NNAG National Neurosciences Advisory Group

THE NEUROLOGICAL ALLIANCE

Association of British Neurologists

Optimal clinical pathway for adults: Neurogenetics

National Neurosciences Advisory Group (NNAG)

Published: November 2023

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Overview: About the optimal pathway

This pathway is part of a suite of optimal neuroscience clinical pathways that have been developed by the neurological community, with the support of NHS England and the National Neurosciences Advisory Group (NNAG).

The development of this pathway was overseen by NNAG, with input from professional bodies and patient organisations. A 6 week public consultation was held to gather input, views and experience from people affected by neurological conditions and wider stakeholders.

The pathways set out what good treatment, care and support looks like. This includes treatment and support for people who may be experiencing the first symptoms of a neurological condition, right through to people who have lived with a condition for a long time. They set out the aspirations for good care, support improvement of services and enable commissioning of quality services, locally and nationally.

Optimal Clinical Neuroscience Pathways

NEUROSCIENCE

- SUBARACHNOID/INTRACRANIAL HAEMMORHAGE
- PITUITARY TUMOUR
- BRAIN TUMOURS
- MULTIPLE SCLEROSIS (MS)
- EPILEPSY
- AUTOIMMUNE
- HEADACHE & FACIAL PAIN
- NEUROMUSCULAR CONDITIONS
- MOVEMENT DISORDERS
- MOTOR NEURONE DISEASE (MND)
- FUNCTIONAL NEUROLOGICAL DISORDER (FND)
- TRAUMATIC BRAIN INJURY (TBI)

CROSS-CUTTING

- TRANSITION FROM CHILDREN TO ADULT SERVICES
- NEUROGENETICS
- MENTAL HEALTH
- REHABILITATION

FIND OUT MORE

Optimal clinical pathways and resources (NHS England and NHS Improvement. NHS log in required): www.future.nhs.uk/about

FutureNHS

VISIT WEBSITE

Optimal clinical pathways and resources (NNAG): www.nnag.org.uk/optimum-clinical-pathways

NNAG National Neurosciences Advisory Group

VISIT WEBSITE

Neurological patient organisation websites & resources (Neurological Alliance): www.neural.org.uk/membership/our-members

THE NEUROLOGICAL ALLIANCE

VISIT WEBSITE

Genomic medicine

- Genomics has been identified as a priority in the NHS Long Term Plan the NHS People Plan (2019) and the Topol Review (2019)

- Neurology has the largest number of adult-onset genetic conditions when compared to other specialties

- Emphasis is now on mainstreaming provision of genomics throughout the NHS:
  - NHS Genomic Medicine Service (GMS) established in 2018, integrating genomic testing and clinical services (see next page for infrastructure overview)
  - Seven NHS Genomic Laboratory Hubs (GLHs) delivering genomic testing, analysis and interpretation
  - Seven NHS GMS Alliances, established in 2020, providing multidisciplinary clinical leadership to embed genomics across pathways
  - Genomic tests commissioned by NHS England set out in National Genomic Test Directory (see following slide)
  - NHS GMS collaboration with Health Education England to support workforce development, training and education
  - Aim to mainstream genomic testing into routine clinical practice and ensure equity of access for patients

NHS genomic medicine service

Overarching aim

To enable the NHS to harness the power of genomic technology and scientific advances to improve population health and patient outcomes

7 NHS GMS Alliances to provide multidisciplinary clinical leadership to embed genomic medicine across end-to-end pathways

1. **Patient is referred for genomic testing by 'mainstream' clinicians or clinical genetics service**
2. **7 NHS Genomic Laboratory hubs perform genomic testing, analysis and interpretation and feed back results to clinicians**
3. **Genomics England National Genomic Research Library – consented patient data currently for WGS**

*Currenting updating the clinical genomics service specification

Clinical Genomics Services support complex care and other clinical teams. Input into genomic MDTS

Informed by the National Genomic Test Directory that covers full repertoire of genomic testing

- **National provision for WGS testing**
- **WGS bioinformatics**
- **Underpinning informatics platform via Genomics England**

Enables ongoing research and discovery from approved researchers, academia and industry

NHS GMS Research Collaborative

Facilitate and scale genomic research in the NHS

Collaboration with NHS England to support workforce development, training and education

