Guidelines on who to recruit from a rare disease family

26/02/2018 Version 2.1

Contents

1 Introduction

1.1 Purpose

This document contains guidance for the selection of families and probands for the rare disease arm of the main programme of the 100,000 Genomes Project. It is designed for use in the clinical environment by recruiting teams.

A glossary is provided with explanation of key terms.

1.2 Changes from previous version

This document is derived from v1.1 guidelines (dated 8/7/16). Changes in this document have been made with the approval of the Scientific Advisory Committee and include:

- Cessation of recruitment of unaffected siblings to create a trio; previously recommended if one or both parents were unavailable
- Simplification of the layout of the guidance for ease of reference
- An update of the disease categories that are considered to typically display non-penetrance

2 Who to recruit in a rare disease family

This depends on whether the disorder is fully penetrant (Group A), i.e. always occurs if someone has the causative variant(s), or is frequently non-penetrant (Group B) i.e. sometimes does not occur when a person has the causative variant(s). The guidance in section 2.1 and 2.2 clarifies the optimal family structure for recruitment in Group A and Group B disorders respectively.

Section 3 contains a table detailing each recruitment category and whether it is considered to be typically penetrant (Group A) or non-penetrant (Group B), for reference as required.

2.1 Who to recruit in a rare disease family: Group A disorders (fully penetrant)

Group A disorders: Fully penetrant

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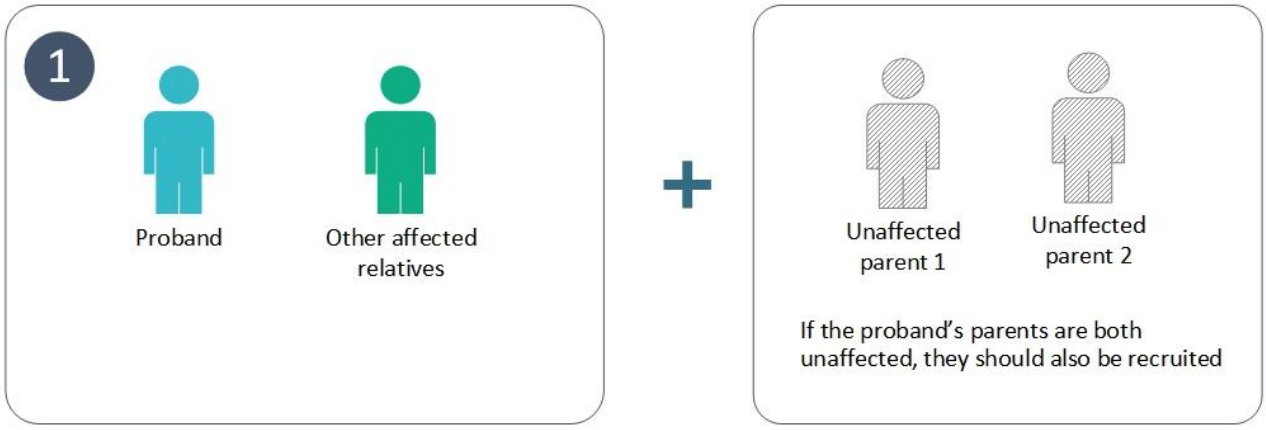
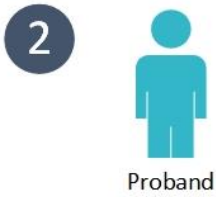


- **DO NOT RECRUIT** relatives whose disease status is unknown
- Relatives marked unaffected **must** be unaffected

LEAST PREFERABLE



2.2 Who to recruit in a rare disease family: Group B disorders (incomplete penetrance)

Group B disorders: Incomplete penetrance

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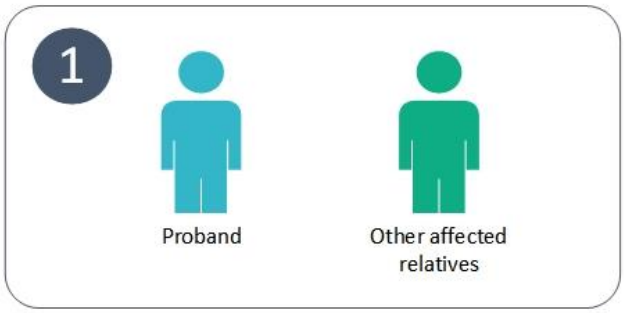
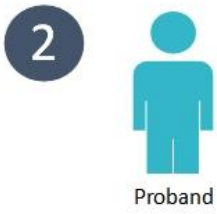


- **DO NOT RECRUIT** relatives whose disease status is unknown
- **DO NOT RECRUIT unaffected** relatives

LEAST PREFERABLE



NOTE: If a condition is typically a group B (incompletely penetrant disorder) but it presents as severe early onset or syndromic disease it can be recruited as per group A's guidance at the recruiting clinician's discretion.

