Attachment 1

New Test Recommendations for 2015/16 Commissioning Year

Evaluation number as assigned during the process	Test Name	Laboratory	Disease description	Utility of test in the NHS	Consequences of not testing
RECOMMENDATIONS TO BE CONSIDERED FOR FUNDING					
#185	Lipoprotein Lipase Deficiency (LPL)	**Aberdeen RGC**	A severe disorder with potentially severe complications and fatal outcome. Individuals with 2 copies (homozygote) of the altered gene present with a childhood onset of chylomicronaemia: • build-up of fat in the blood • severe abdominal pain • loss of appetite • musculoskeletal pain • general failure to thrive As the disease progresses, additional symptoms may include: • recurrent episodes of pancreatitis • development of type 2 diabetes • enlargement of liver and spleen Individuals with one copy (heterozygote) of altered gene present with similar symptoms but usually as an adult. **Death often occurs due to recurrent pancreatitis and associated complications**	• Allows treatment using a novel gene therapy (Alipogene tiparvovec; Glybera) in homozygotes • Will determine likelihood of drug response to certain drugs e.g. fibrates (LPL, apopC2 synthesis activators through PPAR-alpha) in heterozygotes • Will determine possible eligibility for more novel specific treatments for orphan disorders e.g. Lomitapide in heterozygotes	• Patients would not be offered gene therapy • Elligibility for the off-label prescription of Lomitapide (Juxtapid) in severe hypertriglyceidaemia cannot be determined • Diagnosis only possible using a difficult, insensitive and poorly standardised assay to measure Lipoprotein lipase activity
#186	Chromosome Breakage 89 Gene Panel Test	**Bristol RGC**	• **Chromosome Breakage Syndromes** are rare disorders of DNA repair which affects multiple organs : • It is associated with an increased predisposition to cancer and have a high incidence of other congenital abnormalities (e.g. short forearms, small head circumference) often with learning difficuties • **The Inherited Bone Marrow Failure Syndromes** underlie varying defects in the production of red blood cells, white blood cells, and/or platelets leading to low blood counts. • Some patients are at increased risk of developing blood and solid malignancies.	**Chromosome Breakage Syndromes** Provides an accurate diagnosis essential for appropriate and tailored management: • Prognosis and outcome • Further investigation • Treatment • Advice regarding recurrence risks • DNA based prenatal testing • Avoids the use of reagents associated with radiation risk thus avoiding health and safety risk to laboratory staff • Traditional culture methods are extremely labour intensive **The Inherited Bone Marrow Failure Syndromes** • Determination of appropriateness of HSCT treatment • Genetic counselling about familial recurrence risk • Exclusion of disease in potential matched sibling donors can be undertaken	• No definitive diagnosis with patients undiagnosed after many years • Inappropriate treatment or suboptimal choice of conditioning chemotherapy and HSCT strategy • Unnecessary screening strategies for complications related to condition • Recurrences are more likely to occur with potentially major healthcare and financial consequences for the wider NHS • Cheaper and faster parallel testing of multiple genes would not be available
#187 (RARE)	GATA2 deficiency	**Bristol RGC**	This disorder variably causes a range of potentially serious problems including: • Congenital hearing loss and sever limb swelling • Severe or frequent infections (warts, mycobacterial infections) • Bone marrow problems (low blood counts, myelodysplasia or acute myeloid leukaemia) • Excessive risk of blood clots or blood vessel aneurysms	• Allows selection for reduced intensity conditioning chemotherapy to minimise post-transplant complications and earlier discharge from hospital • Early diagnosis will allow selection for bone marrow aspirate surveillance to monitor progression of condition • Will allow accurate genetic counselling and option of antenatal diagnostics in future pregnancies • Offer of vaccination against HPV to reduce the risk of HPV associated carcinomas	• Inappropriate investigation, management or treatment of the complications • Lower chance of survival due to a late recognition of complications such as carcinoma or acute myeloid leukaemia. • Inappropriate choice of conditioning chemotherapy for hemopoietic stem cell transplantation. • Children born with risk of early morbidity and mortality

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#188	Very Early Onset Inflammatory Bowel Disease 40 Gene Panel Test	**London North East RGC GOSH**	A group of conditions with a very early onset of inflammatory bowel disease (VEO-IBD) affecting the gut but also other tissues. • Persistent inflammation and treatment side effects affect other organs e.g. liver. • Children are often not able to tolerate food and frequently rely on nutrition given in a central vein. • Patients presenting in the first two years of life have generally a very poor prognosis with high mortality and morbidity.	**Allows early diagnosis and identification of patients with a "transplantable" condition to enable timely bone marrow transplantation which cures the disease** Early diagnosis prevents exposure to long-term immunosuppression, GI surgery, parenteral nutrition (PN)	• Lack of definitive diagnosis • Delay of treatment by bone marrow transplantation • Long term admissions, surgery and treatment • Inadequate treatment of recurrent infections • Huge negative impact on the psychological and socio-economic integrity of families
#190	Syndromic & Non Syndromic Hearing Loss 95 Gene Panel Test	**London North East RGC GOSH**	A group of conditions including early onset non-syndromic hearing loss (i.e. without other features) and syndromic hearing loss associated with specific additional features. Syndromic forms of hearing loss account for 30% of deafness The presentation for patients with these conditions is variable and in some cases may appear to be isolated hearing loss.	• Genetic diagnosis will determine course of patient management: • **Enables appropriate identification of patients for early cochlear implantation (CI) with aural rehabilitation in patients where this treatment will be successful** • Ensure that long-term ophthalmic, neurological, thyroid or renal follow-up is implemented in appropriate patients • Avoidance of severe surgical complication from cochlear implantation such as meningitis in POU3F4 mutation positive patients	• Lack of definitive diagnosis and accurate genetic counselling • OTOF mutation positive patients not offered CI • Uncertainty as to whether patient is at risk of blindness
#193	HYPOCALCIURIC HYPERCALCEMIA, FAMILIAL, TYPE III; HHC3	**Oxford RGC**	FHH is characterised by lifelong hypercalcaemia, it is generally considered a benign condition. The prognosis is good.	• Allows key distinction of patients with FHH from familial forms of primary hyperparathyroidism which is not benign. • Avoidance of unnecessary parathyroid surgery	Ineffective and unnecessary parathyroid surgery
#194 (RARE)	Rhabdoid Tumour Predisposition Syndrome 1	**London North East RGC GOSH**	• Rhabdoid tumour predisposition syndrome is a rare condition occurring in infancy and early childhood. • **These tumours carry a poor prognosis** • Tumours develop in the brain and spinal cord and/or soft tissues and may present as apparently sporadic tumuors in multiple sites • **Rhabdoid tumours are highly resistant to conventional chemotherapies and radiotherapy, patients frequently succumb rapidly to disease** • One third of cases are due to germline mutations.	• Facilitates diagnosis of children with a germline mutation • Facilitates genetic counselling • Inform option of prenatal diagnosis • Influences intensity of chemotherapy treatment	• Prenatal or post-natal diagnosis would not be offered • Risk of further children being born with condition

