Rare Disease Conditions Eligibility Criteria

100,000 Genomes Project

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Contents

1. Document Version History

Version	Author	Date approved	Summary of main changes and reasons
1.9.0	Andrew Devereau	April 2018	Final Version

2. Purpose of this document

The aim of this document is to provide an up-to-date list of eligibility criteria for conditions approved for recruitment within the Genomics England Rare Diseases Programme.

3. Summary of Changes

The follow table summarises the changes in Rare Disease version 1.9. Only additions have been made to the catalogue: two new diseases have been added to the existing Categories, and a new Category – 'Genomic Medicine Service Indications' – has been added containing a new subcategory 'Whole Genome Sequencing Indications' and 22 new diseases. These new items are highlighted in yellow. The Genomic Medicine Service Indications will be available as first line tests in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use them as a first line test or in parallel to, or following, current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria.

Category	Subcategory	Disease
Motor and Sensory Disorders of the PNS (10991)	Motor and sensory disorders of the PNS (10991)	Pain channelopathies (82148)
Renal and urinary tract disorders (11000)	Syndromes with prominent renal abnormalities (11001)	Familial IgA nephropathy and IgA vasculitis (82147)
Genomic medicine service indications (82157)	Whole genome sequencing indications (82159)	GMS R14 Acutely unwell infants with a likely monogenic disorder (82160)
		GMS R27 Congenital malformation and dysmorphism syndromes - likely monogenic (82161)
		GMS R69 Floppy infant with a likely central cause (82162)
		GMS R29 Moderate, severe or profound intellectual disability (82163)
		GMS R89 Ultra-rare and atypical monogenic disorders (82164)
		GMS R100 Rare syndromic craniosynostosis or isolated multisuture synostosis (82165)

		GMS R104 Skeletal dysplasia (82166)
		GMS R143 Neonatal diabetes (82167)
		GMS R98 Likely inborn error of metabolism - targeted testing not possible (82168)
		GMS R83 Arthrogryposis (82185)
		GMS R84 Cerebellar anomalies (82169)
		GMS R87 Cerebral malformation (82170)
		GMS R61 Childhood onset hereditary spastic paraplegia (82171)
		GMS R109 Childhood onset leukodystrophy (82172)
		GMS R59 Early onset or syndromic epilepsy (82173)
		GMS R54 Hereditary ataxia with onset in adulthood (82174)
		GMS R55 Hereditary ataxia with onset in childhood (82175)
		GMS R85 Holoprosencephaly - NOT chromosomal (82176)
		GMS R86 Hydrocephalus (82177)
		GMS R381 Other rare neuromuscular disorders (82178)
		GMS R88 Severe microcephaly (82179)
		GMS R193 Cystic renal disease (82180)

4. Structure and background to eligibility statements

For each disease listed we provide an "eligibility statement" composed of the following key information:

1. Inclusion criteria – the clinical features, characteristics or investigations that probands with a given disease must have in order to be eligible for recruitment.

2. Exclusion criteria - the clinical features, characteristics or investigation findings that participants with a given disease must not have in order to be eligible for recruitment.

3. Prior genetic testing – this sets out both in general terms, and where appropriate more specifically, the genetic testing which participants with a given disease must have performed prior to recruitment.

Each eligibility statement has been informed by at least one clinician specialising in the field and incorporates comments provided during the consultation period with Genomic Medicine Centres. Therefore, we would like to take this opportunity to thank this community for providing their expertise and understanding of complex disorders so generously.

Given the rapid progress in the understanding of rare diseases worldwide, it is important that the eligibility statements continue to be reviewed and developed over time in light of new discoveries and changes in clinical practice. Therefore we will continue our engagement with the clinical community throughout the lifetime of the project.

5. Rare Disease Conditions Eligibility Criteria

Cardiovascular disorders (10950)

Arteriopathies (33332)

Familial cerebral small vessel disease (36469)

Level 3 Title	Arteriopathies (33332)
Level 4 Title	Familial cerebral small vessel disease (36469)
Eligibility Statement	**Familial cerebral small vessel disease inclusion criteria** • Clinical features consistent with cerebral small vessel disease: either lacunar stroke or vascular cognitive impairment/dementia, AND • MRI confirmed evidence of cerebral small vessel disease as evidenced by; multiple lacunar infarcts and/or confluent white matter hyperintensities, AND • Early onset cerebral SVD (<60 years) without cardiovascular risk factors or affected first degree family member Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Familial cerebral small vessel disease exclusion criteria** • Causes of white matter disease other than cerebral small vessel disease (e.g. multiple sclerosis, vasculitis, leukodystrophy). • Cases with NOTCH3 mutations **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established.

	It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial cerebral small vessel disease prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: NOTCH3 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial Hypercholesterolaemia (33666)

Level 3 Title	Arteriopathies (33332)
Level 4 Title	Familial Hypercholesterolaemia (33666)
Eligibility Statement	**Familial Hypercholesterolaemia inclusion criteria** Lipid levels either pre-treatment or highest on treatment: • Simon Broome criteria 'definite familial hypercholesterolaemia': • Abnormal lipids: -Total cholesterol > 6.7 mmol/l (260 mg/dl), or LDL cholesterol above 4.0 mmol/l in a child < 16 years, OR -Total cholesterol >7.5 mmol/l (290 mg/dl), or LDL cholesterol above 4.9 mmol/l (190 mg/dl) in an adult AND -Tendon xanthomas (TX) in patient, or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt) OR • Abnormal lipids: -Total cholesterol > 6.7 mmol/l (260 mg/dl), or LDL cholesterol above 4.0 mmol/l in a child < 16 years, OR -Total cholesterol >8.5 mmol/l, or LDL cholesterol above 5.5 mmol/l in an adult AND - Family history of myocardial infarction below age of 50 in 2nd degree relative or below age 60 in 1st degree relative, OR - Family history of raised cholesterol: >7.5 mmol/l in adult 1st or 2nd degree relative or > 6.7 mmol/l in child or sibling under 16 AND • Polygenic risk 12-SNP gene score in the bottom two quartiles Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Familial Hypercholesterolaemia exclusion criteria** • Secondary causes of elevated LDL-C. Patients will only be eligible who have elevated LDL-C on measures taken on a fasting blood sample and after secondary causes of hyperlipidaemia have been excluded. • Recessive inheritance. Families showing a recessive pattern of inheritance will not be recruited • Individuals with a fasting plasma Triglyceride level of over 2.5mmol/l will be excluded. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome

	sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial Hypercholesterolaemia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: LDLR, APOB and PCSK9 Polygenic risk 12-SNP gene score **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Severe hypertriglyceridaemia (42185)

Level 3 Title	Arteriopathies (33332)
Level 4 Title	Severe hypertriglyceridaemia (42185)
Eligibility Statement	**Severe hypertriglyceridaemia inclusion criteria** Triglycerides >20mmol/L AND one of Asymptomatic, OR Acute pancreatitis event, OR Eruptive xanthomata Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Severe hypertriglyceridaemia exclusion criteria** Hypertriglyceridaemia secondary to excess alcohol intake (>30 units/week) Hypertriglyceridaemia secondary to uncontrolled diabetes (HbA1c >8%) Known lipodystrophy syndrome- genetic or acquired Known mitochondrial myopathy Use of anti-retroviral drug therapies **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Severe hypertriglyceridaemia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: LPL, APOA5, APOC2, GPIHBP1, LMF1

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Familial Thoracic Aortic Aneurysm Disease (11021)

Level 3 Title	Connective Tissues Disorders and Aortopathies (10951)
Level 4 Title	Familial Thoracic Aortic Aneurysm Disease (11021)
Eligibility Statement	Relevant Diseases: - Familial Thoracic Aortic Aneurysm and dissection - Thoracic aortopathy < 50 years with no other established risk factors - Clinically diagnosed Marfan syndrome with no FBN1 mutation - Loeys-Dietz syndrome and Loeys-Dietz syndrome like conditions - Mutation negative Congenital Contractural Arachnodactyly (Beals syndrome) **Familial Thoracic Aortic Aneurysm Disease inclusion criteria (Conditions)** - patients suspected to have the above conditions Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Familial Thoracic Aortic Aneurysm Disease exclusion criteria:** - Sporadic thoracic aortopathies with risk factors - Family history with no affected proband to test **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial Thoracic Aortic Aneurysm Disease prior genetic testing genes:** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Loeys-Dietz syndrome TGFBR1 and TGFBR2 - Marfan Syndrome FBN1

	- Congenital Contractural Arachnodactyly FBN2 - Isolated familial thoracic aortic aneurysms and dissection - ACTA2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Brugada syndrome (11022)

Level 3 Title	Cardiac arrhythmia (10952)
Level 4 Title	Brugada syndrome (11022)
Eligibility Statement	**Brugada inclusion criteria (clinical diagnosis)** Brugada syndrome diagnosed according to criteria*: - ST segment elevation with type I morphology >= 2 mm in >= 1 lead among the right precordial leads V1,V2 positioned in the 2nd, 3rd, or 4th intercostal space occurring spontaneously OR - Type I ECG morphology as above following a provocative drug test with intravenous administration of Class I antiarrhythmic drugs AND one of - A positive family history of young sudden death OR Brugada syndrome OR - Cardiac arrest with spontaneous type I ECG pattern, OR - Documented history of VF or polymorphic VT, OR - Syncope of likely arrhythmic cause, OR - Nocturnal agonal respiration * Heart Rhythm Society/European Heart Rhythm Association Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Brugada exclusion criteria (unclear diagnosis)** - Unclear diagnosis or history suggestive of a non-genetic cause - Any Brugada syndrome mutation positive (if clearly pathogenic) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established.

	It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Brugada prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: SCN5A **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Long QT syndrome (11023)

Level 3 Title	Cardiac arrhythmia (10952)
Level 4 Title	Long QT syndrome (11023)
Eligibility Statement	**Long QT inclusion criteria** LQTS diagnosed according to criteria*: LQTS risk score >= 3.5 in the absence of a secondary cause for QT prolongation, OR Corrected QT interval for heart rate using Bazett's formula (QTc) >= 500ms in repeated 12 lead electrocardiogram (ECG) and in the absence of a secondary cause for QT prolongation, OR QTc between 480 and 499ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation * Heart Rhythm Society/European Heart Rhythm Association Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Long QT exclusion criteria** - Unclear diagnosis or history suggestive of a non-genetic cause - Any LQTS mutation positive (if clearly pathogenic) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Long QT syndrome prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - KCNQ1, KCNH2 and SCN5A

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Catecholaminergic Polymorphic Ventricular Tachycardia (11024)

Level 3 Title	Cardiac arrhythmia (10952)
Level 4 Title	Catecholaminergic Polymorphic Ventricular Tachycardia (11024)
Eligibility Statement	**Catecholaminergic Polymorphic Ventricular Tachycardia inclusion criteria** CPVT diagnosed according to criteria*: - In the presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine induced bidirectional VT or polymorphic ventricular premature beats (VPBs) or VT in an individual younger than 40 years. OR - In the presence of a structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic VPBs or VT in an individual older than 40 years. * Heart Rhythm Society/European Heart Rhythm Association Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Catecholaminergic Polymorphic Ventricular Tachycardia exclusion criteria** - Unclear diagnosis or history suggestive of a non-genetic cause - Any CPVT mutation positive (if clearly pathogenic) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Catecholaminergic Polymorphic Ventricular Tachycardia prior genetic testing genes**

	Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: RYR2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Unexplained sudden death in the young (38566)

Level 3 Title	Cardiac arrhythmia (10952)
Level 4 Title	Unexplained sudden death in the young (38566)
Eligibility Statement	**Unexplained sudden death in the young inclusion criteria** • Sudden death at age less than or equal to 40 (including Sudden Infant Death Syndrome), AND • No diagnosis established on post mortem examination, AND • Absence of a pre-existing condition to explain the death. • Parents should be recruited under this category in paediatric cases if available • In adult cases the deceased individual should be recruited as a singleton; if surviving relatives have a phenotype which points to a particular condition, they should be the focus of further investigation or recruitment to the programme. • Surviving relatives must be available to provide appropriate consent. **Unexplained sudden death in the young exclusion criteria** • Death in the context of a known diagnosed disease or accident • Cause of death determined by post mortem examination • No post mortem examination carried out • No DNA or frozen tissue stored at post mortem. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Unexplained sudden death in the young prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes listed **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Idiopathic ventricular fibrillation (42161)

Level 3 Title	Cardiac arrhythmia (10952)
Level 4 Title	Idiopathic ventricular fibrillation (42161)
Eligibility Statement	**Idiopathic ventricular fibrillation inclusion criteria** Proband with unexplained documented VF cardiac arrest despite comprehensive clinical evaluation PLUS EITHER A. Juvenile sporadic VF (Age 1-18 years). Recruitment should be as trios. OR B. Idiopathic VF aged 1-45 years with family history of idiopathic VF or SADS in a first, second or third degree relative. In category B, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. **Idiopathic ventricular fibrillation exclusion criteria** Age of disease <1 or >45y in proband or qualifying relative, OR Known inherited arrhythmogenic disorder identified on clinical evaluation **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Idiopathic ventricular fibrillation prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes specified

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Short QT syndrome (55487)

Level 3 Title	Cardiac arrhythmia (10952)
Level 4 Title	Short QT syndrome (55487)
Eligibility Statement	**Short QT syndrome inclusion criteria** QTc interval of less than or equal to 330 ms, OR QTc interval of less than 360 ms AND one or more of • Family history of SQTS • Family history of sudden death at age less than or equal to 40 years • Survival of otherwise unexplained episode of ventricular tachycardia/fibrillation. (derived from: 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. Priori et al. Heart Rhythm 2013 Dec; 10(12): 1932-1963. doi: 10.1016/j.hrthm.2013.05.014.) **Short QT syndrome exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Short QT syndrome prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: KCNH2, KCNQ1, KCNJ2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Arrhythmogenic Right Ventricular Cardiomyopathy (11025)

Level 3 Title	Cardiomyopathy (10953)
Level 4 Title	Arrhythmogenic Right Ventricular Cardiomyopathy (11025)
Eligibility Statement	Relevant diseases: - Arrhythmogenic right ventricular cardiomyopathy (ARVC) - Dilated cardiomyopathy - Dilated cardiomyopathy and conduction defects **Cardiomyopathies inclusion criteria (Plural)** - Patients with a clear diagnosis and at least one affected relative , OR - Patients with no family history who have a clear diagnosis of primary hypertrophic cardiomyopathy under 40 years of age Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Cardiomyopathies exclusion criteria** - Unclear diagnosis or history suggestive of a non-genetic cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Arrhythmogenic Right Ventricular Cardiomyopathy prior genetic testing genes**

	Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - ARVC - PKP2 - DSP - DSG2 - DSC2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Left Ventricular Noncompaction Cardiomyopathy (15044)

Level 3 Title	Cardiomyopathy (10953)
Level 4 Title	Left Ventricular Noncompaction Cardiomyopathy (15044)
Eligibility Statement	Relevant diseases: - Left ventricular non-compaction cardiomyopathy - Dilated cardiomyopathy - Hypertrophic cardiomyopathy **Cardiomyopathies inclusion criteria (Plural)** - Patients with a clear diagnosis and at least one affected relative , OR - Patients with no family history who have a clear diagnosis of primary hypertrophic cardiomyopathy under 40 years of age Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Cardiomyopathies exclusion criteria** - Unclear diagnosis or history suggestive of a non-genetic cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Left Ventricular Noncompaction and Hypertrophic Cardiomyopathy prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - MYBPC3, MYH7, TNNT2 and TNNI3

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Dilated Cardiomyopathy (31340)

Level 3 Title	Cardiomyopathy (10953)
Level 4 Title	Dilated Cardiomyopathy (31340)
Eligibility Statement	**Cardiomyopathies inclusion criteria (Plural)** - Patients with a clear diagnosis and at least one affected relative , OR - Patients with no family history who have a clear diagnosis of primary hypertrophic cardiomyopathy under 40 years of age Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Cardiomyopathies exclusion criteria** - Unclear diagnosis or history suggestive of a non-genetic cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Dilated Cardiomyopathy prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: ABCC9, ACTC1, CSRP3, LMNA, MYH7, PLN, TNNI3, TNNT2, TPM1, TTN, RBM20 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Dilated Cardiomyopathy and conduction defects (11027)

Level 3 Title	Cardiomyopathy (10953)
Level 4 Title	Dilated Cardiomyopathy and conduction defects (11027)
Eligibility Statement	Relevant diseases: - Dilated cardiomyopathy - Dilated cardiomyopathy and conduction defects **Cardiomyopathies inclusion criteria (Plural)** - Patients with a clear diagnosis and at least one affected relative , OR - Patients with no family history who have a clear diagnosis of primary hypertrophic cardiomyopathy under 40 years of age Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Cardiomyopathies exclusion criteria** - Unclear diagnosis or history suggestive of a non-genetic cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Dilated Cardiomyopathy and conduction defects prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: LMNA

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Hypertrophic Cardiomyopathy (11028)

Level 3 Title	Cardiomyopathy (10953)
Level 4 Title	Hypertrophic Cardiomyopathy (11028)
Eligibility Statement	Relevant diseases: - Left ventricular non-compaction cardiomyopathy - Dilated cardiomyopathy - Hypertrophic cardiomyopathy **Cardiomyopathies inclusion criteria (Plural)** - Patients with a clear diagnosis and at least one affected relative , OR - Patients with no family history who have a clear diagnosis of primary hypertrophic cardiomyopathy under 40 years of age Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Cardiomyopathies exclusion criteria** - Unclear diagnosis or history suggestive of a non-genetic cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Left Ventricular Noncompaction and Hypertrophic Cardiomyopathy prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - MYBPC3, MYH7, TNNT2 and TNNI3

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Familial congenital heart disease (42212)

Level 3 Title	Congenital heart disease (10954)
Level 4 Title	Familial congenital heart disease (42212)
Eligibility Statement	**Familial congenital heart disease inclusion criteria** Congenital heart disease AND one or more of the following: One or more first degree relative with congenital heart disease, OR Parental consanguinity Individuals with severe or syndromic disease or with consanguinity and a pedigree in keeping with autosomal recessive inheritance should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Familial congenital heart disease exclusion criteria** Recognised syndromic presentation (e.g. Noonan syndrome) Likely causative environmental insult during gestation **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial congenital heart disease prior genetics testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes specified

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Syndromic congenital heart disease (42213)

Level 3 Title	Congenital heart disease (10954)
Level 4 Title	Syndromic congenital heart disease (42213)
Eligibility Statement	**Syndromic congenital heart disease inclusion criteria** Congenital heart disease, AND One or more malformations outside the cardiovascular system or neurodevelopmental delay **Syndromic congenital heart disease exclusion criteria** Recognised syndromic presentation (e.g. Noonan syndrome) Likely causative environmental insult during gestation **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Syndromic congenital heart disease prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: Microarray genome wide copy number analysis; further testing as dictated by phenotype **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Meige disease (34328)

Level 3 Title	Lymphatic disorders (33334)
Level 4 Title	Meige disease (34328)
Eligibility Statement	**Meige disease inclusion criteria** • Non-congenital lower limb lymphoedema • Multiple affected individuals in the pedigree with family history consistent with autosomal dominant inheritance • Lymphoscintigram (where available) suggestive of deep rerouting with the presence of popliteal nodes **Meige disease exclusion criteria** • Congenital lymphoedema • Lymphoedema of any other segment (e.g. hands/arms/face/genitalia) • Systemic lymphoedema (e.g. intestinal or pulmonary lymphangiectasia, pleural or pericardial effusions) • No family history of lymphoedema • Syndromic lymphoedema including any major structural malformations • Distichiasis (aberrant eyelashes arising from the meibomian glands) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Meige disease prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes listed **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Milroy disease (37604)

Level 3 Title	Lymphatic disorders (33334)
Level 4 Title	Milroy disease (37604)
Eligibility Statement	**Milroy disease inclusion criteria** • Congenital lower limb lymphoedema, AND • Lymphoscintigram (where available) suggestive of functional aplasia **Milroy disease exclusion criteria** • Non-congenital lymphoedema • Lymphoedema of any other segment (e.g. arms/face) • Syndromic lymphoedema or microcephaly or major structural malformation. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Milroy disease prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - FLT4 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Lymphoedema distichiasis (37612)

Level 3 Title	Lymphatic disorders (33334)
Level 4 Title	Lymphoedema distichiasis (37612)
Eligibility Statement	**Lymphoedema distichiasis inclusion criteria** • Non-congenital lower limb lymphoedema, AND • Distichiasis (extra eyelashes arising from the inner eyelid), AND • Family history (if present) consistent with autosomal dominant inheritance, AND • Lymphoscintigram (where available) suggestive of reflux or rerouting **Lymphoedema distichiasis exclusion criteria** • Congenital lymphoedema • Lymphoedema of any other segment (e.g. arms/face) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Lymphoedema distichiasis prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: FOXC2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Lipoedema disease (55456)

Level 3 Title	Lymphatic disorders (33334)
Level 4 Title	Lipoedema disease (55456)
Eligibility Statement	**Lipoedema disease inclusion criteria** Clear clinical diagnosis of lipoedema, AND all of the following: • Female • Onset of abnormal fat distribution at, or around puberty • Waist hip ratio less than 0.80 **Lipoedema disease exclusion criteria** Lymph scan suggestive of underlying lymphoedema **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Lipoedema disease prior genetic testing genes** **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Primary lymphoedema (55517)

Level 3 Title	Lymphatic disorders (33334)
Level 4 Title	Primary lymphoedema (55517)
Eligibility Statement	**Primary lymphoedema inclusion criteria** Lymphoedema of any extremity, face or genital area, AND Lymphoscintigram (where available) suggestive of impaired lymphatic drainage (bilateral in lower limbs or upper limbs), AND One or more of the following: • Family history of lymphoedema in a first or second degree relative • Bilateral involvement • Age of onset less than 40 years • Consanguineous parents **Primary lymphoedema exclusion criteria** Secondary lymphoedema Previously identified causative mutation **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Primary lymphoedema prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: Dependent on phenotype including consideration of FLT4, PIEZO1 or FOXC2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Pulmonary arterial hypertension (55499)

Level 3 Title	Pulmonary heart disease (55662)
Level 4 Title	Pulmonary arterial hypertension (55499)
Eligibility Statement	**Pulmonary arterial hypertension inclusion criteria** Unexplained pulmonary arterial hypertension (PAH) or pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis* The diagnosis of PAH/PVOD is defined by the presence of pre-capillary pulmonary hypertension. This is established at the time of right heart catheterisation by an increase in mean pulmonary arterial pressure (PAPm) greater than 25 mmHg at rest, by a pulmonary artery wedge pressure (PAWP) less than 15 mmHg and a pulmonary vascular resistance (PVR) greater than 3 Wood units (WU) in the absence of other causes of pre-capillary pulmonary hypertension, such as that due to lung diseases, embolic disease, or other rare diseases (see exclusion criteria). **Pulmonary arterial hypertension exclusion criteria** Left heart disease; Lung disease/hypoxaemia; other disease with likely causative role (including myeloproliferative disorders, sarcoidosis, vasculitis, NF1, HIV, sickle cell disease) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Pulmonary arterial hypertension prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: BMPR2, ACVRL1(ALK1), ENG, SMAD9 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Congenital malformations caused by ciliopathies (15091)

Bardet-Biedl Syndrome (11046)

Level 3 Title	Congenital malformations caused by ciliopathies (15091)
Level 4 Title	Bardet-Biedl Syndrome (11046)
Eligibility Statement	**Bardet-Biedl Syndrome inclusion criteria** - unexplained rod-cone dystrophy/ retinal dystrophy OR - at least two of the major diagnostic features associated with Bardet-Biedl syndrome: - Obesity - Polydacyly - Rod-cone dystrophy/ retinal dystrophy/ retinitis pigmentosa - Hypogenitalism - Renal dysplasia **Bardet-Biedl Syndrome exclusion criteria** - non-syndromic retinitis pigmentosa without features suggestive of rod-cone dystrophy/ cone-rod dystrophy - existing molecular confirmation of a diagnosis of Bardet-Biedl syndrome or another ciliopathy **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Bardet-Biedl Syndrome prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) - ARL6, ALMS1, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, MKKS, MKS1 and TTC8 **Closing statement**

	These requirements will be kept under continual review during the main programme and may be subject to change.

