NHSE Genomic Medicine Service

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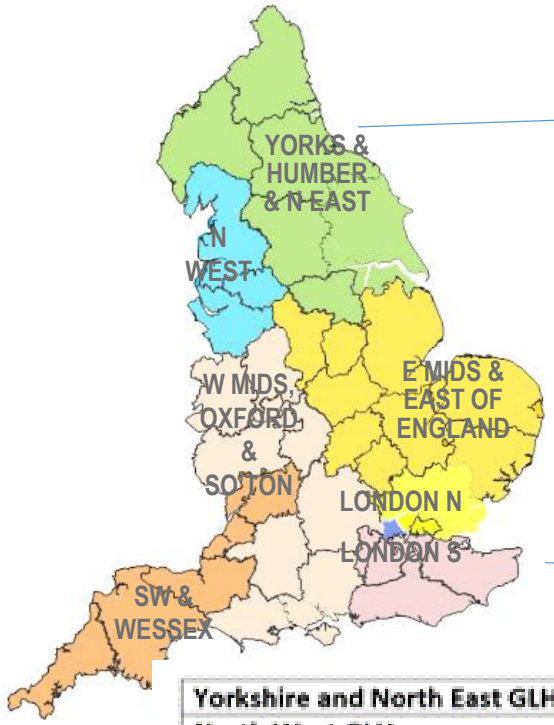
Background

- Annual report by Chief Medical Officer Dame Sally Davies
- Initial plans for the Genomic Medicine Service presented 2017
- Led by Chief Scientific Officer Professor Dame Sue Hill OBE
- Five central tenets:
  - National genomic lab service through a network of 7 hubs
  - National Genomic Test Directory
  - National whole genome sequencing provision
  - Clinical genomics services
  - National co-ordinating body within NHS England, Genomics England
- Due for launch in October 2018!!

Professor Dame Sally C. Davies, Chief Medical Officer for England

7 Genomic Laboratory Hubs (GLH)



Genomic laboratory services are now consolidated into a network of seven *NHS Genomic Laboratory Hubs*

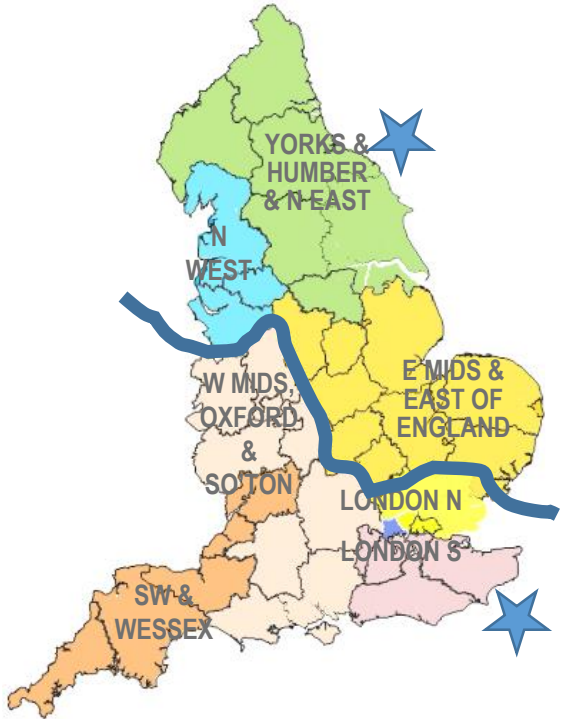
Y&NE: Sheffield, Leeds [Central] (& Leeds HDMS) & Newcastle (& NewGene & Newcastle Mitochondrial lab)

London S: King's College, Guy's and St Thomas' and St George's Hospitals

Yorkshire and North East GLH	Newcastle Hospitals NHSFT
North West GLH	Manchester University NHSFT
East Midlands and East England GLH	Cambridge University Hospitals NHSFT
London North Thames GLH	Great Ormond Street NHSFT
London South GLH	Guy's and St Thomas NHSFT
Wessex, Oxford, and West Midlands GLH	University Hospitals Birmingham NHSFT
South West GLH	North Bristol NHST

Core and specialist services

- Every GLH responsible for “core” tests
- Each GLH bid for specialised services covering broad clinical specialities e.g. Haematology, Renal, Cardiology etc
- 2-4 GLHs awarded each specialised service depending on referral numbers
- **Wilson Disease is within Gastrohepatology SS** awarded to Y&NE & LS GLHs i.e. **Sheffield and Kings College Hospital**
- Sheffield will cover all of North & EMEE
- Kings will cover all of London & SW & WOW



Specialist services

	Cardiology	Endocrinology	Eyes	Gastrohepatology	Haematology	Immunology	Inherited cancer	Metabolic	Mitochondrial	Musculoskeletal	NIPD	Renal	Respiratory	Skin	Hearing	Neurology
YNE				Y	Y		Y		Y	Y			Y			Y
NW	Y		Y		Y	Y	Y	Y							Y	Y
EMEE		Y														Y
WOW	Y	Y	Y		Y		Y	Y	Y	Y	Y		Y			Y
SW	Y	Y										Y				Y
LN			Y			Y	Y	Y	Y	Y	Y	Y		Y	Y	Y
LS	Y			Y	Y								Y	Y		Y

National Test Directory

- https://www.england.nhs.uk/publication/national-genomic-test-directories/
- Also separate test directory for cancer
- TAT currently 6 weeks for diagnostic WD; 2 weeks for familial testing