3 Determining the type of disorder: Penetrant (group A) or non-penetrant (group B)

The following table can be used to determine if the recruited condition is considered to be a Group A disorder (completely penetrant) or Group B disorder (incompletely penetrant).

Please note that if a condition is listed as a group B disorder, but presents as severe early onset or in a syndromic manner, it can be recruited as per group A at the recruiting clinician's discretion.

Category	Subcategory	Disease	Group A or B disorder
Cardiovascular disorders (10950)	Arteriopathies (33332)	Familial cerebral small vessel disease (36469)	B
		Familial Hypercholesterolaemia (33666)	B
		Severe hypertriglyceridaemia (42185)	B
	Connective Tissues Disorders and Aortopathies (10951)	Familial Thoracic Aortic Aneurysm Disease (11021)	B
	Cardiac arrhythmia (10952)	Brugada syndrome (11022)	B
		Long QT syndrome (11023)	B
		Catecholaminergic Polymorphic Ventricular Tachycardia (11024)	B
		Unexplained sudden death in the young (38566)	B*
		Idiopathic ventricular fibrillation (42161)	B
		Short QT syndrome (55487)	B
	Cardiomyopathy (10953)	Arrhythmogenic Right Ventricular Cardiomyopathy (11025)	B
		Left Ventricular Noncompaction Cardiomyopathy (15044)	B
		Dilated Cardiomyopathy (31340)	B
		Dilated Cardiomyopathy and conduction defects (11027)	B

		Hypertrophic Cardiomyopathy (11028)	B
	Congenital heart disease (10954)	Familial congenital heart disease (42212)	B
		Syndromic congenital heart disease (42213)	A
	Lymphatic disorders (33334)	Meige disease (34328)	B
		Milroy disease (37604)	B
		Lymphoedema distichiasis (37612)	B
		Lipoedema disease (55456)	B
		Primary lymphoedema (55517)	B
	Pulmonary heart disease (55662)	Pulmonary arterial hypertension (55499)	B
Ciliopathies (10963)	Congenital malformations caused by ciliopathies (15091)	Bardet-Biedl Syndrome (11046)	A
		Joubert syndrome (36478)	A
		Rare multisystem ciliopathy disorders (36488)	A
	Respiratory ciliopathies (15092)	Primary ciliary dyskinesia (11047)	A
		Non-CF bronchiectasis (11048)	B
Dermatological disorders (10956)	Atopy (15084)	Severe multi-system atopic disease with high IgE (15085)	B
	Autoimmune skin disorders (33336)	Generalised pustular psoriasis (33646)	B
	Ectodermal dysplasias (33338)	Ectodermal dysplasia without a known gene mutation (33699)	A
	Ichthyoses (33340)	Autosomal recessive congenital ichthyosis (33700)	A
	Keratodermas (33342)	Palmoplantar keratoderma and erythrokeratodermas (33701)	B
		Familial disseminated superficial actinic porokeratosis (37644)	B
	Neurocutaneous disorders (33344)	Undiagnosed neurocutaneous disorders (33686)	A
	Skin adnexa disorders (36587)	Familial cicatricial alopecia (36588)	B
		Familial hidradenitis suppurativa (41844)	B
		Non-syndromic hypotrichosis (36849)	B
	Skin fragility disorders (33346)	Epidermolysis bullosa (33684)	A
		Peeling skin syndrome (36540)	A
		Erythropoietic protoporphyria, mild variant (11037)	B

