF	Sanger sequencing	Division of Anatomical Pathology, Pathology, QMH	5 working days
BRAF V600E	Sanger sequencing	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	5 days
BRAF V600E	Sanger sequencing	Molecular Laboratory, Clinical Pathology, PYN	7 working days
Hotspot mutation V600E in BRAF	Allele-specific PCR	Molecular Laboratory, Clinical Pathology, PYN	5 working days
BRAF V600E	Sanger sequencing	Molecular Pathology Laboratory, Pathology, QEH	10 working days
Hotspot mutation V600E in BRAF	Allele-specific qPCR	Molecular Pathology Laboratory, Pathology, QEH	10 working days

Oligodendroglioma 1p19q FISH Test

Suggested Testing Criteria

- Aids in diagnosing
  - Oligodendroglioma and predicting the response to therapy
  - Tumours with a complex "hybrid" morphology requiring differentiation from pure astrocytomas to support the presence of oligodendroglial differentiation/lineage
  - Oligodendroglioma, both low-grade (World Health Organisation WHO, grade II) and anaplastic (WHO, grade III)
  - Mixed oligoastrocytomas

Special Patient and Specimen Requirements

- Nil

Additional Notes

- Co-deletions 1p and 19q also have been associated with response to various chemotherapeutic and radiotherapeutic regimens. These responses have been especially associated with high-grade oligodendrogliomas (anaplastic oligodendrogliomas).
- The presence of gain of chromosome 19 supports a diagnosis of high-grade astrocytoma (glioblastoma multiforme).
- A negative result does not exclude a diagnosis of oligodendroglioma or high-grade astrocytoma.

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
1p deletion 19q deletion	FISH	Division of Anatomical Pathology, Pathology, QMH	7 working days
1p deletion 19q deletion	FISH	Anatomical Pathology Laboratory, Pathology, PMH	10 working days
1p deletion 19q deletion	FISH	Anatomical Pathology Laboratory, Pathology, QEH	14 working days
1p deletion 19q deletion	FISH	Molecular Diagnostic Laboratory (Histopathology), Anatomical and Cellular Pathology, PWH	14 days
1p deletion 19q deletion	FISH	Molecular Laboratory, Clinical Pathology, PYN	7 working days

PTEN Hamartoma Tumour Syndrome

Suggested Testing Criteria

- Establish the diagnosis in patients with hamartomatous tumours presenting as Cowden Syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and/or PTEN-related Proteus-like syndrome
- Family cascade screening as appropriate

Reference:

- *Yehia L, Eng C. PTEN Hamartoma Tumor Syndrome. 2001 Nov 29 [Updated 2021 Feb 11]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.*
  Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK1488/

Special Patient and Specimen Requirements

- Blood collected in EDTA blood container/vacutainer (purple cap), 2 mL
- Two EDTA blood specimens are preferred.
- Blood sample should be collected without recent blood transfusion. Consult pathologist for advice on individual case basis.

Additional Notes

- Nil

Current Tests in GGTD

Test Scope	Method(s)	Test Centre	Turnaround Time
Mutation in PTEN	Sanger sequencing	Chemical Pathology Laboratory, Pathology, QEH	8 weeks

- End -