Joubert syndrome (36478)

Level 3 Title	Congenital malformations caused by ciliopathies (15091)
Level 4 Title	Joubert syndrome (36478)
Eligibility Statement	**Joubert syndrome inclusion criteria** • A confident clinical diagnosis of Joubert syndrome or Joubert syndrome related disorder based on the presence of the characteristic 'molar tooth sign' in axial MRI images confirmed by a neuroradiologist experienced in the diagnosis of Joubert syndrome. With or without other supportive features of Joubert syndrome. OR • Probable 'molar tooth sign' in the presence of additional features of Joubert syndrome: polydactyly, renal cysts, retinal dystrophy, oculomotor apraxia or the characteristic breathing abnormality **Joubert syndrome exclusion criteria** Known genetic cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Joubert syndrome prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: • Joubert syndrome gene panel including AHI1, CC2D2A, CEP290, TMEM67 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Rare multisystem ciliopathy disorders (36488)

Level 3 Title	Congenital malformations caused by ciliopathies (15091)
Level 4 Title	Rare multisystem ciliopathy disorders (36488)
Eligibility Statement	**Rare multisystem ciliopathy disorders inclusion criteria** A clinical diagnosis of a rare multisystem ciliopathy including oral-facial-digital syndromes, cranioectodermal dysplasia OR an unclassified rare multisystem ciliopathy based on the presence of two or more core ciliopathy features: two or more core features indicative of a ciliopathy: • renal dysplasia, polycystic or 'bright' kidneys; • cerebellar hypoplasia (especially vermis where visible) / Dandy-Walker malformation or variant; • polydactyly; • short limbs and/or short ribs; • occipital encephalocele • retinal dystrophy This category would be appropriate for fetuses where they meet the above criteria **Rare multisystem ciliopathy disorders exclusion criteria** • A known genetic cause. • A specific diagnosis of Bardet-Biedl syndrome or other ciliopathy with specific recruitment criteria within the 100,000 Genomes project. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Rare multisystem ciliopathy disorders prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - As dictated by the phenotype including particular consideration of OFD1. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Respiratory ciliopathies (15092)

Primary ciliary dyskinesia (11047)

Level 3 Title	Respiratory ciliopathies (15092)
Level 4 Title	Primary ciliary dyskinesia (11047)
Eligibility Statement	**Primary ciliary dyskinesia inclusion criteria** - Evidence of chronic sinopulmonary disease as indicated by symptoms and signs including a life-long, wet sounding cough and nasal symptoms, neonatal respiratory distress and chest radiograph with chronic abnormalities. - With or without situs inversus totalis or heterotaxy - With or without infertility - If over 4 years of age nasal Nitric Oxide testing available - With high-speed video analysis showing characteristic disordered ciliary motility, or absent cilia on repeat testing - With transmission electron microscopy results available **Primary ciliary dyskinesia exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Primary ciliary dyskinesia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - DNAH5, DNAH11, CCDC103, CCDC39, CCDC40, DNAI1 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Non-CF bronchiectasis (11048)

Level 3 Title	Respiratory ciliopathies (15092)
Level 4 Title	Non-CF bronchiectasis (11048)
Eligibility Statement	**Non-CF bronchiectasis inclusion Critieria** • FEV1< 30% predicted and 4 lobes involved in bronchiectasis < aged 50 OR • Extensive multilobar disease OR • 2 or greater immediate family members affected OR • High chloride in sweat test but CFTR mutation analysis (including extended NHS funded analysis) negative OR • Bronchiectasis with any suspected underlying immunodeficiency aspect to be cross referenced with immunodeficiency GeCiP, e.g. bronchiectasis and recurrent non pulmonary infections OR • Bronchiectasis with any suspected underlying ciliopathy OR • Young's Syndrome OR • Mounier Kuhn syndrome (tracheobronchomegaly) **Non-CF bronchiectasis exclusion Critieria** Late onset, single lobe disease and those where Asthma or COPD are felt much more clearly the primary driver/ aetiology of the bronchiectasis **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Non-CF bronchiectasis prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - CFTR where clinically indicated

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Dermatological disorders (10956)

Atopy (15084)

Severe multi-system atopic disease with high IgE (15085)

Level 3 Title	Atopy (15084)
Level 4 Title	Severe multi-system atopic disease with high IgE (15085)
Eligibility Statement	**Severe multi-system atopic disease with high IgE inclusion criteria** - All of the following are required: - Adult patients only - Onset of patients' medical problems is in early childhood (often < 1 year old) - Severe persistent eczema (severe means requiring treatment over and above safe use of potent topical steroids, e.g. topical calcineurin inhibitors, UV light treatment or systemic immunosuppression: azathioprine, cyclosporine A, methotrexate, mycophenolate). Where topical calcineurin inhibitors are used as first line treatment and achieve good symptom control patients should only be included if serum IgE >10000. - Recurrent or chronic S. aureus skin infections, but this criterion may be absent if the patient is receiving systemic immunosuppressive treatment. - Asthma, but the severity can vary from mild to severe - High IgE levels >5000 - Sensitised to a wide variety of aero-allergens and food allergens as measured by ImmunoCAP tests. **Severe multi-system atopic disease with high IgE exclusion criteria** - Those with systemic infections (unlike patients with classical hyper IgE syndrome) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Autoimmune skin disorders (33336)

Generalised pustular psoriasis (33646)

Level 3 Title	Autoimmune skin disorders (33336)
Level 4 Title	Generalised pustular psoriasis (33646)
Eligibility Statement	**Generalised pustular psoriasis inclusion criteria** • Presence of primary, sterile, macroscopically visible epidermal pustules on non-acral skin • More than one episode of acute pustulation • Diagnosis confirmed by consultant dermatologist **Generalised pustular psoriasis exclusion criteria** • Cases where pustulation is restricted to psoriatic plaques **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Generalised pustular psoriasis prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes listed **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Ectodermal dysplasia without a known gene mutation (33699)

Level 3 Title	Ectodermal dysplasias (33338)
Level 4 Title	Ectodermal dysplasia without a known gene mutation (33699)
Eligibility Statement	**Ectodermal dysplasia without a known gene mutation inclusion criteria** - Ectodermal dysplasia i.e. abnormality of at least two of the following: - nails - teeth - hair - sweating - With or without additional phenotypic features e.g. clefting, limb defects, hearing loss. **Ectodermal dysplasia without a known gene mutation exclusion criteria** • Mutation in known ectodermal dysplasia gene **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Ectodermal dysplasia without a known gene mutation prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - According to phenotype: EDA, EDAR, EDARADD, WNT10A and/or TP63 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Autosomal recessive congenital ichthyosis (33700)

Level 3 Title	Ichthyoses (33340)
Level 4 Title	Autosomal recessive congenital ichthyosis (33700)
Eligibility Statement	**Autosomal recessive congenital ichthyosis inclusion criteria** • Neonates, infants, children and adults with a history of generalised red, dry, peeling skin at birth with a mode of inheritance consistent with autosomal recessive transmission • Diagnosis confirmed by consultant dermatologist **Autosomal recessive congenital ichthyosis exclusion criteria** • Ichthyosis vulgaris • STS-related ichthyosis • Syndromic ichthyosis • Keratinopathic ichthyosis • Acquired ichthyosis **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Autosomal recessive congenital ichthyosis prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: TGM1, ALOXE3, ALOX12B, NIPAL4, CYP4F22 and, where appropriate, STS and ABCA12 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Palmoplantar keratoderma and erythrokeratodermas (33701)

Level 3 Title	Keratodermas (33342)
Level 4 Title	Palmoplantar keratoderma and erythrokeratodermas (33701)
Eligibility Statement	**Palmoplantar keratoderma and erythrokeratodermas inclusion criteria** Diagnosis of one of the following confirmed by consultant dermatologist: • Diffuse palmoplantar keratoderma • Focal keratoderma with or without nail involvement • Pachyonychia congenita phenotype (focal keratoderma with pain and dystrophic nails, oral leukokeratosis and or follicular hyperkeratoses/cysts). • Punctate keratoderma • Striate keratoderma alone • Striate keratoderma with woolly hair • Keratoderma with deafness • Unusual/unique rare keratodermas occuring alone or as part of syndromes. • Erythrokeratoderma **Palmoplantar keratoderma and erythrokeratodermas exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Palmoplantar keratoderma and erythrokeratodermas prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Diffuse palmoplantar keratoderma: KRT9 and KRT1 - Focal keratoderma: KRT16 and KRT6C - Pachyonychia congenital: KRT6A, KRT6B, KRT6C, KRT16 and KRT17 - Striate keratoderma: KRT1 and KRT16 -Striate keratoderma with woolly hair: cardiac panel including desmosomal genes

	-Keratoderma with deafness: GJB2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial disseminated superficial actinic porokeratosis (37644)

Level 3 Title	Keratodermas (33342)
Level 4 Title	Familial disseminated superficial actinic porokeratosis (37644)
Eligibility Statement	**Familial disseminated superficial actinic porokeratosis inclusion criteria** • Clinical diagnosis of DSAP, AND • At least 2 affected members over 2 generations, AND • If there is any clinical doubt, skin biopsy confirmation should be sought **Familial disseminated superficial actinic porokeratosis exclusion criteria** • Mibelli, palmoplantar, punctate, sweat duct naevus-related DSAP **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial disseminated superficial actinic porokeratosis prior genetic testing genes** No genes listed **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Undiagnosed neurocutaneous disorders (33686)

Level 3 Title	Neurocutaneous disorders (33344)
Level 4 Title	Undiagnosed neurocutaneous disorders (33686)
Eligibility Statement	**Undiagnosed neurocutaneous disorders inclusion criteria** All of the following: 1) Abnormal skin pigmentation (café au lait pigmentation, or hypopigmentation, or both) 2) Affected individual has a family history of abnormal skin pigmentation in a first degree relative or is the offspring of a consanguineous relationship 3) Neurological phenotype in at least two of the family members who have skin pigmentary abnormalities (seizures or developmental delay or evidence of congenital abnormality on MRI scan) 4) No diagnosis after assessment by Dermatologist, Neurologist and Geneticist 5) No evidence of chromosomal abnormality on karyotype 6) No pathogenic mutations in the NF1 gene if the child is too young to definitely exclude neurofibromatosis type 1 clinically, and the phenotype could potentially be compatible with that diagnosis **Undiagnosed neurocutaneous disorders exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Undiagnosed neurocutaneous disorders prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: NF1 as indicated above **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial cicatricial alopecia (36588)

Level 3 Title	Skin adnexa disorders (36587)
Level 4 Title	Familial cicatricial alopecia (36588)
Eligibility Statement	**Familial cicatricial alopecia inclusion criteria** • Cicatricial alopecia diagnosed by a consultant dermatologist • Family history of cicatricial alopecia in at least one first or second degree relative **Familial cicatricial alopecia exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial cicatricial alopecia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes listed **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial hidradenitis suppurativa (41844)

Level 3 Title	Skin adnexa disorders (36587)
Level 4 Title	Familial hidradenitis suppurativa (41844)
Eligibility Statement	**Familial hidradenitis suppurativa inclusion criteria** Clinical diagnosis of hidradenitis suppurativa, AND Two or more additional relatives over two generations or more consistent with autosomal dominant inheritance. At least two additional relatives should be available for recruitment. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Familial hidradenitis suppurativa exclusion criteria** Acne vulgaris or nodulocystic acne as an isolated clinical feature **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial hidradenitis suppurativa prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes specified. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Non-syndromic hypotrichosis (36849)

Level 3 Title	Skin adnexa disorders (36587)
Level 4 Title	Non-syndromic hypotrichosis (36849)
Eligibility Statement	**Non-syndromic hypotrichosis inclusion criteria** • Generalised (not patchy) scalp hypotrichosis from 6 months of age or earlier with no improvement, AND • Patient older than three years **Non-syndromic hypotrichosis exclusion criteria** • Patchy hypotrichosis • Patchy or episodic regrowth • Syndromic congenital hypotrichosis including ectodermal dysplasias, alopecia with vitamin D resistant rickets, hypotrichosis with dysmorphic facies, hypotrichosis with spondyloepimetaphyseal dysplasia **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Non-syndromic hypotrichosis prior genetic testing genes** No genes listed **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Epidermolysis bullosa (33684)

Level 3 Title	Skin fragility disorders (33346)
Level 4 Title	Epidermolysis bullosa (33684)
Eligibility Statement	**Epidermolysis bullosa inclusion criteria** • Patients with inherited skin fragility and a clinical diagnosis of EB of unknown cause • Diagnosis confirmed by a consultant dermatologist **Epidermolysis bullosa exclusion criteria** • Non-EB genetic causes including porphyria or photosensitivity syndromes • Acquired causes including EB acquisita and bullous drug reactions **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Epidermolysis bullosa prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: KRT5, KRT14, PLEC, DSP, PKP1, JUP, TGM5, EXPH5, ITGA3, ITGA6, ITGB4, DST, COL17A1, LAMA3, LAMA3A, LAMB3, LAMC2, COL7A1 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Peeling skin syndrome (36540)

Level 3 Title	Skin fragility disorders (33346)
Level 4 Title	Peeling skin syndrome (36540)
Eligibility Statement	**Peeling skin syndrome inclusion criteria** • Generalised peeling skin with or without atopy, OR • Acral peeling skin (TGM5 mutations excluded), OR • Peeling skin in association with other features, OR AND • Diagnosis of peeling skin syndrome confirmed by consultant dermatogist **Peeling skin syndrome exclusion criteria** • Peeling skin cases that have not had the genetic testing below **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Peeling skin syndrome prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - For those with acral peeling skin: TGM5 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Erythropoietic protoporphyria, mild variant (11037)

Level 3 Title	Sun-exposure related conditions (10958)
Level 4 Title	Erythropoietic protoporphyria, mild variant (11037)
Eligibility Statement	**Erythropoietic protoporphyria, mild variant inclusion criteria** - History of episodic photosensitivity; - No evidence of an alternative cause of photosensitivity; - Onset of symptoms >60 mins after sun exposure and/or atypical symptoms compared to classical EPP photosensitivity and/or resolution of symptoms <48 hours - Raised red cell free protoporphyrin concentration **Erythropoietic protoporphyria, mild variant exclusion criteria** - Normal red cell protoporphyrin concentration **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Erythropoietic protoporphyria, mild variant prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - FECH **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Hydroa vacciniforme (15083)

Level 3 Title	Sun-exposure related conditions (10958)
Level 4 Title	Hydroa vacciniforme (15083)
Eligibility Statement	**Hydroa Vacciniforme inclusion criteria** - All six of the following: - Photosensitivity - Papulovesicular eruption - Typical varioliform scarring - Significantly elevated Epstein-Barr viral load in the blood - Positive phototest responses to UVA - clinical diagnosis must be made by an experienced photodermatologist able to differentiate this from other photodermatoses clinically **Hydroa Vacciniforme exclusion criteria** - No evidence of Epstein-Barr viral infection **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Kabuki (28664)

Kabuki syndrome (10960)

Level 3 Title	Kabuki (28664)
Level 4 Title	Kabuki syndrome (10960)
Eligibility Statement	**Kabuki inclusion criteria** - At least 3 of the typical dysmorphic features: - Arched eyebrows - Sparse lateral one third of the eyebrows - Long palpebral fissures - Everted lower eyelids - Ptosis - Blue sclera - Strabismus - Large dysplastic ears - Flat nasal tip - Broad nasal root - Oligodontia - Abnormal dentition - Full lower lip - Pillowed lower lip - Lip nodules - Lip pits - Micrognathia - AND at least 1 of the following: - Developmental delay or Intellectual disability - Any of the following malformations - Cleft palate - Congenital Heart Defect - Renal malformation - Ocular malformation - Gastrointestinal malformation - Feeding difficulties or Growth retardation - Any of the following neurological problems

- Microcephaly
- Seizures
- Any of the following endocrine/metabolic abnormalities
- Early onset prominent breasts/areola
- Hypoglycaemia
- Growth hormone deficiency
- Diabetes insipidus
- Unconjugated hyperbillirubinemia

- Any of the following limb and skeletal anomalies

- Persistent fetal pads
- Brachydactyly or clinodactyly
- Joint dislocation
- Joint hypermobility

- Any of the following immunological abnormalities

- Frequent infections
- Low Immunoglobulins
- Autoimmunity

Kabuki exclusion criteria
- Those with systemic infections (unlike patients with classical hyper IgE syndrome)

Prior genetic testing guidance
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

Kabuki prior genetic testing genes
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
- KMT2D (MLL2)

Closing statement
These requirements will be kept under continual review during the main programme and may be subject to change.

Noonan syndrome (11039)

Level 3 Title	RASopathies (10961)
Level 4 Title	Noonan syndrome (11039)
Eligibility Statement	Relevant diseases: - Noonan syndrome - Noonan syndrome plus other features - Cardio-facio-cutaneous syndrome - LEOPARD syndrome - Costello syndrome - Legius syndrome **RASopathies inclusion** - At least 2 of the suggestive clinical features: - Early feeding difficulty/ failure to thrive - Relative macrocephaly - Short stature - Developmental disability - At least 1 of: - Cardiomyopathy - Congenital heart disease - Arrhythmia - Suggestive malignancy (bladder carcinoma, Rhabdomyosarcoma, Leukaemia, phaeochromocytoma) - Skin abnormalities (hyperkeratosis, cafe au lait patches, ulerythema oophorogenes, keratosis pilaris, excess palmar skin) **RASopathies exclusion criteria** - Low birth weight for gestation **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established.

	It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **RASopathy Prior Testing Prior Testing Prior Testing Prior Testing Prior Testing prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - PTPN11, RAF1, BRAF, SOS1, KRAS, HRAS, NRAS, SHOC2, CBL, SPRED1, MAP2K1, MAP2K2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Noonan syndrome plus other features (11040)

Level 3 Title	RASopathies (10961)
Level 4 Title	Noonan syndrome plus other features (11040)
Eligibility Statement	Relevant diseases: - Noonan syndrome - Noonan syndrome plus other features - Cardio-facio-cutaneous syndrome - LEOPARD syndrome - Costello syndrome - Legius syndrome **RASopathies inclusion** - At least 2 of the suggestive clinical features: - Early feeding difficulty/ failure to thrive - Relative macrocephaly - Short stature - Developmental disability - At least 1 of: - Cardiomyopathy - Congenital heart disease - Arrhythmia - Suggestive malignancy (bladder carcinoma, Rhabdomyosarcoma, Leukaemia, phaeochromocytoma) - Skin abnormalities (hyperkeratosis, cafe au lait patches, ulerythema oophorogenes, keratosis pilaris, excess palmar skin) **RASopathies exclusion criteria** - Low birth weight for gestation **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

	RASopathy Prior Testing Prior Testing Prior Testing Prior Testing Prior Testing prior genetic testing genes Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - PTPN11, RAF1, BRAF, SOS1, KRAS, HRAS, NRAS, SHOC2, CBL, SPRED1, MAP2K1, MAP2K2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Cardio-facio-cutaneous syndrome (11041)

Level 3 Title	RASopathies (10961)
Level 4 Title	Cardio-facio-cutaneous syndrome (11041)
Eligibility Statement	Relevant diseases: - Noonan syndrome - Noonan syndrome plus other features - Cardio-facio-cutaneous syndrome - LEOPARD syndrome - Costello syndrome - Legius syndrome **RASopathies inclusion** - At least 2 of the suggestive clinical features: - Early feeding difficulty/ failure to thrive - Relative macrocephaly - Short stature - Developmental disability - At least 1 of: - Cardiomyopathy - Congenital heart disease - Arrhythmia - Suggestive malignancy (bladder carcinoma, Rhabdomyosarcoma, Leukaemia, phaeochromocytoma) - Skin abnormalities (hyperkeratosis, cafe au lait patches, ulerythema oophorogenes, keratosis pilaris, excess palmar skin) **RASopathies exclusion criteria** - Low birth weight for gestation **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

	RASopathy Prior Testing Prior Testing Prior Testing Prior Testing Prior Testing prior genetic testing genes Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - PTPN11, RAF1, BRAF, SOS1, KRAS, HRAS, NRAS, SHOC2, CBL, SPRED1, MAP2K1, MAP2K2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

LEOPARD syndrome (11042)

Level 3 Title	RASopathies (10961)
Level 4 Title	LEOPARD syndrome (11042)
Eligibility Statement	Relevant diseases: - Noonan syndrome - Noonan syndrome plus other features - Cardio-facio-cutaneous syndrome - LEOPARD syndrome - Costello syndrome - Legius syndrome **RASopathies inclusion** - At least 2 of the suggestive clinical features: - Early feeding difficulty/ failure to thrive - Relative macrocephaly - Short stature - Developmental disability - At least 1 of: - Cardiomyopathy - Congenital heart disease - Arrhythmia - Suggestive malignancy (bladder carcinoma, Rhabdomyosarcoma, Leukaemia, phaeochromocytoma) - Skin abnormalities (hyperkeratosis, cafe au lait patches, ulerythema oophorogenes, keratosis pilaris, excess palmar skin) **RASopathies exclusion criteria** - Low birth weight for gestation **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

	RASopathy Prior Testing Prior Testing Prior Testing Prior Testing Prior Testing prior genetic testing genes Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - PTPN11, RAF1, BRAF, SOS1, KRAS, HRAS, NRAS, SHOC2, CBL, SPRED1, MAP2K1, MAP2K2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Costello syndrome (11043)

Level 3 Title	RASopathies (10961)
Level 4 Title	Costello syndrome (11043)
Eligibility Statement	Relevant diseases: - Noonan syndrome - Noonan syndrome plus other features - Cardio-facio-cutaneous syndrome - LEOPARD syndrome - Costello syndrome - Legius syndrome **RASopathies inclusion** - At least 2 of the suggestive clinical features: - Early feeding difficulty/ failure to thrive - Relative macrocephaly - Short stature - Developmental disability - At least 1 of: - Cardiomyopathy - Congenital heart disease - Arrhythmia - Suggestive malignancy (bladder carcinoma, Rhabdomyosarcoma, Leukaemia, phaeochromocytoma) - Skin abnormalities (hyperkeratosis, cafe au lait patches, ulerythema oophorogenes, keratosis pilaris, excess palmar skin) **RASopathies exclusion criteria** - Low birth weight for gestation **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

	RASopathy Prior Testing Prior Testing Prior Testing Prior Testing Prior Testing prior genetic testing genes Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - PTPN11, RAF1, BRAF, SOS1, KRAS, HRAS, NRAS, SHOC2, CBL, SPRED1, MAP2K1, MAP2K2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Legius syndrome (11044)

Level 3 Title	RASopathies (10961)
Level 4 Title	Legius syndrome (11044)
Eligibility Statement	Relevant diseases: - Noonan syndrome - Noonan syndrome plus other features - Cardio-facio-cutaneous syndrome - LEOPARD syndrome - Costello syndrome - Legius syndrome **RASopathies inclusion** - At least 2 of the suggestive clinical features: - Early feeding difficulty/ failure to thrive - Relative macrocephaly - Short stature - Developmental disability - At least 1 of: - Cardiomyopathy - Congenital heart disease - Arrhythmia - Suggestive malignancy (bladder carcinoma, Rhabdomyosarcoma, Leukaemia, phaeochromocytoma) - Skin abnormalities (hyperkeratosis, cafe au lait patches, ulerythema oophorogenes, keratosis pilaris, excess palmar skin) **RASopathies exclusion criteria** - Low birth weight for gestation **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

	RASopathy Prior Testing Prior Testing Prior Testing Prior Testing Prior Testing prior genetic testing genes Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - PTPN11, RAF1, BRAF, SOS1, KRAS, HRAS, NRAS, SHOC2, CBL, SPRED1, MAP2K1, MAP2K2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Balanced translocations with an unusual phenotype (11045)

Level 3 Title	Balanced translocations (10962)
Level 4 Title	Balanced translocations with an unusual phenotype (11045)
Eligibility Statement	**Balanced translocations with an unusual phenotype inclusion criteria** - De novo translocation where extreme phenotype present - Familial balanced translation that co-segregates with disease - Routine investigations pertaining to the presenting phenotype have been carried out with normal results - Genome-wide copy number variant testing has demonstrated no significant genomic rearrangement at the break points **Balanced translocations with an unusual phenotype exclusion criteria** - Genome-wide copy number variant analysis abnormal and clearly pathogenic **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Balanced translocations with an unusual phenotype prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variant analysis (e.g. aCGH, SNP array or other genomic microarray) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

VACTERL-like phenotypes (10964)

Level 3 Title	Limb disorders (15087)
Level 4 Title	VACTERL-like phenotypes (10964)
Eligibility Statement	**VACTERL-like phenotypes inclusion criteria** - At least three out of the five of the following: - Vertebral anomalies - Oesophageal atresia and tracheo-oesophageal fistula - Cardiac malformation - Renal malformation - Limb defect **VACTERL-like phenotypes exclusion criteria** - severe developmental delay - epibulbar dermoid - pre-auricular tags - bilateral limb defect **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **VACTERL-like phenotypes prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) - EFTUD2 (if suggestive clinical findings, e.g. microcephaly, facial asymmetry, inner ear anomalies) - chromosome breakage/Fanconi studies (if suggestive clinical findings, e.g. IUGR, growth retardation, microcephaly, hypo/hyperpigmentation) **Closing statement**

	These requirements will be kept under continual review during the main programme and may be subject to change.

Cockayne syndrome (36497)

Level 3 Title	DNA repair disorders (10965)
Level 4 Title	Cockayne syndrome (36497)
Eligibility Statement	**Cockayne syndrome inclusion criteria** • A likely diagnosis of Cockayne syndrome. Major criteria: • Microcephaly (pre- or post-natal onset) • Small stature (pre- or post-natal onset) Minor criteria • Persistently cold peripheries • Bilateral hearing loss (conductive, sensorineural or mixed; not unilateral) • Clinical cutaneous photosensitivity (n.b. skin biopsy testing of DNA repair is NOT REQUIRED) • Tremor • Joint contractures • Progressive loss of body fat • Cataracts • Enophthalmia • Brain imaging abnormality: cerebral calcification, dysmyelination or cerebellar hypoplasia (if more than one present, still count as only ONE minor criterion) A likely diagnosis of Cockayne syndrome is defined as both major criteria and 2 minor criteria. **Cockayne syndrome exclusion criteria** • Known molecular genetic diagnosis **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Cockayne syndrome prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT as diagnosis of these disorders carries

	important management implications: - ERCC6 and ERCC8 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Non-Fanconi anaemia (11050)

Level 3 Title	DNA repair disorders (10965)
Level 4 Title	Non-Fanconi anaemia (11050)
Eligibility Statement	**Non-Fanconi anaemia inclusion criteria** - Patients referred for Fanconi anaemia chromosome breakage testing, but who are negative for elevated chromosome breakage with mitomycin C/diepoxybutane - Patients with two or more of the following clinical features which overlap with Fanconi: - Skin: hyperpigmentation; Cafe au lait spots; Hypopigmentation - Microsomia: short stature - Upper limbs: Absent/hypoplastic thumbs or radii - Head and face: Microcephaly; micrognathia - Hypogenitalia in males or females - Renal: Ectopic or pelvic; abnormal, horseshoe - Haematology: Unexplained cytopenia **Non-Fanconi anaemia exclusion criteria** - Patients referred for Fanconi anaemia chromosome breakage testing, who are positive for elevated chromosome breakage with mitomycin C/diepoxybutane. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Non-Fanconi anaemia Gene** - chromosome breakage analysis with mitomycin C/diepoxybutane **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Xeroderma Pigmentosum-like disorders (15089)

Level 3 Title	DNA repair disorders (10965)
Level 4 Title	Xeroderma Pigmentosum-like disorders (15089)
Eligibility Statement	**Xeroderma Pigmentosum-like inclusion Critiera** - Patients with typical facial lentigines and/or XP-like pattern of photosensitivity - XP has been excluded based on normal unscheduled DNA synthesis and no mutations identified in any of the known XP genes. **Xeroderma Pigmentosum-like exclusion Critiera** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Xeroderma Pigmentosum-like prior genetic testing genes** No genes listed **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Primary Microcephaly - Microcephalic Dwarfism Spectrum (36505)

Level 3 Title	DNA repair disorders (10965)
Level 4 Title	Primary Microcephaly - Microcephalic Dwarfism Spectrum (36505)
Eligibility Statement	**Primary Microcephaly - Microcephalic Dwarfism Spectrum inclusion criteria** • Occipitofrontal circumference (OFC) >2 standard deviations (SD) below mean at birth AND progressive microcephaly to >4SD, OR • OFC >4SD below mean at birth, OR • OFC >3SD below mean at birth AND length >3SD below mean at birth **Primary Microcephaly - Microcephalic Dwarfism Spectrum exclusion criteria** • A known genetic cause. • Dysmorphic physical features or MRI brain indicative of an alternative diagnosis • Evidence of an environmental cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Primary Microcephaly - Microcephalic Dwarfism Spectrum prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT as diagnosis of these disorders carries important management implications: - Array or equivalent genome-wide copy number analysis. - ASPM and other genes dictated by the phenotype **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Vici Syndrome and other autophagy disorders (11051)

Level 3 Title	Autophagy disorders (10966)
Level 4 Title	Vici Syndrome and other autophagy disorders (11051)
Eligibility Statement	**Vici Syndrome and other autophagy disorders inclusion criteria** - at least 3 major criteria below OR - at least 1 major criteria and 3 minor criteria below OR - vacuolar myopathy and any other criterion (major or minor) - Major criteria - Agenesis of the corpus callosum - Cataracts - Cardiomyopathy - Hypopigmentation - Combined immunodeficiency - Minor criteria - Microcephaly - Sensorineural deafness - Failure to thrive - Myopathy - Neuropathy - Movement disorder **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

	Vici Syndrome and other autophagy disorders prior genetic testing genes Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Coarse facial features including Coffin-Siris-like disorders (36596)

Level 3 Title	Dysmorphic disorders (36595)
Level 4 Title	Coarse facial features including Coffin-Siris-like disorders (36596)
Eligibility Statement	**Coarse facial features including Coffin-Siris-like disorders inclusion criteria** • Coarse facial features warranting further investigation -particularly those with other medical problems, additional dysmorphic facial features or intellectual disability, AND • Previous investigations to exclude metabolic disorder including a minimum of plasma amino acids, urine organic acids and urine GAGs, AND **Coarse facial features including Coffin-Siris-like disorders exclusion criteria** • Known genetic aetiology • Untreated congenital hypothyroidism • Metabolic investigations indicative of likely inborn error of metabolism (these individuals should follow a metabolic pathway of investigation and recruitment) • Clinical features of an insulin resistance / lipodystrophy disorder, RASopathy or overgrowth disorder (these individuals should be investigated and recruited to the relevant specific rare disorder) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Coarse facial features including Coffin-Siris-like disorders prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Guided by phenotype. There should be a low threshold for Ras-MAPK gene testing, and 11p15 methylation analysis should be considered - If clinical diagnosis of Pallister-Killian syndrome is considered likely, a skin biopsy for chromosome analysis should be performed prior to recruitment **Closing statement**

	These requirements will be kept under continual review during the main programme and may be subject to change.