	Sun-exposure related conditions (10958)	Hydroa vacciniforme (15083)	B
Dysmorphic and congenital abnormality syndromes (10959)	Kabuki (28664)	Kabuki syndrome (10960)	A
	RASopathies (10961)	Noonan syndrome (11039)	A
		Noonan syndrome plus other features (11040)	A
		Cardio-facio-cutaneous syndrome (11041)	A
		LEOPARD syndrome (11042)	A
		Costello syndrome (11043)	A
		Legius syndrome (11044)	A
	Balanced translocations (10962)	Balanced translocations with an unusual phenotype (11045)	A
	Limb disorders (15087)	VACTERL-like phenotypes (10964)	A
	DNA repair disorders (10965)	Cockayne syndrome (36497)	A
		Non-Fanconi anaemia (11050)	A
		Xeroderma Pigmentosum-like disorders (15089)	A
		Primary Microcephaly - Microcephalic Dwarfism Spectrum (36505)	A
	Autophagy disorders (10966)	Vici Syndrome and other autophagy disorders (11051)	A
	Dysmorphic disorders (36595)	Coarse facial features including Coffin-Siris-like disorders (36596)	A
		Familial non-syndromic cleft lip and or familial cleft palate (37565)	B
		Syndromic cleft lip and or cleft palate (37573)	A
		PHACE(S) syndrome (37578)	A
		Radial dysplasia (37636)	A
	Fetal disorders (38586)	Fetal hydrops (37586)	A
		Unexplained monogenic fetal disorders (38665)	A
Endocrine disorders (10967)	Adrenal disorders (10969)	Congenital adrenal hypoplasia (11053)	A
	Disorders of calcium homeostasis (10970)	Familial or syndromic hypoparathyroidism (11054)	B*
		Disorders of sex development (36852)	A

	Gonadal and sex development disorders (36923)	Early onset familial premature ovarian insufficiency (36851)	B
	Growth hormone disorders (10971)	IUGR and IGF abnormalities (11057)	A
	Hypothalamic and pituitary disorders (42204)	Idiopathic hypogonadotropic hypogonadism (41827)	B
	Obesity syndromes (10973)	Significant early-onset obesity with or without other endocrine features and short stature (11060)	A
	Rare subtypes of diabetes (15099)	Familial young-onset non-insulin-dependent diabetes (15103)	B
		Hyperinsulinism (15105)	A
		Neonatal diabetes (diagnosed less than 6 months) (30553)	A
		Diabetes with additional phenotypes suggestive of a monogenic aetiology (30559)	A
		Insulin resistance (including lipodystrophy) (30561)	A
		Multi-organ autoimmune diabetes (30563)	B
	Thyroid disorders (42208)	Congenital hypothyroidism (41908)	A
		Resistance to thyroid hormone (41916)	A
Gastroenterological disorders (38581)	Gastrointestinal disorders (38582)	Infantile enterocolitis and monogenic inflammatory bowel disease (37490)	A
		Gastrointestinal epithelial barrier disorders (37772)	A
		Non-syndromic familial congenital anorectal malformations (41868)	B
		Early onset or familial intestinal pseudo obstruction (41876)	B
		Familial Hirschsprung Disease (55463)	B
	Liver disease (55663)	Ductal plate malformation (55469)	A
		Neonatal cholestasis (71744)	A

Growth disorders (10974)	Beckwith-Wiedemann syndrome (BWS) and other congenital overgrowth disorders (10975)	Classical Beckwith-Wiedemann syndrome (11063)	A
		Atypical Beckwith-Wiedemann syndrome (11064)	A
		Simpson-Golabi-Behmel syndrome (11065)	A
		Sotos syndrome (11066)	A
		Weaver syndrome (11067)	A
	Growth restriction (38585)	Silver Russell syndrome (37553)	A
Haematological and immunological disorders (10977)	Anaemias and red cell disorders (10979)	Congenital anaemias (11075)	A
		Hereditary erythrocytosis (55505)	A
	Primary immunodeficiency disorders (10978)	Primary immunodeficiency (55674)	A
	Haemostasis disorders (55664)	Inherited bleeding and or platelet disorders (55475)	A
		Monogenic venous thrombosis (55523)	B
	Myeloid and marrow failure disorders (71739)	Cytopenia and pancytopenia (71752)	A
Hearing and ear disorders (10980)	Non-syndromic hearing loss (10981)	Congenital hearing impairment (11076)	A
		Auditory Neuropathy Spectrum Disorder (30607)	A
		Autosomal dominant deafness (36848)	B
	Deafness and congenital structural abnormalities (10982)	Bilateral microtia (11077)	A
		Familial hemifacial microsomia (37649)	A
		Ear malformations with hearing impairment (37657)	A
	Other hearing and ear disorders (71738)	Familial Meniere Disease (71748)	B
Infectious diseases (42209)	Bacterial disorders (42210)	Disseminated non-tuberculous mycobacterial infection (41932)	A
	Sepsis (55671)	GAinS study (55665)	B
Metabolic disorders (10983)	Specific metabolic abnormalities (10984)	Ketotic hypoglycaemia (11080)	A
		Lactic acidosis (11081)	A
		Cerebral folate deficiency (11083)	A