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Evaluation number as assigned during the process	Test Name	Laboratory	Disease description	Utility of test in the NHS	Consequences of not testing
#201 (multi gene) (Evaluate with #213 - Guy's Panel Test)	Urea cycle disorders (UCDs)	**Sheffield RGC**	The urea cycle is the body's only method of disposing of waste nitrogen from broken-down proteins, by converting ammonia into urea. Severe defects in this process cause • The rapid build-up of ammonia which is highly toxic to the body, especially the brain • lethargy, seizures, coma and death in the first few days of life if untreated • Less severe forms can present at any age, sometimes in adulthood, and cause failure to thrive, lethargy and neurological or psychiatric problems. • Treatment involves life-long drug and dietary management; liver transplantation is required in some severe cases	• Allows optimised therapy to be delivered, in addition to the generic treatment of the hyperammonaemia using ammonia-scavenging drugs. • Liver biopsy for enzymological testing would not be necessary, thus avoiding an invasive and distressing procedurefor the patient and the parents. • It also allows definitive and rapid carrier, predictive, perinatal, prenatal or preimplantation testing for affected families	• Diagnoses may be delayed, or missed. • Sub-optimal management of therapy, resulting in a poorer prognosis • Families may have limited reproductive choices • Liver biopsies which can be a distressing medical procedure with associated risk of complications may be required • CPS1 deficiency and NAGS deficiency will not be able to be distinguished
#202	Monogenic Diabetes 14 Gene Panel Test	**Exeter RGC**	Monogenic diabetes is a clinically and genetically heterogeneous group of disorders characterised by: • **Early onset diabetes in slim individuals that are not insulin dependent** • Diagnosis under the age of 35 years with a minimum two generation family history of diabetes • Age of diagnosis, clinical features, severity of disease and penetrance are variable	Definitive diagnosis to determine clinical management and prognosis including: • Transfer from Insulin to Low dose sulfonylureas treatment for patients with HNF1A/HNF4A-MODY • Statin therapy for HNF1A and HNF4A MODY patients as at risk of microvascular and macrovascular complications • Renal imaging and renal function in patients with HNF1 mutations • Serial fetal abdominal scans in women with GCK MODY to identify excessive fetal growth • Improved glycaemic control reduces the risk of diabetes complications with fewer hospital admissions or clinic appointments	• **Unnecessary insulin treatment in MODY patients** • **Poor diabetes control and increased risk of developing diabetic complications** • Macrosomia and associated complications in pregnancy/during delivery (including stillbirth) • Leptin therapy will also not be made available for FPLD • Lack of access to appropriate health surveillance
#203	Neonatal Diabetes ~~20~~ 22 Gene Panel Test	**Exeter RGC**	A heterogeneous group of neonatal diabetes subtypes. Subtypes have symptoms that may include: • Pancreatic and cerebellar Agenesis • Spectrum of autoimmune features • Congenital cardiac defects • Congenital biliary tract Abnormalities • Gut development disorders • Thyroid dysfunction • Neurocognitive abnormalities Clinical diagnosis may be difficult due to variable symptoms and age onset.	• Allows a definitive genetic diagnosis before a clinical diagnosis is possible • Transfer from Insulin to Low dose sulfonylureas treatment • Defines the diagnostic subtype • Predicts prognosis and determines the most appropriate treatment • Informs families of sibling recurrence risk or risk of diabetes in future offspring • Clinical management of the additional features in syndromic subtypes and informs prognosis	• Life expectancy of patients would be reduced • Delayed diagnosis and early treatment • Unnecessary insulin treatment in MODY patients • Prenatal and pre-implantation genetic testing would not be possible