Familial non-syndromic cleft lip and or familial cleft palate (37565)

Level 3 Title	Dysmorphic disorders (36595)
Level 4 Title	Familial non-syndromic cleft lip and or familial cleft palate (37565)
Eligibility Statement	**Familial Non-syndromic cleft lip and or familial cleft palate inclusion criteria** • Familial cleft lip with or without cleft palate, or cleft palate alone AND • At least 4 affected family members over at least 3 generations, OR • At least 3 affected siblings with no additional family history AND • At least 3 affected individuals available to participate in the study **Familial Non-syndromic cleft lip and or familial cleft palate exclusion criteria** • Van der Woude syndrome or Stickler syndrome clinically diagnosed • Syndromic clefting disorders (see syndromic clefting disorders eligibility criteria) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial Non-syndromic cleft lip and or familial cleft palate prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - aCGH or equivalent - IRF6 if lip pits in any member or cleft lip AND palate present in the family **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Syndromic cleft lip and or cleft palate (37573)

Level 3 Title	Dysmorphic disorders (36595)
Level 4 Title	Syndromic cleft lip and or cleft palate (37573)
Eligibility Statement	**Syndromic cleft lip and or cleft palate inclusion criteria** • Cleft palate and/or cleft lip palate AND • At least one additional structural malformation, OR • Height/length or head circumference >3SDs from the mean, OR • Dysmorphism, OR • Intellectual disability – moderate or more severe, OR • Autism spectrum disorder **Syndromic cleft lip and or cleft palate exclusion criteria** • Known teratogenic or genetic cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Syndromic cleft lip and or cleft palate prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - aCGH or equivalent - IRF6 if suspected Van der Woude syndrome; COL2A1, COL11A1 and COL11A2 in suspected Stickler syndrome (as guided by ocular phenotype) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

PHACE(S) syndrome (37578)

Level 3 Title	Dysmorphic disorders (36595)
Level 4 Title	PHACE(S) syndrome (37578)
Eligibility Statement	**PHACE(S) syndrome inclusion criteria** • Haemangioma on the scalp or face of >5cm, AND at least 1 major or 2 minor criteria: • MAJOR: Anomaly of major cerebral arteries; Posterior fossa anomaly; Aortic arch anomaly; Ocular posterior segment anomaly; sternal defect • MINOR: Persistent embryonic artery other than trigeminal artery; Enhancing extra-axial lesion with features consistent with intracranial haemangioma or midline anomaly or neuronal migration defect; Ventricular septal defect or right aortic arch; Ocular anterior segment anomaly; Hypopituitarism/ectopic thyroid **PHACE(S) syndrome exclusion criteria** • Clinical features suggestive of Sturge-Weber syndrome **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **PHACE(S) syndrome prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - aCGH or equivalent **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Radial dysplasia (37636)

Level 3 Title	Dysmorphic disorders (36595)
Level 4 Title	Radial dysplasia (37636)
Eligibility Statement	**Radial dysplasia inclusion criteria** • Bilateral radial dysplasia, OR • Unilateral radial dysplasia with positive family history, parental consanguinity or additional syndromic features (such as at least one additional structural malformation, height/length or head circumference >3SDs from the mean, dysmorphism, moderate or worse intellectual disability or autism spectrum disorder) **Radial dysplasia exclusion criteria** • Known genetic cause • Known teratogenic cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Radial dysplasia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - aCGH or equivalent - Fanconi breakage testing (if features suggestive of Fanconi anaemia) - TBX5 (if phenotype suggestive of Holt-Oram syndrome) - RBM8A (if aCGH or clinical features suggestive of TAR syndrome) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Fetal hydrops (37586)

Level 3 Title	Fetal disorders (38586)
Level 4 Title	Fetal hydrops (37586)
Eligibility Statement	**Fetal hydrops inclusion criteria** • Non-immune fetal hydrops surviving >16 weeks gestation, AND • Normal infection screen (including parvovirus, CMB, rubella +- syphilis, VZV), AND • No evidence of Rh or other blood group incompatibility, AND • Haemoglobinopathy excluded where present in parent, AND • Normal fetal +- neonatal amniotic fluid screen for storage disorders (glycosaminglycans), AND • If IUGR: normal placental artery dopplers AND middle cerebral artery Doppler <1.5MoM Please note: samples from ongoing pregnancies should NOT be included **Fetal hydrops exclusion criteria** • Isolated structural cardiac anomaly or cardiac arrhythmia • Fetal tumour • Fetal lung mass • Maternal pre-eclampsia • Poorly controlled maternal DM/hypothyroidism • Twin-twin transfusion **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Fetal hydrops prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Consideration of RASopathy screen (low threshold for PTPN11 exons 3 & 8) - Low threshold Niemann Pick analysis if splenomegaly or Ashkenazi ancestry

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Unexplained monogenic fetal disorders (38665)

Level 3 Title	Fetal disorders (38586)
Level 4 Title	Unexplained monogenic fetal disorders (38665)
Eligibility Statement	**Unexplained monogenic fetal disorders inclusion criteria** Fetuses with a normal chromosome test considered likely to have a monogenic disease by a clinician expert in fetal genetics Please note: samples from ongoing pregnancies should NOT be included **Unexplained monogenic fetal disorders exclusion criteria** • Likely teratogenic, infectious or chromosomal cause • Likely placental cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Unexplained monogenic fetal disorders prior genetic testing genes** Where rapid aneuploidy testing and/or detailed chromosome testing (e.g. microarray) is indicated, this should be completed PRIOR TO RECRUITMENT. Further genetic testing in line with current local practice should be considered in parallel with recruitment but is NOT required prior to recruitment. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Adrenal disorders (10969)

Congenital adrenal hypoplasia (11053)

Level 3 Title	Adrenal disorders (10969)
Level 4 Title	Congenital adrenal hypoplasia (11053)
Eligibility Statement	**Congenital adrenal hypoplasia inclusion criteria** - Combined primary glucocorticoid and mineralocorticoid insufficiency OR - Isolated primary glucocorticoid insufficiency OR - Isolated primary mineralocorticoid insufficiency **Congenital adrenal hypoplasia exclusion criteria** - Congenital adrenal hyperplasia - Autoimmune Addison disease - Secondary adrenal insufficiency - Iatrogenic adrenal suppression due to glucocorticoid use - Post-infective adrenal dysfunction/haemorrhage/infiltrative disease - Metabolic adrenal insufficiency (X-linked adrenoleukodystrophy, mitochondrial disorders, Wolman syndrome) - Confirmed diagnosis of salt loss (e.g. pseudohypoaldosteronism type I or II, UTI, urethral values, renal conditions, cerebral salt loss etc.) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Congenital adrenal hypoplasia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - NR0B1 for boys with combined glucocorticoid and mineralocorticoid insufficiency with a family history consistent with an X-linked disorder

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Familial or syndromic hypoparathyroidism (11054)

Level 3 Title	Disorders of calcium homeostasis (10970)
Level 4 Title	Familial or syndromic hypoparathyroidism (11054)
Eligibility Statement	**Familial or syndromic hypoparathyroidism inclusion criteria** - Hypocalcaemia, congenital or acquired - High normal or raised serum phosphate - Low or low-normal plasma parathyroid hormone in the presence of hypocalcaemia - Normal serum 25-OH vitamin D - Low serum magnesium may be present, but is not required for diagnosis AND - At least one first degree relative with hypoparathyroidism, OR - At least one additional congenital anomaly or unexplained medical disorder likely to be causally related to the hypoparathyroidism **Familial or syndromic hypoparathyroidism exclusion criteria** - Significant renal failure (estimated creatinine clearance < 30 mls/min), renal dysplasia, sensorineural deafness (HDR syndrome). - Skeletal manifestations of pseudohypoparathyroidism. - Elevated parathyroid hormone. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial or syndromic hypoparathyroidism prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - CASR **Closing statement**

	These requirements will be kept under continual review during the main programme and may be subject to change.

Gonadal and sex development disorders (36923)

Disorders of sex development (36852)

Level 3 Title	Gonadal and sex development disorders (36923)
Level 4 Title	Disorders of sex development (36852)
Eligibility Statement	**Disorders of sex development inclusion criteria** 46,XX disorder of sex development • Normal 46,XX karyotype following microarray testing, AND • Absence of SRY, AND • At least one of (a) genital ambiguity, (b) absence or anomaly of the Mullerian structures, or (c) gonadal dysgenesis 46,XY disorder of sex development • Normal 46,XY karyotype following microarray testing, AND • Presence of SRY, AND • At least one of (a) ambiguity of the external genitalia, (b) presence of Mullerian structures, or (c) gonadal dysgenesis **Disorders of sex development exclusion criteria** 46,XX disorder of sex development • Antenatal history suggestive of non-genetic cause, e.g. maternal androgen exposure • Biochemical or genetic evidence of 21-hydroxylase deficiency, 11-hydroxylase deficiency, 3 beta hydroxysteroid dehydrogenase deficiency type 2, cytochrome P450 reductase (POR) related disorders and 17 alpha hydroxylase deficiency. 46,XY disorder of sex development • Isolated hypospadias • Biochemical or genetic evidence of 5 alpha reductase deficiency, 3 beta hydroxysteroid dehydrogenase deficiency type 2, cytochrome P450 reductase (POR) related disorders, aromatase deficiency and androgen insensitivity syndrome. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established.

	It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Disorders of sex development prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: 46,XX disorder of sex development • In situ study to exclude presence of SRY • Exclusion of CNV associated with 46 XX DSD • CYP21A2 and CYP11B1 if indicated by steroid biochemistry - steroid biochemistry to assess whether these disorders needed genetic testing would be a requirement before inclusion. 46,XY disorder of sex development • In situ study to prove presence of SRY • Exclusion of CNV associated with 46 XY DSD • Obligatory endocrinological assessment and steroid biochemistry (including testosterone, DHT) and where indicated from biochemical investigations analysis of HSD17B3, SRD5A2 and Androgen receptor) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Early onset familial premature ovarian insufficiency (36851)

Level 3 Title	Gonadal and sex development disorders (36923)
Level 4 Title	Early onset familial premature ovarian insufficiency (36851)
Eligibility Statement	**Early onset familial premature ovarian insufficiency inclusion criteria** • 4 consecutive months of amenorrhoea (primary or secondary), AND • Elevated serum FSH of >30IU/L on two separate occasions at least 6 weeks apart, AND • Age of onset is <30 years, AND • At least one other close family member (sister, mother, aunt or first cousin) with POF, AND • Availability of at least 1 additional affected family member to take part in the project No male relatives should be recruited to this disorder. Unaffected female relatives should only be recruited if they are aged over 45 years, AND menstruation ceased after the age of 45 years. **Early onset familial premature ovarian insufficiency exclusion criteria** • X chromosome abnormality such as Turner syndrome • Presence of FMR1 premutation • Iatrogenic cause (bilateral oophorectomy, chemotherapy, radiotherapy or any other iatrogenic cause) • Presence of thyroid or adrenal auto-antibodies **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Early onset familial premature ovarian insufficiency prior genetic testing genes** Testing for fragile X premutation and chromosome abnormalities is strongly recommended PRIOR TO RECRUITMENT as these may not be reliably detected by WGS using current analysis techniques. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Growth hormone disorders (10971)

IUGR and IGF abnormalities (11057)

Level 3 Title	Growth hormone disorders (10971)
Level 4 Title	IUGR and IGF abnormalities (11057)
Eligibility Statement	**IUGR inclusion criteria** - Height Standard Deviation Score (SDS) <-3 (very significant short stature - well below the 0.4th centile) AND - At least one of: - being born small for gestational (birth weight and/or length <-2SDS), ± a history of intra-uterine growth restriction - Body disproportion - e.g. discrepancy between stature and head size, limb to spine disproportion, limb asymmetry - Dysmorphic features e.g. facial dysmorphism, polydactyly/syndactyly, ear abnormalities - Aberration in the GH-IGF axis (evidence of GH insensitivity or deficiency) - Other pituitary hormonal deficiencies - Family history (short stature that is explained or idiopathic in parents, affected siblings,cousins) and/or consanguinity - Other features such as cleft palate, hearing loss, visual impairment with eye abnormalities including anophthalmia/microphthalmia, optic nerve hypoplasia, retinal dystrophy, forebrain abnormalities and learning difficulties - For all patients with no abnormalities of the GH-IGF-I axis classified as Idiopathic Short Stature or who are small for gestational age with failure of catch up growth, a skeletal survey should be performed. **IUGR exclusion criteria** - Acquired causes of short stature, e.g. autoimmune, intracranial neoplasia, infective causes such as Group B Streptococcal meningitis, Langerhans cell Histiocytosis, trauma, previous treatment for malignancy including irradiation, exogenous glucocorticoid use, psychosocial growth failure, chronic disease - Syndromes associated with short stature such as Turner syndrome, Noonan syndrome, Down syndrome, other chromosomal disorders. However, if the patient has a clinical diagnosis of, e.g. Noonan syndrome, and testing of known genes associated with the syndrome has not identified a pathogenic mutation, then they should be included in the 100000 genomes study. - Foetal alcohol syndrome - Genetically proven skeletal dysplasias such as hypochondroplasia or achondroplasia - Genetically proven Silver-Russell syndrome **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to

	the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **IUGR prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - All patients with short stature and other features such as developmental delay and dysmorphism should have a DNA microarray with no pathogenic copy number variants detected prior to enrolment - Additional genetic testing should have been performed as appropriate **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Idiopathic hypogonadotropic hypogonadism (41827)

Level 3 Title	Hypothalamic and pituitary disorders (42204)
Level 4 Title	Idiopathic hypogonadotropic hypogonadism (41827)
Eligibility Statement	**Idiopathic hypogonadotropic hypogonadism inclusion criteria** Delayed or absent puberty with low or suppressed gonadotropins (including primary amenorrhoea, oligo/azoospermia with low testosterone. Bilateral cryptorchidism with micophallus is suggestive of congenital IHH) AND at least one of the following, Parental consanguinity, OR One or more similarly affected first, second or third degree relative, OR Syndromic features such as anosmia, cleft lip or palate, deafness, renal agenesis, neurological disorders Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Idiopathic hypogonadotropic hypogonadism exclusion criteria** Acquired structural hypothalamo-pituitary disease History of anabolic steroid use, recent history of glucocorticoid or opiate use Severe intercurrent illness, anorexia, or other forms of undernourishment Evidence of primary hypogonadism Co-existent pituitary hormone deficiency Features of Bardet Biedl, CHARGE syndromes, or other complex syndromes for which UKGTN testing exists **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

	Idiopathic hypogonadotropic hypogonadism prior genetic testing genes Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes specified **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Significant early-onset obesity with or without other endocrine features and short stature (11060)

Level 3 Title	Obesity syndromes (10973)
Level 4 Title	Significant early-onset obesity with or without other endocrine features and short stature (11060)
Eligibility Statement	**Obesity inclusion criteria** - Syndromic or non-syndromic severe obesity (BMI > 3SD above the mean) - Onset before age 5 years **Obesity exclusion criteria** - Known cause of obesity, e.g. steroid treatment **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Obesity prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) - Where the phenotype is recognisable and is caused by 1-2 principle genes, these should have been tested prior to recruitment **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial young-onset non-insulin-dependent diabetes (15103)

Level 3 Title	Rare subtypes of diabetes (15099)
Level 4 Title	Familial young-onset non-insulin-dependent diabetes (15103)
Eligibility Statement	**Diabetes inclusion criteria** - Diagnosis of diabetes <35 years of age - Not insulin dependent (>=1 years without insulin treatment) - Non-obese (BMI <30) Unaffected family members should only be recruited if they have had testing to rule out diabetes (e.g. normal HbA1c) at or over the age of 40. **Diabetes exclusion criteria** - One or more autoantibodies positive **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial young-onset non-insulin-dependent diabetes prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes listed **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Hyperinsulinism (15105)

Level 3 Title	Rare subtypes of diabetes (15099)
Level 4 Title	Hyperinsulinism (15105)
Eligibility Statement	**Hyperinsulinism inclusion criteria** - Hypoglycaemia onset before 12 years of age - Drug-treated for >=3 months or pancreatectomy - Intravenous glucose infusion rate required to maintain normoglycaemia >8mg/kg/min - Detectable serum insulin or C-Peptide when blood glucose is less than 3mmol/L **Hyperinsulinism exclusion criteria** - Hypoglycaemia in the neonatal period which resolved without treatment - Hypoglycaemia in the context of systemic neonatal disease e.g. sepsis **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Neonatal diabetes (diagnosed less than 6 months) (30553)

Level 3 Title	Rare subtypes of diabetes (15099)
Level 4 Title	Neonatal diabetes (diagnosed less than 6 months) (30553)
Eligibility Statement	**Neonatal diabetes inclusion criteria** - Neonatal diabetes diagnosed < 6 months NOTE: diabetes diagnosed before 6 months of age almost universally has a monogenic aetiology. Families should be recruited if diabetes is diagnosed according to WHO criteria before the age of 6 months, and the diagnostic panel of known genes is negative. **Neonatal diabetes exclusion criteria** - One or more pancreatic autoantibodies (GAD, IA2, ICA) positive (titre >99th population centile) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Neonatal diabetes prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT as WGS will not detect treatable mutations quickly enough to prevent irreversible neurological damage in a subset of patients: Neonatal diabetes screen which is offered at the Exeter Molecular Genetics Laboratory or an equivalent genetic test. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Diabetes with additional phenotypes suggestive of a monogenic aetiology (30559)

Level 3 Title	Rare subtypes of diabetes (15099)
Level 4 Title	Diabetes with additional phenotypes suggestive of a monogenic aetiology (30559)
Eligibility Statement	**Monogenic diabetes inclusion criteria** - Developmental disorder phenotype (e.g. CNS, renal or cardiac) AND - Diagnosis of diabetes <25 years AND - Not insulin dependent (>=3 years without insulin treatment) AND - Non-obese (BMI <30) **Monogenic diabetes exclusion criteria** - One or more pancreatic autoantibodies (GAD, IA2, ICA) positive (titre >99th population centile) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Monogenic diabetes prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - MTTL1 testing - Other appropriate single gene tests as suggested by the phenotype, eg HNF1B if renal malformation, WFS1 if diabetes insipidus or optic atrophy, ALMS1 if obesity or cone-rod dystrophy - If the appropriate prior genetic testing is unclear, please go to www.diabetesgenes.org for further information, or consider carrying out a panel test of known diabetes genes. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Insulin resistance (including lipodystrophy) (30561)

Level 3 Title	Rare subtypes of diabetes (15099)
Level 4 Title	Insulin resistance (including lipodystrophy) (30561)
Eligibility Statement	**Insulin resistance inclusion criteria** - Diagnosis of diabetes <25 years AND - Not insulin dependent (>=3 years without insulin treatment) AND - Non-obese (BMI <30) AND - Acanthosis nigricans AND - Biochemical confirmation of severe insulin resistance. **Insulin resistance exclusion criteria** - One or more pancreatic autoantibodies (GAD, IA2, ICA) positive (titre >99th population centile) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change. **Insulin resistant prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - LMNA if partial lipodystrophy phenotype

Multi-organ autoimmune diabetes (30563)

Level 3 Title	Rare subtypes of diabetes (15099)
Level 4 Title	Multi-organ autoimmune diabetes (30563)
Eligibility Statement	**Autoimmune diabetes inclusion criteria** - Diabetes AND - >=2 autoimmune disorders with >=2 of these diagnosed <10 years. **Autoimmune diabetes exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Autoimmune Diabetes prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - AIRE if Addison's disease is present **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Congenital hypothyroidism (41908)

Level 3 Title	Thyroid disorders (42208)
Level 4 Title	Congenital hypothyroidism (41908)
Eligibility Statement	**Congenital hypothyroidism inclusion criteria** Congenital Hypothyroidism defined biochemically as: Primary CH: neonatal or early onset elevated TSH with subnormal or normal thyroid hormone levels Central CH: neonatal or early onset subnormal thyroid hormone levels with normal or subnormal TSH Preferred inclusion criteria – cases from multicase families or consanguineous backgrounds or (in primary CH) with additional extra-thyroidal features. **Congenital hypothyroidism exclusion criteria** A high likelihood that the phenotype is completely explained by an acquired aetiology (eg autoimmunity, maternal autoantibodies, iodine deficiency) A pathogenic mutation in a known causative gene which completely explains the phenotype. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Congenital hypothyroidism prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: Consideration of FOXE1, GNAS, SLC26A4, TSHR, TPO, DUOX2, TG **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Resistance to thyroid hormone (41916)

Level 3 Title	Thyroid disorders (42208)
Level 4 Title	Resistance to thyroid hormone (41916)
Eligibility Statement	**Resistance to thyroid hormone inclusion criteria** Resistance to thyroid hormone defined biochemically as elevated levels of T3 and/or T4 with non-suppressed TSH levels **Resistance to thyroid hormone exclusion criteria** A high likelihood that the phenotype is completely explained by an acquired aetiology (eg drugs, assay interference, iodine deficiency, TSH-secreting pituitary tumour). A pathogenic mutation in a known causative gene which completely explains the phenotype. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Resistance to thyroid hormone prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: Elevated T3, low/normal T4 and/or clinical features suggestive of Allan-Herndon-Dudley syndrome: SLC16A2 (MCT8) Elevated T3, low/normal T4, and/or clinical features suggestive of RTHalpha: THRA Raised T4, normal/low T3, high reverse T3, low plasma selenium: SECISBP2, TRNAU1 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Gastroenterological disorders (38581)

Gastrointestinal disorders (38582)

Infantile enterocolitis and monogenic inflammatory bowel disease (37490)

Level 3 Title	Gastrointestinal disorders (38582)
Level 4 Title	Infantile enterocolitis and monogenic inflammatory bowel disease (37490)
Eligibility Statement	**Infantile enterocolitis and monogenic inflammatory bowel disease inclusion criteria** - Chronic inflammatory bowel disease and inflammatory bowel disease like intestinal inflammation - Age of onset intestinal inflammation less than complete 2 years of age. - Histology confirmed intestinal inflammation with first endoscopy (less than 2.5 years of age). **Infantile enterocolitis and monogenic inflammatory bowel disease exclusion criteria** - Acute infectious gastroenteritis/enterocolitis due to common pathogens (Rotavirus, Norovirus, Salmonella etc.) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Infantile enterocolitis and monogenic inflammatory bowel disease prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - In case of enterocolitis less than 3 month of age IL10, IL10RA and IL10RB signalling defects should be excluded. - In case of enterocolitis with infantile diabetes and autoimmunity IPEX (FOXP3) should be excluded. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Gastrointestinal epithelial barrier disorders (37772)

Level 3 Title	Gastrointestinal disorders (38582)
Level 4 Title	Gastrointestinal epithelial barrier disorders (37772)
Eligibility Statement	NB. Clinical test guidance: General biopsy refers to biopsy of abnormal intestinal features Inflammatory markers refers to C reactive protein General Imaging Diagnostics refers to Endoscopy **Gastrointestinal epithelial barrier disorders inclusion criteria** • Proven histological evidence of epithelial disorder on gut biopsy: Epithelial dysmorphology characterised by e.g. epithelial detachment abnormal epithelial cell polarisation, epithelial cell crowding/tufting and increased apoptotic activity of the epithelial layer. **Gastrointestinal epithelial barrier disorders exclusion criteria** • Evidence of primary immune deficiency. • Histopathology in keeping with conventional GI disorders such as IBD without features described above. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Gastrointestinal epithelial barrier disorders prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: • EPCAM, MYO5B, ADAM17, IKBKG **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Non-syndromic familial congenital anorectal malformations (41868)

Level 3 Title	Gastrointestinal disorders (38582)
Level 4 Title	Non-syndromic familial congenital anorectal malformations (41868)
Eligibility Statement	**Non-syndromic familial congenital anorectal malformations inclusion criteria** Congenital anorectal malformation regardless of phenotype severity (imperforate anus through to cloaca) AND At least one first or second degree relative with an anorectal malformation. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. Unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Non-syndromic familial congenital anorectal malformations exclusion criteria** Additional clinical features suggestive of a multisystem syndrome other than VACTERL association. For example, please do not recruit cases with clinical diagnoses of Currarino syndrome, Townes-Brockes syndrome or Pallister-Hall syndrome. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Non-syndromic familial congenital anorectal malformations prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes specified **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Early onset or familial intestinal pseudo obstruction (41876)

Level 3 Title	Gastrointestinal disorders (38582)
Level 4 Title	Early onset or familial intestinal pseudo obstruction (41876)
Eligibility Statement	**Early onset or familial intestinal pseudo obstruction inclusion criteria** A. Chronic visceral dilatation including part or all of the small intestine (chronic intestinal pseudo-obstruction) AND one of: B1. Diagnosis within first year of life (majority will have symptoms from the neonatal period) B2. Diagnosis at any age but with at least one first or second degree relative with a diagnosis of either IPO or another severe digestive motility disorder (enteric dysmotility; oesophageal achalasia, megacolon, megarectum). Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Early onset or familial intestinal pseudo obstruction exclusion criteria** Proven mitochondrial myopathy (MNGIE) [by MRI / muscle biopsy in suspected cases] Proven early onset secondary cause e.g. muscular dystrophy or cystic fibrosis [with relevant testing if clinical suspicion] **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Early onset or familial intestinal pseudo obstruction prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes specified

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Familial Hirschsprung Disease (55463)

Level 3 Title	Gastrointestinal disorders (38582)
Level 4 Title	Familial Hirschsprung Disease (55463)
Eligibility Statement	**Familial Hirschsprung Disease inclusion criteria** Diagnosis of Hirschsprung disease (HSCR) as proven with histology AND ONE OR MORE OF 1. Family history of HSCR, at least 2 affected first or second degree members, OR 2. Parental consanguinity, OR 3. HSCR occurring as part of a syndrome or with other anomalies **Familial Hirschsprung Disease exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial Hirschsprung Disease prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: RET and other tests as relevant if additional features are present e.g. microarray, ZEB2 (Mowat-Wilson syndrome). **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Ductal plate malformation (55469)

Level 3 Title	Liver disease (55663)
Level 4 Title	Ductal plate malformation (55469)
Eligibility Statement	**Ductal plate malformation inclusion criteria** Ductal plate malformation as defined by an individual diagnosis of or any combination of multiple biliary hamartomas, Caroli's disease, choledochal cyst, polycystic liver disease or congenital hepatic fibrosis Radiological and/or histological evidence supportive of DPM as the primary liver diagnosis. In addition, the clinical entity of idiopathic non-cirrhotic portal hypertension where a liver explant/representative liver biopsy is defined histologically using any of these interchangeable terms: hepatoportal sclerosis, incomplete septal cirrhosis, non-cirrhotic portal fibrosis. **Ductal plate malformation exclusion criteria** Where ductal plate malformation is part of a complex phenotype – recruit such cases to relevant ciliopathy disease group Extrahepatic portal vein thrombosis, nodular regenerative hyperplasia, Budd-Chiari syndrome, sinusoidal obstruction syndrome. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Ductal plate malformation prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: If polycystic renal disease, PKD1, PKD2 (autosomal dominant), PKHD1 (autosomal recessive). **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Neonatal cholestasis (71744)

Level 3 Title	Liver disease (55663)
Level 4 Title	Neonatal cholestasis (71744)
Eligibility Statement	**Neonatal cholestasis eligibility inclusion criteria** Neonatal cholestasis in which a known genetic disease has been excluded and in which a monogenic cause is considered likely by a specialist Liver Unit. **Neonatal cholestasis eligibility exclusion criteria** Infective causes after excluding known genetic disease. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Neonatal cholestasis eligibility prior genetic testing genes** **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Growth disorders (10974)

Beckwith-Wiedemann syndrome (BWS) and other congenital overgrowth disorders (10975)

Classical Beckwith-Wiedemann syndrome (11063)

Level 3 Title	Beckwith-Wiedemann syndrome (BWS) and other congenital overgrowth disorders (10975)
Level 4 Title	Classical Beckwith-Wiedemann syndrome (11063)
Eligibility Statement	Relevant diseases: - Classical Beckwith-Wiedemann syndrome - Atypical Beckwith-Wiedemann syndrome **Beckwith-Wiedemann syndrome inclusion criteria** Clinical diagnosis of BWS meeting standard clinical diagnostic criteria EXCEPT THOSE WITH UPD 11p15, UNBALANCED TRANSLOCATIONS OR OTHER 11p15 COPY NUMBER DEFECTS OR CDKN1C MUTATIONS Eligible patients will include those with No detectable cause Balanced chromosomal aberration (translocation/inversion) Multilocus methylation defect consistent with an in trans imprinting defect Isolated/single locus 11p15 methylation defect Recruitment of families with Isolated/single locus methylation defects without a family history or BWS or other imprinted disorder should only occur as proband-mother-father trios. **Beckwith-Wiedemann syndrome exclusion criteria** Those with: UPD 11p15 Unbalanced translocations or other 11p15 copy number defects CDKN1C mutations **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established.