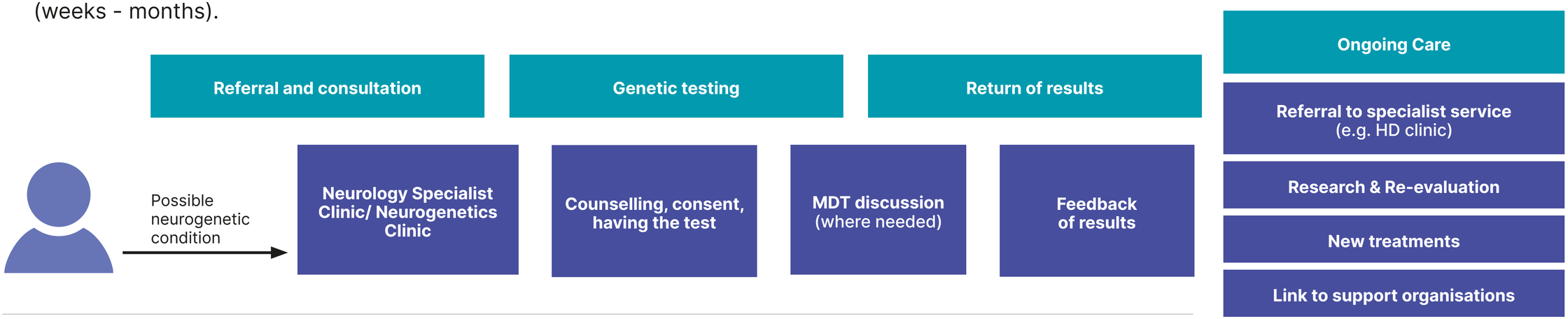
Key principles

- Be **clinically and scientifically led**
- Have **patients and public involved** at all levels
- Ensure **equity of access** for all patients
- To enable rapid access to **precision and targeted treatments**
- Have a **standardised** model of delivery and commissioning across the country
- **Be responsive** to innovation and new technologies
- Inform and drive change using **data led insights**

GMS Genomic Medicine Service **MDTS** Multi-disciplinary teams **WGS** Whole genome sequencing

Overarching principles

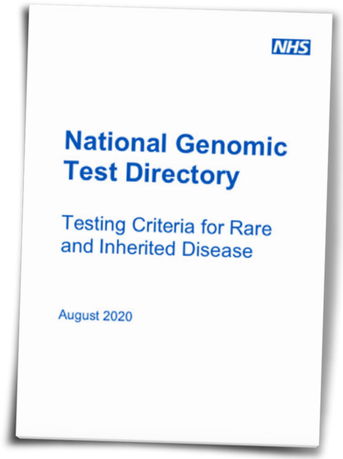
- Diagnostic testing for genetic conditions should be undertaken in by clinicians in neurology/ neurogenetics/ psychiatry clinics who have the appropriate knowledge and training.
- For more common neurogenetic conditions e.g. CMT1A, HNPP, CADASIL, particularly where whole genome sequencing is not required, and the phenotype is clear, clinicians should consider requesting genetic tests rather than simply referring straight to a specialist service for diagnostic testing.
- Appropriate time should be allocated in clinics for consenting patients, and attendance at relevant MDTs should be job planned and renumerated.
- Predictive testing should be undertaken by clinical genetics services.
- Patients should be counselled as to potential implications of test results for themselves, family members and likely time to receiving result (weeks - months).
- Consent for genetic testing and enrolling in the National Genomic Research Library should be documented in the medical notes.
- Support for consenting patients should be provided e.g. through recruitment of genetic counsellors/ specialist nurses/ genomic practitioners, and development of video-consenting clinics.
- Where whole genomic sequencing is undertaken, record of discussion forms need to be completed and uploaded as part of the patient record.
- Clinicians requesting tests should have access to a multi-disciplinary MDT where test results can be discussed with neurogenetics specialists, laboratory scientists and bioinformatics experts.
- The National Genomics Research Library and enhanced bioinformatics expertise should foster research and development on a local and national scale to improve diagnosis and treatment of genetic conditions.