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Evaluation number as assigned during the process	Test Name	Laboratory	Disease description	Utility of test in the NHS	Consequences of not testing
#204	Hereditary Cancer and Fanconi Anaemia TruSIGHT 94 Gene Panel Test	**Sheffield RGC**	**Hereditary Predisposition to Cancer** is characterised by: • Increased overall lifetime risk of developing cancer • Associated significant morbidity and mortality • Earlier age of onset than is typical for multiple primary cancers • Clustering of rare cancers **Fanconi Anaemia** is a hereditary disorder characterised by: • Lack of blood cell production (bone marrow failure) • Predisposition to certain malignancies • Physical malformations • Short stature • Skin abnormalities • Cognitive developmental disability	<u>Hereditary Predisposition to Cancer</u> • Offers a significantly improved service leading to rapid diagnosis • Allows risk determination in pre-symptomatic at-risk relatives • Relatives with an increased risk can opt for prophylactic surgery • Informs reproductive decisions • Allows regular detailed screening (e.g. by MRI rather than ultrasound) to enable early effective treatment • Relatives not at an increased risk can be reassured and discontinue screening <u>Fanconi Anaemia</u> • Allows rapid definitive diagnosis • Assesses suitability of possible related donor for bone marrow transplantation	<u>Hereditary Predisposition to Cancer</u> • Delayed diagnosis using a less sensitive, expensive and time consuming test • Relatives with undetermined risk will continue to have unnecessary screening tests, sometimes invasive • Relatives with increased risk will not have regular and detailed screening <u>Fanconi Anaemia</u> • Delayed diagnosis through sequential testing • Potential related donors will not be identified
#207	Primary Ciliary Dyskinesia 18 Gene Panel Test	**Leeds RGC**	PCD causes significant respiratory distress and bronchiectasis (widening of the airways associated with excessive mucus production) and is generally detected in early infancy. Symptoms include: • nasal congestion • sinus problems • recurrent chest, ear and sinus infection • Situs inversus, (internal organs are reversed **End-stage lung disease and early mortality can occur in adulthood.**	• Reduces repeated equivocal biopsy results reducing discomfort and inconvenience • Reduces delays in a definitive diagnosis • Allows appropriate management improving health outcomes. • Enables carrier and prenatal testing to be offered to family members • Pre-conception carrier testing could be offered to high risk couples	• Lack of definitive diagnosis • Inappropriately management resulting in poor health outcomes. • Carrier and prenatal testing would not be available to at-risk relatives
#209 (RARE)	Nonsyndromic Holoprosencephaly	**Exeter RGC**	Nonsyndromic holoprosencephaly is an abnormality of brain development that can also affect the development the head and face. Holoprosencephaly occurs when the brain fails to divide properly into the right and left hemispheres.	The results of genetic test will provide a definitive diagnosis and will influence genetic counselling and may enable prenatal diagnosis.	Prenatal diagnosis or genetic counselling would not be offered
#210 (RARE)	Congenital fibrosis of the extraocular muscles 2 (CFEOM2)	**Exeter RGC**	• Individuals with congenital fibrosis of the extraocular muscles type 2 are born with sever bilateral ptosis (droopy lids), with their eyes partially or completely fixed in an outward (exotropic) position. • Eye movements are severely limited or absent in all directions. • Significant impact on vision and risk of infections	• Allows a definitive diagnosis to be made • Early diagnosis will allow proactive treatment usually by specialist surgery to prevent secondary complications	Unable to provide a definitive diagnosis and accurate genetic counselling

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Evaluation number as assigned during the process	Test Name	Laboratory	Disease description	Utility of test in the NHS	Consequences of not testing
#211	Primary pigmented nodular adrenocortical disease (PPNAD)	**Exeter RGC**	• Patients with PPNAD have nodules on their adrenal glands that result in excess hormone being released leading to severe health implications • Patients present with Cushing syndrome (rapid weight gain, thin skin that bruises easily, muscle weakness, excessive sweating and slowed growth in children). • Left untreated, Cushing syndrome can cause high blood pressure which increases the risk of heart attack and stroke.	• Genetic testing provides a definitive diagnosis of PPNAD and enables accurate genetic counselling for family members. • The identification of a PRKAR1A mutation enables screening for other cancers associated with Carney complex	• Delay in diagnosis • Clinical misdiagnosis of Carney Complex with unnecessary screening for symptoms of this condition in patient and family members
#213 (Evaluate with #201 - Sheffield multi gene)	Urea Cycle Defects (UCD) 9 Gene Panel Test	**London South East RGC GSTT**	Urea cycle disorders are a group of disorders resulting from failure of protein breakdown. • Toxic metabolites build up in blood which adversely affect brain and liver function • Damage is irreversible • Age of presentation can be from first day of life to adulthood	• Definite diagnosis of primary hyperammonemia due to a urea cycle defect • Replaces time consuming enzyme analysis • Informs clinical management in the individual situation e.g. arginase deficient patients may need an urgent liver transplant • Allows dietetic management and avoidance of hospital admission due to encephalopathy • Improves cognitive outcome minimising additional support by the local services	• The inheritance pattern would remain unclear. • Unable to advise on recurrent risk or identify appropriate relatives for cascade screening. • Morbidity and even death in patients due to an undiagnosed encephalopathy **• Lack of appropriate surveillance to avoid complications such as recurrent hyperammonemia and neurocognitive decline**
#214	Alport Syndrome 5 Gene Panel Test	**London South East RGC GSTT**	Alport syndrome is an inherited nephritis (kidney condition) that inevitably causes renal failure in young adults associated with nerve deafness and eye problems affecting the lens and the cornea.	**• Kidney biopsy no longer required and associated risks of morbidity and mortality are avoided** • Relatives can be offered predictive testing, carrier testing, prenatal diagnosis (PND) and pre-implantation genetic diagnosis (PGD) **• Early diagnosis and intervention with ACE inhibitors extends renal health by an average of 13 additional years**	• Invasive kidney biopsies would be required with associated risks of morbidity and mortality • The option of prenatal diagnosis or preimplantation genetic diagnosis (PGD) cannot be offered. • Unable to carry out early intervention with ACE inhibitors • Earlier renal failure increasing number of organ transplant
#215	Methymalonic acidemia (MMA) 11 Gene Panel Test	**London South East RGC GSTT**	The presentation can be at any age from newborn to adulthood with intermittent episodes. Neonatal presentation: • Vomiting and lethargy • Encephalopathy associated with raised ammonia and ketones • Invariably leading to death Childhood presentation: • Poor feeding and failure to thrive • Developmental delay and recurrent episodes of vomiting and dehydration Adult presentation: • anorexia and impaired cognitive ability • renal failure, abnormal movements (dystonia) • immune function abnormalities and visual impairment	• Provides a definitive diagnosis • Improves clinical management • Earlier prenatal diagnosis can be offered • Allows earlier diagnosis to enable provision of advice regarding emergency care • Allows dietary manipulation and supportive treatment to be initiated to minimise complications such as liver and renal failure and delay the need for transplantation	• Delayed definitive diagnosis • Carrier testing or prenatal diagnosis could not be offered • Expensive biochemical studies on cultured fibroblasts would be only method offered for diagnosis in adults