	It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Beckwith-Wiedemann syndrome prior genetic testing genes** 11p15 methylation testing is required PRIOR TO RECRUITMENT as molecular diagnosis determines eligibility and surveillance, and methylation abnormalities cannot be detected on WGS. - Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: CDKN1C **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Atypical Beckwith-Wiedemann syndrome (11064)

Level 3 Title	Beckwith-Wiedemann syndrome (BWS) and other congenital overgrowth disorders (10975)
Level 4 Title	Atypical Beckwith-Wiedemann syndrome (11064)
Eligibility Statement	Relevant diseases: - Classical Beckwith-Wiedemann syndrome - Atypical Beckwith-Wiedemann syndrome **Beckwith-Wiedemann syndrome inclusion criteria** Clinical diagnosis of BWS meeting standard clinical diagnostic criteria EXCEPT THOSE WITH UPD 11p15, UNBALANCED TRANSLOCATIONS OR OTHER 11p15 COPY NUMBER DEFECTS OR CDKN1C MUTATIONS Eligible patients will include those with No detectable cause Balanced chromosomal aberration (translocation/inversion) Multilocus methylation defect consistent with an in trans imprinting defect Isolated/single locus 11p15 methylation defect Recruitment of families with Isolated/single locus methylation defects without a family history or BWS or other imprinted disorder should only occur as proband-mother-father trios. **Beckwith-Wiedemann syndrome exclusion criteria** Those with: UPD 11p15 Unbalanced translocations or other 11p15 copy number defects CDKN1C mutations **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Beckwith-Wiedemann syndrome prior genetic testing genes** 11p15 methylation testing is required PRIOR TO RECRUITMENT as molecular diagnosis determines eligibility and surveillance, and methylation abnormalities cannot be detected on WGS.

	- Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: CDKN1C **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Simpson-Golabi-Behmel syndrome (11065)

Level 3 Title	Beckwith-Wiedemann syndrome (BWS) and other congenital overgrowth disorders (10975)
Level 4 Title	Simpson-Golabi-Behmel syndrome (11065)
Eligibility Statement	Relevant diseases: • Simpson-Golabi-Behmel syndrome • Sotos syndrome • Weaver syndrome **Simpson-Golabi-Behmel syndrome inclusion criteria** Clinical diagnosis of non-BWS overgrowth disorders (e.g. Sotos, Weaver, Simpson-Golabi-Behmel syndromes) without detectable germline mutation in relevant genes (e.g. EZH2, NSD1, GPC3). **Simpson-Golabi-Behmel exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Sotos syndrome (11066)

Level 3 Title	Beckwith-Wiedemann syndrome (BWS) and other congenital overgrowth disorders (10975)
Level 4 Title	Sotos syndrome (11066)
Eligibility Statement	Relevant diseases: • Simpson-Golabi-Behmel syndrome • Sotos syndrome • Weaver syndrome **Simpson-Golabi-Behmel syndrome inclusion criteria** Clinical diagnosis of non-BWS overgrowth disorders (e.g. Sotos, Weaver, Simpson-Golabi-Behmel syndromes) without detectable germline mutation in relevant genes (e.g. EZH2, NSD1, GPC3). **Simpson-Golabi-Behmel exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Weaver syndrome (11067)

Level 3 Title	Beckwith-Wiedemann syndrome (BWS) and other congenital overgrowth disorders (10975)
Level 4 Title	Weaver syndrome (11067)
Eligibility Statement	Relevant diseases: • Simpson-Golabi-Behmel syndrome • Sotos syndrome • Weaver syndrome **Simpson-Golabi-Behmel syndrome inclusion criteria** Clinical diagnosis of non-BWS overgrowth disorders (e.g. Sotos, Weaver, Simpson-Golabi-Behmel syndromes) without detectable germline mutation in relevant genes (e.g. EZH2, NSD1, GPC3). **Simpson-Golabi-Behmel exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Growth restriction (38585)

Silver Russell syndrome (37553)

Level 3 Title	Growth restriction (38585)
Level 4 Title	Silver Russell syndrome (37553)
Eligibility Statement	**Silver Russell syndrome inclusion criteria** A. All 4 core features of Silver-Russell syndrome (SRS) present and no cause found B. 3 or more features present and family history of SRS or other imprinting disorder; or recurrent fetal loss with IUGR C. 3 or more features present and multilocus imprinting defect D. Isolated/single locus 11p15 methylation defect (H19 loss of methylation) with a family history of Silver-Russell syndrome. Recruitment of relatives in these families should follow standard guidance. OR E. Isolated/single locus 11p15 methylation defect (H19 loss of methylation) without a family history of Silver-Russell syndrome. Recruitment to families in group E should occur only as proband-mother-father trios. Core clinical features of Silver-Russell syndrome: 1. small for gestational age (birth weight and/or length <-2SDS) +- history of intrauterine growth retardation; 2. post-natal short stature (<-2 SDS) 3. body asymmetry 4. marked feeding difficulties in infancy / childhood +/- BMI 1.5 SDS relative to birth weight / length). **Silver Russell syndrome exclusion criteria** • Other known short stature syndrome • Causative UPD (including UPD7, UPD14, UPD16, UPD20) • Causative chromosome rearrangement • Isolated methylation defect other than in familial cases **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing.

	PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Silver Russell syndrome prior genetic testing genes** UPD7 testing and 11p15 methylation testing are required PRIOR TO RECRUITMENT as molecular diagnosis determines eligibility and methylation abnormalities cannot be detected on WGS. Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Multi-locus methylation testing **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Congenital anaemias (11075)

Level 3 Title	Anaemias and red cell disorders (10979)
Level 4 Title	Congenital anaemias (11075)
Eligibility Statement	Relevant diseases: - Early onset pancytopenia and red cell disorders - Congenital anaemias **Congenital anaemias inclusion criteria** - Anaemia on more than one occasion **Congenital anaemias exclusion criteria** - Evidence that the anaemia is acquired (e.g. low B12, folate or ferritin or cytogenetic abnormalities) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Congenital anaemias prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - As appropriate based on presentation - e.g. Sideroblastic anaemia - ALAS2, SLC25A38; - Congenital Dyserythropoietic Anemia - C15orf41, CDAN1, GATA1 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Hereditary erythrocytosis (55505)

Level 3 Title	Anaemias and red cell disorders (10979)
Level 4 Title	Hereditary erythrocytosis (55505)
Eligibility Statement	**Hereditary erythrocytosis inclusion criteria** Unexplained elevated haematocrit (greater than 50%) and HB (greater than 185 g/l in men, greater than 170 g/l in women or above the 95th centile for age in children) with or without pulmonary arterial hypertension or raised erythropoietin levels. **Hereditary erythrocytosis exclusion criteria** Chronic hypoxia that preceded erythrocytosis Acquired JAK2 mutation causing polycythaemia rubra vera Kidney disease (e.g. a renal tumour or cysts) resulting in elevated renal EPO production Abnormal oxygen-haemoglobin dissociation **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Hereditary erythrocytosis prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: VHL **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Primary immunodeficiency (55674)

Level 3 Title	Primary immunodeficiency disorders (10978)
Level 4 Title	Primary immunodeficiency (55674)
Eligibility Statement	**Primary immunodeficiency inclusion criteria** - Suspected primary immunodeficiency diagnosed by a consultant immunologist, particularly if familial. - Appropriate available diagnostic tests should have ruled out mutations in relevant known genes. - All cases must be discussed and approved by the PID-MDT at the recruiting GMC Recruitment under these criteria would be appropriate for individuals with the following: Combined immunodeficiency, with or without associated/syndromic features Predominantly antibody deficiencies Diseases of immune dysregulation (includes HLH) Congenital defects of phagocyte number, function or both Defects in intrinsic and innate immunity Autoinflammatory disorders Complement deficiencies **Primary immunodeficiency exclusion criteria** - Known genetic cause already identified in proband or family member with similar phenotype. - Secondary immunodeficiency likely **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Primary immunodeficiency prior genetic testing genes** **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Inherited bleeding and or platelet disorders (55475)

Level 3 Title	Haemostasis disorders (55664)
Level 4 Title	Inherited bleeding and or platelet disorders (55475)
Eligibility Statement	**Inherited bleeding and or platelet disorders inclusion criteria** Diagnosis of a bleeding and/or platelet disorder* of unknown cause before the age of 50 and following haematological consultation, AND family history or consanguineous parents, OR syndromic features (incl. neurodevelopmental, immunological, nephrology, skeletal, hearing, etc.), OR early onset severe childhood case of unknown cause OR deficiency of coagulation factor without causal coding variants in the corresponding gene *Platelet disorder is defined as one or more of the following: Platelet count greater than 400x10e9/L or less than 100x10e9/L Mean Platelet Volume (MPV) greater than 13 fL and /or macrothrombocytopenia, or MPV less than 7fL Abnormal platelet morphology, ideally confirmed by high resolution microscopy Abnormal platelet function test, replicated on an independent sample **Inherited bleeding and or platelet disorders exclusion criteria** 1. Acquired bleeding and /or platelet disorders 2. Cases with platelet counts greater than 400x10e9/L and age less than 30 must be tested and found to be negative for somatic mutations in JAK2 and CALR 3. Use of prescription or over-the-counter drugs known to be associated with abnormal platelet (function) phenotypes and/or bleeding disorders, including a. anticoagulant medications b. aspirin, clopidogrel, dipyridamole, etc. c. nonsteroidal anti-inflammatory drugs (incl. COX-2 selective anti-inflammatory drugs) 4. Patients with evidence of an autoimmune or other systemic condition known to affect haemostasis and platelet homeostasis, including a. Autoimmune thrombocytopenia (ITP) b. Other autoimmune disorders, e.g. SLE 5. Other medical conditions known to be associated with abnormal platelet count and volume and / or abnormal platelet function a. Acute viral infection b. Bone marrow aplasia c. DIC (Disseminated intravascular coagulation)

	d. Hepatic failure e. HIV positivity and/or AIDS f. HUS (Haemolytic-uraemic syndrome) g. Malignancies, particularly those compromising haematopoiesis h. Splenomegaly i. TTP (Thrombotic thrombocytopenia purpura) j. Uraemia **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Inherited bleeding and or platelet disorders prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Monogenic venous thrombosis (55523)

Level 3 Title	Haemostasis disorders (55664)
Level 4 Title	Monogenic venous thrombosis (55523)
Eligibility Statement	**Monogenic venous thrombosis inclusion criteria** Unprovoked venous thrombosis (including in pregnancy) occurring before the age of 40, confirmed by imaging and following consultation with a Haemophilia or Thrombosis Centre Consultant Haematologist, AND ONE OR MORE OF • Family history of thrombotic events before the age of 40, OR • Consanguineous parents, OR • Syndromic features, OR • Early onset severe childhood / adolescence cases before the age of 25 with multiple independent unprovoked thrombotic events, OR • Unexplained (mutation negative) deficiency of an Antithrombin [SERPINC1], Protein C [PROC] or Protein S [PROS1] **Monogenic venous thrombosis exclusion criteria** Abnormality on thrombophilia testing that would explain the phenotype Acquired thrombotic disorders including 1. Anti-phospholipid antibodies (anti-beta2-glycoprotein I), including during pregnancy 2. Thrombotic event occuring after trauma/surgical challenge **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Monogenic venous thrombosis prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: SERPINC1, PROC, PROS1, SERPIND1, HRG, PLG, THBD, PLAT **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Cytopenia and pancytopenia (71752)

Level 3 Title	Myeloid and marrow failure disorders (71739)
Level 4 Title	Cytopenia and pancytopenia (71752)
Eligibility Statement	**Cytopenia and pancytopenia inclusion criteria** A suspected or likely diagnosis of a genetic disorder causing persistent or recurrent cytopenia or pancytopenia of unknown cause following review by a haematologist. Cases should be particularly considered for enrolment if there is a relevant family history, consanguinity, syndromic features and/or early onset severe disease. For patients with isolated thrombocytopenias, see Haemostasis disorders For patients with isolated lymphopenias, see Primary immunodeficiency disorders **Cytopenia and pancytopenia exclusion criteria** Acquired causes of cytopenia or pancytopenia including drugs, viral infections and clear-cut autoimmune cytopenias **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Cytopenia and pancytopenia prior genetic testing genes** **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Hearing and ear disorders (10980)

Non-syndromic hearing loss (10981)

Congenital hearing impairment (11076)

Level 3 Title	Non-syndromic hearing loss (10981)
Level 4 Title	Congenital hearing impairment (11076)
Eligibility Statement	**Congenital hearing impairment inclusion criteria** Moderate or worse hearing loss that is congenital and/or prelingual, bilateral and apparently non-syndromic **Congenital hearing impairment exclusion criteria** - Proven or suspected congenital CMV infection - Post-meningitis - Auditory neuropathy with concomitant neonatal hypoxia, jaundice, or prematurity **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Congenital hearing impairment prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT: - GJB2 (coding region plus splice site and GJB6 deletion); SLC26A4 if enlarged vestibular aqueducts **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Auditory Neuropathy Spectrum Disorder (30607)

Level 3 Title	Non-syndromic hearing loss (10981)
Level 4 Title	Auditory Neuropathy Spectrum Disorder (30607)
Eligibility Statement	**Auditory Neuropathy Spectrum Disorder inclusion criteria** - Diagnosis of ANSD (based on evidence from ABR testing, OAEs and tympanometry) - Apparently non-syndromic - Completed Visual Evoked Potentials examination - Normal vestibulocochlear nerves and cochlear morphology on MRI scanning - Absence of clinically apparent peripheral neuropathy **Auditory Neuropathy Spectrum Disorder exclusion criteria** - Prematurity (<37 weeks gestation or requiring >48 hours NICU) - Severe jaundice - Known syndrome - Peripheral neuropathy **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Auditory Neuropathy Spectrum Disorder prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - OPA1 if VEP prolonged **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Autosomal dominant deafness (36848)

Level 3 Title	Non-syndromic hearing loss (10981)
Level 4 Title	Autosomal dominant deafness (36848)
Eligibility Statement	**Autosomal dominant deafness inclusion criteria** • Non-syndromic hearing loss in proband, AND • Two or more additional affected family members in at least two generations, of which one must be a first degree relative of the proband and a have a similar or compatible audiometric hearing loss, AND • Audiometry must be provided on 2 or more affected individuals. Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Autosomal dominant deafness exclusion criteria** • Features of known syndrome **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Autosomal dominant deafness prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - All patients must have dominant monoallelic or recessive bi-allelic mutations in GJB2 excluded - UKGTN gene panel testing is available and should be encouraged **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Bilateral microtia (11077)

Level 3 Title	Deafness and congenital structural abnormalities (10982)
Level 4 Title	Bilateral microtia (11077)
Eligibility Statement	**Bilateral microtia inclusion criteria** - Microtia affecting both ears (includes unilateral microtia with pre auricular tags or pits affecting the contralateral side) - Normal microarray - Ifpre auricularpits,renal scan and EYA1/SIX1 testing should be done **Bilateral microtia exclusion criteria** - Maternal diabetes - Treacher-Collins syndrome and EFTUD2 clinically - The following syndromes should also be excluded clinically,unless mutationanalysishas been performed and is negative: LAMMsyndrome (labrytinthine aplasia, microtia and microdontia), BOR syndrome, BOF syndrome, Fraser syndrome, Miller syndrome, Nager syndrome, LADD syndrome, Meier Gorlin syndrome and Townes Brocks syndrome. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Bilateral microtia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Where the phenotype is recognisable and is caused by 1-2 principle genes, these should have been tested prior to recruitment **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial hemifacial microsomia (37649)

Level 3 Title	Deafness and congenital structural abnormalities (10982)
Level 4 Title	Familial hemifacial microsomia (37649)
Eligibility Statement	**Familial hemifacial microsomia inclusion criteria** • Proband with either HFM, Goldenhar or Oculoauriculovertebral spectrum, AND • At least two other relatives with features of first and second branchial arch anomalies especially macrostomia, epibulbar dermoid, asymmetric mandiular hypoplasia or microtia/ significant external ear anomaly (but not isolated preauricular pits or minor ear anomalies). **Familial hemifacial microsomia exclusion criteria** • Known cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial hemifacial microsomia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: • aCGH or equivalent • Preauricular pits: EYA1, SIX1 • SALL1 (if abnormal thumbs or anal anomaly) • SALL4, EFTUD2 and SF3B4 (if abnormal thumbs) • TCOF1 (if bilateral microtia) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Ear malformations with hearing impairment (37657)

Level 3 Title	Deafness and congenital structural abnormalities (10982)
Level 4 Title	Ear malformations with hearing impairment (37657)
Eligibility Statement	**Ear malformations with hearing impairment inclusion criteria** • Unexplained bilateral ear malformation associated with bilateral hearing loss Examples include cochlear hypoplasia/aplasia, incomplete partitioning of the cochlea, dilated vestibule, dilated vestibular aqueducts, dilated, hypolplastic or absent semicircular canals, hypoplastic or absent VIIIth nerve, duplicated or absent IAM (internal auditory meatus). **Ear malformations with hearing impairment exclusion criteria** • Bilateral lateral semicircular canal dysplasia is excluded. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Ear malformations with hearing impairment prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: • Enlarged vestibular aqueducts: SLC26A4 • Cochlear hypoplasia and preauricular pits in any family member: EYA1/SIX1 • Inner ear agenesis (absent cochlea or vestibule): FGF3 • Absent semi-circular canals: consider CHD7 • Vestibular/semicircular canal dysplasia: consider SOX10 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial Meniere Disease (71748)

Level 3 Title	Other hearing and ear disorders (71738)
Level 4 Title	Familial Meniere Disease (71748)
Eligibility Statement	**Familial Meniere Disease inclusion criteria** A diagnosis of Meniere made by either an ENT or an Audiovestibular Medicine (AVM) consultant. The full clinical triad of symptoms (vertigo, tinnitus and sensorineural hearing loss). At least 3 affected relatives with confirmed diagnosis of Meniere's disease (fitting the clinical criteria) of whom two should be first degree relatives. Unaffected individuals should not be recruited. **Familial Meniere Disease exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial Meniere Disease prior genetic testing genes** **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Infectious diseases (42209)

Bacterial disorders (42210)

Disseminated non-tuberculous mycobacterial infection (41932)

Level 3 Title	Bacterial disorders (42210)
Level 4 Title	Disseminated non-tuberculous mycobacterial infection (41932)
Eligibility Statement	**Disseminated non-tuberculous mycobacterial infection inclusion criteria** Individuals with disseminated (multiple lymph nodes, liver, spleen, bone or other organs) or progressive disease (including progressive skin or lymph node infection at the site of BCG due to BCG or non-tuberculous mycobacteria **Disseminated non-tuberculous mycobacterial infection exclusion criteria** Underlying immunodeficiency (PID, CGD); HIV Infection; Infection following bone marrow transplantation or cancer chemotherapy. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Disseminated non-tuberculous mycobacterial infection prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes specified **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GAinS study (55665)

Level 3 Title	Sepsis (55671)
Level 4 Title	GAinS study (55665)
Eligibility Statement	**GAinS study inclusion criteria** RECRUITMENT TO THIS CATEGORY IS ONLY APPROVED VIA OXFORD GMC GAinS study participants who are previously healthy individuals, with minimal or no co-morbidities or smoking history who have been admitted to intensive care with sepsis aged over 18 years but less than 50 years old due to community-acquired pneumonia and developed organ dysfunction OR GAinS study participants specifically nominated as extreme responders to Sepsis for other reason **GAinS study exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **GAinS study prior genetic testing genes** **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Metabolic disorders (10983)

Specific metabolic abnormalities (10984)

Ketotic hypoglycaemia (11080)

Level 3 Title	Specific metabolic abnormalities (10984)
Level 4 Title	Ketotic hypoglycaemia (11080)
Eligibility Statement	Specific metabolic abnormalities eligibility statements. **Specific Metabolic Abnormalities inclusion criteria** - Evidence of inborn error of metabolism as demonstrated by findings in at least 2 of the following areas: - Clinical presentation - Biochemical - Haematological - Radiological - Biochemical testing and genetic testing completed for relevant known inborn errors of metabolism **Specific Metabolic Abnormalities exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Specific Metabolic Abnormalities prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genetic testing completed for relevant known inborn errors of metabolism **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Lactic acidosis (11081)

Level 3 Title	Specific metabolic abnormalities (10984)
Level 4 Title	Lactic acidosis (11081)
Eligibility Statement	Specific metabolic abnormalities eligibility statements. **Specific Metabolic Abnormalities inclusion criteria** - Evidence of inborn error of metabolism as demonstrated by findings in at least 2 of the following areas: - Clinical presentation - Biochemical - Haematological - Radiological - Biochemical testing and genetic testing completed for relevant known inborn errors of metabolism **Specific Metabolic Abnormalities exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Specific Metabolic Abnormalities prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genetic testing completed for relevant known inborn errors of metabolism **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Cerebral folate deficiency (11083)

Level 3 Title	Specific metabolic abnormalities (10984)
Level 4 Title	Cerebral folate deficiency (11083)
Eligibility Statement	Specific metabolic abnormalities eligibility statements. **Specific Metabolic Abnormalities inclusion criteria** - Evidence of inborn error of metabolism as demonstrated by findings in at least 2 of the following areas: - Clinical presentation - Biochemical - Haematological - Radiological - Biochemical testing and genetic testing completed for relevant known inborn errors of metabolism **Specific Metabolic Abnormalities exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Specific Metabolic Abnormalities prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genetic testing completed for relevant known inborn errors of metabolism **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Undiagnosed metabolic disorders (37620)

Level 3 Title	Specific metabolic abnormalities (10984)
Level 4 Title	Undiagnosed metabolic disorders (37620)
Eligibility Statement	**Undiagnosed metabolic disorders inclusion criteria** • Any patient seen in a metabolic clinic considered likely to have a monogenic disorder by a consultant Metabolic physician **Undiagnosed metabolic disorders exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Undiagnosed metabolic disorders prior genetic testing genes** Genetic testing in line with current local practice should be considered in parallel with recruitment but is NOT required prior to recruitment. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Congenital disorders of glycosylation (37628)

Level 3 Title	Specific metabolic abnormalities (10984)
Level 4 Title	Congenital disorders of glycosylation (37628)
Eligibility Statement	**Congenital disorders of glycosylation inclusion criteria** • Repeated abnormal pattern on transferrin isolelectric focussing in a child of >3 months, AND • Clinically multisystem disease with abnormal protein C and / or S; AND Factor VIII and/or factor XI and /or ATIII (abnormal) OR • Muscle biopsy with abnormal dystroglycan pattern OR • Normal transferrin isolelectric focussing but patient thought to have CDG after assessment by metabolic or neurometabolic specialist and exclusion of abnormalities of VLCFA or 7DHC **Congenital disorders of glycosylation exclusion criteria** • Known genetic cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Congenital disorders of glycosylation prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: • Transferrin isoelectric focussing and, if abnormal, confirmed on a second sample and PMM2 deficiency excluded • Those with normal IEF should be assessed by metabolic or neurometabolic specialist for inclusion; 7DHC should be normal; VLCFA should be normal; protein C and S, factor VIII and XI and ATIII, T4 and TSH should be measured; for suspected isolated O glycosylation or combined N- and O-glycosylation defect ApoC III should be measured. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Hyperammonaemia (11079)

Level 3 Title	Urea Cycle disorders (15108)
Level 4 Title	Hyperammonaemia (11079)
Eligibility Statement	**Hyperammonaemia inclusion criteria** - Evidence of inborn error of metabolism as demonstrated by findings in at least 2 of the following areas: - Clinical presentation - Biochemical - Haematological - Radiological - Biochemical testing and genetic testing completed for relevant known inborn errors of metabolism **Hyperammonaemia exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Hyperammonaemia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genetic testing completed for relevant known inborn errors of metabolism **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Mucopolysaccharideosis, Gaucher, Fabry (11084)

Level 3 Title	Lysosomal storage disorders (10985)
Level 4 Title	Mucopolysaccharideosis, Gaucher, Fabry (11084)
Eligibility Statement	**Mucopolysaccharideosis, Gaucher, Fabry inclusion criteria** - Evidence of inborn error of metabolism as demonstrated by findings in at least 2 of the following areas: - Clinical presentation - Biochemical - Haematological - Radiological - Biochemical testing and genetic testing completed for relevant known inborn errors of metabolism **Mucopolysaccharideosis, Gaucher, Fabry exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Mucopolysaccharideosis, Gaucher, Fabry prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genetic testing completed for relevant known inborn errors of metabolism **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Mitochondrial disorders (11085)

Level 3 Title	Mitochondrial (10986)
Level 4 Title	Mitochondrial disorders (11085)
Eligibility Statement	**Mitochondrial inclusion criteria** - Unexplained multi-system progressive disorder usually involving the central nervous system and/or neuromuscular system - Contributory laboratory findings may include but are not restricted to: - characteristic brain MR imaging, e.g. brainstem or basal ganglia involvement, infarction not confined to typical vascular territory, leukoencephalopathy - raised serum, CSF or urinary organic acid biomarkers (e.g. lactate, 3-MGA) - evidence of mitochondrial dysfunction in diagnostic biopsies including histochemical (COX-deficient fibres, ragged-red fibres) and biochemical (respiratory chain enzyme deficiencies) markers of disease pathology. **Mitcohondrial exclusion criteria** - Mitochondrial DNA and common nuclear genetic causes (e.g. POLG) excluded (m.3243A>G, POLG) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Mitcohondrial prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Mitochondrial DNA - Common nuclear genetic causes as appropriate **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Peroxisomal biogenesis disorders (11086)

Level 3 Title	Peroxisomal disorders (10987)
Level 4 Title	Peroxisomal biogenesis disorders (11086)
Eligibility Statement	**Peroxisoomal inclusion criteria** - Evidence of inborn error of metabolism as demonstrated by findings in at least 2 of the following areas: - Clinical presentation - Biochemical - Haematological - Radiological - Biochemical testing and genetic testing completed for **Peroxisomal exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Peroxisomal Prior Testing prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genetic testing completed for relevant known inborn errors of metabolism **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Other peroxisomal disorders (15109)

Level 3 Title	Peroxisomal disorders (10987)
Level 4 Title	Other peroxisomal disorders (15109)
Eligibility Statement	**Peroxisoomal inclusion criteria** - Evidence of inborn error of metabolism as demonstrated by findings in at least 2 of the following areas: - Clinical presentation - Biochemical - Haematological - Radiological - Biochemical testing and genetic testing completed for **Peroxisomal exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Peroxisomal Prior Testing prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genetic testing completed for relevant known inborn errors of metabolism **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Cerebellar hypoplasia (36512)

Level 3 Title	Motor Disorders of the CNS (10989)
Level 4 Title	Cerebellar hypoplasia (36512)
Eligibility Statement	**Cerebellar hypoplasia inclusion criteria** • Cerebellar or ponto-cerebellar hypoplasia on MRI brain scan **Cerebellar hypoplasia exclusion criteria** • Findings characteristic of Joubert syndrome (in which case recruit to Joubert syndrome category) • Known genetic cause • Evidence of causative prenatal infection such as CMV (this usually causes more widespread brain abnormalities such as calcification not just cerebellar hypoplasia) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Cerebellar hypoplasia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Gene panel including ITPR1, SPTBN2, KCNC3, CASK, OPHN1 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Hereditary ataxia (11087)

Level 3 Title	Motor Disorders of the CNS (10989)
Level 4 Title	Hereditary ataxia (11087)
Eligibility Statement	**Hereditary ataxia inclusion criteria** - Unexplained cerebellar ataxia progressing over >2 years +/- spasticity, peripheral neuropathy, or bulbar dysfunction. Individuals with syndromic disease or disease onset <30 years should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Hereditary ataxia exclusion criteria** - No structural or inflammatory (MS-like) lesions on brain MRI. - No history of alcohol excess. - Normal thyroid function. - No evidence of malignancy. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Hereditary ataxia prior genetic testing genes** Testing for genes which are affected by trinucleotide repeats is strongly recommended PRIOR TO RECRUITMENT as these will not be reliably detected by WGS using current analysis techniques including: - Common trinucleotide repeat disorders excluded (ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7, TBP, ATN1, FXN (only recessive history), FMR1) **Closing statement**

	These requirements will be kept under continual review during the main programme and may be subject to change.