		Undiagnosed metabolic disorders (37620)	A
		Congenital disorders of glycosylation (37628)	A
	Urea Cycle disorders (15108)	Hyperammonaemia (11079)	A
	Lysosomal storage disorders (10985)	Mucopolysaccharideosis, Gaucher, Fabry (11084)	A
	Mitochondrial (10986)	Mitochondrial disorders (11085)	A
	Peroxisomal disorders (10987)	Peroxisomal biogenesis disorders (11086)	A
		Other peroxisomal disorders (15109)	A
Neurology and neurodevelopmental disorders (10988)	Motor Disorders of the CNS (10989)	Cerebellar hypoplasia (36512)	A
		Hereditary ataxia (11087)	B
		Early onset dystonia (11088)	A
		Hereditary spastic paraplegia (11089)	B
		Neurotransmitter disorders (37779)	A
		Structural basal ganglia disorders (37786)	A
	Inherited Epilepsy Syndromes (10990)	Genetic Epilepsies with Febrile Seizures Plus (11091)	A
		Familial Genetic Generalised Epilepsies (11092)	B
		Familial Focal Epilepsies (11093)	B
		Epileptic encephalopathy (11094)	A
		Epilepsy plus other features (41924)	A
	Motor and Sensory Disorders of the PNS (10991)	Charcot-Marie-Tooth disease (15111)	B
		Paediatric motor neuronopathies (11099)	A
	Neurodegenerative disorders (10992)	Early onset and familial Parkinson's Disease (11100)	B
		Complex Parkinsonism (includes pallido-pyramidal syndromes) (15112)	B
		Early onset dementia (15113)	B
		Amyotrophic lateral sclerosis or motor neuron disease (15114)	B

	Neurodevelopmental disorders (10993)	Classical tuberous sclerosis (11101)	A
		Intellectual disability (11102)	A
		Holoprosencephaly (36519)	A
		Rhomboencephalosynapsis (36603)	A
		Malformations of cortical development (36526)	A
		Fetal structural CNS abnormalities (36850)	A
		Pontine tegmental cap dysplasia (55493)	A
	Neuromuscular disorders (10994)	Congenital muscular dystrophy (15135)	A
		Congenital myopathy (11103)	A
		Congenital myaesthenia (15136)	A
		Rhabdomyolysis and metabolic muscle disorders (15137)	B
		Distal myopathies (11104)	A
		Arthrogryposis (15138)	A
		Limb girdle muscular dystrophy (11106)	A
	Channelopathies (11097)	Skeletal Muscle Channelopathies (15139)	A
		Brain channelopathy (15140)	B
	Sleep disorders (10995)	Kleine-Levin syndrome and other inherited sleep disorders (11108)	B
	Cerebrovascular disorders (36610)	Moyamoya disease (36611)	A
		Vein of Galen malformation (42174)	A
	Parenchymal brain disorders (36618)	Intracerebral calcification disorders (36619)	A
	White matter disorders (36626)	Inherited white matter disorders (36627)	A
Ophthalmological disorders (10996)	Anterior segment abnormalities (10997)	Corneal abnormalities (11110)	A
		Glaucoma (developmental) (11111)	A
		Cataracts (11112)	A
	Posterior segment abnormalities (10998)	Inherited optic neuropathies (11114)	A
		Rod-cone dystrophy (29268)	A
		Rod Dysfunction Syndrome (29269)	A