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#216	Inherited Ataxias 57 Gene Panel Test	**Oxford RGC**	Inherited ataxias are a highly heterogeneous group of neurological disorders affecting individuals of all age groups. Clinical manifestations: • Poor coordination of movement and a wide-based unsteady gait • Poor coordination of hands, speech and eye movements • Many forms are progressive; others affect children from birth and are lifelong conditions. • The prognosis is variable but all genetic forms are associated with significant disability and in many cases early death.	• Reduction in the delay to diagnosis • Will enable accurate prognosis as this is variable depending on cause • Avoid numerous unnecessary and often costly investigations • Development of therapeutic strategies • Facilitates accurate counselling for recurrence and reproductive risk	• Unnecessary investigations • Delays in molecular diagnosis resulting in uncertainty for the families • Delayed detection and treatment in some conditions. • Carrier or pre-symptomatic testing will not be available.
#217	KBG syndrome (short stature, macrodontia, characteristic facies, skeletal abnormalities and developmental delay	**Bristol RGC**	KBG syndrome is a rare dominant genetic disorder characterized by distinctive features: • Triangular-shaped face, widely-spaced eyes, drooping eyelids and abnormal teeth. • Short stature, curved spine (scoliosis) • Developmental delay, seizures and intellectual disability.	• Provide an accurate diagnosis and determination of whether mutation is inherited • Provide testing to at-risk relatives and allow genetic counselling • Allows focused medical investigations and management • Avoidance of on-going investigations e.g MRI	• Patients remain undiagnosed and associated complications such as curvature of the spine may be missed • Lack of a diagnosis limits access to focused investigations and management • Family unable to make informed reproductive decisions
#221 (RARE)	CHILD syndrome	**Exeter RGC**	CHILD syndrome is a multisystem disorder characterised by: • Unilateral inflammatory, scaly skin and limb defects • Underdevelopment of the brain, lungs and kidneys • Heart defects and calcification of cartilage (seen on X-ray) The disorder is present at birth and is associated with male lethality	• Provides an answer for families that offers a complete explanation for their child's problems • The ability to direct the family towards a specific support group • Provide testing of other at risk family members, and, where applicable, a pre-natal diagnostic test	• Lack of molecular confirmation of diagnosis • Unable to provide testing to at risk family members
#222 (RARE)	Familial hyperphosphatemic tumoral calcinosis (HFTC)	**Exeter RGC**	• Hyperphosphatemic Familial Tumoral Calcinosis (HFTC) **is a severe metabolic disorder characterised by growths (calcifications) occurring mainly around the hip, elbow or shoulder, high serum phosphate level** (hyperphosphatemia) and normal or elevated levels of vitamin D. • Onset is within the first decade of life. **• Growths can be extremely painful and require surgical intervention.**	• Allow a definitive diagnosis and the appropriate early intervention and treatment to be given • Provide early diagnosis allowing earlier treatment to prevent surgical intervention	• Lack of molecular confirmation of diagnosis • Treatment by painful and disabling surgery to remove calcification masses

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#223	Osteopetrosis 21 Gene Panel test	**Bristol RGC**	In osteopetrosis, osteoclast cells responsible for regulating bone formation either cannot be made or fail to function properly. This has devastating consequences for: • Formation of bone marrow cavities • Preventing bone fractures • The health of nerves which pass through holes in the skull **Untreated, two thirds of children with this disease die before the age of 10 years.**	• Allows the different forms of Osteopetrosis to be distinguished in infancy • Informs clinical management and early intervention with HSCT • Patients with forms of Osteopetrosis unsuitable for HSCT may be spared inappropriate and life-threatening therapy. • Parents can also be offered timely genetic counselling and antenatal diagnosis in future pregnancies.	• Poor decisions and inappropriate instances of transplantation will continue • Different forms of Osteopetrosis will be indistinguishable in children • Carrier and antenatal testing will not be offered
#224 (RARE)	Galactosialidosis	**London South East RGC GSTT**	Galactosialidosis is a rare condition affecting many parts of the body including: • Heart, liver and spleen • Eye involvement causing early blindness • Nervous system **The early onset forms of the condition are often life limiting whilst the later onset form may be associated with a normal life expectancy though with significant medical problems.**	• Confirmation of biochemical and clinical diagnosis • Allows carrier testing • Informed reproductive choices • Informs appropriate care and support to the affected individual and family members	• Carrier testing will not be available as unable to determine by biochemical testing • Test will not be offered to consanguineous families to identify those at risk of affected children (and also prenatal diagnosis) • Prenatal diagnosis and pre-implantation genetic diagnosis (PGD) would not be available • It would not be possible to offer carrier testing to other family members • Unnecessary prenatal diagnosis using enzyme assay would be be carried out
#225	GM1 gangliosidosis and mucopolysaccharidosis type IVB	**London South East RGC GSTT**	GM1-gangliosidosis and Mucopolysaccharidosis are two phenotypically distinct recessive disorders caused by deficiency of the enzyme beta-galactosidase GM1-gangliosidosis is associated with neurological decline and has a variable range of onset Mucopolysaccharidosis type IVB is characterized by: • skeletal changes- short stature and skeletal dysplasia • Normal intellect unless there is spinal cord compression leading to central nervous system compromise. Treatment for both disorders is mainly supportive	• Confirmation of biochemical and clinical diagnosis • Allows carrier testing and reproductive choices to be made • Allows health care professionals to provide appropriate care and support to the affected individual and family members	• Carrier testing will not be available as unable to determine by biochemical testing • Test will not be offered to consanguineous families to identify those at risk of affected children (and also prenatal diagnosis) • Prenatal diagnosis and pre-implantation genetic diagnosis (PGD) would not be available • It would not be possible to offer carrier testing to other family members • Unnecessary prenatal diagnosis using enzyme assay will be carried out