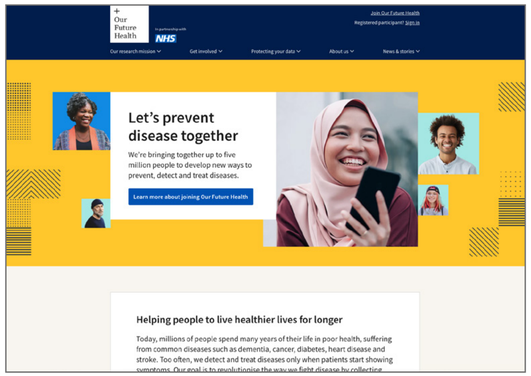
HD Huntington's disease **MDT** multi-disciplinary team

Ordering genomic tests

- The National Genomic Test Directory specifies which genomic tests are commissioned by NHS England, and the technology used for these tests, and through eligibility criteria outlines which patients should be tested.



- Where appropriate chromosomal tests (microarray/ karyotype) should be considered in addition to single gene/ panel tests and whole genome sequencing.
- There is an annual review process for the Test Directory: anyone can submit a proposal for an update to be made, including for new clinical indications or changes to existing clinical indications.
- Where multiple genes are tested via a panel, the online NHS GMS PanelApp tool can be used for information about specific genes included in panel.
- The local NHS GLH should be contacted in case of queries regarding tests.
- Testing for polygenic conditions where there is an interaction between multiple genes and environmental factors such as trauma, diet, and exercise is not possible in current NHS pathways. However, this is a rapidly changing field, and new tests are likely to be available in future, particularly following completion of the national 'Our Future Health' research programme'.



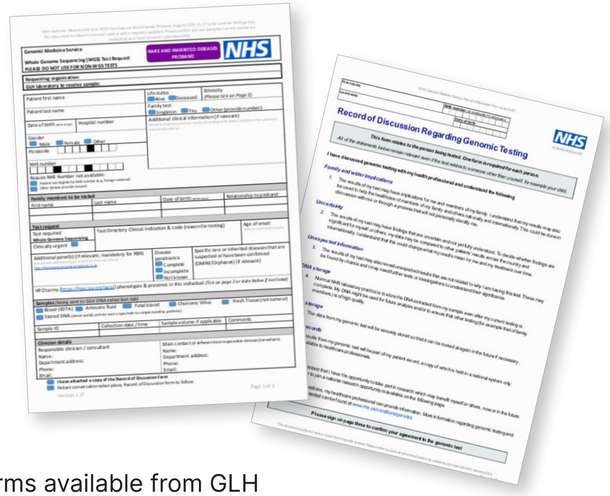
GLH Genomic Laboratory Hub **GMS** Genomic Medicine Service

Whole genome sequencing

Introduced to NHS in England in 2020 (Phase 1).
Phase 2 clinical indications introduced April 2022.

See National Genomic Test Directory for current Neurology conditions eligible for WGS

Note: WGS for specific conditions undertaken as ‘virtual panels’ applied to sequenced DNA for the relevant clinical indication. Variants for unrelated conditions are not looked for or returned.

