East Genomic Laboratory Hub

NHS East Genomic Laboratory Hub
Cambridge Genomics Laboratory
Cambridge University Hospitals Foundation Trust
Cambridge, CB2 0QQ

19th December 2022

RE: IMPORTANT Change in delivery of Neurology Rare Disease Clinical Indications

Dear Colleagues

I would like to inform you of a change in service delivery for some Neurology rare disease genomic tests in the East GLH region as part of the Genomic Medicine Service. The associated Rare Disease Test Directory Clinical Indications are listed in Table 1 below.

Whole Genome Sequencing (WGS) is now the preferred strategy for delivering diagnostic testing for these Neurology Clinical Indications. Improvements to the WGS analysis workflow mean that analysis of short tandem repeat (STR) disorders can now also be performed alongside small variant and copy number variant analysis. This improved workflow will provide a standalone WGS test for patients, supporting streamlined testing in the East GLH and will provide the opportunity for patients to participate in the National Genomic Research Library.

This change in delivery strategy means that NGS gene panel testing will no longer be available for these Neurology Clinical Indications and that STR testing using targeted PCR will only be available for certain disorders.

Diagnostic Testing

From the 23rd January 2023, WGS will be used for diagnostic testing of patients referred for the Neurology Clinical Indications listed in Table 1. STR expansions that are identified near to or above the normal size threshold will be confirmed using PCR testing prior to reporting. Analysis and reporting of WGS will be performed by both the Cambridge and Nottingham Clinical Scientist Teams using standardised processes and reporting templates.

After the 23rd January 2023, samples received for gene panel testing without a WGS specific test order will be extracted, stored and no testing will be performed. A report will be issued requesting the WGS test order process is completed (see below).

To support this transition, testing patients using targeted PCR will remain available for the common STRs until April 1st 2023 (Table 1, column 4). We recommend that this testing pathway is only used for patients with a high likelihood of a specific STR disorder.

Some Neurology Clinical Indications in the Test Directory list STR as the only associated test and therefore these will remain available to order as standalone PCR tests (Table 2). Furthermore, where there is strong clinical suspicion of Friedreich ataxia or X-Linked Spinal

and Bulbar Muscular Atrophy type 1 (Kennedy's disease), in addition to a family history consistent with the mode of inheritance of the disorder, then PCR testing will remain available for these patients (Table 2).

A list of all disorders associated with STR expansions are listed in Table 3.

Familial Testing for STR disorders
Testing for known familial STR disorders will be delivered using targeted PCR tests at the East Genomics Laboratory Hub or a partner Genomic Laboratory Hub.

WGS ordering requirements
Clinical Indications delivered by WGS must be ordered using a WGS test order form or using the WGS specific CUH EPIC process. A WGS Patient Choice Record of Discussion Form (consent form) must be completed and sent to the laboratory for each individual tested.

We recognise that the ordering process for WGS is a notable change to current practise. We have collated details of the Clinical Indications and instructions for referral, including flow charts, test order forms and remote consenting guidance, on the East GLH website: https://www.eastgenomics.nhs.uk/for-healthcare-professionals/genomic-tests/rare-and-inherited-diseases/genome-sequencing/

Training for the Patient Choice Consent Framework is available online and should be completed prior to ordering WGS:
https://elearning.cam-pgmc.ac.uk/course/index.php?categoryid=13

Please contact the Cambridge Genomics Laboratory with any queries, feedback or to request additional training for ordering WGS using the email address emee.glh@nhs.net (please include 'Rare Disease WGS' in the subject heading).

Yours sincerely

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Table 1.
Neurology Clinical Indications WGS and associated STR Expansion disorders