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#227	Lysosomal acid lipase deficiency	**London South East RGC GSTT**	Lysosomal acid lipase (LAL) deficiency is a lipid storage disease that can result in:- 1) **An early onset form, Wolman disease that is fatal in the first year of life.** 2) A less severe form, cholesteryl ester storage disease (CESD): • liver disease/failure • increased risk of strokes	• Confirmation of biochemical and clinical diagnosis • Informed reproductive choices • Implementation of supportive therapies to slow disease progress • Treatment with Cholesterol lowering drugs • Liver transplantation in some severe cases. • Provide early diagnosis to inform early management	• Enzyme testing cannot be used to identify carriers of these conditions • Prenatal diagnostic options unavailable • Carrier testing unavailable • Unnecessary prenatal or partner enzyme assays will be performed • Milder, later onset forms of the disorder will not be detected and managed
#228 (RARE)	Neuraminidase deficiency	**London South East RGC GSTT**	The disorder is broadly classified into types 1 and 2. Type 1 is the less severe form and patients present in their teens or twenties: • Gait disturbance • Reduced visual acuity • Sudden involuntary muscle contractions (myoclonus) • Ataxia and leg tremors • Seizures Type 2 is more severe and progressive in nature: • Excessive swelling throughout the body before birth • Abnormal enlargement of the liver and spleen after birth • Abnormal bone development and coarse facial features **Failure to thrive and recurrent respiratory infection and death before the age of one year.**	• Confirmation of biochemical and clinical diagnosis • Allows carrier testing and reproductive choices to be made • Enables appropriate management to be put in place at an earlier stage which will lessen complications and improves prognosis. Treatment is mainly supportive.	• Carrier testing will not be available as unable to determine by biochemical testing • Test will not be offered to consanguineous families to identify those at risk of affected children (and also prenatal diagnosis) • Prenatal diagnosis and pre-implantation genetic diagnosis (PGD) would not be available • It would not be possible to offer carrier testing to other family members • Unnecessary prenatal diagnosis using enzyme assay will be carried out
#229	Pyruvate carboxylase deficiency	**London South East RGC GSTT**	Pyruvate carboxylase deficiency causes developmental delay and failure to thrive starting in the neonatal or early infantile period. The disorder is generally classified into three types with the only common feature of metabolic acidosis. Type A (infantile form) : • Infantile with a severe course Type B: • Very severe course with a fatal outcome in early infancy Type C: • Episodic metabolic acidosis, without any neurologic symptoms.	• Enables accurate identification of carriers facilitating cascade screening • Offers informed reproductive choices • Supportive treatment (pharmacologic and dietary supplementations) can be offered to prevent any secondary complications.	• Enzyme analysis in cultured cells is the only method available • Carrier testing will not be available • Prenatal diagnosis cannot be offered

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#234	Paediatric Cardiomyopathy 73 Gene Panel Test	**Bristol RGC**	Paediatric cardiomyopathy is a heterogeneous group of disorder: • Chronic and sometimes progressive • Heart muscle becomes abnormally enlarged, stretched, thickened or stiffened • Irregular heartbeats and heart failure may occur. **One-third of children with a cardiomyopathy will die or require transplantation.**	• Enables accurate rapid genetic diagnosis • Aids decisions about treatment management and prognosis • Provides advice for family members regarding reproductive risks and clinical screening • Identifies non-risk relatives that can be discharged from cardiac screening • Prenatal diagnosis can be offered	• Delayed diagnosis with sequential clinical, metabolic, biopsy and genetic testing. • Family members (parents and siblings) would require clinical cardiac screening by ECG, ECHO potentially on a recurrent basis. • Unable to offer test to family members • Family will not be able to make informed reproductive decisions
#236	Neurogenetic Disorders 95 Gene Panel Test	**Sheffield RGC**	**ATAXIA:** **A group of progressive neurological disorders affecting balance, coordination, and speech. Some forms of ataxia are treatable.** **HEMIPLEGIC MIGRAINE (HM)** • A rare form of migraine: • Perceptual disturbance (aura) • Motor aura (weakness) • Speech difficulties • Head pain **HEREDITARY SPASTIC PARAPLEGIA (HSP):** A group of inherited progressive disorders that cause weakness and stiffness of the leg muscles, due to deterioration of spinal nerves which control voluntary movement. **AMYOTROPHIC LATERAL SCLEROSIS (ALS) / FRONTOTEMPORAL DEMENTIA (FTD)** ALS, also known as Motor Neurone Disease (MND) is a progressive disease that attacks the motor neurones, or nerves, in the brain and spinal cord. **DYSTONIA**: A neurological movement disorder involving uncontrollable and sometimes painful muscle spasms caused by incorrect signals from the brain.	• Allows a definitive diagnosis • Allows treatment to be offered e.g. Familial isolated vitamin E deficiency (ataxia) can be treated with vitamin E supplements and a specialised diet • Allows determination of the mode of inheritance clarifying risk to other family member • Long-term care plans can be initiated • Allows the option of prenatal diagnosis if required. • Expensive neuroimaging will no longer be required • Biochemical testing may longer required where appropriate	• Unable to provide a definitive diagnosis • Costly or invasive means of diagnosis will continue to be carried out: o neuroimaging o biopsy and lumbar puncture. • Prognosis of condition will not be clarified • Prenatal diagnosis and carrier testing will not be offered
#239	Congenital Anaemia 33 Gene Panel Test	**Oxford Haemoglobinopathy**	A group of rare disorders which can be extremely severe usually manifesting at birth resulting from: • Either intrinsic defect in the way red blood cells develop in the bone marrow • Or due to deficiencies in the enzymes critical for mature red blood cells maintenance Children are transfusion dependent for life, which carries serious health risks of iron overload and heart failure.	• Allows a definitive diagnosis to be made • Reduces anxiety for parents and patient • Allows patient to be treated with the appropriate therapy for their condition if availlable eg IFN-a for CDA-1 • Allows carrier status testing, appropriate genetic counselling and prenatal diagnosis.	• Delayed diagnosis through sequential testing of some of genes at different centres • Novel variants in a patients presenting with an atypical phenotype may be overlooked • Anxiety due to difficulty making decisions regarding further children • Lack of access to specific therapies in some cases • Carrier testing and prenatal diagnosis could not be offered