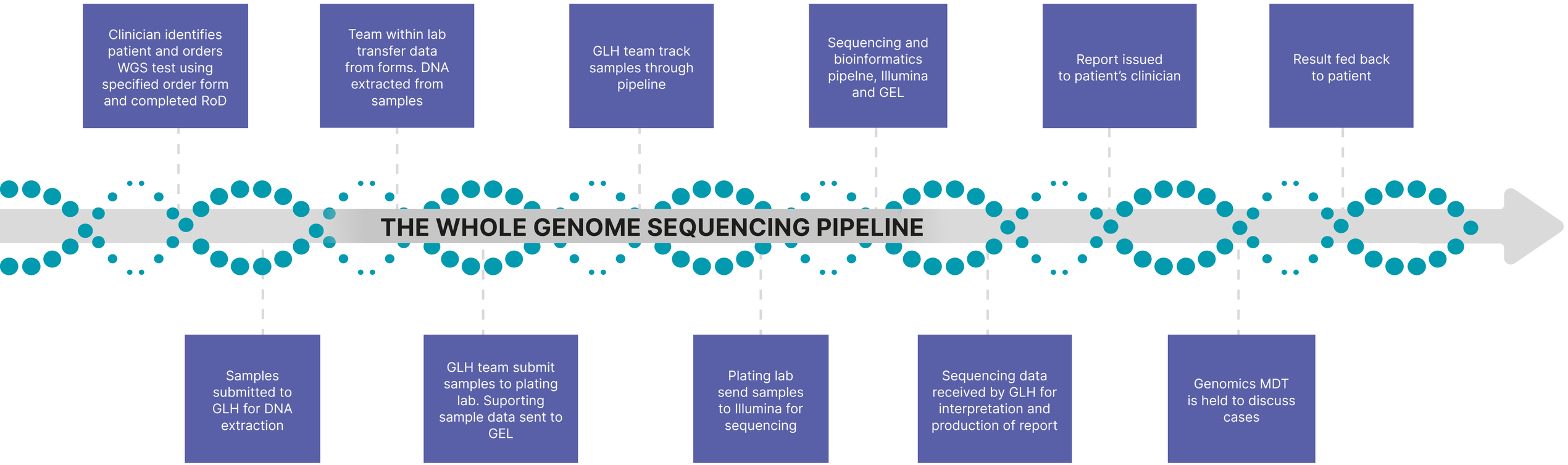


* forms available from GLH Clinical Leads for Neurogenetics

	Responsibilities: Clinicians in Neurology	Responsibilities: Local Genomic Laboratory Hub
■ Pre-test	Confirm eligibility, patient choice discussion, counselling Where necessary, refer to Genomics England PanelApp website to ensure the correct test or panel for the condition is selected	
■ Ordering	For proband and family members, send off: ■ Germline DNA (2-5mls EDTA) ■ Test order form* ■ Record of Discussion Form* ■ Clinical consent for WGS ■ Research consent to donate genomic and medical data to National Genomic Research Library	Transcribe test order form into NGIS, confirm RoD
■ Form completion Dx & HPO terms	incomplete information may affect interpretation. Aim for 3-6+ HPO terms. Discussion with Neurogenetics MDT/ clinical lead where support needed with test selection	Transcribe into NGIS
■ Results	Discuss at Neurogenetics MDT in case of queries Disclose results to patient	Analysis and reporting
■ Post-results	Refer to Genetics if indicated (eg predictive testing for family members) Links to research trials	

GLH Genomic Laboratory HubsHPO: Human Phenotype Ontology **MDT** Multi-Disciplinary Team **NGIS** National Genomic Information System **RoD** Record of discussion **WGS** Whole genome sequencing

Whole genome sequencing



GEL Genomics England **GLH** Genomic Laboratory Hub **RoD** record of discussion **WGS** Whole genome sequencing

Genomic testing across neurology and neurosurgery pathways

	PATHWAY	EXAMPLES OF CONDITIONS FOR WHICH GENETIC TESTING MAY BE APPROPRIATE	IMPLICATIONS FOR CURRENT AND FUTURE SERVICE DEVELOPMENT
Neurology	Epilepsy	• Clinical features in keeping with specific epilepsy syndromes • Childhood and infantile onset epilepsy • Syndromic epilepsy with autism/ learning disability	• Development of transition clinics • Jiong diagnostic review clinics /MDT with clinic genetics • Access to appropriate medications (eg for Dravet syndrome)
	Headache	• CADASIL/CARASIL • Familial Hemiplegic Migraine	• Review of cases in neuroradiology MDT • Access to leukodystrophy MDT/ Clinic
	Movement disorders	• Hereditary Ataxia • Huntington's Disease & other choreiform disorders • Young onset Parkinson's Disease	• Tertiary Movement Disorders clinics with neurogenetics expertise • Access to specialised commissioned clinics for new treatments such as ASO therapies
	MND and Neuromuscular	• FTD-ALS • Myotonic/Muscular dystrophy • Distal myopathies • Hereditary spastic paraplegia	• Nurse specialists in MND and Muscular dystrophies • Joint clinics with cardiac/respiratory specialists • Access to specialised commissioned clinics for new treatments such as ASO therapies (SMA)
	Dementia	• Frontotemporal dementia • Genetic prion diseases • Familial Alzheimer's Disease	• Nurse specialists in young onset / familial dementia • Access to disease modifying therapies • Tertiary MDT dementia clinics with genetics expertise • Access to testing for psychiatrists with appropriate skills
	Acute Neurology and Stroke	• Fabry's disease • MELAS • CADASIL/ CARASIL • Homocystinuria	• Neuroradiology MDT review of cases • Links with cardiology services where appropriate
	Neuro-developmental	• Intellectual disability • Congenital malformation /dysmorphic syndromes • Neuroprogressive conditions	• Access to research clinics for patients with no diagnosis • Link with metabolic services • Review at transition to adult services
Neurosurgery	Brain tumours	• Tuberous sclerosis • Neurofibromatosis • Von-Hippel Lindau • **overlap with oncology and tumour genetics	• Neuro-oncology MDT with links to neurogeneticists /oncologists with genetics expertise
	Intracerebral haemmorhage	• Familial Multiple Cavernomas • Collagen Type IV vasculopathy • Hereditary Amyloid Angiopathy	• Neuro-radiology MDT discussion • Links with neurogenetics /neurosurgery specialists with genetics expertise

