Specialist Clinic Referral Guidelines
CLINICAL GENETICS AND GENOMICS SERVICE

AlfredHealth

General practitioners and Medical specialists are encouraged to refer eligible patients to the Alfred Hospital Clinical Genetics and Genomics Service (CGGS) for evaluation of suspected genetic or inherited predispositions. These guidelines aim to streamline the referral process and ensure comprehensive assessment and advice.

To refer a patient, please submit a referral electronically through one of the following mechanisms:

- Direct to CGGS at genetics@alfred.org.au or via **fax to (03) 9076 8546.**
- Via Alfred Health Outpatient referral in team op.referrals@alfred.org.au or via fax (03) 9076 6938.

Urgent Outpatient referrals; please include in the referral sufficient clinical details regarding the reason AND specific the nature of the urgency. Examples include; patient deterioration likely within 3 months AND/OR where genetic testing results will change immediate management

Please include in the referral:

Demographic details: • Date of birth • Patient's contact details including mobile phone number • Referring GP details • If an interpreter is required • Medicare number	**Clinical information:** • Reason for referral Relevant investigations and correspondence to facilitate a thorough evaluation • Where a pathogenic variant is known to be present in a family, please provide relation to the family member and service where family member tested

Exclusion criteria

The following cases are not within the scope of CGGS;

- Children or adolescents <18yrs of age (Please refer to paediatric genetic services)
- Individuals with a personal or family history of a health condition where a monogenic cause has not been established
- Individuals with a personal or family history of a health condition explained by confirmed/likely somatically acquired pathogenic variants
- Individuals who are pregnant or require prenatal genetic counselling and care
- Individuals seeking or considering 'direct to consumer' genetic testing, pharmacogenetic or paternity testing
- Common genetic conditions (e.g., hemochromatosis, MTFHR mutation carriers or Factor V Leiden Thrombophilia) not within the scope of CGGS
- Referrals for individuals with Ehlers-Danlos syndrome, type 3 / hypermobility / joint laxity will not be accepted unless there are additional and proven clinical features suggestive of a specific connective tissue disorder. Additional features may include; hernias, spontaneous internal organ rupture/collapse, aortic/arterial aneurysm or dissection, arterial tortuosity, cleft palate, craniosynostosis, ectopia lentis, easy fractures, dysmorphic features that may indicate conditions such as Marfan syndrome, vascular EDS, Loeys Dietz syndrome, TAAD, or arterial tortuosity syndrome.

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Referral Indications – summary for GPs

Referral to the CGGS may be indicated for individuals with a relevant personal and/or family history of conditions including, but not limited to:

- Familial cancer syndromes (e.g., hereditary breast and ovarian cancer, Lynch syndrome)
- Neurological and muscle disorders (e.g., Huntington's disease, muscular dystrophy, epilepsies)
- Cardiac conditions with suspected genetic basis (e.g., long QT syndrome, cardiomyopathies)
- Familial aortopathies and connective tissue disorders (e.g., Marfan's syndrome, Loeys-Dietz syndrome)
- Renal conditions suggestion of genetic aetiology (e.g., polycystic kidney disease)
- Immune or autoinflammatory disorders (e.g. Familial Mediterranean fever, primary immunodeficiencies)
- Inherited pulmonary conditions (e.g., Cystic Fibrosis)
- Intellectual disability with suspected genetic cause
- Dysmorphic features or congenital anomalies suggestive of a genetic syndrome
- Patients with an established genetic or chromosomal diagnosis requiring further evaluation
- Predictive testing for individuals with a known pathogenic variant in a family member

For a more detailed explanation please see RACGP Genomics in general practice

Please note there are DH statewide referral criteria for advice on inherited breast cancer (high risk patients)

Inquiries about referral criteria or specific cases, please contact CGGS on phone number (03) 9076 8554 and ask to speak to the genetic counsellor on duty.

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Hypermobile Ehlers-Danlos Syndrome

Joint hypermobility is common in the general population and often familial. The diagnosis of hypermobile Ehlers-Danlos syndrome (hEDS) is made based on clinical features, as the genetic basis is not yet understood. Because of this, we do not offer genetic testing to patients with hEDS. A clinical diagnosis can be made by a GP or other medical specialists involved in the patients care and does not require attending a genetics service for this purpose. The 2017 International Diagnostic Criteria provides guidance regarding making a clinical diagnosis. The checklist can be found at The Ehlers-Danlos Society website (https://www.ehlers-danlos.com/heds-diagnostic-checklist/).