Early onset dystonia (11088)

Level 3 Title	Motor Disorders of the CNS (10989)
Level 4 Title	Early onset dystonia (11088)
Eligibility Statement	**Early onset dystonia inclusion criteria** - Dystonia affecting any body part, usually spreading to involve multiple body regions (e.g. multifocal, segmental, generalised) - Age at onset <31 years or later onset with family history of early onset dystonia - May be paroxysmal/episodic dystonia - May be associated with myoclonus as in myoclonic dystonia This disease category includes dopa responsive dystonia. **Early onset dystonia exclusion criteria** - Underlying cause for clinical syndrome identified, e.g. cerebral palsy, structural brain lesion, Wilson disease, psychogenic dystonia **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Early onset dystonia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - TOR1A **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Hereditary spastic paraplegia (11089)

Level 3 Title	Motor Disorders of the CNS (10989)
Level 4 Title	Hereditary spastic paraplegia (11089)
Eligibility Statement	**Hereditary spastic paraplegia inclusion criteria** - Unexplained spastic paraplegia progressing over >2 years +/-, peripheral neuropathy, or ataxia. Individuals with syndromic disease or disease onset <30 years should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Hereditary spastic paraplegia exclusion criteria** - No structural or inflammatory (MS-like) lesions on brain MRI. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Hereditary spastic paraplegia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - SPAST, ATL1 - Normal very long chain fatty acid studies **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Neurotransmitter disorders (37779)

Level 3 Title	Motor Disorders of the CNS (10989)
Level 4 Title	Neurotransmitter disorders (37779)
Eligibility Statement	**Neurotransmitter disorders inclusion criteria** • Patient with an abnormal CSF neurotransmitter profile indicating an abnormal HVA, HIAA or pterin profile • Patients with symptoms suspicious of dopamine/serotonin deficiency (e.g. movement disorder, gait abnormalities, hypotonia, autonomic features and neurodevelopmental delay) **Neurotransmitter disorders exclusion criteria** • CSF neurotransmitter highly suggestive of a primary neurotransmitter that would warrant exclusion of this condition e.g. a CSF profile consistent with AADC deficiency would warrant AADC enzyme activity and DDC genetic testing before patient would be eligible • Normal CSF neurotransmitter profile • No clinical features of a neurotransmitter disorder **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Neurotransmitter disorders prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: • As determined by CSF profile **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Structural basal ganglia disorders (37786)

Level 3 Title	Motor Disorders of the CNS (10989)
Level 4 Title	Structural basal ganglia disorders (37786)
Eligibility Statement	**Structural basal ganglia disorders inclusion criteria** • Patient with structural, preferably symmetrical radiological abnormalities on MR imaging affecting the striatum, globus pallidus and/or substantia nigra, AND • Neurological symptoms e.g. movement disorder **Structural basal ganglia disorders exclusion criteria** • Evidence of an acquired disorder (e.g. basal ganglia stroke or autoimmune aetiology) • No neurological symptoms • Known genetic cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Structural basal ganglia disorders prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - As dictated by phenotype **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Genetic Epilepsies with Febrile Seizures Plus (11091)

Level 3 Title	Inherited Epilepsy Syndromes (10990)
Level 4 Title	Genetic Epilepsies with Febrile Seizures Plus (11091)
Eligibility Statement	**Genetic Epilepsies with Febrile Seizures Plus inclusion criteria** Families with: - autosomal dominant inheritance (with at least 2 first degree family members or 3 generations affected) - electrographically-proven generalised seizures, which may, or may not be associated with intellectual impairment; and febrile seizures or febrile seizures plus; AND where: - focal seizures form are a minor part of the family phenotype **Genetic Epilepsies with Febrile Seizures Plus exclusion criteria** - SCN1A positive; - No family history of febrile seizures (recruit under familial GGE); - No family history of generalised seizure disorder; - Suspected acquired cause of epilepsy based on history or imaging; - Previously identified genetic cause of epilepsy **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial Genetic Generalised Epilepsies (11092)

Level 3 Title	Inherited Epilepsy Syndromes (10990)
Level 4 Title	Familial Genetic Generalised Epilepsies (11092)
Eligibility Statement	**Familial Genetic Generalised Epilepsies inclusion criteria** - Electrographically-proven generalised epilepsy - At least two first degree relatives or affected family members across three generations who have generalised epilepsy - All forms of generalised epilepsy are permissible **Familial Genetic Generalised Epilepsies exclusion criteria** - Suspected acquired cause of epilepsy - Focal neurological deficit - MRI demonstrates structural substrate for epilepsy - EEG demonstrates definite focal discharges **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial Focal Epilepsies (11093)

Level 3 Title	Inherited Epilepsy Syndromes (10990)
Level 4 Title	Familial Focal Epilepsies (11093)
Eligibility Statement	**Familial Focal Epilepsies inclusion criteria** - Patients with focal epilepsy not thought to be acquired in aetiology - At least two first degree relatives or affected family members across three generations who have focal epilepsy that is not thought to be acquired in aetiology - All forms of focal epilepsy are permissible **Familial Focal Epilepsies exclusion criteria** - Suspected acquired cause of epilepsy - EEG demonstrates definite generalised epileptiform discharges **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Epileptic encephalopathy (11094)

Level 3 Title	Inherited Epilepsy Syndromes (10990)
Level 4 Title	Epileptic encephalopathy (11094)
Eligibility Statement	**Epileptic encephalopathy inclusion criteria** - Recurrent seizures with onset of epilepsy prior to two years of age AND - Negative genome wide microarray copy number analysis **Epileptic encephalopathy exclusion criteria** - Major structural brain malformation such as cortical malformation, neuronal migration defect AND/OR - Known clear biochemical, enzymatic or molecular genetic evidence of underlying metabolic cause, e.g. organic aciduria, vitamin B6 metabolism defect **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Epilepsy plus other features (41924)

Level 3 Title	Inherited Epilepsy Syndromes (10990)
Level 4 Title	Epilepsy plus other features (41924)
Eligibility Statement	**Epilepsy plus other features inclusion criteria** Established diagnosis of epilepsy, confirmed by a neurologist AND with at least one additional phenotype from: intellectual disability, autism spectrum disorder, structural abnormality (e.g. dysmorphism, cerebral or somatic malformation), unexplained cognitive/memory decline OR Consanguineous parents **Epilepsy plus other features exclusion criteria** Case falls into one of the other GeL epilepsy disease categories Focal, unilateral cerebral malformations **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Epilepsy plus other features prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: As dictated by local practice and clinical phenotype including consideration of SCN1A **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Charcot-Marie-Tooth disease (15111)

Level 3 Title	Motor and Sensory Disorders of the PNS (10991)
Level 4 Title	Charcot-Marie-Tooth disease (15111)
Eligibility Statement	**Charcot-Marie-Tooth disease inclusion criteria** - Unexplained peripheral neuropathy affecting motor, sensory or autonomic nerves progressing over >2 years +/- additional neurological signs. **Charcot-Marie-Tooth disease exclusion criteria** - History of trauma - Known acquired metabolic, vascular, inflammatory or immunological cause - History of alcohol excess - Evidence of malignancy - ENG/EMG suggest acquired pathology **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Charcot-Marie-Tooth disease prior genetic testing genes** Testing for the chromosome 17p11.2 duplication is strongly recommended PRIOR TO RECRUITMENT as this may not be reliably detected by WGS using current analysis techniques; other tests below should be considered where this is in line with current local practice including: - PMP22 point mutations, GJB1, MPZ, MFN2 (MFN2 axonal only) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Paediatric motor neuronopathies (11099)

Level 3 Title	Motor and Sensory Disorders of the PNS (10991)
Level 4 Title	Paediatric motor neuronopathies (11099)
Eligibility Statement	Relevant diseases: - Brown-Vialetto-Van Laere syndrome - Spinal muscular atrophy syndromes - Fazio-Londe syndrome **Paediatric motor neuronopathies inclusion criteria** Motor neuronopathy OR bulbar palsy with or without respiratory insufficiency due to diaphragmatic paralysis +/-sensory neuropathy, optic atrophy and sensorineural hearing loss - Congenital or presentation in early childhood most commonly (presentation can occur in adult life, but is rare) - EMG consistent with motor neuron involvement **Paediatric motor neuronopathies exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Paediatric motor neuronopathies prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: Testing of SMN1 if a clinical diagnosis of spinal muscular atrophy is being considered **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Pain channelopathies (null)

Level 3 Title	Motor and Sensory Disorders of the PNS (10991)
Level 4 Title	Pain channelopathies (null)
Eligibility Statement	**Pain channelopathies inclusion criteria** Individuals with clinical features of a monogenic neuropathic pain disorder or other pain channelopathy **Pain channelopathies exclusion criteria** Features suggestive of an acquired cause including: History of trauma Known acquired metabolic, vascular, inflammatory or immunological cause for neuropathy History of alcohol excess likely to explain neuropathy Evidence of malignancy likely to explain neuropathy ENG/EMG suggest acquired pathology **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Pain channelopathies prior genetic testing genes** As determined by clinical presentation but consideration of testing for Fabry where relevant **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Early onset and familial Parkinson's Disease (11100)

Level 3 Title	Neurodegenerative disorders (10992)
Level 4 Title	Early onset and familial Parkinson's Disease (11100)
Eligibility Statement	**Early onset and familial Parkinson's Disease inclusion criteria** - Early onset (<= 45 years of age) or history of other family member with Parkinson's Disease - Bradykinesia plus at least one of rigidity, rest tremor and gait disturbance - May have concurrent dystonia (common in early onset PD) - May have positive family history or consanguinity - If complex features, e.g. spasticity, early dementia, gaze palsy, Neurodegeneration with Brain Iron Accumulation, please recruit to Complex Parkinsonism - May develop Lewy Body/PD type dementia Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Early onset and familial Parkinson's Disease exclusion criteria** - Underlying cause for clinical syndrome identified, e.g. cerebral palsy, dopa-responsive dystonia, structural brain lesion, Wilson disease, psychogenic dystonia **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Early onset and familial Parkinson's Disease prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: LRRK2 G2019S (dominant), PARK2 (parkin, recessive) and PINK1 (recessive). Clinical phenotype and family history

	to guide testing. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Complex Parkinsonism (includes pallido-pyramidal syndromes) (15112)

Level 3 Title	Neurodegenerative disorders (10992)
Level 4 Title	Complex Parkinsonism (includes pallido-pyramidal syndromes) (15112)
Eligibility Statement	**Complex Parkinsonism inclusion criteria** - Progressive motor syndrome with parkinsonism (bradykinesia with one of tremor, gait disorder, stiffness) - Additional features may include spasticity, gaze palsy, early dementia, early bulbar failure, dyspraxia, ataxia, postural hypotension, cortical sensory loss, brain iron accumulation on MRI brain - Age at onset <= 45 years or later onset with family history of similar condition in other family members Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Complex Parkinsonism exclusion criteria** - Underlying cause not identified, e.g. structural brain lesion, Wilson disease **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Complex Parkinsonism prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - C9ORF72, GRN, MAPT in cases with a clinical presentation suggestive of cortico-basal/PSP syndrome **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Early onset dementia (15113)

Level 3 Title	Neurodegenerative disorders (10992)
Level 4 Title	Early onset dementia (15113)
Eligibility Statement	**Early onset dementia inclusion criteria** - Progressive cognitive deterioration with change in memory, vision, behaviour or language with functional impairment - Age at onset <60 years OR - Later onset with family history of dementia of the same type in a first or second degree relative Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Early onset dementia exclusion criteria** - Identified underlying cause, e.g. structural brain lesion. NB in uncertain cases with anxiety/depression brain atrophy on imaging, CSF findings or EEG abnormalities should be available to support the diagnosis of a primary degenerative syndrome **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Early onset Dementia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Clinical syndrome Alzheimer disease: PSEN1, APP - Clinical syndrome FTLD: MAPT, C9ORF72, GRN - Clinical syndrome Prion disease: PRNP **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Amyotrophic lateral sclerosis or motor neuron disease (15114)

Level 3 Title	Neurodegenerative disorders (10992)
Level 4 Title	Amyotrophic lateral sclerosis or motor neuron disease (15114)
Eligibility Statement	**Amyotrophic lateral sclerosis or motor neuron disease inclusion criteria** - Progressive upper and/or lower motor neuron disease degeneration with clinical features of amyotrophy, spasticity, bulbar/pseudo-bulbar involvement - EMG/NCS consistent with MND - Positive family history of other affected family members with ALS or with FTD/ALS like phenotype or disease onset below 40 years. Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Amyotrophic lateral sclerosis or motor neuron disease exclusion criteria** - Identified underlying cause for clinical syndrome e.g. multi-focal motor neuropathy, lymphoma **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Amyotrophic lateral sclerosis or motor neuron disease prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - C9ORF72, SOD1 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Classical tuberous sclerosis (11101)

Level 3 Title	Neurodevelopmental disorders (10993)
Level 4 Title	Classical tuberous sclerosis (11101)
Eligibility Statement	**Classical tuberous sclerosis inclusion criteria** 2 major or 1 major and >=2 minor criteria: - Major features - Hypomelanotic macules (>=3 at least 5-mm diameter) - Angiofibromas (>=3) or fibrous cephalic plaque - Ungual fibromas (>=2) - Shagreen patch - Multiple retinal hamartomas - Cortical dysplasias (tubers or cerebral white matter radial migration lines) - Subependymal nodules - Subependymal giant cell astrocytoma - Cardiac rhabdomyoma - Lymphangioleiomyomatosis (LAM) - Renal angiomyolipomas (>=2) - Minor features - Confetti skin lesions - Dental enamel pits (>3) - Intraoral fibromas (>=2) - Retinal achromic patch - Multiple renal cysts - Nonrenal hamartomas AND - Participants who have not undergone prior genetic testing of TSC1 and TSC2 should be recruited initially as singletons. In families where analysis as a singleton does not lead to identification of the underlying causative mutation, recruitment of additional affected family members is encouraged. **Classical tuberous sclerosis exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.

	- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Classical tuberous sclerosis prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: TSC1, TSC2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Intellectual disability (11102)

Level 3 Title	Neurodevelopmental disorders (10993)
Level 4 Title	Intellectual disability (11102)
Eligibility Statement	NB. Clinical test guidance: Imaging diagnostics refers to MRI brain and/or medical photographs of facial features and other physical features as appropriate **Intellectual disability inclusion criteria** - Moderate to Severe/ Profound ID disproportionate to parental IQ unless the family history is consistent with an X-linked disorder - Congenital onset - Developmental Delay - +/- clinical features suggestive of a specific syndrome - Metabolic causes have been excluded **Intellectual disability exclusion criteria** - Antenatal history suggestive of non-genetic cause - Proven congenital or neonatal infections - Known genetic cause already identified - Microarray analysis abnormal and clearly pathogenic **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Intellectual disability prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - For syndromes where the cause of disease is 1-2 genes these need to be excluded before Genomics England recruitment, e.g. for Kabuki syndrome, MLL2 (KMT2D) and KDM6A should have been tested **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Holoprosencephaly (36519)

Level 3 Title	Neurodevelopmental disorders (10993)
Level 4 Title	Holoprosencephaly (36519)
Eligibility Statement	**Holoprosencephaly inclusion criteria** Holoprosencephaly: one major and one minor Major: • 1. Holoprosencephaly • 2. Single central incisor Minor: • 1. Unilateral or bilateral choanal stenosis/atresia • 2. Ptosis • 3. Small head circumference • 4. Learning difficulties • 5. Dysmorphic features • 6. Hypopituitarism **Holoprosencephaly exclusion criteria** Chromosome rearrangement consistent with the diagnosis **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Holoprosencephaly prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Rhomboencephalosynapsis (36603)

Level 3 Title	Neurodevelopmental disorders (10993)
Level 4 Title	Rhomboencephalosynapsis (36603)
Eligibility Statement	**Rhomboencephalosynapsis inclusion criteria** Rhombencephalosynapsis • 1. MRI findings indivative of rhombencephalosynapsis reviewed by an experienced neuroradiologist **Rhomboencephalosynapsis exclusion criteria** Chromosome rearrangement consistent with the diagnosis **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Rhomboencephalosynapsis prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Malformations of cortical development (36526)

Level 3 Title	Neurodevelopmental disorders (10993)
Level 4 Title	Malformations of cortical development (36526)
Eligibility Statement	**Malformations of cortical development inclusion criteria** • Evidence of diffuse or focal cortical brain malformation on brain MRI or pathology, AND • MCD the cardinal feature, AND • Appropriate known gene, if testing available via UKGTN, excluded , AND • Congenital infection, especially CMV, has been excluded if suggested by phenotype **Malformations of cortical development exclusion criteria** • Brain MRI or pathology not available • Known genetic cause • Evidence of congenital infection • Known metabolic condition • Raised CK levels indicative of muscle-eye-brain disease • Diagnosis of Tuberous Sclerosis • MCD clearly part of a known MCA syndrome with a known cause • Fetal cases – these should be recruited to the fetal structural brain anomaly category **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Malformations of cortical development prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - 1. Microarray - 2. Exclusion of PAFAH1B1 and DCX gene deletions using MLPA or similar method where appropriate. - 3. Single MCD gene or MCD gene panel testing as guided by phenotype. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Fetal structural CNS abnormalities (36850)

Level 3 Title	Neurodevelopmental disorders (10993)
Level 4 Title	Fetal structural CNS abnormalities (36850)
Eligibility Statement	**Fetal structural CNS abnormalities inclusion criteria** Neuronal migration abnormality: Bilateral neuronal migration abnormality, confirmed on MRI or pathology, normal TORCH screen Posterior fossa abnormality: Cerebellar vermis agenesis /hypoplasia < 5th percentile and / or bilateral cerebellar hemisphere hypoplasia /atrophy Midline brain abnormalities: Absent cavum septum pellucidum or holoprosencephaly or complete / partial agenesis of the corpus callosum Severe ventriculomegaly with posterior ventricle measuring > 15mm: non-obstructive, normal spine anatomy, normal TORCH screen Microcephaly: Head circumference measuring <3rd percentile, normal TORCH & VZV screen. For all: Both parents MUST be available to provide a blood sample for testing. **Fetal structural CNS abnormalities exclusion criteria** Midline brain abnormalities: maternal exposure to illicit drugs and alcohol Severe ventriculomegaly: intracranial haemorrhage of any underlying cause; twin pregnancy related problems. Microcephaly: Parental head circumference measuring <3rd percentile, normal HC/AC and HC/FL ratios. For all: A known genetic or chromosomal cause. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Fetal structural CNS abnormalities prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: • chromosome microarray • ASPM and other genes dictated by the phenotype **Closing statement**

	These requirements will be kept under continual review during the main programme and may be subject to change.

Pontine tegmental cap dysplasia (55493)

Level 3 Title	Neurodevelopmental disorders (10993)
Level 4 Title	Pontine tegmental cap dysplasia (55493)
Eligibility Statement	**Pontine tegmental cap dysplasia inclusion criteria** Diagnosis of PTCD on MRI brain scan - characteristic neuroimaging features are flattening of ventral pons, dorsal pontine 'cap', hypoplastic or absent middle and inferior cerebellar peduncles and hypoplastic vermis. Sensorineural deafness due to absence of 8th cranial nerve with or without corneal anaesthesia due to trigeminal sensory dysfunction. **Pontine tegmental cap dysplasia exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Pontine tegmental cap dysplasia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: Microarray **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Congenital muscular dystrophy (15135)

Level 3 Title	Neuromuscular disorders (10994)
Level 4 Title	Congenital muscular dystrophy (15135)
Eligibility Statement	Relevant diseases: - Congenital muscular dystrophy **Congenital muscular dystrophy inclusion criteria** - Muscle weakness with onset in infancy or early childhood AND - elevated creatine kinases or muscle biopsy with dystrophic changes - Availability of CK and muscle biopsy results - Dystrophic changes on muscle biopsy **Congenital muscular dystrophy exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Congenital myopathy (11103)

Level 3 Title	Neuromuscular disorders (10994)
Level 4 Title	Congenital myopathy (11103)
Eligibility Statement	Relevant diseases: - Congenital myopathy **Congenital myopathy inclusion criteria** - Muscle weakness - ne or more of the following histopathological features - type 1 predominance or uniformity - congenital fibre type disproportion - central cores - multi-minicores - nemaline rods - central nuclei - Availability of CK, muscle CT/MR imaging, muscle biopsy and neurophysiological studies **Congenital myopathy exclusion criteria** - Absence of muscle weakness - CK more than 5x normal - dystrophic features on muscle biopsy **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Congenital myaesthenia (15136)

Level 3 Title	Neuromuscular disorders (10994)
Level 4 Title	Congenital myaesthenia (15136)
Eligibility Statement	**Congenital myaesthenia inclusion criteria** - Patients at any age with fatigable weakness and fluctuating motor symptoms - Clinical neurophysiology revealing a neuromuscular transmission defect (repetitive nerve stimulation, or Single fibre EMG) - Review of patient data by CMS NHS Highly Specialised Services for Rare Diseases service **Congenital myaesthenia exclusion criteria** - Response to immunosuppressive treatment - Presence of anti- AChR or MuSK antibodies - Muscle biopsy indicative of mitochondrial disorder. Muscle biopsy giving clear indication of dystrophy or other muscle disorder **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Rhabdomyolysis and metabolic muscle disorders (15137)

Level 3 Title	Neuromuscular disorders (10994)
Level 4 Title	Rhabdomyolysis and metabolic muscle disorders (15137)
Eligibility Statement	**Rhabdomyolysis and metabolic muscle disorders inclusion criteria** - At least 2 of the criteria listed below: - Symptom triggers: Exercise, fasting, fever and heat - Variable CK with exacerbations >10x above basal value - Myoglobinuria (tea or coca cola coloured urine) - In patient treatment for acute rhabdomyolysis with or without acute renal failure - Muscle weakness is progressive - Usually muscle pain associated with atrophy and weakness - Malignant Hyperpyrexia syndrome - Neuroleptic Malignant syndrome - Acute compartment Syndrome Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Rhabdomyolysis and metabolic muscle disorders exclusion criteria** - Non exercise related limb pain - Muscle biopsy with histochemical enzyme or sarcolemmal protein deficiencies to indicate a diagnosis of GSDV, GSDVII or muscular dystrophy (Becker or LGMD) - Abnormal fasting blood acyl carnitines and/or urine organic acids consistent with a known FAODD - Confirmed viral induced myositis without myoglobinuria - Prescribed (e.g. statin) or recreational drug triggers - Severe trauma **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Distal myopathies (11104)

Level 3 Title	Neuromuscular disorders (10994)
Level 4 Title	Distal myopathies (11104)
Eligibility Statement	**Distal myopathies inclusion criteria** - Unexplained predominantly distal muscle weakness, onset at any age - Acquired myopathies excluded by relevant clinical investigations - Serum creatine kinase (CK) assessment - Muscle Biopsy with immunohistochemistry (IH) - Neurophysiology performed - Muscle MRI (optional) - Dried blood spot test for Pompe disease performed **Distal myopathies exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Distal myopathies prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - DMD analysis by MLPA or equivalent - DUX1 and DMPK exclusion by conventional genetic testing - Exclusion by genetic testing of any gene indicated by IH. - In the presence of evidence of myofibrillar myopathy on muscle biopsy IH exclusion of LDB3, MYOT, DES, CRYAB by sequencing **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Arthrogryposis (15138)

Level 3 Title	Neuromuscular disorders (10994)
Level 4 Title	Arthrogryposis (15138)
Eligibility Statement	**Arthrogryposis inclusion criteria** - Multiple congenital bilateral joint contractures - EMG/NCV completed - Creatinine kinase measured - MRI brain if developmentally delayed or otherwise clinically indicated - TORCH screen if developmentally delayed and less than 6 months old - Maternal anti-acetylcholine receptor antibodies - Consideration of skeletal survey to exclude skeletal dysplasia **Arthrogryposis exclusion criteria** - Isolated talipes/clubfoot - Oligohydramnios - Major structural CNS abnormalities likely to be causative of phenotype - Confident clinical diagnosis of amyoplasia **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Arthrogryposis prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - If associated with other abnormalities, genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Limb girdle muscular dystrophy (11106)

Level 3 Title	Neuromuscular disorders (10994)
Level 4 Title	Limb girdle muscular dystrophy (11106)
Eligibility Statement	**Limb girdle muscular dystrophy inclusion criteria** - Unexplained predominantly proximal muscle weakness, onset at any age. - Acquired myopathies excluded by relevant clinical investigations. - Serum creatine kinase (CK) assessment. - Muscle Biopsy with immunohistochemistry (IH) performed. - Dried blood spot test for Pompe disease performed. - Muscle MRI (optional). - Review of patient data by LGMD NHS Highly Specialised Services for Rare Diseases service **Limb girdle muscular dystrophy exclusion criteria** - Phenotypes suggestive of FSHD, DM1 or DM2. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Limb girdle muscular dystrophy prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - 'DMD analysis by MLPA or equivalent, LMNA, ANO5, CAPN3 and FKRP by sequencing. - Exclusion by genetic testing of any gene indicated by IH. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Skeletal Muscle Channelopathies (15139)