		Cone Dysfunction Syndrome (29270)	A
		Inherited macular dystrophy (29271)	A
		Leber Congenital Amaurosis or Early-Onset Severe Retinal Dystrophy (29272)	A
		Developmental macular and foveal dystrophy (29273)	A
		Familial exudative vitreoretinopathy (41900)	A
	Ocular malformations (10999)	Anophthalmia or microphthamia (11115)	A
		Ocular coloboma (15141)	A
	Ocular movement disorders (33350)	Infantile nystagmus (33662)	A
Psychiatric disorders (71735)	Schizophrenia and other psychotic disorders (71736)	Schizophrenia plus additional features (71740)	B
	Feeding and eating disorders (71737)	Severe familial anorexia (29278)	B
Renal and urinary tract disorders (11000)	Syndromes with prominent renal abnormalities (11001)	Proteinuric renal disease (30732)	B
		Familial haematuria (30733)	B
		Atypical haemolytic uraemic syndrome (33489)	B
		Primary membranoproliferative glomerulonephritis (55481)	B
	Structural renal and urinary tract disease (11003)	Cystic kidney disease (11120)	B
		Congenital Anomaly of the Kidneys and Urinary Tract (CAKUT) (29277)	B
	Disorders of function (11004)	Renal tubular acidosis (11123)	B
		Renal tract calcification (or Nephrolithiasis or nephrocalcinosis) (11124)	B
		Extreme early-onset hypertension (15142)	B
		Unexplained kidney failure in young people (36855)	B
Respiratory disorders (33353)	Interstitial lung disorders (33354)	Familial pulmonary fibrosis (33671)	B
	Vascular lung disorders (33355)	Hereditary haemorrhagic telangiectasia (33674)	B

		Familial and multiple pulmonary arteriovenous malformations (33677)	B
	Structural lung disorders (42203)	Familial primary spontaneous pneumothorax (41819)	B
Rheumatological disorders (11009)	Multi-system inflammatory or autoimmune disorders (11008)	Periodic fever syndromes and amyloidosis (11127)	A
		Juvenile dermatomyositis (29219)	B
	Connective tissues disorders (36930)	Kyphoscoliotic Ehlers-Danlos syndrome (36853)	A
		Classical Ehlers-Danlos Syndrome (41860)	A
Skeletal disorders (11005)	Skeletal dysplasias (11007)	Multiple Epiphyseal Dysplasia (11125)	A
		Chondrodysplasia punctata (15143)	A
		Thoracic dystrophies (11126)	A
		Stickler syndrome (11129)	A
		Osteogenesis imperfecta (30627)	A
		Unexplained skeletal dysplasia (36854)	A
		Amelogenesis imperfecta (55449)	B
	Craniosynostosis (30775)	Craniosynostosis syndromes (11006)	A
	Choanal anomalies (31500)	Choanal atresia (11078)	A
Tumour syndromes (11012)	Breast and endocrine (11013)	Familial breast and or ovarian cancer (11131)	B
		Multiple endocrine tumours (11132)	B
		Neuro-endocrine Tumours- PCC and PGL (11133)	B
		Parathyroid cancer (30611)	B
		Inherited non-medullary thyroid cancer (41884)	B
	GI tract (11014)	Familial colon cancer (11135)	B
		Multiple bowel polyps (30615)	B
		Peutz-Jeghers syndrome (36533)	B
	Muscle and nerve (11015)	Familial rhabdomyosarcoma or sarcoma (11138)	B

		Familial tumour syndromes of the central and peripheral nervous system (30619)	B
		Neurofibromatosis Type 1 (38874)	B**
	Skin (11016)	Genodermatoses with malignancies (30623)	B
	Young onset tumour syndromes (30781)	Paediatric congenital malformation-dysmorphism-tumour syndromes (30686)	A
		Exceptionally young adult onset cancer (41892)	B
	Multiple Primaries (30782)	Multiple Tumours (30685)	B
Ultra-rare disorders (30783)	Undescribed disorders (30784)	Ultra-rare undescribed monogenic disorders (30785)	A
	Multi-system groups (38589)	Neonatal or paediatric intensive care admission with a likely monogenic disease (38558)	A
		Single autosomal recessive mutation in rare disease (38672)	A
		Undiagnosed monogenic disorder seen in a specialist genetics clinic (42193)	A/B

Key:

B* - if the individual presents with severe early onset or syndromic disease, recruitment as per category A can be selected at the discretion of the recruiting clinician.

B** - if the NF1 gene has not been sequenced in the family before, please only recruit a single affected proband. Affected relatives can be recruited where there has been no diagnosis from standard sequencing approaches.

A/B - depends on the individual clinical scenario and is at the discretion of the recruiting clinician.

Disorder-specific guidance is given in the **Rare Disease Eligibility Statements** which can be found on the Genomics England website (http://www.genomicsengland.co.uk/) in the section 'For Health Professionals (Information for GMC staff', 'Important documents – Rare Disease'.

Guidelines on who to recruit from a rare disease family:

4 Specific guidance

4.1 Unaffected relatives

The recruiting clinician must be confident that any relatives recruited as unaffected are genuinely unaffected. They should do this by considering the age of onset and penetrance of the phenotype, and arranging any clinically indicated physical examination or investigation to look for early or mild features of the condition.