In general, treatment for hEDS should support patients to manage and alleviate symptoms. Patients may benefit from specific medical and allied health services such as, physiotherapy, psychology. Low impact exercise is advisable. Management of symptoms should be through referral to relevant medical and allied health specialists. Guidelines for managing patients with hEDS, as well as the clinical features and natural history, can be found at The Ehlers-Danlos Society website (https://www.ehlers-danlos.com/).

Other types of Ehlers-Danlos syndrome

There are at least 12 other types of EDS, some of which are associated with life-threatening complications (such as arterial or organ rupture). Clinical genetics assessment and testing is available for other types of EDS, as well as other connective tissue disorders associated with arterial dissection/aneurysm (such as Marfan Syndrome or Loeys-Dietz syndrome) where there is proven clinical features present and genetic testing is clinically indicated.

Where a patient has proven clinical features such as those listed below, referral to a Clinical Genetics can be made:

- Extensive widened atrophic scars
- Significant sagging skin
- Recurrent large hernias
- Significant kyphoscoliosis
- Personal or family history of spontaneous internal organ rupture/collapse
- Aortic/arterial aneurysm or dissection
- Arterial tortuosity
- Cleft palate
- Craniosynostosis
- Ectopia lentis
- Easy fractures
- Dysmorphic features that may indicate conditions such as Marfan syndrome
- Vascular EDS
- Loeys Dietz syndrome
- Recurrent pneumothoraces
- Hand and foot deformities
- TAAD
- arterial tortuosity syndrome.

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Referral Indications for specialists

A number of detailed specialist guidelines can be found in the links for the following specialities:

- Cardiology
- Endocrine
- Familial Cancer
- Immunology
- Neurology
- Renal
- Respiratory

In addition, referral to the CGGS may be indicated for individuals with a relevant personal and/or family history of conditions including, but not limited to:

- Inherited haematological conditions
- Intellectual disability with suspected genetic cause
- Dysmorphic feature of congenital anomalies suggestive of a genetic syndrome
- Patients with an established genetic or chromosomal diagnosis requiring further evaluation
- Predictive testing for individuals with a known pathogenic variant in a family member

Inquiries about referral criteria or specific cases, please contact CGGS and ask to speak to the genetic counsellor on duty.

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ALFRED HEALTH CARDIOLOGY GENETICS REFERRAL GUIDELINES

Referral Indicators *NOTE: Prior to referring please exclude traditional causes (CAD etc) AND complete cardiac phenotypic work up PRIOR to referral*
Pathogenic variant identified in the family
Untested adult blood relative of a person with an identified pathogenic variant in a gene known to predispose to an inherited cardiac or connective tissue disorder.
Cardiomyopathy
An individual with ANY of the following • Likely diagnosis of ARVC using Task Force Criteria[1] • Unexplained non-ischaemic cardiomyopathy with LVEF 35-50% and one of the following (i) MRI scar (ii) conduction disease (iii) clinically significant arrhythmias (iv) positive FHx in first degree relatives. • Hypertrophic cardiomyopathy • Amyloid cardiomyopathy (Note: patients must have been seen in specialist amyloid clinic prior to referral to genetics)
Arrhythmia
An individual with ANY of the following ○ Likely diagnosis of LQTS/CPVT/Brugada ○ Unexplained VT/VF/cardiac arrest
Vasculopathy
An individual with ANY of the following ○ Thoracic aortic dissection < 60y of age ○ Clinical diagnosis of Marfan syndrome ○ SCAD affected >1 individual in the same family or in individuals <35y of age

[1] Corrado D et al Diagnosis of arrhythmogenic cardiomyopathy: The Padua criteria. Int J Cardiol. 2020 Nov 15;319:106-114. doi: 10.1016/j.ijcard.2020.06.005. Epub 2020 Jun 16. PMID: 32561223.