Level 3 Title	Channelopathies (11097)
Level 4 Title	Skeletal Muscle Channelopathies (15139)
Eligibility Statement	**Skeletal Muscle Channelopathies inclusion criteria** - Episodic flaccid paralysis or weakness and/or myotonia - May develop progressive, usually proximal, weakness - Electrophysiology including long and short exercise testing - Intra-attack potassium documented whenever possible - Normal renal function and thyroid function **Skeletal Muscle Channelopathies exclusion criteria** - Primary renal or endocrine problem that may be causative - Associated loss of consciousness with attacks **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Skeletal Muscle Channelopathies prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Myotonia: DMPK, CNBP, SCN4A, CLCN1 (including MLPA) - Episodic weakness: CACNA1S, SCN4A, KCNJ2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Brain channelopathy (15140)

Level 3 Title	Channelopathies (11097)
Level 4 Title	Brain channelopathy (15140)
Eligibility Statement	**Brain channelopathy inclusion criteria** - Episodic disorder that often causes a combination of ataxia with walking problems, abnormal extra movements, stiff legs, weakness, headache and nausea. - Episodes lasting a few minutes or hours. - There may be a dystonic component and some patients are exhausted for many hours afterwards. - Attacks are not always the same, even with the same genetic defect. - Arms can be affected like legs - Migraine type headaches are frequently associated as is dysarthria - Some patients have a primary headache in the form of hemiplegic migraine (FHM), cluster headache, SUNCT or SUNA - MRI brain and cord to exclude common causes such as tumours, discs, demyelinating causes - Family history of often present in AD or AR forms, X linked pattern rare - Often drugs such as Lamotrigine or acetazolamide are effective Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Brain channelopathy exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Brain channelopathy prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - KCNA1, PRRT2 as appropriate

	- CACNA1A (only in dominant, long duration episodic ataxia) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Kleine-Levin syndrome and other inherited sleep disorders (11108)

Level 3 Title	Sleep disorders (10995)
Level 4 Title	Kleine-Levin syndrome and other inherited sleep disorders (11108)
Eligibility Statement	NB. Clinical test guidance: Imaging diagnostics refers to Brain MRI **Kleine-Levin syndrome and other inherited sleep disorders inclusion criteria** -Recurrent hypersomnia: -Recurrent episodes of excessive daytime sleepiness lasting for 2 days-4 weeks -Episodes recur at least once per year -Alertness, cognitive function and behavior are normal between episodes -Hypersomnia -AND at least 1 of the following: -Cognitive abnormalities – ex confusion, derealisation(“déjà vu” during episodes, dream-like state or experiencing out of body hallucinations -Abnormal behaviour – irritability, aggression -Hyperphagia OR -Recurrent daytime hypersomnia: -Sudden onset of sleep or "sleep attacks" -Other symptoms can include cataplexy, hypnagogic hallucinations and Sleep paralysis -A positive family history OR -Involuntary kicking and jerking movements of the legs and arms often repeated 100s of times during the night -Unaware of their multiple night-time awakenings unless they are witnessed by a bed partner -In extreme cases these brief arousals following the leg movements disturb sleep so much that they cause excessive daytime sleepiness -A +ve family history OR -The symptoms of parasomnias: -Sleepwalking—takes place during deep sleep, not REM sleep when dreams typically occur -Night terrors—these severe attacks cause people, usually children, to appear to wake up and scream in fear or panic -Sleep-eating disorders—these episodes occur during partial awakenings from deep sleep and cause individuals to eat without any knowledge of what they are doing. -A +ve family history Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall

	singleton monitoring metrics applied to GMCs. **Kleine-Levin syndrome and other inherited sleep disorders exclusion criteria** - No structural or inflammatory (MS-like) lesions on brain MRI. - No atypical depression - No sleep disorders (exclude Narcolepsy and Menstruation-related hypersomnia) - No substance abuse (particularly benzodiazepine) - No temporal lobe epilepsy - Metabolic Encephalopathy - Lyme disease - Acute intermittent porphyria **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Moyamoya disease (36611)

Level 3 Title	Cerebrovascular disorders (36610)
Level 4 Title	Moyamoya disease (36611)
Eligibility Statement	**Moyamoya disease inclusion criteria** • Bilateral intracranial occlusive arteriopathy, with or without basal collaterals, confirmed by review by an expert neuroradiologist **Moyamoya disease exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Moyamoya disease prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes listed **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Vein of Galen malformation (42174)

Level 3 Title	Cerebrovascular disorders (36610)
Level 4 Title	Vein of Galen malformation (42174)
Eligibility Statement	**Vein of Galen malformation inclusion criteria** Vein of Galen malformation diagnosed by an expert neuroradiologist **Vein of Galen malformation exclusion criteria** Vein of Galen aneurysmal dilatation Other brain AVM **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Vein of Galen malformation prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes specified **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Intracerebral calcification disorders (36619)

Level 3 Title	Parenchymal brain disorders (36618)
Level 4 Title	Intracerebral calcification disorders (36619)
Eligibility Statement	**Intracerebral calcification disorders inclusion criteria** • Intracerebral calcification identified on brain imaging in the absence of a known genetic cause. **Intracerebral calcification disorders exclusion criteria** • Known genetic diagnosis. • Evidence of causative environmental cause, for example infection • Phenotype indicative of other recruitable rare disorder, for example Cockayne syndrome **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Intracerebral calcification disorders prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Guided by phenotype, for example UKGTN Aidcardi-Goutieres syndrome gene panel testing **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Inherited white matter disorders (36627)

Level 3 Title	White matter disorders (36626)
Level 4 Title	Inherited white matter disorders (36627)
Eligibility Statement	**Inherited white matter disorders inclusion criteria** • Patients with a proven or suspected inherited white mater disorder on the basis of abnormal white matter on MR imaging reviewed by an expert neuroradiologist. • Relevant metabolic investigations completed, for example very long chain fatty acids, white cell enzymes and urine organic acids where indicated **Inherited white matter disorders exclusion criteria** • Known genetic cause • Evidence of causative environmental cause, for example infection, hypoxia or inflammation • Phenotype indicative of other recruitable rare disorder, for example Cockayne syndrome or intracerebral calcification indicative of Aicardi-Goutiere's syndrome, or a peroxisomal disorder, in which case recruit to relevant category **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Inherited white matter disorders prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Guided by phenotype, for example PLP1 in males with a phenotype suggestive of Pelizaeus-Merzbacher disease or GJA1 in the presence of phenotypic features of oculodentodigital dysplasia. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Ophthalmological disorders (10996)

Anterior segment abnormalities (10997)

Corneal abnormalities (11110)

Level 3 Title	Anterior segment abnormalities (10997)
Level 4 Title	Corneal abnormalities (11110)
Eligibility Statement	**Corneal abnormalities inclusion criteria** - Bilateral corneal signs - Prior consultation with ophthalmologist who has a specialist interest in corneal dystrophies **Corneal abnormalities exclusion criteria** - Corneal opacity likely secondary to inflammatory disease or trauma (including surgical) - Age-related corneal endothelial failure - Keratoconus **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Corneal abnormalities prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - TGFBI (BIGH3) gene screening in anterior corneal dystrophies (which accounts for approximately 80% of such families) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Glaucoma (developmental) (11111)

Level 3 Title	Anterior segment abnormalities (10997)
Level 4 Title	Glaucoma (developmental) (11111)
Eligibility Statement	**Glaucoma inclusion criteria** - Diagnosis of developmental glaucoma confirmed (preferably) by an ophthalmologist with a sub-specialist expertise in childhood glaucoma - Availability of relevant phenotypic information including: - structural assessment of anterior segment - optic nerve head characteristics - intraocular pressure at first presentation - highest ever recorded IOP, where available - slit lamp assessment of anterior segment - pachymetry - ERG and VEP (if appropriate) - Availability of non-ocular phenotypic information if appropriate: - Presence/absence of maxillary hypoplasia - umbilical anomaly - cardiac anomalies (from history) - growth delay - dental anomalies - metabolic disease (from history) **Glaucoma exclusion criteria** - Features of adult-onset glaucoma - Suggestion of secondary (acquired) glaucoma, i.e. following trauma, intraocular neoplasm, uveitis, lens-related (subluxation, spherophakia, phacolytic), following lensectomy, drug-induced (corticosteroids), secondary to rubeosis, angle closure, associated with increased venous pressure, or following intraocular infection. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Glaucoma prior genetic testing genes**

	Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - MYOC in cases of juvenile open angle glaucoma - CYP1B1 in cases of primary congenital glaucoma - PAX6 in cases of aniridia **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Cataracts (11112)

Level 3 Title	Anterior segment abnormalities (10997)
Level 4 Title	Cataracts (11112)
Eligibility Statement	**Cataracts inclusion criteria** - Congenital cataracts, or cataracts diagnosed in childhood - Bilaterally affected individuals - Isolated or complex **Cataracts exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Posterior segment abnormalities (10998)

Inherited optic neuropathies (11114)

Level 3 Title	Posterior segment abnormalities (10998)
Level 4 Title	Inherited optic neuropathies (11114)
Eligibility Statement	**Inherited optic neuropathies inclusion criteria** - Optic atrophy occurring either in isolation or in association with other multisystemic features - Evidence of optic nerve dysfunction on clinical examination - Additional objective evidence of primary retinal ganglion cell dysfunction with optical coherence tomography imaging and/or visual electrophysiology performed to ISCEV standards **Inherited optic neuropathies exclusion criteria** - Acquired causes of an optic neuropathy have been fully excluded with the relevant investigations, including neuroimaging - Optic atrophy secondary to inherited outer retinal disease **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Inherited optic neuropathies prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Testing for mitochondrial DNA mutations **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Rod-cone dystrophy (29268)

Level 3 Title	Posterior segment abnormalities (10998)
Level 4 Title	Rod-cone dystrophy (29268)
Eligibility Statement	**Rod-cone dystrophy inclusion criteria** - Retinal degeneration as shown by decreased rod / cone responses on an ISCEV ERG and / or clear phenotypic evidence of retinal degeneration as shown by clinical features, e.g. retinal bone spicules, retinal thinning on OCT scans, typical visual field defects such as mid peripheral retinal scotoma. - Evidence of bilateral retinal degeneration. **Rod-cone dystrophy exclusion criteria** - History of retinal detachment or an inflammatory process (e.g. syphilis or tuberculosis infection) masquerading as unilateral retinal degeneration. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Rod Dysfunction Syndrome (29269)

Level 3 Title	Posterior segment abnormalities (10998)
Level 4 Title	Rod Dysfunction Syndrome (29269)
Eligibility Statement	Relevant diseases: - Poor night vision from infancy / early childhood with no evidence of progression - Congenital stationary night blindness - Oguchi disease - Åland Island eye disease - Fundus albipunctatus **Rod Dysfunction Syndrome inclusion criteria** - Presentation from infancy / early childhood including some of these features: nystagmus, reduced visual acuity, and poor night vision. - ISCEV standard ERG has been performed. - Normal fundus appearance except for fundus albipunctatus (multiple discrete white dots scattered throughout the retina at the level of the RPE - most numerous in the mid-periphery and are usually absent at the macula) and Oguchi disease (greyish or green-yellow discoloration of the fundus, which reverts to normal on prolonged dark adaptation) **Rod Dysfunction Syndrome exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Cone Dysfunction Syndrome (29270)

Level 3 Title	Posterior segment abnormalities (10998)
Level 4 Title	Cone Dysfunction Syndrome (29270)
Eligibility Statement	Relevant diseases: - Complete achromatopsia - Incomplete achromatopsia - Blue cone monochromatism - Oligocone trichromacy - Bradyopsia - Borholm eye disease **Cone Dysfunction Syndrome exclusion criteria** **Cone Dysfunction Syndrome inclusion criteria** - Absent or severely reduced cone function from birth / early infancy with no significant evidence of rod involvement. - Presentation from birth / early infancy ÔÇô including some of these features: nystagmus, photophobia, reduced visual acuity, and reduced/absent colour vision. - Absent or severely reduced cone function with no significant rod dysfunction on ISCEV standard ERGs - Assessment of colour vision using tests that probe the 3 axes of colour **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Inherited macular dystrophy (29271)

Level 3 Title	Posterior segment abnormalities (10998)
Level 4 Title	Inherited macular dystrophy (29271)
Eligibility Statement	- Available phenotype data including ISCEV ERG, OCT and AF imaging - Diagnosis confirmed preferably by an ophthalmologist with a sub-specialist expertise in inherited retinal disease. **Inherited macular dystrophy inclusion criteria** - Available phenotype data including ISCEV ERG, OCT and AF imaging - Diagnosis confirmed preferably by an ophthalmologist with a sub-specialist expertise in inherited retinal disease. **Inherited macular dystrophy exclusion criteria** - Features of age-related macular degeneration (any two of - onset over 60 years, soft drusen, CNV, RPE atrophy) - Features of readily testable single gene disorders such as Doyne/dominant drusen (p.R345W in EFEMP1), Best (dominant or recessive alleles in BEST1), RDS (typical macular dystrophy associated with such alleles as p.R172W in RDS). These phenotypes are eligible if there is evidence of negative testing of the associated gene. - Unilateral disease - Suggestion of chloroquine, hydroxychlorquine or other retinotoxic drug aetiology - Signs suggestive of an inflammatory aetiology such as toxocara, toxoplasmosis. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Inherited macular dystrophy prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - EFEMP1 in cases of Doyne/dominant drusen - BEST1 in cases of Best macular dystrophy - PRPH2 (RDS) in cases of typical macular dystrophy **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Leber Congenital Amaurosis or Early-Onset Severe Retinal Dystrophy (29272)

Level 3 Title	Posterior segment abnormalities (10998)
Level 4 Title	Leber Congenital Amaurosis or Early-Onset Severe Retinal Dystrophy (29272)
Eligibility Statement	Relevant diseases: - Leber Congenital Amaurosis (LCA) - Early-Onset Severe Retinal Dystrophy (EOSRD) **Leber Congenital Amaurosis or Early-Onset Severe Retinal Dystrophy inclusion criteria** - Severe disorders in which there is progressive loss of rod and later cone photoreceptor function leading to severe visual impairment - Usually occurring as an isolated retinal abnormality but can be syndromic (e.g. Joubert syndrome, peroxisomal disorders, and Senior-Loken syndrome) - LCA: presentation from birth / early infancy with nystagmus, absence / marked reduction in pupillary responses, and severely reduced vision. ISCEV ERG undetectable or severely reduced. - EOSRD: presentation within the first 5 years of life with reduced visual acuity, poor night vision, and markedly reduced ISCEV ERG with greater rod than cone system involvement. **Leber Congenital Amaurosis or Early-Onset Severe Retinal Dystrophy exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Developmental macular and foveal dystrophy (29273)

Level 3 Title	Posterior segment abnormalities (10998)
Level 4 Title	Developmental macular and foveal dystrophy (29273)
Eligibility Statement	**Developmental macular and foveal dystrophy inclusion criteria** - Absence of the fovea (synonym foveal hypoplasia - defined by preservation of inner retinal layers throughout the macula) OR - Congenital abnormality of the macula such as that seen in North Carolina Macular dystrophy, Bifocal chorioretinopathy and Sorsby syndrome OR - Congenital foveal retinoschisis **Developmental macular and foveal dystrophy exclusion criteria** - Foveal retinoschisis compatible with XL RS1 disease in a male (unless screened negative for RS1 mutations - Unilateral disease - Signs suggestive of an inflammatory aetiology such as toxocara and toxoplasmosis **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Developmental macular and foveal dystrophy prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - GPR143 if foveal hypoplasia is in the context of albinism confined to the eye and there is an X-linked history or typical carrier signs - PAX6 if foveal hypoplasia is in the context of aniridia - RS1 in males with foveal schisis **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial exudative vitreoretinopathy (41900)

Level 3 Title	Posterior segment abnormalities (10998)
Level 4 Title	Familial exudative vitreoretinopathy (41900)
Eligibility Statement	**Familial exudative vitreoretinopathy inclusion criteria** All probands should be diagnosed with bilateral retinopathy consistent with familial exudative vitreoretinopathy following detailed retinal examination and include at least one of the following features: - peripheral retinal avascularity (preferably demonstrated through fluorescein angiography) - subretinal or intraretinal exudation - retinal detachment - neovascularisation with or without vitreous haemorrhage Examination of parents, when available to distinguish recessive disease from dominant disease with variable expressivity. Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Familial exudative vitreoretinopathy exclusion criteria** Birth weight below 1500g or under 32 weeks gestational age at birth. Unilateral retinopathy Localised retinal telangiectasia Coat's disease Peripheral angiomatous retinal malformation **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial exudative vitreoretinopathy prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local

	practice: No genes specified **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Anophthalmia or microphthamia (11115)

Level 3 Title	Ocular malformations (10999)
Level 4 Title	Anophthalmia or microphthamia (11115)
Eligibility Statement	Relevant diseases: - Anophthalmia/microphthalmia Anophthalmia (clinical absence of the eye) and severe microphthalmia (congenital reduction in the overall size of the globe) represent clinically significant inborn errors of early development. **Anophthalmia inclusion criteria** - Unilateral or bilateral anophthalmia or microphthalmia **Anophthalmia exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Anophthalmia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variation (e.g. aCGH, SNP array or other genomic microarray) - SOX2, OTX2 (severe, bilateral cases) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Ocular coloboma (15141)

Level 3 Title	Ocular malformations (10999)
Level 4 Title	Ocular coloboma (15141)
Eligibility Statement	**Ocular coloboma inclusion criteria** - Ocular coloboma taken to represent failure of the optic fissure to close with awide spectrum of clinical severity asa consequence of variation in the site and extent of the closure defect. - Unilateral or bilaterally affected individuals. **Ocular coloboma exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Ocular movement disorders (33350)

Infantile nystagmus (33662)

Level 3 Title	Ocular movement disorders (33350)
Level 4 Title	Infantile nystagmus (33662)
Eligibility Statement	**Infantile nystagmus inclusion criteria** • Nystagmus with onset in early infancy, AND • Normal ophthalmological examination with normal VEP and ERG **Infantile nystagmus exclusion criteria** • Anterior segment disorders • Retinal dystrophies • Abnormal ERG and VEP • Acquired nystagmus • Grade 2 to 4 foveal hypoplasia • Structural abnormality found on MRI brain scan **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Infantile nystagmus prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: FRMD7 unless inheritance through paternal line **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Feeding and eating disorders (71737)

Severe familial anorexia (29278)

Level 3 Title	Feeding and eating disorders (71737)
Level 4 Title	Severe familial anorexia (29278)
Eligibility Statement	**Severe familial anorexia inclusion criteria** - Anorexia nervosa restricting or binge/purge type - Duration of >5 years - At least one first- or two second- degree relative affected - Minimum BMI should have reached 16 kg/m2 or below during the course of the illness - Maintenance of low BMI - Other indices of starvation may be present such as amenorrhea (in women), lanugo, bradycardia, hypotension, hypoleptinemia, The optimal family structure for Severe familial anorexia is to recruit the affected proband, their parents, and any affected siblings; outside this structure, no other unaffected relatives should be recruited. **Severe familial anorexia exclusion criteria** - Acute onset after head injury - Primary Adrenal insufficiency, Crohns, inflammatory bowel disease, cealiac disease, ulcerative colitis **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Severe familial anorexia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes listed

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Schizophrenia plus additional features (71740)

Level 3 Title	Schizophrenia and other psychotic disorders (71736)
Level 4 Title	Schizophrenia plus additional features (71740)
Eligibility Statement	**Schizophrenia plus additional features inclusion criteria** A clinical diagnosis of schizophrenia plus at least one of: - Age of onset below 18 years (where trio/nuclear family are recruited) OR - Familial disease in a first-or second degree relative OR - Related parents OR - Neurological signs (that pre-dates drug treatment), seizures or MRI abnormalities OR - Other clinical features suggesting a genomic cause (e.g. narcolepsy, severe cardiac/cardiomyopathy, autoimmune disorders, skeletal abnormalities, deafness, dysmorphic features). Individuals with syndromic disease should be recruited according to standard guidance, typically as trios. In other cases, unaffected individuals should not be recruited. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Schizophrenia plus additional features exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Schizophrenia plus additional features prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: Consideration of microarray for 22q11 deletion **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Renal and urinary tract disorders (11000)

Syndromes with prominent renal abnormalities (11001)

Proteinuric renal disease (30732)

Level 3 Title	Syndromes with prominent renal abnormalities (11001)
Level 4 Title	Proteinuric renal disease (30732)
Eligibility Statement	**Proteinuric renal disease inclusion criteria** - Urinary protein:creatinine ratio >100 mg/mmol OR albumin:creatinine ratio >30 mg/mmol on 2 or more occasions over more than 1 month AND one or more of - Family history of renal failure or proteinuria by the above criteria, parental consanguinity or syndromic features - Kidney biopsy in at least one family member showing Diffuse Mesangial Sclerosis, FSGS or glomerular pathology of likely genetic cause (e.g. glomerular basement membrane disorder or fibronectin deposition etc.) - Steroid sensitive nephrotic syndrome diagnosed aged <5 years - Steroid resistant nephrotic syndrome (Urinary protein:creatinine ratio > 300 mg/mmol or >3g day proteinuria; Hypoalbuminaemia; oedema persistent after 6 weeks' or more treatment with steroids) Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Proteinuric renal disease exclusion criteria** - Orthostatic proteinuria - Proteinuria present only within 6 months of pregnancy - Proteinuric renal disease attributable to obesity or systemic disorder (including but not limited to: diabetes mellitus, SLE or other autoimmune disease, infection, malignancy, paraproteinaemia, amyloidosis, Fabry disease, cystinosis, drugs etc) - Proteinuria or FSGS secondary to other identified primary renal disorder (e.g. MPGN, IgA nephropathy etc) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool

	to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Proteinuric renal disease prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - No gene accounts for >10% of cases. Consideration of sequencing with (UKGTN approved) SRNS gene panel of 33 genes, which detected a mutation in ~20% of cases. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial haematuria (30733)

Level 3 Title	Syndromes with prominent renal abnormalities (11001)
Level 4 Title	Familial haematuria (30733)
Eligibility Statement	**Familial haematuria inclusion criteria** - Persistent microscopic haematuria AND one or both of: - Family history of kidney failure or microscopic haematuria - Kidney biopsy showing characteristic electron micrographic features of Alport syndrome or thin glomerular basement membrane nephropathy Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Familial haematuria exclusion criteria** - Known or suspected renal or urinary tract malignancy - Known or suspected renal calculi - Known monogenic cause of microscopic haematuria **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial haematuria prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: COL4A3, COL4A4 and COL4A5 where indicated by the phenotype. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Atypical haemolytic uraemic syndrome (33489)

Level 3 Title	Syndromes with prominent renal abnormalities (11001)
Level 4 Title	Atypical haemolytic uraemic syndrome (33489)
Eligibility Statement	**Atypical haemolytic uraemic syndrome inclusion criteria** • Renal biopsy showing a thrombotic microangiopathy, OR • the classic triad of microangiopathic haemolytic anaemia, thrombocytopenia, renal failure. **Atypical haemolytic uraemic syndrome exclusion criteria** • Shiga toxin associated HUS • Secondary causes – drugs, infection (HIV, Streptococcus pneumonia), transplantation (bone marrow, liver, lung, cardiac but not de-novo renal), cobalamin deficiency, SLE, APL Ab syndrome, scleroderma • ADAMTS13 activity <10% or anti-ADAMTS13 autoantibodies **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Atypical haemolytic uraemic syndrome prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: CFH, CFI, CD46 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Primary membranoproliferative glomerulonephritis (55481)

Level 3 Title	Syndromes with prominent renal abnormalities (11001)
Level 4 Title	Primary membranoproliferative glomerulonephritis (55481)
Eligibility Statement	**Primary membranoproliferative glomerulonephritis inclusion criteria** Kidney biopsy showing MPGN or C3 Glomerulopathy (defined as glomerular inflammation with immunoreactivity for complement C3 greater than 2x immunoreactivity for immunoglobulins) with or without hypocomplementaemia or an identified C3 Nephritic Factor (should both be tested for), AND Proteinuria or haematuria lasting longer than 3 months. **Primary membranoproliferative glomerulonephritis exclusion criteria** Likely or proven underlying malignant, autoimmune or infectious disorder (for example, but not limited to, hepatitis virus infection, systemic lupus erythematosus, cryoglobulinaemia, paraproteinaemia etc) OR Self-limiting post-infectious glomerulonephritis **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Primary membranoproliferative glomerulonephritis prior genetic testing genes** **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial IgA nephropathy and IgA vasculitis (null)

Level 3 Title	Syndromes with prominent renal abnormalities (11001)
Level 4 Title	Familial IgA nephropathy and IgA vasculitis (null)
Eligibility Statement	**Familial IgA nephropathy and IgA vasculitis inclusion criteria** Renal biopsy proven IgA nephropathy or IgA vasculitis (formerly Henoch Schoenlein Purpura) AND one or more first or second degree relative with renal biopsy proven IgA nephropathy or IgA vasculitis **Familial IgA nephropathy and IgA vasculitis exclusion criteria** IgA nephropathy attributable to secondary cause (eg liver disease) in index case or relative **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial IgA nephropathy and IgA vasculitis prior genetic testing genes** **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Cystic kidney disease (11120)

Level 3 Title	Structural renal and urinary tract disease (11003)
Level 4 Title	Cystic kidney disease (11120)
Eligibility Statement	**Cystic kidney disease inclusion criteria** Patients with cystic renal disease (>5 cysts affecting one or both kidneys) with one of the following features: - Clinically not characteristic of ADPKD, OR - Onset before the age of 10, OR - Combined with other syndromic features, OR - A genetic diagnosis is required to influence management (and hasn't been achieved on an NHS test) AND - Unaffected individuals have undergone appropriate screening for cryptic disease e.g. renal ultrasound scan - Individuals with severe or syndromic disease should be recruited according to standard guidance, preferably as trios - In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. AND - Participants with features suggestive of classical ADPKD (autosomal dominant polycystic kidney disease) who have not undergone prior genetic testing of PKD1 and PKD2 should be recruited initially as singletons. In families where analysis as a singleton does not lead to identification of the underlying causative mutation, recruitment of additional affected family members is encouraged. **Cystic kidney disease exclusion criteria** - Advanced or end-stage kidney failure due to identified (non-cystic) disease - Multicystic dysplastic kidney(s) (see CAKUT) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

	Cystic kidney disease prior genetic testing genes Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: PKD1 and PKD2 if kidneys enlarged for age (or >12cm in length in adults). PKHD1 if family history and phenotype consistent with AR PKD. These genes need not be tested if other phenotypic features make them unlikely to be causative. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Congenital Anomaly of the Kidneys and Urinary Tract (CAKUT) (29277)

Level 3 Title	Structural renal and urinary tract disease (11003)
Level 4 Title	Congenital Anomaly of the Kidneys and Urinary Tract (CAKUT) (29277)
Eligibility Statement	**CAKUT inclusion criteria** - CAKUT with syndromic manifestations in other organ systems, OR - Isolated CAKUT with a first degree relative with CAKUT or unexplained ESKD, OR - Multiple distinct renal/urinary tract abnormalities or CAKUT with unexplained ESKD before age 25 - Unaffected individuals have undergone appropriate investigation for cryptic disease e.g. renal ultrasound scan - Individuals with severe or syndromic disease should be recruited according to standard guidance, preferably as trios - In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **CAKUT exclusion criteria** - Clinical or molecular diagnosis of autosomal dominant or autosomal recessive polycystic kidney disease - Known causative genetic or chromosomal abnormality **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **CAKUT prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - HNF1B if personal or family history of diabetes mellitus - SALL1 if 2 out of imperforate anus, ear abnormalities, thumb abnormalities **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Renal tubular acidosis (11123)