Equitable access to genomic testing
Education and training of healthcare staff in line with mainstreaming

Epilepsy case study

Claire had a history of epilepsy since her early teenage years, as well as some difficulties with coordination and sports at school. Her condition deteriorated at the age of 29, following the birth of her son. She was seen by several neurologists over the course of the next few years who noted her ataxia and myoclonus. MRI imaging showed atrophy of the cerebellum. Blood tests did not show any reversible cause for her ataxia.

In view of her history of epilepsy, myoclonic jerks and ataxia, a diagnosis of a progressive myoclonic epilepsy (Ramsay Hunt Syndrome) was made. She tried several antiseizure medications, including Phenytoin, Valproate and Clonazepam. Whilst her epilepsy remained stable, there was limited improvement in her myoclonus, and her gait continued to deteriorate.

Claire was re-reviewed in 2019, at the age of 61. By this time, she was requiring the use of a wheelchair. Examination revealed cerebellar ataxia; her gait was wide based, and she could manage only a few unsteady steps. There was a bilateral upper limb cerebellar tremor present. Reflexes were preserved with no signs of spasticity. Her cognition was intact. Repeat MRI Brain showed unchanged appearances of the cerebellar atrophy. Her myoclonus was not well controlled, and she required full assistance with activities of daily living. She also felt that the combination of the Clonzepam and Valproate, whilst helping to control her symptoms, made her feel quite tired.

On review of the family history, Claire reported that her sister, Mary, was also affected with epilepsy and walking difficulties, for which no cause had been identified. Neither parent, or any other family members, had similar symptoms. At this stage, she was referred to a neurogenetics clinic.

Following review in the neurogenetics clinic, Claire consented for whole genome sequencing for early onset and syndromic epilepsy (panel R59). This confirmed that she was heterozygous for two variants in the CO8QA gene. Biallelic pathogenic variants in COQ8 are associated with primary coenzyme Q10 deficiency. This is an autosomal recessive cerebellar ataxia with mitochondrial respiratory chain dysfunction. Affected individuals typically present with early onset exercise intolerance, progressive cerebellar ataxia. The phenotype is variable and patients may also have developmental regression, myoclonus and seizures. Treatment with Ubidecarenone (a coenzyme Q10 supplement) can, in some cases, be very effective in ameliorating symptoms.

Undergoing genetic testing was life changing for Claire; not only did she have a clear diagnosis for her condition, treatment with Ubidecarenone improved her myoclonus, enabling a reduction in the dose of clonazepam, and an improvement in her energy levels and well being. It was also a relief for her to know that due to the recessive nature of the condition, her son would be a carrier, but would not be expected to develop symptoms as she had.

Clinical lead and acknowledgements

Clinical lead

Dr Helen Grote, Consultant Neurologist,
Chelsea and Westminster Hospital NHS Foundation Trust

Thank you to the health professionals, professional bodies, patient organisations and representatives of the NHS England Genomics clinical reference group who inputted into the development of the pathway through the consultation and stakeholder meetings

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National Neurosciences Advisory Group c/o The Neurological Alliance (England)
www.nnag.org.uk

The Neurological Alliance is a coalition working together to improve treatment, care and support for people affected by neurological conditions. Together we campaign to ensure people affected by neurological conditions can access high quality, joined up care and support to meet their individual needs, at every stage of their life.

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