Under some eligibility criteria there is specific guidance regarding the recruitment of unaffected relatives.

4.2 Affected relatives

All relatives who are marked as affected must be considered to have the same disorder as the proband, otherwise they should be assigned a different disorder. All relatives recruited as affected must be blood relations of each other.

4.3 If the proband sample fails sample process

If a proband has failed DNA quality control (QC), proband designation can be switched to an alternative affected individual (if available) and the remaining samples sent for sequencing. Changes to the proband must be updated in all accompanying systems and documentation.

4.4 Waiting for additional family samples

Once a complete family unit is submitted to the UK Biorepository, that group of samples will proceed together for sequencing, analysis and reporting. It is therefore recommended that all family samples are held at the GMC(s) until the family unit is complete, and submitted together.

If a sample from an additional family member becomes available greater than two months after submission of the family unit, please contact the Genomics England helpdesk for advice.

4.5 Monozygotic twins

If a family includes a pair of monozygotic twins (who are affected with the same disorder), only one of the twins should be recruited. However, information may become available which is of relevance to the health of the other twin, and therefore the clinician may wish to check whether the other twin is aware of this possibility.

5 General notes

- If a proband sample is not sent through with appropriate family member samples, it will be treated as a singleton.
- Step-parents or other non-biological relations (e.g. aunts/uncles by marriage) are not to be included.
- All affected individuals must be blood relations of each other.
- Individuals (proband and family members) will only be included if their DNA sample passes the quality control standards set by the sequencer.
- Samples taken from unaffected relatives may not be sent for sequencing. For example, if the proband sample is unavailable or has not passed DNA quality controls, then parental samples will not be sent for sequencing, unless a replacement proband sample is provided.
- If the disease-specific eligibility criteria for the proband's phenotype require a particular number or pattern of affected relatives for recruitment, that criterion must be met and this over-rides the general guidance provided in this document.
- Deceased probands and relatives are eligible for inclusion in the programme subject to the following conditions:
    - A stored DNA sample is available which passes quality control tests
    - A relative in a qualifying relationship is available to provide appropriate consent
    - The consent obtained from the deceased individual at the time of sampling does not preclude use of the sample for the benefit of family members
    - Surviving relatives under the care of the NHS in England will benefit in terms of healthcare or reproductive options if a diagnosis is made.
- The proband needs to meet all eligibility criteria for the condition they are recruited with. Relatives are considered to be affected if their clinician thinks that they have the same condition, whether or not they meet the eligibility criteria independently.
- Only one affected family member needs to have had the required prior genetic testing.

6 General Enquiries Form

For clinical enquiries we would ask GMCs to contact the project's helpdesk (Telephone: 0808 281 9535 or E-mail: ge-servicedesk@genomicsengland.co.uk), providing the following information as a minimum:

- The Disorder Category and how the patient meets the Eligibility Criteria
- Where the family fits within the Guidelines for Family and Proband Selection
- The nature of the query regarding eligibility or recruitment
- What genetic testing has already been carried out
- Confirm that the GMC Rare Disease lead supports the request

7 Glossary

Consanguinity: a consanguineous family is one in which related individuals have had children together, e.g. parents are first or second cousins.

Monozygotic twins: genetically identical twins.

Penetrance: probability that a person with the disease-causing genotype or combination of genotypes will show clinical signs of the disease. For a fully penetrant disease, 100% of people with the genotype will have clinical features, usually at a young age. Diseases with incomplete penetrance can appear to skip generations.

Permanently unobtainable: where a member of the family is deceased or has permanently and irreversibly lost contact with the wider family, or has definitively decided not to take part in the project.

Phenotype: the clinical features of a disease or condition, which result from a combination of genotype (the individual's genetic make-up) and environmental or lifestyle factors.

Predictive test: offering a genetic test to a healthy, asymptomatic person to give them information about whether they may be at risk of developing the specific genetic condition identified in their family at some time in the future.

Proband: variably used to mean the first person in a family to be identified as being affected by a genetic condition, or the youngest or most seriously affected; in the 100,000 Genomes Project, the proband must be in the youngest generation from which samples are collected (see section 6 above).

Singleton: an individual recruited to the project without any family members; singletons may be the only affected person in the family (a simplex case), or they may be recruited as singletons because other affected family members are not available for recruitment (see section 5.2 above).