Level 3 Title	Disorders of function (11004)
Level 4 Title	Renal tubular acidosis (11123)
Eligibility Statement	Relevant diseases: - Distal renal tubular acidosis - Renal Fanconi syndrome - Gitelman and Bartter type 3 syndrome (Hypokalaemic alkalosis with hypomagnesaemia & hypocalcalciuria) - Bartter syndrome type 1, 2 & 4 (Hypokalaemic alkalosis with hypercalciuria) - Liddle syndrome (hypertensive hypokalaemic alkalosis) - Gordon syndrome (hypertensive hyperkalaemic acidosis) - Glucocorticoid remediable hypertension - Apparent Mineralocorticoid excess - Pseudohypoaldosteronism type1 **Renal tubular acidosis inclusion criteria** - Renal acid-base or other electrolyte disorders of unknown aetiology. AND - Unaffected individuals have undergone appropriate screening for cryptic disease - Individuals with severe or syndromic disease should be recruited according to standard guidance, preferably as trios - In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Renal tubular acidosis exclusion criteria** - Prior genetic testing that identifies a pathogenic mutation in a gene known to cause one or more of the diseases detailed above. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

	Renal tubular acidosis prior genetic testing genes Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Distal renal tubular acidosis: SLC4A1, ATP6V0A4, ATP6V1B1 - Hypokalaemic alkalosis with hypomagnesaemia & hypocalciuria: SLC12A3, CLCNKB - Hypokalaemic alkalosis with hypercalciuria: SLC12A1, KCNJ1, BSND **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Renal tract calcification (or Nephrolithiasis or nephrocalcinosis) (11124)

Level 3 Title	Disorders of function (11004)
Level 4 Title	Renal tract calcification (or Nephrolithiasis or nephrocalcinosis) (11124)
Eligibility Statement	**Renal tract calcification inclusion criteria** - Nephrolithiasis or nephrocalcinosis AND one or more of: - Age of first episode under 21 - Positive family history of stones/nephrocalcinosis in first or second degree relative - Hyper/hypocalcaemia - Abnormal PTH in setting of normal eGFR - Metabolic acidosis/alkalosis - Hypercalciuria - Hyperphosphaturia - Hyperoxaluria - Aminoaciduria - Hypocitraturia - Hypermagnesuria AND - Unaffected individuals have undergone appropriate screening for cryptic disease e.g. renal ultrasound scan, AND Individuals with severe or syndromic disease should be recruited according to standard guidance, preferably as trios - In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Renal tract calcification exclusion criteria** - Excluding infection stones **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Renal tract calcification prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local

	practice: - AGXT, GRHPR, HOGA1 if Hyperoxaluria - ATP6V1B1, ATP6V0A4, SLC4A1 if distal renal tubular acidosis - SLC3A1, SLC7A9 if cystinuria - CASR if hypocalciuric hypercalcaemia **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Extreme early-onset hypertension (15142)

Level 3 Title	Disorders of function (11004)
Level 4 Title	Extreme early-onset hypertension (15142)
Eligibility Statement	**Extreme early-onset hypertension inclusion criteria** - Hypertension (defined in adults by blood pressure > 160/100 in clinic AND average BP of 150/95 on ambulatory blood pressure monitoring) occurring below the age of 30. **Extreme early-onset hypertension exclusion criteria** - Primary hyperaldosteronism, phaeochromocytoma, Cushing's syndrome and hyper/hypothyroidism **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Unexplained kidney failure in young people (36855)

Level 3 Title	Disorders of function (11004)
Level 4 Title	Unexplained kidney failure in young people (36855)
Eligibility Statement	**Unexplained kidney failure in young people inclusion criteria** • Requirement for renal replacement therapy (dialysis or kidney transplantation) at age < 50 years in the absence of an identified cause Recruitment guidance: • Unaffected individuals have undergone appropriate screening for cryptic disease • Individuals with paediatric onset of kidney failure or evidence of syndromic disease should be recruited according to standard guidance. • In other cases, unaffected individuals should not be recruited. • Recruitment in such families should favour families with multiple affected individuals available to participate in the study over singletons. These singleton recruits will not contribute to the overall singleton monitoring metrics applied per GMC but will be capped across the study at one third of the total genomes for the disorder. **Unexplained kidney failure in young people exclusion criteria** • Likely or proven diabetic nephropathy • Likely or proven renovascular disease • Identified glomerular disorder on kidney biopsy (other than glomerulocystic disease, ischaemic changes or secondary glomerulosclerosis) • Evidence autoimmune, infectious, malignant, metabolic or other systemic disorder likely to be responsible for kidney disease • Renal sarcoidosis or tuberculosis • Paraproteinaemia (unless kidney biopsy shows no evidence of renal monoclonal deposition) • Exposure to nephrotoxin (drug or toxin) suspected of causing renal dysfunction • Obstructive uropathy • Significant proteinuria (>1g/day; uPCR >100) at presentation (see proteinuric renal disease inclusion criteria) • Identified tubular/electrolyte/acid base disorder (see RTA/electrolyte disorder eligibility criteria) • >5 kidney cysts (see cystic renal disease eligibility statement) • Nephrolithiasis (see renal stone disease eligibility criteria) • Congenital anomaly of kidney and urinary tract including reflux nephropathy (see CAKUT eligibility criteria) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool

	to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Unexplained kidney failure in young people prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: • If personal or family history of gout under age of 30 in the absence of CKD stage 3, 4 or 5: UMOD • If diabetes: HNF1B **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Respiratory disorders (33353)

Interstitial lung disorders (33354)

Familial pulmonary fibrosis (33671)

Level 3 Title	Interstitial lung disorders (33354)
Level 4 Title	Familial pulmonary fibrosis (33671)
Eligibility Statement	**Familial pulmonary fibrosis inclusion criteria** • Clinical syndrome consistent with interstitial lung disease: Breathlessness on exertion or cough, bilateral crepitations on examination, AND • A High Resolution CT Scan with evidence of interstitial lung disease, AND • A first degree relative with an interstitial lung disease **Familial pulmonary fibrosis exclusion criteria** • A respiratory disease other than an interstitial lung disease • Any cystic lung disease **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial pulmonary fibrosis prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: SFTPB, SFTPC in childhood onset cases **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Hereditary haemorrhagic telangiectasia (33674)

Level 3 Title	Vascular lung disorders (33355)
Level 4 Title	Hereditary haemorrhagic telangiectasia (33674)
Eligibility Statement	**Hereditary haemorrhagic telangiectasia inclusion criteria** Three or more of: 1) Nosebleeds from nasal telangiectasia 2) Mucocutaneous telangiectasia 3) Visceral telangiectasia such as pulmonary, cerebral, hepatic AVMs or gastrointestinal telangiectasia 4) First degree relative with HHT Individuals with syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Hereditary haemorrhagic telangiectasia exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Hereditary haemorrhagic telangiectasia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: ENG, ACVRL1, and SMAD4 **Closing statement**

	These requirements will be kept under continual review during the main programme and may be subject to change.

Familial and multiple pulmonary arteriovenous malformations (33677)

Level 3 Title	Vascular lung disorders (33355)
Level 4 Title	Familial and multiple pulmonary arteriovenous malformations (33677)
Eligibility Statement	**Familial and multiple pulmonary arteriovenous malformations inclusion criteria** • Multiple PAVMs confirmed by chest x-ray, thoracic CT scan, other cross sectional imaging or angiography OR • Single PAVM, AND • Family history of PAVM in first or second degree relative, AND • Clear evidence of an additional phenotype segregating in the family. Individuals with syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Familial and multiple pulmonary arteriovenous malformations exclusion criteria** • Known disease causing mutation in ENG, ACVRL1, or SMAD4. • Single PAVM with no indication of additional genetic phenotypes in family • Radiological "PAVM mimics" such as pulmonary artery aneurysms, pulmonary varices, bronchocoeles or vascular tumours; • Positive contrast echocardiographic studies detecting right to left shunting in the absence of radiological evidence of PAVMs. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial and multiple pulmonary arteriovenous malformations prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:

	ENG, ACVRL1, and SMAD4 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial primary spontaneous pneumothorax (41819)

Level 3 Title	Structural lung disorders (42203)
Level 4 Title	Familial primary spontaneous pneumothorax (41819)
Eligibility Statement	**Familial primary spontaneous pneumothorax inclusion criteria** Primary spontaneous pneumothorax, AND One or more first, second or third degree relative with primary spontaneous pneumothorax Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. Unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Familial primary spontaneous pneumothorax exclusion criteria** Syndromic pneumothorax (following review within by specialist respiratory/genetics service) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial primary spontaneous pneumothorax prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: Consideration of FLCN and FBN1 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Multi-system inflammatory or autoimmune disorders (11008)

Periodic fever syndromes and amyloidosis (11127)

Level 3 Title	Multi-system inflammatory or autoimmune disorders (11008)
Level 4 Title	Periodic fever syndromes and amyloidosis (11127)
Eligibility Statement	**Periodic fever syndromes and amyloidosis inclusion criteria** - Biopsy proven amyloid deposition in any organ OR - Recurrent or continuous attacks of systemic inflammation with evidence of a significantly raised CRP (> 30 mg/L with attacks) and at least 2 of the following features: onset before age 40, family history of similar symptoms, rash, fever > 38°C, serositis (synovial, peritoneal, pleuritic, pericardial or meningitic), arthralgia/myalgia, arthritis. **Periodic fever syndromes and amyloidosis exclusion criteria** - Evidence of underlying infectious, autoimmune or malignant cause - Paraproteinaemia or haematological dyscrasia - Known monogenic cause of periodic fever syndrome or amyloidosis **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Periodic fever syndromes and amyloidosis prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - FGA, apolipoprotein A-I, lysozyme, - If recurrent or continuous inflammation: MEFV, MVK, TNFRSFIA, NLRP3, NLRP12 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Juvenile dermatomyositis (29219)

Level 3 Title	Multi-system inflammatory or autoimmune disorders (11008)
Level 4 Title	Juvenile dermatomyositis (29219)
Eligibility Statement	**Juvenile dermatomyositis inclusion criteria** - Any child/young person aged 18 years or younger that has been diagnosed with one of the following: - Definite/probable juvenile dermatomyositis (JDM) - Definite/probable polymyositis - JDM or polymyositis overlap with scleroderma, chronic polyarthritis, mixed connective tissue disease or systemic lupus erythematosus - Mixed connective tissue disease - Other idiopathic inflammatory myopathy - Focus will be in specific endo-phenotypes (e.g. calcinosis, lipodystrophy) **Juvenile dermatomyositis exclusion criteria** - Entry into another registry - Children diagnosed with other types of myositis (e.g. septic myositis of infectious cause) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Kyphoscoliotic Ehlers-Danlos syndrome (36853)

Level 3 Title	Connective tissues disorders (36930)
Level 4 Title	Kyphoscoliotic Ehlers-Danlos syndrome (36853)
Eligibility Statement	**Kyphoscoliotic Ehlers-Danlos syndrome inclusion criteria** Presumed Kyphoscoliotic Ehlers Danlos Syndrome with no genetic diagnosis with two or more of the following features: • Significant Joint hypermobility and dislocations • Skin fragility and hyperextensibility • Kyphoscoliosis • Increased length at birth with wrist drop • Muscular hypotonia • Criss-cross lines on palm and soles • Hearing impairment • Ocular fragility **Kyphoscoliotic Ehlers-Danlos syndrome exclusion criteria** • Known genetic aetiology • Kyphoscoliosis as part of an underlying genetic / syndromal diagnosis • Symptomatic joint hypermobility without additional confirmed diagnostic features such as kyphoscoliosis **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Kyphoscoliotic Ehlers-Danlos syndrome prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - PLOD1 - If seen in Specialist EDS Centres (London/ Sheffield): Kyphoscoliotic targeted gene panel

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Classical Ehlers-Danlos Syndrome (41860)

Level 3 Title	Connective tissues disorders (36930)
Level 4 Title	Classical Ehlers-Danlos Syndrome (41860)
Eligibility Statement	**Classical Ehlers-Danlos Syndrome inclusion criteria** A working or confirmed diagnosis of Classical Ehlers Danlos Syndrome **Classical Ehlers-Danlos Syndrome exclusion criteria** Known genetic aetiology Other forms of Ehlers Danlos syndrome **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Classical Ehlers-Danlos Syndrome prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: COL5A1, COL5A2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Skeletal disorders (11005)

Skeletal dysplasias (11007)

Multiple Epiphyseal Dysplasia (11125)

Level 3 Title	Skeletal dysplasias (11007)
Level 4 Title	Multiple Epiphyseal Dysplasia (11125)
Eligibility Statement	**Multiple Epiphyseal Dysplasia inclusion criteria** - Radiological evidence of MED, as determined by expert skeletal dysplasia radiologist - Clinical manifestations of MED within this context, including mild short stature, genu valgum/varum, joint hypermobility +/- brachydactyly. **Multiple Epiphyseal Dysplasia exclusion criteria** - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) showing a chromosome imbalance indicating an alternative aetiology - MED as a feature of another skeletal dysplasia condition e.g. spondyloepiphyseal dysplasia **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Multiple Epiphyseal Dysplasia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) - COMP (if appropriate) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Chondrodysplasia punctata (15143)

Level 3 Title	Skeletal dysplasias (11007)
Level 4 Title	Chondrodysplasia punctata (15143)
Eligibility Statement	**Chondrodysplasia punctata inclusion criteria** - CDP reported by skeletal dysplasia expert and/or radiologist - Radiological features of a CDP condition, as determined by skeletal dysplasia expert, after stippling would be expected to have resolved (after 2nd birthday usually), e.g. rhizomelia, remnants of vertebral body clefting, short tibiae and metacarpals - Biochemical evidence of abnormal metabolism, i.e. VLCFA profile, abnormal cholesterol biosynthesis, abnormal arylsulphatase E **Chondrodysplasia punctata exclusion criteria** - Maternal factors excluded (i.e. Mixed connective tissue disease, Hyperemesis gravidarum, fetal exposure to warfarin) - Radiology not consistent - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) demonstrating an imbalance that explains the condition **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Chondrodysplasia punctata prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Thoracic dystrophies (11126)

Level 3 Title	Skeletal dysplasias (11007)
Level 4 Title	Thoracic dystrophies (11126)
Eligibility Statement	**Thoracic dystrophies inclusion criteria** - Isolated thoracic dystrophy - Thoracic dystrophy with multisystem involvement: renal cysts, hepatic cysts, retinal dystrophy, laterality defect, polydactyly (>1 limb) - Thoracic dystrophy with skeletal dysplasia (e.g. pelvic dysplasia) - Thoracic dystrophy with laryngeal stenosis **Thoracic dystrophies exclusion criteria** - Established molecular diagnosis of ciliopathy - Radiology consistent with abnormal methylation pattern at chromosome 14q34 **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Thoracic dystrophies prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Stickler syndrome (11129)

Level 3 Title	Skeletal dysplasias (11007)
Level 4 Title	Stickler syndrome (11129)
Eligibility Statement	**Stickler syndrome inclusion criteria** 3 or more of: - Cleft palate - Characteristic retinal or vitreous changes - High frequency sensorineural hearing loss - Characteristic facial features (malar hypoplasia, broad or flat nasal bridge, and micro/retrognathia) - Musculoskeletal features: femoral head failure (slipped epiphysis or Legg-Perthes-like disease), radiographically demonstrated osteoarthritis before age 40, scoliosis, spondylolisthesis, Scheuermann-like kyphotic deformity or joint hypermobility **Stickler syndrome exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Stickler syndrome prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - COL2A1, COL11A1 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Osteogenesis imperfecta (30627)

Level 3 Title	Skeletal dysplasias (11007)
Level 4 Title	Osteogenesis imperfecta (30627)
Eligibility Statement	**Osteogenesis imperfecta inclusion criteria** - Clinical diagnosis of osteogenesis imperfecta based on the presence of childhood onset bone fragility (>1 fracture and/or fractures associated with low impact trauma) AND one or more of: - Short stature (not associated with any other syndromal diagnosis) - Dentinogenesis Imperfecta - Blue sclerae - Joint hypermobility - Deafness - Facial Dysmorphism characteristic of OI/ bone fragility - Joint contractures with an unexplained genetic aetiology AND - Individuals with features suggestive of classical mild osteogenesis imperfecta (OI type I) who have not undergone prior genetic testing of COL1A1 and COL1A2 should be recruited initially as singletons. In families where analysis as a singleton does not lead to identification of the underlying causative mutation, recruitment of additional affected family members is encouraged. **Osteogenesis imperfecta exclusion criteria** - Known genetic aetiology of OI - Other syndromal short stature without bone fragility - Secondary causes of bone fragility such as prolonged treatment with steroids; cerebral palsy; reduced mobility contributing to fractures **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Osteogenesis imperfecta prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:

	COL1A1, COL1A2, c-14C>T IFITM5 testing or UKGTN Osteogenesis Imperfecta panel (16 genes) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Unexplained skeletal dysplasia (36854)

Level 3 Title	Skeletal dysplasias (11007)
Level 4 Title	Unexplained skeletal dysplasia (36854)
Eligibility Statement	**Unexplained skeletal dysplasia inclusion criteria** Unexplained skeletal dysplasia as determined by one of the following: • Unknown/undefined skeletal dysplasia detected on skeletal survey by a radiologist with expertise in skeletal dysplasias [expertise is available via DREAMS (http://d-reams.org by contacting: DREAMS@sheffield.ac.uk] OR • Skeletal phenotype on skeletal survey consistent with a known disorder for which the common gene mutations for that disorder have been excluded **Unexplained skeletal dysplasia exclusion criteria** • Known aetiology • Disproportionate short stature with non-skeletal aetiology • Short stature (<0.4th centile) for other non-skeletal reason (e.g. growth hormone deficiency) • Skeletal dysplasia within remit of other 100,000 Genomes Project disorder **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Unexplained skeletal dysplasia prior genetic testing genes** No genes listed **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Amelogenesis imperfecta (55449)

Level 3 Title	Skeletal dysplasias (11007)
Level 4 Title	Amelogenesis imperfecta (55449)
Eligibility Statement	**Amelogenesis imperfecta inclusion criteria** Amelogenesis Imperfecta confirmed through clinical evaluation (including dental radiographs) by a specialist dentist with an interest in developmental enamel abnormalities. **Amelogenesis imperfecta exclusion criteria** Developmental enamel abnormalities attributable to other causes including Molar Incisor Hypomineralisation, iatrogenic causes (e.g. chemotherapy), severe systemic illness and fluorosis. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Amelogenesis imperfecta prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: Gene panel that includes AMELX, FAM83H, ENAM, c4orf26, KLK4, MMP20, WDR72, GPR68, LAMB3, LAMA3, ITGB4, COL17A1, LTBP3, FAM20A, FAM20C, DLX3, STIM1, LAMC2, PEX1, PEX6 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Craniosynostosis syndromes (11006)

Level 3 Title	Craniosynostosis (30775)
Level 4 Title	Craniosynostosis syndromes (11006)
Eligibility Statement	**Craniosynotosis inclusion criteria** - Any combination of more than one major cranial vault suture fused at original presentation (from metopic, sagittal, left coronal, right coronal, left lambdoid, right lambdoid) - Single suture synostosis accompanied by either (a) dysmorphic features or at least one major extracranial abnormality; (b) significant learning disability; (c) first or second degree relative with craniosynostosis, or offspring of consanguineous union **Craniosynotosis exclusion criteria** - Evidence of likely secondary cause. This is most likely to comprise (a) extreme prematurity <28 weeks' gestation; (b) complications of severe perinatal asphyxia; (c) teratogenic exposure, most commonly sodium valproate; (d) compelling history of intrauterine growth restriction; (e) documented rickets (genetic or acquired) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Craniosynostosis prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) - DNA sequencing of FGFR3-P250R, FGFR2 exons IIIa (8) and IIIc (10), TWIST1 exon 1 in all cases - Additional tests available for other genes as clinically indicated (nationally commissioned testing). These tests will most commonly include the EFNB1, ERF and TCF12 genes (mutations in each of these genes contribute >=1% of craniosynostosis overall), and MLPA of TWIST1. Additional testing is currently offered for FGFR1, FGFR2 (extended screen), IL11RA, POR, RAB23 and ZIC1. **Closing statement**

	These requirements will be kept under continual review during the main programme and may be subject to change.

Choanal atresia (11078)

Level 3 Title	Choanal anomalies (31500)
Level 4 Title	Choanal atresia (11078)
Eligibility Statement	**Choanal atresia inclusion criteria** - Bilateral bony choanal atresia OR - Unilateral bony choanal atresia with stenosis of the contralateral side - As above, with or without additional malformations - Skull X-rays excluding sclerosing bone dysplasias **Choanal atresia exclusion criteria** - Teratogens (e.g. Carbimazole, fluconazole) **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Choanal atresia prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) - CHD7 if additional malformations suggestive of CHARGE syndrome - FGFR2, FGFR3 and other genes linked to craniosynostosis if appropriate **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial breast and or ovarian cancer (11131)

Level 3 Title	Breast and endocrine (11013)
Level 4 Title	Familial breast and or ovarian cancer (11131)
Eligibility Statement	**Familial breast and or ovarian cancer inclusion criteria** Multiplex cases: Proband is affected by invasive breast cancer (age <50) - 3 family members (FDR, SDR, TDR) affected by invasive breast cancer (average age of BCs <60). - Samples available and to be collected from >= 2 affected relatives Proband only recruitment: - Proband is affected by breast cancer (age <50) or ovarian cancer (any age). - Manchester Score of family >22 - Cases of ovarian cancer (any age) and breast cancer (<40) have been confirmed. - Ovarian cancers demonstrated to be invasive epithelial; mucinous and borderline tumours non-eligible (where histology available) - Family is not eligible for recruitment to the multiplex families breast cancer eligibility. - Samples to be supplied from: proband only. Unaffected individuals should not be recruited in this disorder. **Familial breast and or ovarian cancer exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial breast and or ovarian cancer prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families

	with readily detectable mutations in known disease genes: - BRCA1 - BRCA2 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Multiple endocrine tumours (11132)

Level 3 Title	Breast and endocrine (11013)
Level 4 Title	Multiple endocrine tumours (11132)
Eligibility Statement	**Multiple endocrine tumours inclusion criteria** - Proband is affected by endocrine tumour (age <60) - >=1 additional endocrine tumour (any age) in patient or family member (FDR, SDR, TDR) (age <60). Sample should be sought from affected family members if alive [endocrine tumours: parathyroid hyperplasia, pituitary adenoma, GIT neuroendocrine tumour, carcinoid tumours, adrenocortical tumours, medullary thyroid carcinoma, phaeochromocytoma] Unaffected individuals should not be recruited in this disorder. Recruitment should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Multiple endocrine tumours exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Multiple endocrine tumours prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families with readily detectable mutations in known disease genes: - MEN1 (MEN1-like spectrum) - MEN1 and AIP (if pituitary tumours only) - RET (MEN2-like spectrum) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Neuro-endocrine Tumours- PCC and PGL (11133)

Level 3 Title	Breast and endocrine (11013)
Level 4 Title	Neuro-endocrine Tumours- PCC and PGL (11133)
Eligibility Statement	**Neuro-endocrine Tumours- PCC and PGL inclusion criteria** - proband is affected by PCC/PGL (age <60) AND >= 1 family member (FDR, SDR, TDR) affected by PCC/PGL (any age) AND sample available from >= 1 affected family member OR - proband is affected by multiple PCC/PGL (first diagnosis age <60) Unaffected individuals should not be recruited in this disorder. Recruitment should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Neuro-endocrine Tumours- PCC and PGL exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Neuro-endocrine Tumours- PCC and PGL prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families with readily detectable mutations in known disease genes: - SDHB, SDHD, RET, VHL, SDHC, SDHAF2, MAX and TMEM127 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Parathyroid cancer (30611)

Level 3 Title	Breast and endocrine (11013)
Level 4 Title	Parathyroid cancer (30611)
Eligibility Statement	**Parathyroid Cancer inclusion criteria** - proband affected by parathyroid carcinoma (age <60) Unaffected individuals should not be recruited in this disorder. Recruitment should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Parathyroid Cancer exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Parathyroid cancer prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families with readily detectable mutations in known disease genes: CDC73 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Inherited non-medullary thyroid cancer (41884)

Level 3 Title	Breast and endocrine (11013)
Level 4 Title	Inherited non-medullary thyroid cancer (41884)
Eligibility Statement	**Inherited non-medullary thyroid cancer inclusion criteria** Proband non-medullary thyroid cancer <60 years AND one of One or more first degree relative with non-medullary thyroid cancer <60 years OR One or more first, second or third degree relatives with non-medullary thyroid cancer AND a second first, second or third degree relative with another thyroid pathology (e.g. multinodular goitre, thyroiditis). Unaffected individuals should not be recruited to this category **Inherited non-medullary thyroid cancer exclusion criteria** Known genetic cause **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Inherited non-medullary thyroid cancer prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: No genes specified **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial colon cancer (11135)

Level 3 Title	GI tract (11014)
Level 4 Title	Familial colon cancer (11135)
Eligibility Statement	**Familial colon cancer inclusion criteria** PREFERABLY: proband is affected by colorectal cancer (age <50) Additional 3 family members (FDR, SDR, TDR) affected by colorectal cancer (average age <60) Samples to be supplied from proband AND >=2 affected relatives OR proband is affected by colorectal or Lynch-related cancer (age <50) Additional 2 family members (FDR or SDR of each other) affected by colorectal or Lynch-related cancer (average age <60). If proband's tumour is colorectal cancer, the tumour must exhibit microsatellite instability. Cancer diagnosis confirmed in >= 2 family members Proband has <=1 living affected family members (ie ineligible for multiplex CRC) Samples to be supplied from: proband only (Lynch-related tumours: Colorectal cancer Endometrial cancer Ovarian cancer Pancreatic cancer Ureter cancer Benign skin tumours Sebaceous adenoma Sebaceous epithilioma Keratoacanthoma Skin cancers Sebaceous carcinoma Transitional cell cancer of renal pelvis Gastric cancer Hepatobiliary tract cancer Small bowel cancer Glioblastoma)

	Unaffected individuals should not be recruited in this disorder. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Familial colon cancer exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial colon cancer prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families with readily detectable mutations in known disease genes: MULTIPLEX FAMILY RECRUITED - GENES TO BE EXCLUDED ON PRIOR TESTING: - MLH1, MSH2, MSH6 AND - +PMS2 (if IHC shows isolated loss of PMS2) LYNCH SYNDROME TESTING ONLY REQUIRED IF TUMOURS IN THE FAMILY SHOW MICROSATELLITE INSTABILITY, AND - +APC (if proband has >10 adenomatous polyps) PROBAND-ONLY RECRUITMENT – GENES TO BE EXCLUDED ON PRIOR TESTING: - MLH1, MSH2, MSH6 AND - +PMS2 (if IHC shows isolated loss of PMS2) AND - +APC (if proband has >10 adenomatous polyps) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Multiple bowel polyps (30615)