CI ID	Clinical Indication	STR disorders in Clinical Indication delivered via WGS	In house STR PCR tests available until 01/04/2023
R54	Hereditary ataxia with onset in adulthood	DRPLA, FXTAS, FRDA, SCA1, SCA2, SCA3, SCA36, SCA6, SCA7, SCA10, SCA12, SCA17, ULD	DRPLA, FRDA, SCA1, SCA2, SCA3, SCA6, SCA7, SCA17
R55	Hereditary ataxia with onset in childhood	FRDA, SCA2, SCA7, ULD	FRDA, SCA2, SCA7
R56	Adult onset dystonia, chorea or related movement disorder	DRPLA, FTDASE1, HDL-2, SCA17	DRPLA, FTDASE1, SCA17
R57	Childhood onset dystonia, chorea or related movement disorder	SCA2, SCA17, ULD	SCA2, SCA17
R58	Adult onset neurodegenerative disorder	FTDASE1, HD, SMAX1	FTDASE1, HD
R59	Early onset or syndromic epilepsy	DRPLA, ULD	
R60	Adult onset hereditary spastic paraplegia	FRDA, SCA1, SCA2, SCA3, SCA6, SCA7, SCA12, SCA17	FRDA, SCA1, SCA2, SCA3, SCA6, SCA7, SCA17
R61	Childhood onset hereditary spastic paraplegia	FRDA	FRDA
R78	Hereditary neuropathy or pain disorder -NOT PMP22 copy number	SMAX1	
R84	Cerebellar anomalies	FRDA, SCA2, SCA7, ULD	FRDA, SCA2, SCA7
R109	Childhood onset leukodystrophy	DM1, FRAX, FRDA	
R381	Other rare neuromuscular disorders	DM1, SMAX1	DM1

Table 2.
STR disorder testing available as standalone PCR tests

CI ID	Clinical Indication	STR	Gene_Repeat
R72	Myotonic dystrophy type 1	DM1	DMPK_CTG
R410	Myotonic dystrophy type 2 (DM2)	DM2	CNBP_CCTG
R68	Huntington disease	HD	HTT_CAG
R75	Oculopharyngeal muscular dystrophy	OPMD	PABPN1_GCG
R53	Fragile X	FMR1 STR	FMR1_CGG
R54, R55, R60, R61, R84	Friedreich Ataxia. Where there is a strong clinical suspicion and a family history consistent with an autosomal recessive mode of inheritance.	FRDA	FXN_GAA
R58, R78, R381	X-Linked Spinal and Bulbar Muscular Atrophy type 1 (Kennedy's disease). Where there is a strong clinical suspicion and a family history consistent with an X-linked mode of inheritance.	SMAX1	AR_CAG

Table 3. STR Expansion disorders tested in the Genomic Medicine Service

STR	Disorder	Gene_Repeat	Inheritance
DM1	Myotonic dystrophy 1	DMPK_CTG	AD
DM2	Myotonic dystrophy type 2	CNBP_CCTG	AD
DRPLA	Dentatorubral-pallidoluysian atrophy	ATN1_CAG	AD
FRAX	Fragile X syndrome	FMR1_CGG	X Linked
FXTAS	Fragile X tremor/ataxia syndrome	FMR1_CGG	X Linked
FRDA	Friedreich ataxia	FXN_GAA	AR
FTDASE1	Frontotemporal dementia and/or amyotrophic lateral sclerosis 1	C9orf72_GGGGCC	AD
HD	Huntington Disease	HTT_CAG	AD
HDL-2	Huntington disease-like 2	JPH3_CTG	AD
OPMD	Oculopharyngeal muscular dystrophy	PABPN1_GCG	AD
SCA1	Spinocerebellar ataxia type 1	ATXN1_CAG	AD
SCA2	Spinocerebellar ataxia type 2	ATXN2_CAG	AD
SCA3	Spinocerebellar ataxia type 3	ATXN3_CAG	AD
SCA6	Spinocerebellar ataxia type 6	CACNA1A_CAG	AD
SCA7	Spinocerebellar ataxia type 7	ATXN7_CAG	AD
SCA10	Spinocerebellar ataxia type 10	ATXN10_ATTCT	AD
SCA12	Spinocerebellar ataxia type 12	PPP2R2B_CAG	AD
SCA17	Spinocerebellar ataxia type 17	TBP_CAG	AD
SCA36	Spinocerebellar ataxia type 36	NOP56_GGCCTG	AD
SMAX1	X-Linked Spinal and Bulbar Muscular Atrophy type 1	AR_CAG	X Linked
ULD	Myoclonic Epilepsy of Unverricht and Lundborg	CSTB_CCCCGCCCCGCG	AR