DATE: 12th October 2021

Title:

Explanatory document to accompany documents published by NHS England and NHS Improvement on 4th October 2021:

- National Genomic Test Directory for rare and inherited disease
- Rare and inherited disease eligibility criteria

Available online:
https://www.england.nhs.uk/publication/national-genomic-test-directories/

Please note:

A separate document accompanies the updates to the Test Directory for Cancer.

This explanatory note provides details of:

- The major changes that have been made to the Test Directory for Rare and Inherited Disease and associated eligibility criteria, recently published on the website (https://www.england.nhs.uk/publication/national-genomic-test-directories/).

- Further updates that are planned to be made to the Test Directory for Rare and Inherited Disease during 2021/22.

When will the new tests be available to order and the other changes implemented?

- The Genomic Laboratory Hubs are asked to implement the changes at the earliest opportunity, but no later than 3-months following the publication date of the 2021/2022 Test Directory.

What has changed in the Test Directory published on 4 October 2021?

Clinical Indications moving to Whole Genome Sequencing:

Please note that these Clinical Indications may not all be ready for testing by WGS and therefore requestors should contact their local GLH prior to consenting and ordering for patients to check the state of readiness. If WGS is not yet being delivered, please continue with your usual practice for ordering testing.

Speciality	Clinical Indication moving to Whole Genome Sequencing
Cardiology	**R135** Paediatric or syndromic cardiomyopathy (page 25)
Neurology	**R60** Adult onset hereditary spastic paraplegia (page 291) **R58** Adult onset neurodegenerative disorder (page 289) **R62** Adult onset leukodystrophy (page 293) **R78** Hereditary neuropathy or pain disorder – NOT PMP22 copy number (page 302) **R56** Adult onset dystonia, chorea or related movement disorder (page 287) **R57** Childhood onset dystonia, chorea or related movement disorder (page 288)
Renal	**R257** Unexplained paediatric onset end-stage renal disease (page 337)
Immunology	**R15** Primary immunodeficiency (page 163)
Ophthalmology	**R32** Retinal disorders (page 89) **R33** Possible X-linked retinitis pigmentosa (page 90) **R34** Sorsby retinal dystrophy (page 91) **R35** Doyne retinal dystrophy (page 92) **R31** Bilateral congenital or childhood onset cataracts (page 88) **R36** Structural eye disease (page 93)

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New Clinical Indications:

R412 Fetal anomalies with a likely genetic cause - non urgent (page 106)
R413 Autoinflammatory Disorders (page 165)
R414 APC associated Polyposis (page 184)
R415 Cleidocranial Dysplasia (page 269)
R416 Syndromic and non syndromic craniosynostosis involving midline sutures only (metopic, sagittal, metopic & sagittal) (page 272)

Clinical Indications that have been removed or merged with others:

R408 **Idiopathic ventricular fibrillation** (merged with R138 and renamed from "Molecular autopsy following sudden unexplained death" to "Sudden unexplained death or survivors of a cardiac event")
R210 **Inherited MMR deficiency** (Lynch syndrome; MSI and BRAF V600E testing have been removed as these are covered by the Cancer Test Directory)
R266 **Neuromuscular arthrogryposis**, (a panel of genes was never created for this Clinical Indication as the phenotypes are encompassed in other panel tests)
R193 **Cystic renal disease** (the PKD1 gene test is now included in the panel test).

Other key changes:

Specialty	CI number	Clinical Indication name	Change in name and scope
Developmental Disorders	**R29**	Intellectual disability – microarray and sequencing	removed Fragile X testing from this indication as there is a separate test specifically for Fragile X (R53) (page 34)
Endocrinology	**R223**	Inherited phaeochromocytoma and paraganglioma excluding NF1	name changed to be clear that this Clinical Indication is excluding testing for NF1 (page 81)
Gastrohepatology	**R177**	Hirschsprung disease	extended scope by removing the requirement for the patient to have an affected 1st or 2nd degree relative (page 127)
Gastrohepatology	**R331**	Intestinal failure or congenital diarrhoea	This testing now includes congenital diarrhoea and criteria have been updated accordingly. Please check with the lab first if the genes you require testing for congenital diarrhoea are available whilst this testing is being established (page 128)
Immunology	**R15**	Primary Immunodeficiency and monogenic inflammatory bowel disease	This testing now includes monogenic inflammatory bowel disease and criteria have been updated accordingly. Please check with the lab first if the genes you require for mIBD are included whilst the test is being established (page 163)