Level 3 Title	GI tract (11014)
Level 4 Title	Multiple bowel polyps (30615)
Eligibility Statement	**Multiple bowel polyps inclusion criteria** FAMILIAL ADENOMAS: • proband affected with >10 adenomatous polyps (all diagnosed age <50) AND first degree-relative affected by >10 adenomatous polyps (all diagnosed age <50) AND • >=3 adenomas have been histologically confirmed in each of proband and affected first degree relative • Samples should be available and obtainable from proband AND affected first degree-relative • Samples may also be obtained from any additional affected first/second degree-relatives with > 5 adenomatous polyps (all diagnosed age <50) • Note: Adenomas can be synchronous OR metachronous • Presumed inheritance model: dominant ISOLATED (PRESUMED RECESSIVE) POLYPOSIS: • Proband affected with: - (a) >25 polyps (all diagnosed age <50) OR - (b) >10 polyps (all diagnosed age <25) OR - (c) >10 polyps (all diagnosed age <40 and parents consanguineous) • Samples should be obtained on proband • Samples may also be obtained for any additional family members affected with >10 polyps (all diagnosed age <50) • Where samples can be obtained from both parents, they should be sought. • Note: Polyps can be synchronous OR metachronous. Polyps can include adenomas, hyperplastic polyps or serrated polyps. Polyp histology should be detailed in clinical data model • Presumed inheritance model: recessive or de novo JUVENILE POLYPOSIS: • Proband affected with >2 juvenile polyps AND >=2 juvenile polyps have been histologically confirmed in proband • Samples should be obtained on proband AND both parents • Samples may be obtained on any additional family members affected with juvenile polyposis • Note: Juvenile polyps can arise anywhere in the GI tract Unaffected individuals should not be recruited in this disorder (with the exception of parents in recessive and juvenile polyposis). Recruitment should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Multiple bowel polyps exclusion criteria**

	Prior genetic testing guidance - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Multiple bowel polyps prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families with readily detectable mutations in known disease genes: • APC, biallelic mutations in MUTYH (familial adenomas) • APC, biallelic mutations in MUTYH, MLH1, MSH2, MSH6 (isolated polyposis) • SMAD4, BMPR1A (juvenile polyposis) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Peutz-Jeghers syndrome (36533)

Level 3 Title	GI tract (11014)
Level 4 Title	Peutz-Jeghers syndrome (36533)
Eligibility Statement	**Peutz-Jeghers syndrome inclusion criteria** • Two or more histologically confirmed PJS-type hamartomatous polyps OR • Any number of PJS-type polyps detected in one individual who has a confirmed family history of PJS in FDR OR • Characteristic mucocutaneous pigmentation in an individual who has a confirmed family history of PJS OR • Any number of PJS-type polyps in an individual who also has characteristic mucocutaneous pigmentation. Unaffected individuals should not be recruited in this disorder. Recruitment should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Peutz-Jeghers syndrome exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Peutz-Jeghers syndrome prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families with readily detectable mutations in known disease genes: - STK11 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial rhabdomyosarcoma or sarcoma (11138)

Level 3 Title	Muscle and nerve (11015)
Level 4 Title	Familial rhabdomyosarcoma or sarcoma (11138)
Eligibility Statement	**Familial rhabdomyosarcoma or sarcoma inclusion criteria** - Proband is affected by rhabdomyosarcoma or sarcoma - >= 1 family member (FDR, SDR, TDR) affected by rhabdomyosarcoma or sarcoma (any age). Sample should be sought if patient alive Unaffected individuals should not be recruited in this disorder. Recruitment should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Familial rhabdomyosarcoma or sarcoma exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Familial rhabdomyosarcoma or sarcoma prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families with readily detectable mutations in known disease genes: - TP53 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Familial tumour syndromes of the central and peripheral nervous system (30619)

Level 3 Title	Muscle and nerve (11015)
Level 4 Title	Familial tumour syndromes of the central and peripheral nervous system (30619)
Eligibility Statement	**Familial Tumours Syndromes of the central and peripheral Nervous system inclusion criteria** [See separate eligibility criteria for Neurofibromatosis type 1] A. Proband has clinical features diagnostic of Von Hippel Lindau syndrome. Samples to be obtained from proband and any affected family members, OR B. Proband has clinical features diagnostic of Neurofibromatosis type 2, AND >= 1 family member (FDR, SDR) affected with NF2. Samples to be available and obtainable from proband and >= 1 affected family member OR C. Proband has >=2 nonintradermal schwannomas, at least one with histologic confirmation, AND >= 1 family member (FDR, SDR) affected by >= 2 nonintradermal schwannomas. Samples to be available and obtainable from proband and >= 1 affected family member OR D. Proband diagnosed with glioma/meningioma/astrocytoma (aged <60, histologically confirmed)) AND >= 1 family member (FDR, SDR) affected by a brain tumour of the same histology (histologically confirmed). Samples must be available and obtainable from proband and >= 1 affected family member. Unaffected individuals should not be recruited in this disorder. Recruitment should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Familial Tumours Syndromes of the central and peripheral Nervous system exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

	Familial Tumours Syndromes of the central and peripheral Nervous system prior genetic testing genes Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families with readily detectable mutations in known disease genes: - NF2, VHL, SMARCB1 as appropriate **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Neurofibromatosis Type 1 (38874)

Level 3 Title	Muscle and nerve (11015)
Level 4 Title	Neurofibromatosis Type 1 (38874)
Eligibility Statement	**Neurofibromatosis Type 1 inclusion criteria** A. Proband with a clinically confirmed diagnosis of Neurofibromatosis type 1, OR B. Proband with multiple café-au-lait patches but no non-pigmentary features Where the NF1 gene has not been tested before recruitment, participants should be recruited initially as singletons. In families where analysis as a singleton does not lead to identification of the underlying causative mutations, recruitment of additional affected family members is encouraged. **Neurofibromatosis Type 1 exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Neurofibromatosis Type 1 prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families with readily detectable mutations in known disease genes: - In case A above (clinically confirmed diagnosis of NF1) prior testing as below is strongly recommended to allow appropriate management. - In case B above (no non-pigmentary features) testing of the following genes should be considered but is not required prior to recruitment: NF1 **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Genodermatoses with malignancies (30623)

Level 3 Title	Skin (11016)
Level 4 Title	Genodermatoses with malignancies (30623)
Eligibility Statement	**Genodermatoses with malignancies inclusion criteria** - proband has clinical features diagnostic or resulting in an operational diagnosis for Gorlin syndrome or Cowden syndrome OR - proband has colorectal cancer (diagnosed age <60) AND >= 1 sebaceous adenoma, sebaceous carcinoma or epithelioma (histologically confirmed, diagnosed age <60) Unaffected individuals should not be recruited in this disorder. Recruitment should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Genodermatoses with malignancies exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Genodermatoses with malignancies prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families with readily detectable mutations in known disease genes: - PTCH1 (Gorlin), PTEN (Cowden), MLH1, MSH2, MSH6 (Muir Torre) **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Paediatric congenital malformation-dysmorphism-tumour syndromes (30686)

Level 3 Title	Young onset tumour syndromes (30781)
Level 4 Title	Paediatric congenital malformation-dysmorphism-tumour syndromes (30686)
Eligibility Statement	**Paediatric congenital malformation-dysmorphism-tumour inclusion** - proband is affected with childhood neoplasia (diagnosed age <=16) AND - proband has significant congenital malformation OR - premorbid growth abnormality (>=3SD from mean) OR - FDR is affected with childhood malignancy (diagnosed age <= 16) OR - significant facial dysmorphism (ascertained by clinical geneticist) OR - Proband (child <16) with bilateral tumours **Paediatric congenital malformation-dysmorphism-tumour exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Paediatric congenital malformation-dysmorphism-tumour prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families with readily detectable mutations in known disease genes: - any genetic testing for which patient is eligible by local guidance on account of personal/family history. - including for Wilms tumour – WT1 and 11p15 methylation studies; Adrenocortical carcinoma – TP53; Hepatoblastoma – 11p15 methylation studies; consideration of Fanconi breakage testing according to clinical presentation **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Exceptionally young adult onset cancer (41892)

Level 3 Title	Young onset tumour syndromes (30781)
Level 4 Title	Exceptionally young adult onset cancer (41892)
Eligibility Statement	**Exceptionally young adult onset cancer inclusion criteria** Proband only (index case does not qualify under family history criteria) N.B. young cancer plus family history would be recruited under the family history category Proband has developed a common adult cancer diagnosed at age 30 or younger; this category is for cancer that are typically of later onset e.g. breast, colorectal, renal, lung. Individuals with syndromic disease should be recruited according to standard guidance, typically as trios. In other cases, unaffected individuals should not be recruited. Singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Exceptionally young adult onset cancer exclusion criteria** Probands with tumours of characteristically young onset tumours such as germ cell tumours (teratoma, seminoma), osteosarcoma and Hodgkins disease. Borderline or mucinous ovarian tumours Squamous cervical cancer **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Exceptionally young adult onset cancer prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: As dictated by the tumour type. Breast cancer: BRCA1, BRCA2, TP53 (for HER2+ cancers); Colorectal cancer: mutYH, FAP, hMLH1, hMSH2 (depending on cancer features including IHC and MSI); Lung cancer: TP53; Serous ovarian cancer: BRCA1, BRCA2

	Closing statement These requirements will be kept under continual review during the main programme and may be subject to change.

Multiple Primaries (30782)

Multiple Tumours (30685)

Level 3 Title	Multiple Primaries (30782)
Level 4 Title	Multiple Tumours (30685)
Eligibility Statement	**Multiple tumour inclusion criteria** - proband is affected with (a) 2 or more primary malignancies (both diagnosed aged <50) OR (b) 3 or more primary malignancies (all diagnosed aged <70), not including the following malignancies after the age of 50 years: breast, prostate, lung, colorectal, cervix, head and neck, mesothelioma, anal, Kaposi sarcoma, unknown primary - Note: Non-melanoma skin cancers are not included in this definition of primary malignancy Unaffected individuals should not be recruited in this disorder. Recruitment should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs. **Multiple tumours exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Multiple Tumour prior genetic testing genes** Testing as below is strongly recommended PRIOR TO RECRUITMENT to allow appropriate management of families with readily detectable mutations in known disease genes: - any genetic testing for which patient is eligible by local guidance on account of personal/family history. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Ultra-rare undescribed monogenic disorders (30785)

Level 3 Title	Undescribed disorders (30784)
Level 4 Title	Ultra-rare undescribed monogenic disorders (30785)
Eligibility Statement	**Ultra-rare undescribed monogenic disorders inclusion criteria** - Rare distinctive phenotype - There is a high chance of a monogenic basis for the disorder as assessed by presentation and family history - Phenotype can include distinctive, undescribed imaging, biopsy or biochemical findings - Family has been reviewed by a 100,000 Genomes Project-focused multidisciplinary team (MDT) within the GMC and approved for recruitment - The GMC recruiting the patient has not exceeded its cap on recruitment to ultra-rare undescribed monogenic disorders. It is the responsibility of the GMC rare disease lead to oversee adherence to this cap - The depth of phenotype data supplied is equivalent to the disease-specific data models - The disorder has been allocated to a disease-facing GeCIP domain to provide support for clinical interpretation **Ultra-rare undescribed monogenic disorders exclusion criteria** - Patient would be eligible for recruitment under existing disease-specific Eligibility Criteria - Multiple families with similar phenotypes are available for recruitment; this phenotype should be proposed using the disease nomination form to develop disease-specific eligibility criteria - (Please contact chiefscientist@genomicsengland.co.uk for advice if this is unclear for this family) - Patient's phenotype has been previously assessed by Genomics England and considered out of scope for the programme **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

	Ultra-rare undescribed monogenic disorders prior genetic testing genes Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: - As per phenotype, according to recommendation of GMC MDT **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Neonatal or paediatric intensive care admission with a likely monogenic disease (38558)

Level 3 Title	Multi-system groups (38589)
Level 4 Title	Neonatal or paediatric intensive care admission with a likely monogenic disease (38558)
Eligibility Statement	**Neonatal or paediatric intensive care admission with a likely monogenic disease inclusion criteria** • The proband is <18 years old and is currently admitted to neonatal or paediatric intensive care, AND • A monogenic disease is considered likely following assessment by a consultant experienced in genetic diagnostics for the relevant phenotype, AND • The underlying cause is not known, AND • Given frequent unavailability of DNA for genetic testing in ICU patients due to the frequent use of blood products & high mortality, units should introduce DNA storage at admission to ICU as standard practice **Neonatal or paediatric intensive care admission with a likely monogenic disease exclusion criteria** • Reasons for admission unlikely have a monogenic cause including: isolated prematurity; isolated intrauterine growth retardation of likely placental aetiology; trauma; admission following a surgical procedure for a disorder unlikely to have a monogenic cause. • Participants with disorders already covered by a 100,000 Genomes Project rare disease would typically be expected to fulfil the relevant disease category. For example, a child with congenital heart disease would only be recruited if there was a positive family history, parental consanguinity or syndromic features. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Neonatal or paediatric intensive care admission with a likely monogenic disease prior genetic testing genes** Where rapid aneuploidy testing and/or detailed chromosome testing (e.g. microarray) is indicated, this should be completed PRIOR TO RECRUITMENT. Further genetic testing in line with current local practice should be considered in parallel with recruitment but is NOT required prior to recruitment. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Single autosomal recessive mutation in rare disease (38672)

Level 3 Title	Multi-system groups (38589)
Level 4 Title	Single autosomal recessive mutation in rare disease (38672)
Eligibility Statement	**Single autosomal recessive mutation in rare disease inclusion criteria** - Proband has a rare autosomal recessive monogenic disease, AND - A likely pathogenic variant* has been identified on one allele, AND - No likely pathogenic variant has been detected on the second allele, AND - Standardly available clinical testing has been performed of full coding regions (including MLPA where available) Where the disease falls into another disease category, please recruit to that category *a likely pathogenic variant corresponds to an ACMG class 4 or 5 variant **Single autosomal recessive mutation in rare disease exclusion criteria** **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Single autosomal recessive mutation in rare disease prior genetic testing genes** No genes listed **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Undiagnosed monogenic disorder seen in a specialist genetics clinic (42193)

Level 3 Title	Multi-system groups (38589)
Level 4 Title	Undiagnosed monogenic disorder seen in a specialist genetics clinic (42193)
Eligibility Statement	**Undiagnosed monogenic disorder seen in a specialist genetics clinic inclusion criteria** A patient seen in a Clinical Genetics or other specialist Genetics clinic with a likely monogenic disorder for whom standard current testing has not identified a molecular cause and in whom whole genome sequencing is considered suitable as a next investigation by the consultant in charge. **Undiagnosed monogenic disorder seen in a specialist genetics clinic exclusion criteria** Patients with conditions covered by existing eligibility categories should not be recruited using this category and should adhere to the existing recruitment guidelines. **Prior genetic testing guidance** - Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition. - Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the 'Genetic investigations' section of the data capture tool to allow comparison of WGS with current standard testing. PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out. **Undiagnosed monogenic disorder seen in a specialist genetics clinic prior genetic testing genes** Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice: As dictated by phenotype **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

Genomic medicine service indications (82157)

Whole genome sequencing indications (82159)

GMS R14 Acutely unwell infants with a likely monogenic disorder (82160)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R14 Acutely unwell infants with a likely monogenic disorder (82160)
Eligibility Statement	**Acutely unwell infants with a likely monogenic disorder inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Acutely unwell infants admitted to intensive care or high dependency care with a likely monogenic disorder. Optimal family structure: Trio. Where in pathway: Acutely unwell infants admitted to intensive care or high dependency care with a likely monogenic disorder. NOTE: Consider microarray in parallel depending on clinical features (copy number analysis is not yet live in 100k pipeline. Expected for diagnostic service). Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R14 Acutely unwell infants with a likely monogenic disorder exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R27 Congenital malformation and dysmorphism syndromes - likely monogenic (82161)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R27 Congenital malformation and dysmorphism syndromes - likely monogenic (82161)
Eligibility Statement	**R27 Congenital malformation and dysmorphism syndromes - likely monogenic inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Congenital malformations and/or dysmorphism suggestive of an underlying monogenic disorder where targeted genetic testing is not possible Testing of individuals with syndromic overgrowth or overgrowth in combination with intellectual disability or developmental delay would also be appropriate under this indication Optimal family structure: Trio. Where in pathway: At presentation following discussion with Consultant in Clinical Genetics or other relevant subspecialist approved by Genomic Laboratory Hub. NOTE: Consider microarray in parallel depending on clinical features (copy number analysis is not yet live in 100k pipeline. Expected for diagnostic service). Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R27 Congenital malformation and dysmorphism syndromes - likely monogenic exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R69 Floppy infant with a likely central cause (82162)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R69 Floppy infant with a likely central cause (82162)
Eligibility Statement	**R69 Floppy infant with a likely central cause inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Neonates or infants with unexplained hypotonia where the clinical picture is suggestive of a central cause, i.e. particularly where the baby is not alert, but lethargic or sleepy. Optimal family structure: Trio. Where in pathway: At presentation after exclusion of sepsis or hypoglycaemia as causes. NOTE: Consider targeted testing in parallel depending on clinical features including: - Microarry for copy number abnormality (Copy number pipeline not yet live in 100k pipeline. Expected for diagnostic service). - Myotonic dystrohy+E13 - Prader-Willi syndrome (PWS methylation out of scope of WGS). - Spinal muscular atrophy (SMN1 small variant and copy number analysis not validated for 100k pipeline. Not currently expected for diagnostic service). Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R69 Floppy infant with a likely central cause exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R29 Moderate, severe or profound intellectual disability (82163)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R29 Moderate, severe or profound intellectual disability (82163)
Eligibility Statement	**GMS R29 Moderate, severe or profound intellectual disability inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Unexplained moderate or worse intellectual disability or global developmental delay. Optimal family structure: Trio. Where in pathway: At presentation following discussion with Consultant in Clinical Genetics or other relevant subspecialist approved by Genomic Laboratory Hub. NOTE: Consider microarray in parallel depending on clinical features (copy number analysis is not yet live in 100k pipeline. Expected for diagnostic service). Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R29 Moderate, severe or profound intellectual disability exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R89 Ultra-rare and atypical monogenic disorders (82164)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R89 Ultra-rare and atypical monogenic disorders (82164)
Eligibility Statement	**GMS R89 Ultra-rare and atypical monogenic disorders inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Individuals with ultra-rare disorders or atypical manifestations of recognised monogenic disorders that make broad genomewide analysis the optimal approach. Optimal family structure: Singleton or Trio depending on clinical setting (see family selection guidance). Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R89 Ultra-rare and atypical monogenic disorders exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R100 Rare syndromic craniosynostosis or isolated multisuture synostosis (82165)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R100 Rare syndromic craniosynostosis or isolated multisuture synostosis (82165)
Eligibility Statement	**GMS R100 Rare syndromic craniosynostosis or isolated multisuture synostosis inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Rare syndromic craniosynostosis syndrome or isolated multisuture synostosis where clinical features are not consistent with mutations in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1. Optimal family structure: Trio. Where in pathway: At presentation **GMS R100 Rare syndromic craniosynostosis or isolated multisuture synostosis exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R104 Skeletal dysplasia (82166)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R104 Skeletal dysplasia (82166)
Eligibility Statement	**GMS R104 Skeletal dysplasia inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Clinical features indicative of a likely monogenic skeletal dysplasia. Optimal familiy structure: Trio. Where in pathway: Following review of clincial features and x-rays by a Clinical Geneticist or Radiologist expert in skeletal dysplasias. Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R104 Skeletal dysplasia exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R143 Neonatal diabetes (82167)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R143 Neonatal diabetes (82167)
Eligibility Statement	**GMS R143 Neonatal diabetes inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Diabetes mellitus diagnosed below the age of 6 months Optimal family structure: Trio. Where in pathway: Start with treatment response screen for sulphonylurea-sensitive genes by Sanger sequencing Continue to WGS test if negative Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R143 Neonatal diabetes exclusion criteria** **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change. **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria.

GMS R98 Likely inborn error of metabolism - targeted testing not possible (82168)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R98 Likely inborn error of metabolism - targeted testing not possible (82168)
Eligibility Statement	**GMS R98 Likely inborn error of metabolism - targeted testing not possible inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Clinical feature of a likely inborn error of metabolism where targeted testing is not possible Optimal family structure: Trio. Where in pathway: At presentation following clinically relevant, rapidly available investigations Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R98 Likely inborn error of metabolism - targeted testing not possible exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R83 Arthrogryposis (82185)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R83 Arthrogryposis (82185)
Eligibility Statement	**GMS R83 Arthrogryposis inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Clinical features that indicate arthrogryposis of monogenic aetiology. Optimal family structure: Trio. Where in pathway: At presentation following assessment by a Neurologist or Clinical Geneticist and following serum CK estimation. Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R83 Arthrogryposis exclusion criteria** **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change. **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria.

GMS R84 Cerebellar anomalies (82169)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R84 Cerebellar anomalies (82169)
Eligibility Statement	**GMS R84 Cerebellar anomalies inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Likely monogenic cerebellar malformation, cerebellar or pontocerebellar hypoplasia or childhood-onset cerebellar atrophy. Optimal family structure: Trio. Where in pathway: At presentation following MRI brain and assessment by a Neurologist or Clinical Geneticist. Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R84 Cerebellar anomalies exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R87 Cerebral malformation (82170)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R87 Cerebral malformation (82170)
Eligibility Statement	**GMS R87 Cerebral malformation inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Cerebral malformation such as cortical malformation or porencephaly with features suggestive of a monogenic cause Optimal family struture: Trio. Where in pathway: At presentation. NOTE: Consider targeted testing for mosaic mutations causative of cerebral malformation as part of segmental overgrowth disorders where clincial features are suggestive (WGS pipeline does not have high sensitivity to low level mosacism). Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R87 Cerebral malformation exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R61 Childhood onset hereditary spastic paraplegia (82171)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R61 Childhood onset hereditary spastic paraplegia (82171)
Eligibility Statement	**GMS R61 Childhood onset hereditary spastic paraplegia inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Unexplained spastic paraplegia of likely monogenic aetiology with onset in childhood. Optimal family structure: Trio. Where in pathway: At presentation following assessment by a Neurologist or Clinical Geneticist. NOTE: Consider targeted STR testing for SCA loci in parallel if clinically relevant (STR analysis is in development but not yet live in 100k pipeline. Expected for diagnostic service). Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R61 Childhood onset hereditary spastic paraplegia exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R109 Childhood onset leukodystrophy (82172)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R109 Childhood onset leukodystrophy (82172)
Eligibility Statement	**GMS R109 Childhood onset leukodystrophy inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Unexplained leukodystrophy on neuroimaging with onset in childhood. Optimal family structure: Trio. Where in pathway: At presentation following review of neuroimaging by Neuroradiologist. Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R109 Childhood onset leukodystrophy exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R59 Early onset or syndromic epilepsy (82173)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R59 Early onset or syndromic epilepsy (82173)
Eligibility Statement	**GMS R59 Early onset or syndromic epilepsy inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. 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 Optimal family structure: Trio. Where in pathway: At presentation. Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R59 Early onset or syndromic epilepsy exclusion criteria** **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change. **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria.

GMS R54 Hereditary ataxia with onset in adulthood (82174)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R54 Hereditary ataxia with onset in adulthood (82174)
Eligibility Statement	**GMS R54 Hereditary ataxia with onset in adulthood inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Unexplained ataxia with onset in adulthood including where the differential diagnosis encompasses STR loci. Optimal family stsructure: Singleton. Where in pathway: At presentation following assessment by a Neurologist. NOTE: Consider targeted STR testing for SCA loci in parallel if clinically relevant (STR analysis is in development but not yet live in 100k pipeline. Expected for diagnostic service). Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R54 Hereditary ataxia with onset in adulthood exclusion criteria** **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change. **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria.

GMS R55 Hereditary ataxia with onset in childhood (82175)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R55 Hereditary ataxia with onset in childhood (82175)
Eligibility Statement	**GMS R55 Hereditary ataxia with onset in childhood inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Unexplained hereditary ataxia with onset in childhood including where the differential diagnosis encompasses STR loci. Optimal family structure: Trio. Where in pathway: At presentation following assessment by a Neurologist. NOTE: Consider targeted STR testing for SCA loci in parallel if clinically relevant (STR analysis is in development but not yet live in 100k pipeline. Expected for diagnostic service). Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R55 Hereditary ataxia with onset in childhood exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R85 Holoprosencephaly - NOT chromosomal (82176)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R85 Holoprosencephaly - NOT chromosomal (82176)
Eligibility Statement	**GMS R85 Holoprosencephaly - NOT chromosomal inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Liveborn individuals with unexplained holoprosencephaly in whom a chromosomal cause has been excluded by microarray or equivalent. Optimal family structure: Trio. Where in pathway: At presentation following chromosome microarray (which may have followed rapid aneuploidy screening). Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R85 Holoprosencephaly - NOT chromosomal exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R86 Hydrocephalus (82177)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R86 Hydrocephalus (82177)
Eligibility Statement	**GMS R86 Hydrocephalus inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Unexplained hydrocephalus with a likely monogenic cause, i.e. where secondary causes such as congenital infection and intraventricular haemorrhage are unlikely to be causative. Optimal family structure: Trio. Where in pathway: At presentation after relevant acquired causes have been excluded where feasible. Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R86 Hydrocephalus exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R381 Other rare neuromuscular disorders (82178)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R381 Other rare neuromuscular disorders (82178)
Eligibility Statement	**GMS R381 Other rare neuromuscular disorders inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Clinical features of rare neuromuscular disorder not covered by more specific indications Optimal family structure: Singleton or Trio. Where in pathway: At presentation. Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R381 Other rare neuromuscular disorders exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R88 Severe microcephaly (82179)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R88 Severe microcephaly (82179)
Eligibility Statement	**GMS R88 Severe microcephaly inclusion critieria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. Individuals with severe microcephaly of likely monogenic aetiology. Optimal family structure: Trio. Where in pathway: At presentation. Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R88 Severe microcephaly exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.

GMS R193 Cystic renal disease (82180)

Level 3 Title	Whole genome sequencing indications (82159)
Level 4 Title	GMS R193 Cystic renal disease (82180)
Eligibility Statement	**GMS R193 Cystic renal disease inclusion criteria** This indication and the criteria set out here are based on those to be included in the NHS Genomic Test Directory as part of the NHS Commissioned Service. 1. Patients with non-syndromic cystic renal disease (excluding acquired cystic disease due to chronic or end stage kidney disease) which is EITHER 2. Clinically not characteristic of ADPKD and underlying diagnosis is required for management purposes, OR 3. Clinically symptomatic disease presenting before the age of 18, OR 4. Clinical diagnosis of ADPKD where a genetic diagnosis is required to influence management Overlapping conditions: 'Congenital malformation and dysmorphism syndromes – likely monogenic' or 'Ultra-rare and atypical monogenic disorders' tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations Optimal family structure: Singleton. Where in pathway: At presentation, or when clinical management decision depending on molecular diagnosis is required NOTE: Consider testing in parallel using an accredited diagnostic test pending finalisation of validation data from WGS Testing should principally be targeted at those where a molecular diagnosis will guide management or alter advice. **GMS R193 Cystic renal disease exclusion criteria** **Prior genetic testing guidance - GMS** This indication will be available as a first line test in the new NHS Genomic Medicine Service. Prior to that, local clinical teams can use it as a first line test or in parallel to or following current diagnostic testing according to the clinical setting, noting that the 100,000 Genomes Project pipeline does not yet report on all variant types that will be available in the NHS pipeline and is not accredited. Other tests that should be considered are listed in the 'Where in pathway' section of the Inclusion criteria. **Closing statement** These requirements will be kept under continual review during the main programme and may be subject to change.