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ALFRED HEALTH ENDOCRINE GENETICS REFERRAL GUIDELINES

Referral Indicators
Glucose and Insulin Homeostasis Disorders
Severe, recurrent and unexplained hypo-hyperglycaemia +/- syndromic features e.g. congenital hyperinsulinaemia, inborn errors of metabolism, glycogen storage disorders Possible Mature Onset Diabetes of the Young (MODY) – with • Diagnosis of diabetes <35y with negative auto-antibodies, normal BMI and low normal C-peptide (> 0.2 nmol/L) AND • Family history in a first degree relative of a diagnosis of diabetes <35y For MODY referrals, please ensure that HbA1c, C-peptide, and negative autoantibody results are available in Powerchart and MODY calculator score is documented in referral or clinical notes - https://www.diabetesgenes.org/exeter-diabetes-app/ AND advise if patient has any renal cysts, structural or other urogenital abnormalities
Calcium and Phosphate Homeostasis Disorders
Osteogenesis imperfecta Hypophosphatemic rickets Familial hypocalcaemia Suspected familial hypocalciuric hypercalcaemia Familial hypoparathyroidism Multiglandular or familial primary hyperparathyroidism
Genetic Pituitary Hormone Disorders
Suspected familial isolated pituitary adenoma disorder Combined pituitary hormone deficiency - GH deficiency and at least one other pituitary hormone deficiency +/- intellectual disability +/- craniofacial, dental, skeletal and/or urogenital anomalies Congenital hypogonadotrophic hypogonadism either in isolation (normosmic CHH) or in association with anosmia (Kallmann syndrome) or with syndromic features (e.g. Prader-Willi syndrome) Hormone resistance disorders e.g. thyroid hormone resistance, Laron syndrome, pseudo hypoaldosteronism, familial glucocorticoid deficiency

ALFRED HEALTH ENDOCRINE GENETICS REFERRAL GUIDELINES cont.

Growth, obesity, metabolism disorders – *referral is appropriate if diagnosis is required for management, or counselling patient/ family regarding reproductive risk/planning*
Undiagnosed adult with clinical features or a previous diagnosis of a genetic syndrome where no genetic testing has occurred e.g. Prader Willi Syndrome, Noonan syndrome Unexplained short or tall stature, failure to thrive in childhood or severe familial obesity
Adrenal disorders
Such as congenital adrenal hyperplasia, bilateral macronodular adrenal hyperplasia
Sex Development and Maturation
Suspected/confirmed disorder of sexual development (DSD)
Pancreas
Suspected hereditary pancreatitis
Familial Hypercholesterolaemia
An individual with any of the following • A Dutch Lipid Clinic Network (DLNC) Score of 6 of more (“probable” or “definite” FH) (https://www.athero.org.au/fh/wp-content/uploads/Dutch-Lipid-Clinic-Network-Score2.pdf); OR • An isolated LDL-cholesterol level of ≥ 6.5mmol/L (DLNC Score of 5); OR • An LDL-cholesterol level of 5 – 6.4mmol/L with signs of premature or accelerated atherogenesis (DLNC Score of at least 4)

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ALFRED HEALTH FAMILIAL CANCER GENETICS REFERRAL GUIDELINES

Individuals may access genetic testing to assist cancer management and inform relatives risk. Referrals to CGGS should be considered for all people meeting the categories as outlined by the eviQ guidelines. The most up to date guidelines can be found at:

https://www.eviq.org.au/cancer-genetics/referral-guidelines

To make an inquiry about these guidelines please contact the clinic at genetics@alfred.org.au or call 9076 8554 and request to speak with the Duty Genetic Counsellor prior to making a referral in Cerner.

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ALFRED HEALTH IMMUNOLOGY GENETICS REFERRAL GUIDELINES

Referral Indicators
Pathogenic variant identified in the family
Untested adult blood relative of a person with an identified pathogenic variant in a gene known to predispose to an immunological condition.
An individual diagnosed with ANY of the following
Monogenic causes of immunodeficiency disorders are increasingly recognised but variable penetrance/expressivity is recognised. An individual with ANY of the following increased susceptibility to ○ recurrent infections from broad range of organisms, or narrow range of infections with unusual presentation ○ autoinflammatory disease ○ immune dysregulation including lymphoproliferation and autoimmunity ○ Systemic autoimmune disease with early-onset or severe involvement • These individuals may have abnormalities in routinely available immunology tests including decreased serum antibody levels or lymphocyte enumeration, and may fit with phenotypic immunodeficiencies described in the IUIS 2022 that include ○ Predominantly antibody deficiency ○ Combined immunodeficiency ○ Immune regulation disorders ○ Innate immunity – complement, phagocytes • 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity DOI: 10.1007/s10875-022-01352-z