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#240	Iron Regulatory 16 Gene Panel Test	**Oxford Haemoglobinopathy**	A group of disorders with disrupted systemic iron regulation leading to pathological conditions: • Iron deficiency or defective iron trafficking (anaemia) • Iron overload can affect many organs leading to multi system disease (haemochromatosis). • Misregulation of cellular iron metabolism • Brain iron overload in neurodegenerative disorders. **These various diseases of iron metabolism can generate both significant morbidity and mortality**.	• A definitive diagnosis enables disease and subtype confirmation • Allows initiation of appropriate management • Facilitates carrier testing in other at risk family members especially where there is consanguity. • Reduces long term complications of iron overload and associated costs • Allows determination of digenic inheritance in patients with severe or early onset haemochromatosis to enable earlier treatment	• A definitive diagnosis will not be provided • Carrier testing will not be available • Genetic counselling and advice cannot be provided • Appropriate surveillance will not be available • Long term complications from iron overload will not be reduced
#242 (Resub from last year #155) **(RARE)**	HYPEREKPLEXIA, HEREDITARY 1; HKPX1 HYPEREKPLEXIA 3; HKPX3 HYPEREKPLEXIA 2; HKPX2	**Cardiff RGC**	Hyperkplexia is a rare disorder that is most severe in early life and is characterised by: • Susceptibility to environmental triggers such as noise, touching and visual stimuli • Abnormal tone (typically their trunk and limbs are stiff) • Startling with a stimulus can prolong an attack where patient becomes 'stiff as a board' • In the more severe cases there are recurrent infantile apnoea attacks and a spectrum of learning disability that includes intellectual disability in more severe cases Medication is partially helpful in most and very helpful in some	• Allow correct management of the condition with the appropriate medication (benzodiazapines) • Prevent the use of unnecessary and ineffective medications • Prevent patient from being subjected to unnecessary clinical tests (Repeated EEG/ MRI under general anaesthetic) • Allow focused education to enable management of repeated and frequent neonatal apnoeas • Allows access any additional support from local services. • Allows prognosis prediction • Allows targeted genetic counselling and testing for families. • Allows parents to meet and provide peer support at patient support groups	• A number of clinical tests will be done to exclude other potential diagnoses without reaching a definitive answer • Families are left in limbo and unable to access local services • Misdiagnosis could lead to prolonged exposure to inappropriate medications and impact on lifestyle • Prognosis will not be predictable • Carrier testing will not be available
#250	Early Infantile Epileptic Encephalopathy (EIEE) 45 Gene Panel Test	**London North East RGC GOSH**	The early infantile epileptic encephalopathies (EIEE) are a group of disorders characterised by **early onset seizures and developmental delay.** • **Many are associated with intractable seizures, severe developmental delay and need for lifelong care.** • Early mortality is common in severe forms due to seizures and/or respiratory tract infections.	• Allows a definitive diagnosis of this heterogenous group of disorders. • Informs medical management e.g. tailoring of antiepileptic regimens in individuals with SCN1A mutations or the introduction of early preventative physiotherapy for lower limb spasticity in patients with SLC9A6 mutations • Allows accurate assessment of recurrence risk so families may consider prenatal diagnosis/Preimplantation genetic diagnosis • Reduced cost of diagnostic investigations. e.g. extensive neurometabolic investigations (including blood, urine, skin, muscle and CSF specimens)	**Lack of availability of a diagnosis:** • Ongoing parental anxiety in the absence of a specific diagnosis • Lack of accurate genetic counselling • Unnecessary diagnostic investigations would continue • Appropriate counselling, family testing and prenatal diagnosis may not be made available.

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#251	Cancer 83 Gene Panel Test	**Leeds RGC**	Characteristics of hereditary cancers include: • Most are autosomal dominant, first-degree relatives are at 50% risk • Earlier age of onset multiple primary cancers in an individual, • Clustering of rare cancers, • Those that do not have the familial mutation have the general population risk for cancer.	• Provides an earlier diagnosis as many genes analysed in parallel • Allows diagnosis by analysis of genes not highly targeted to a particular cancer phenotype • **The cost of the package of genes is significantly cheaper than the total cost of testing individual genes, or small groups of genes in a stepwise approach** • Allows investigation of potentially multiple genetic explanations for a family history of suspicious of a cancer/tumour syndrome. • Allows identification of germ line mutations facilitating risk assessment in patients and relatives • Will allow better targeted cancer screening, and/or risk-reducing strategies. • Family members undergoing a negative predictive test may be spared additional screening e.g colonoscopy and examination or MRI scan	• Patients and family members would continue to be offered tests which are highly targeted to particular cancer phenotypes, but likely to miss important genetic diagnoses • Some patients would continue to be offered sequential testing of different genes, leading to delays in completion of testing, increased costs and anxiety • An accurate genetic basis for a potential hereditary cancer may not be defined
#253	Cardiac 67 Gene Panel Test	**Manchester RGC**	**Sudden cardiac death (SCD) is a natural death from cardiac causes heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms.** **Drug treatment for sudden cardiac death has improved over the years, and implantable cardiac defibrillators can be extremely effective in at risk individuals.**	**Cardiac gene testing should be performed on all children and young adults that suffer a SCD or resuscitation from unexplained cardiac arrest (Heart 2008;94;502-507).** • Allows a rapid genetic diagnosis to be made • Allows a definitive diagnosis by molecular autopsy in individuals (<40 years) that do not have a pathologic diagnosis at the time of SCD • Informs clinical management e.g. Fabry's disease as alters recurrence risk as X-linked recessive condition and clinical assessment of other potentially involved organ systems • Assessment for enzyme replacement therapy • Allowed accurate cascade testing of at risk family members within the family • Allows removal of clinical interventions not required e.g. Removal of an ICD from a previously at risk individual who was shown not to carry the familial mutation for SCN5A in Long QT with consequent cost savings	• Where no cause of a SCD is determined there is uncertainty and lack of an explanation for the devastating clinical event in the family with significant psychological sequelae. • Accurate risk estimation and cardiac screening and treatment in at risk first degree relatives is not possible • Definitive cascade screening in at risk family members not feasible
GENE DOSSIERS SUBMITTED AND RECOMMENDED FOR HIGHLY SPECIALISED SERVICES (PREVIOUSLY NSCT) FUNDING					
#189	Bardet-Biedl Syndrome 13 Gene Panel Test	**London North East RGC GOSH**	Bardet-Biedl syndrome (BBS) is multisystem disorder comprising polydactyly (extra digits on the hands or feet), obesity, learning and behavioural difficulties, genital abnormalities, blindness and kidney abnormalities. • **Visual problems tend to develop in childhood with the majority of patients being registered legally blind by the age of 20.** • Kidney abnormalities can **be structural or functional and in addition to obesity are the largest cause of morbidity and mortality in patients with BBS**	• Provides a definitive diagnosis in patients who may have had features for years • Emerging genotype-phenotype correlations in the patient allows clinicians to provide a more accurate prognosis • A molecular diagnosis in the family will also allow for prenatal diagnosis if required	• Prenatal diagnosis or Preimplantation genetic diagnosis would not be possible • Appropriate surveillance for known complications would not be possible