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Specialty	CI number	Clinical Indication name	Change in eligibility criteria
Endocrinology	**R141**	Monogenic diabetes	Significant changes in eligibility criteria (page 44)
Endocrinology	**R142**	Glucokinase-related fasting hyperglycaemia	Significant changes in eligibility criteria (page 46)
Endocrinology	**R143**	Neonatal diabetes	Age threshold changed from 6 months to 9 months (page 47)
Audiology	**R67**	Monogenic hearing loss	Name has changed from "Non-syndromic hearing loss" and the eligibility criteria has been updated to include unilateral hearing loss in specific circumstances, see the criteria for full details (page 161)
Inherited cancer	**R212**	Peutz Jegher Syndrome	Additional criteria added 1) Sex cord tumours with annular tubules (SCAT) at any age and 2) Adenoma malignum of the cervix at any age (page 185)
Inherited cancer	**R214**	Nevoid Basal Cell Carcinoma Syndrome or Gorlin syndrome	Change to the number of major or minor criteria required for testing, has made it less restrictive (page 188)
Inherited cancer	**R358**	Familial rhabdoid tumours	Criteria now includes "Small cell carcinoma of the ovary, hypercalcaemic type (SCCOHT) (any age)" (page 193)
Inherited cancer	**R364**	DICER1-related cancer predisposition	Major changes, see the criteria document (page 199)
Respiratory	**R186**	Hereditary haemorrhagic telangiectasia	Includes more details around AVMs (page 344)
Ultra-rare and atypical monogenic disorders	**R89**	Ultra-rare and atypical monogenic disorders	More detail provided in the criteria (page 366)
Multi purpose tests	**R246**	Carrier testing at population risk for partners of known carriers of nationally agreed autosomal recessive disorders	Significant new guidance provided in the criteria (page 370)

Requesting specialties

Additional requesting specialties were added to various clinical indications in the eligibility criteria. Please note that where a clinical specialty is not listed for that clinical indication, the GLH can process that test if it is deemed appropriate as per their agreed local pathways and the eligibility criteria for the clinical indication is being met. Further detail is provided on page 3 of the eligibility criteria.

Further planned updates:

Not all the supported changes were included in the publication on 4th October given some of the changes require a longer timeframe for implementation.

- The 2021/22 updates to the Test Directory are to be published in three separate stages before the end of the financial year with the 4th October publication being stage 1.
- The table below lists the Clinical Indications for which there are further updates planned to the Test Directory for Rare and Inherited Disease. Should individuals be considering submitting an application to update the Test Directory as part of the next application round (closing on 29 October 2021), please contact the Genomics Unit (contact details below) who will be able to provide further detail to avoid submission of duplicate applications.

Further planned updates to the Test Directory for Rare and Inherited Disease:		
Specialty Group	**Clinical Indication name**	**Clinical Indication code**
Cardiology	Long QT Syndrome	R127
Cardiology	Dilated & Arrhythmogenic Cardiomyopathy	R132
Cardiology	Arrhythmogenic Right Ventricular Cardiomyopathy	R133
Metabolic	Gaucher Disease Type 1	R272
Endocrinology	Albright hereditary osteodystrophy, pseudohypoparathyroidism and pseudopseudohypoparathyroidism	R293
Endocrinology	Multi Locus Imprinting Disorder	New CI
Endocrinology	Familial hyperparathyroidism	R151
Mosaic and structural chromosomal disorders	Possible structural chromosomal rearrangement - karyotype	R297
Core Inherited Cancers	Inherited ovarian cancer without breast cancer	R207
Core Inherited Cancers	Inherited breast cancer and ovarian cancer	R208
Core Inherited Cancers	Inherited Polyposis	R211
Core Inherited Cancers	Inherited colorectal cancer	R209
Specialist Inherited Cancers	Multilineage cytopenias with marrow dysplasia or marrow failure in children and adults <40 years	New CI
Specialist Inherited Cancers	BAP1 Associated Tumour Disposition Syndrome	New CI
Specialist Inherited Cancers	CDH1 Related Cancer Syndrome	R215
Specialist Inherited Cancers	Li Fraumeni Syndrome	R216
Specialist Inherited Cancers	Wilms tumour with features of suggestive predisposition	R220
Specialist Inherited Cancers	Familial Melanoma	R254
Specialist Inherited Cancers	Neurofibromatosis Type 2 & Schwannomatosis	R221 & R393
Gastrohepatology	Cholestasis	R171
Gastrohepatology	Pancreatitis	R175
Immunology	Hereditary Alpha Tryptasaemia	New CI
Neurology	Acute Rhabdomyolysis	New CI
Neurology	Adult onset neurodegenerative disorder	R58
Neurology	Motor Neuron Disease (Amyotrophic Lateral Sclerosis) (ALS)	New CI

Neurology	Duchenne or Becker muscular dystrophy	R73
Neurology	Neurofibromatosis type 1	R222
Neurology	Hereditary ataxia with onset in adulthood	R54
Neurology	Tuberous Sclerosis	R228
Ophthalmology	Retinal disorders	R32
Ophthalmology	Pseudoxanthoma Elasticum	New CI
Respiratory	Pulmonary Fibrosis, Familial	New CI
Respiratory	Pulmonary arterial hypertension	R188
Respiratory	Hereditary haemorrhagic telangiectasia	R186
Respiratory	Cystic fibrosis diagnostic test & Cystic Fibrosis Carrier Testing	R184, R185
Mitochondrial	Possible mitochondrial disorder - mitochondrial DNA rearrangement testing	R299
Fetal (including NIPD)	NIPD for Retinoblastoma	New CI
Fetal (including NIPD)	Common Aneuploidy testing - prenatal	R401
Dermatology	Subcutaneous Panniculitis T-Cell Lymphoma	New CI
Haematology	Inherited predisposition to acute myeloid leukaemia (AML)	R347

Further queries or questions:

The Evaluation and Testing Team within the Genomics Unit at NHS England and NHS Improvement are working hard to action the roll out of the first annual cycle of Test Directory updates. Any questions in relation to the Test Directory should be directed via email to the Genomics Unit within NHS England and NHS Improvement (england.testevaluation@nhs.net).

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