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ALFRED HEALTH NEUROLOGY GENETICS REFERRAL GUIDELINES

Referral Indicators Patients with at least one of the following are appropriate for referral to the genetics clinic – they are likely to be offered funded genomic testing:
Pathogenic variant identified in the family
Untested adult blood relative of a person with an identified pathogenic variant in a gene known to predispose to an inherited cardiac or connective tissue disorder.
Epilepsy
• Severe epilepsy/epileptic encephalopathy • Drug-resistant epilepsy with no known acquired cause (e.g. stroke, injury etc) AND where there is a strong suspicion of a genetic cause • Syndromic epilepsy (epilepsy + intellectual disability, congenital abnormalities, movement disorder, other neurological co-morbidities (e.g. neuropathy, myopathy) • MRI-B abnormalities (e.g. leukodystrophy, cortical malformation) • Associated paroxysmal ataxia, movement disorder (e.g. dyskinesia, dystonia, chorea) and/or hemiplegic migraine • 1+ first degree relative with a similar epilepsy phenotype AND where there is a strong suspicion of a genetic cause
Movement and Neuromuscular Disorders
An individual with a diagnosis of ANY of the following: • Muscular dystrophies (Duchenne, Becker, limb-girdle, facioscapulohumeral, myotonic, Emery-Dreyfuss etc) • Ataxias (spinocerebellar, Friedreich etc) • Spinal muscular atrophy • Early onset dystonia • Periodic paralysis • Congenital myasthenic syndromes • Hereditary neuropathies (Charcot-Marie Tooth etc) • Hereditary spastic paraplegia • Early onset Parkinson's disease
Neurodegenerative disorders
An individual with a diagnosis of ANY of the following: • Huntington's disease • Motor neuron disease dx <65 or any age with a family history • Early onset dementias (Alzheimer disease, frontotemporal, vascular, Lewy body) dx <65y or any age with a family history • Lysosomal or metabolic disorders • Leukodystrophy or brain malformations • CADASIL

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ALFRED HEALTH RENAL GENETICS REFERRAL GUIDELINES

Referral Indicators
ESKD <50yrs with unclear cause
Multiple renal cysts
Suspected Alport syndrome (*e.g. haematuria, proteinuria, sensory hearing loss etc*) or thin basement membrane nephropathy
>6 months haematuria with no obvious cause – if renal biopsy is not indicated or biopsy is not diagnostic
Haemolytic uraemic syndrome – consider where there are any of the following; • family history of kidney disease • responsive to C5 inhibitor therapy and considering discontinuation • prior to transplant
Patient with chronic or ESKD with previous genetic testing AND where no identified pathogenic variant/s were detected. Consider referral in the following circumstances • Condition has deteriorated and/or where new symptoms have evolved • Requires transplant and a related donor is being considered • Family planning • Genetic testing occurred >3 yrs ago (may be eligible for reanalysis)
Suspected genetic kidney disease based on family history AND/OR presence of ANY of other features; *presentation <35yrs, family history of kidney disease, parental consanguinity, syndromic features including congenital abnormalities, intellectual disability, MODY*
Congenital abnormalities of kidney and urinary tract
UNTESTED patient from a family with a known pathogenic variant/variants in a gene associated with inherited kidney disease/syndrome

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ALFRED HEALTH RESPIRATORY GENETICS REFERRAL GUIDELINES

Referral Indicators
Patients suspected to have an inherited condition such as (but not limited to); • Inherited forms of interstitial lung disease • Primary ciliary dyskinesia • Pulmonary arterial hypertension • Respiratory symptoms, malformations, ID +/- features suggested of inherited syndromic conditions • Cystic Fibrosis
UNTESTED patient from a family with a known pathogenic variant/variants in a gene associated with inherited respiratory disease/syndrome

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