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Evaluation number as assigned during the process	Test Name	Laboratory	Disease description	Utility of test in the NHS	Consequences of not testing
#195 (PART)	Connective Tissue Disorders 67 Gene Panel Test	**Sheffield RGC**	• Connective tissue support organs and other parts of the body and can be described as the 'biological glue' that gives tissues form and strength, as well as helping them function **• Connective tissue disorders can be multisystem disorders often affecting bones, muscles, and skin although organs such as the eyes, heart, lungs, kidneys, brain, gastrointestinal tract, and blood vessels can also be involved.** • Symptoms of a connective tissue disorder can include bone growth problems leading to deformity and brittle bones, skin symptoms including poor wound healing, kidney disease, brain lesions, and weak blood vessels that can easily rupture. • These disorders can be severely disabling with pain and impaired mobility. **• In severe cases connective tissue disorders are life threatening and can lead to death shortly after birth.**	**General:** • Accurate diagnosis allowing appropriate, effective treatment and improved surveillance • Identification and counselling of at risk relatives • First trimester prenatal diagnosis made possible **The availability of a panel test will result in a significant cost saving due to the removal of the need for sequential gene testing, biochemistry and possible need for skin/kidney/muscle/bone biopsy and will facilitate much quicker diagnosis for the patient.** **Alport** • Enables appropriate relatives to be identified who wish to act as a living kidney donor **Collagen VI - related myopathy** • Provides information on whether cardiac screening is required. **Cutis Laxa** • Patients can be appropriately managed according to the organ systems affected in that type if mutation is defined • Presymptomatic testing to identify individuals at risk for cardiovascular and pulmonary disease is made available. **EDS** Some subtypes have a risk of sudden death and these patients need appropriate monitoring. The confirmation of a subtype with no life threatening features means that further investigations and particularly expensive cardiovascular monitoring are not required. **COL4A1-related disorders** • Allows differentiation of familial porencephaly from alternate causes to inform pregnancy management and recurrence risk • e.g. Allows Cesarean delivery of fetuses at risk for a COL4A1-related disorder to prevent brain vascular injury • Anticoagulant usage can be avoided **FTAA** •Diagnosis of these conditions will allow for prompt appropriate and potentially life-saving treatment. •Non-invasive screening for sites of arterial aneurysm may reduce morbidity and mortality. •For some patients elective surgery may be discouraged due to increased tissue fragility resulting in a high risk of surgical complications. •Allows pregnancy to be managed in a high risk obstetric program. **Osteogenesis Imperfecta** • Late prenatal testing is sometimes requested for delivery management. • Molecular diagnosis also allows rapid predictive analysis of the newborn (2 weeks) and reduced parental anxiety. OI is one of the rare genetic conditions where there is treatment available in the form of bisphosphonates which has dramatically changed **Stickler:** Allows appropriate follow up e.g. annual examination by a vitreoretinal specialist.	**General:** • Can be difficult to assess potential clinical outcome and therefore develop appropriate monitoring and/or management plans, leading to poorer outcome. • Lack of accurate identification of the mode of inheritance would not allow appropriate counselling of at risk family members and carrier, presymptomatic and prenatal testing is not possible. • Unable to determine recurrence risk in some of these conditions **Alports syndrome:** • Unable to identify relatives for live kidney donation. **Collagen 4A1-related disorders:** • Patients with myopathy would not be differentiated into subtype Unnecessary cardiac screening might occur **Cutis Laxa and EDS** Under or over management would be likely **Collagen IV-related disorders**: Pregnancies might not be managed correctly. **FTAA:** Appropriate organisation of elective surgery may not be possible. The need for referral to high risk obstetric program may not be identified. **OI:** Lack of precise form of OI hampers prediction of treatment outcomes, especially for patients with milder form of the condition. **Stickler Syndrome** • Unable to advise on possibility of severe eye phenotype • Unnecessary investigations will continue
#198 (PART)	GSD 32 Gene Panel	**Sheffield RGC**	Glycogen storage diseases mainly affect the liver and/or muscles, and can range from severe liver, muscle and heart disease that require frequent feeding and liver transplantation, to mild symptoms, requiring only minor dietary changes.	• Allows accurate molecular genetic diagnosis of the to inform management • Allows definitive and rapid carrier, predictive, perinatal, prenatal or preimplantation testing fto be done • Result in a significant cost saving due to the removal of the need for sequential gene testing, enzymology and possible associated need for tissue biopsy leading to a more rapid diagnosis. • Detection of the correct sub-type of GSD will alter the management of the patient by dietary modifications and other interventions. • Will clarify the inheritance pattern and determine associated recurrence risks	• Investigations including a possible tissue (muscle, liver, skin) biopsy would continue to be done which is distressing • Delayed diagnosis • Misdiagnosis leading to sub-optimal treatment of the underlying metabolic disorder. • Sub-optimal management of therapy, as a result of an incorrect or non-specific diagnosis, may result in a poorer prognosis.
#199 (RARE)	CEROID LIPOFUSCINOSIS, NEURONAL, 7; CLN7	**London North East RGC GOSH**	CLN7 is one of several genetically heterogeneous neurodegenerative disorders known as neuronal ceroid-lipofuscinoses (NCL) / Batten disease. **• The clinical course includes progressive intellectual and motor deterioration, seizures, and early death** • Visual loss is a feature of most forms • The NCLs are the most common childhood onset neurodegenerative disorders and are currently incurable • CLN7 mutations cause a variant form of NCL, which is usually late-infantile in onset and can be life-limiting	• No effective treatment is currently available for CLN7 although confirmation of diagnosis may give an indication of prognosis • Testing is predominantly to confirm the diagnosis and determine which gene is involved for future prenatal diagnosis (or PGD) in the family and carrier testing of other family members • Confirmation of a diagnosis may give an indication of prognosis • Carrier testing for the common mutation could be offered to partners of carriers within the Roma population	• In the absence of a test the affected individual may undergo repeated clinical investigations to establish a diagnosis • Prenatal diagnosis (and PGD) would not be available for parents of affected children and carrier testing of other adult relatives would not be available

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#205	CRANIOSYNOSTOSIS AND DENTAL ANOMALIES; CRSDA	**Oxford RGC**	This disorder is characterized by: • Craniosynostosis (premature fusion of the growth plates of the skull) Maxillary hypoplasia (under-development of the upper jaw) and dental anomalies • Some patients also display minor digit anomalies	• Enable appropriate genetic counselling and prenatal testing to be offered • Planned monitoring of patient for dental anomalies • Further molecular analysis no longer required	• Unable to provide definite diagnosis and accurate genetic counselling • Unable to offer prenatal diagnosis
#206 (PART)	Primary Immune Deficiencies 72 Gene Panel Test (part HSS)	**London North East RGC GOSH**	Primary immunodeficiency (PID) is a group of genetic disorders in which part or all of the immune system is missing or non-functional. **Patients with PID are effectively left defenceless against dangerous, life-threatening pathogens**, in addition to normal infections that could affect everyone. This creates a pattern of repeated infections, severe infections and/or infections that are unusually hard to cure. Depending on the type, these infections may attack the skin, respiratory system, the ears, the brain or spinal cord, or the urinary or gastrointestinal tracts.	Test will enable rapid diagnosis and optimal treatment & therapy for patients. The test will enable carrier screening for adult relatives, PGD if requested and early diagnosis of family members. By knowing the underlying genetic defect, patients can be o Appropriately referred for haematopoietic stem cell transplant (HSCT) (e.g. patients with confirmed haemophagocytic lymphohistiocytosis (HLH) will undergo HSCT whereas if they have secondary HLH, HSCT is not appropriate. o Appropriate conditioning prior to HSCT (T cell only, myeloid, etc.) o Appropriate chemotherapy treatment as (e.g. DNA ligase IV patients are very susceptible to alkylation agents). **Family donors for HSCT can be screened to ensure that an affected family member is not used as a HSCT donor.** **Knowing the genetic diagnosis is a requirement for gene therapy. Gene therapy is offered for 4 of the conditions tested in the PID panel.** **Early diagnosis results in reduced hospital stays, lower morbidity and lower mortality**	• Inappropriate chemotherapy may be given resulting in increased morbidity and mortality • Gene therapy cannot be provided genetic defect unknown • A transplant might be undertaken inappropriately • PGD, prenatal screening and carrier testing could not be offered
#248 (RARE) (PART)	Short Syndrome	**Cambridge RGC**	SHORT syndrome describes combination of moderate short stature, characteristically abnormal facial appearance, with deep set eyes and a relatively small jaw, and other features including developmental anomalies in the front part of the eye, hyperextensible joints, delayed teething, and impaired development of adipose tissue. **Many patients have severe resistance to insulin, with a high risk of diabetes.**	• Provides a definitive diagnosis • Allows precise prediction of recurrence in children, and family-based testing • Allows surveillance for clinical features such as iridal abnormalities, glaucoma, severe insulin resistance and diabetes mellitus • Savings will arise from abolishing the need for further genetic or endocrine testing	• Patient is unlikely to receive the best specialist management as the disease is very rare • Family members will not be assessed and diagnosed promptly • Patients may also experience substantial psychological distress as a result of misdiagnosis and mismanagement which frequently occurs without a specific diagnosis.
NON-INVASIVE PRENATAL DIAGNOSIS (NIPD) - FOR NEW CONDITIONS					
#191 (NIPD)	Cystic Fibrosis; CF	**London North East RGC GOSH**	Cystic Fibrosis (CF) is a complex multisystem disease affecting: • Epithelia of the respiratory tract • Exocrine pancreas • Intestine • Male genital tract, • Hepatobiliary system • Exocrine sweat glands Pulmonary disease is the major cause of morbidity and mortality in CF: • Reduced life expectancy of around 35 years.	• Offer a safe non-invasive DNA test from as early as 9 weeks gestation to families where the paternal mutation is known to be different to the maternal mutation • Reduced risk of miscarriage as non-invasive • Diagnosis at this stage of pregnancy allows women to undergo surgical termination of pregnancy if they wish. • Enable planning and preparation for the birth of an affected child. • Allow early paediatric intervention which is thought to improve longer term prognosis.	All pregnant couples at-risk of having a CF child could only be offered an invasive procedure with the associated risk of miscarriage

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#200 (NIPD)	Apert syndrome- using cell free fetal DNA (cffDNA) for non-invasive prenatal diagnosis (NIPD) for 2 common FGFR2 mutations.	**London North East RGC GOSH**	Apert syndrome is severe disorder characterised by: • Cleft palate • Severe eye problems (e.g. crossed eyes, drooping eyelids) • Fusion of upper and lower arm bones and restricted elbow movement • Abnormal fusion of the bones of the hands and feet • Intellectual disability • Heart, gastrointestinal, or urinary system problems • Fused cervical vertebrae. Presentation of symptoms depends on type of mutation in causative gene.	• Women with an at risk pregnancy can be offered a safe non-invasive DNA test from as early as 9 weeks gestation • Provides a definitive diagnosis without miscarriage risk • Allows accurate prenatal counselling and avoidance of inappropriate interventions. • Allows definitive diagnosis without jeopardising the safety of the normal fetus in a multiple pregnancy • Offers a test with improved sensitivity as covers known mutations	All pregnant couples at-risk of having an Apert child could only be offered an invasive procedure with the associated risk of miscarriage.