	A	B	C	D	E	F	G
1	*National Genomic Test Directory for rare and inherited disease, August 2020: © NHS in England 2020: All rights reserved*						
2	**Clinical indication ID**	**Clinical Indication**	**Eligibility Criteria**	**Test ID**	**Target/Genes**	**Test Method**	**Clinical Group**
148	R168	Non-acute porphyrias	114	R168.1	Non-acute porphyrias (513)	Small panel	Gastrohepatology
149	R169	Acute intermittent porphyria	115	R169.1	HMBS	Single gene sequencing >=10 amplicons	Gastrohepatology
150	R170	Variegate porphyria	116	R170.1	PPOX	Single gene sequencing >=10 amplicons	Gastrohepatology
151	R171	Cholestasis	117	R171.1	Cholestasis (544)	WES or Medium Panel	Gastrohepatology
152	R172	Wilson disease	118	R172.1	ATP7B	Single gene sequencing >=10 amplicons	Gastrohepatology
153	R173	Polycystic liver disease	119	R173.1	Polycystic liver disease interim (653)	WES or Small Panel	Gastrohepatology
154	R175	Pancreatitis	120	R175.1	Pancreatitis (386)	Small panel	Gastrohepatology
155				R175.2	CFTR common mutations	Targeted mutation testing	Gastrohepatology
156	R176	Gilbert syndrome	121	R176.1	UGT1A1	Targeted mutation testing	Gastrohepatology
157	R177	Hirschsprung disease - familial	122	R177.1	RET	Single gene sequencing >=10 amplicons	Gastrohepatology
158	R331	Intestinal failure	123	R331.1	Intestinal failure (514)	WES or Small Panel	Gastrohepatology
533							

Eligibility criteria

- https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-Inherited-Disease-Eligibility-Criteria-November-2020-21.pdf

R172 Wilson disease

Testing Criteria

High suspicion of Wilson disease, as evidenced by some or all of low caeruloplasmin, high liver copper, high urinary copper, high free copper, Kayser–Fleischer rings

Overlapping indications

- R98 Likely inborn error of metabolism - targeted testing is not possible, R27 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with atypical features in whom a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Hepatology
- Metabolic Medicine

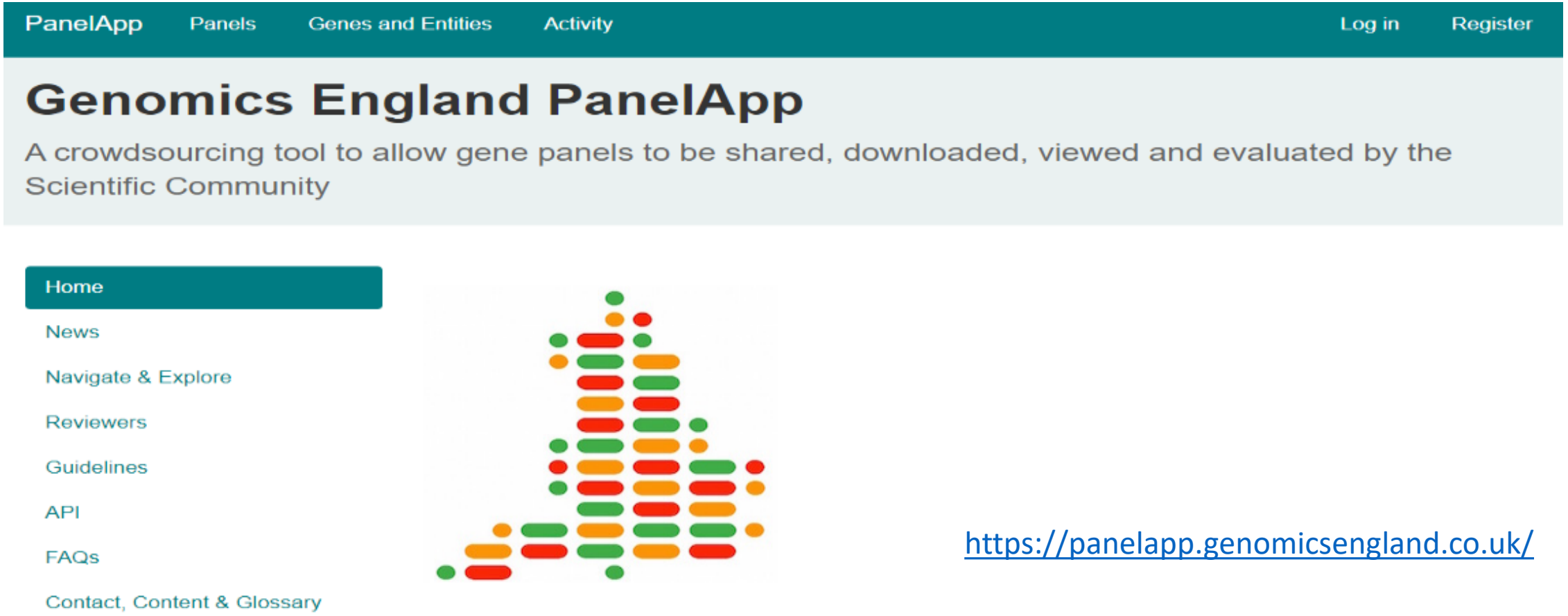
Specialist Service Group

- Gastrohepatology

Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R172.1	ATP7B Single gene sequencing	Singleton	Small variants	Single gene(s)	ATP7B	Single gene sequencing >=10 amplicons

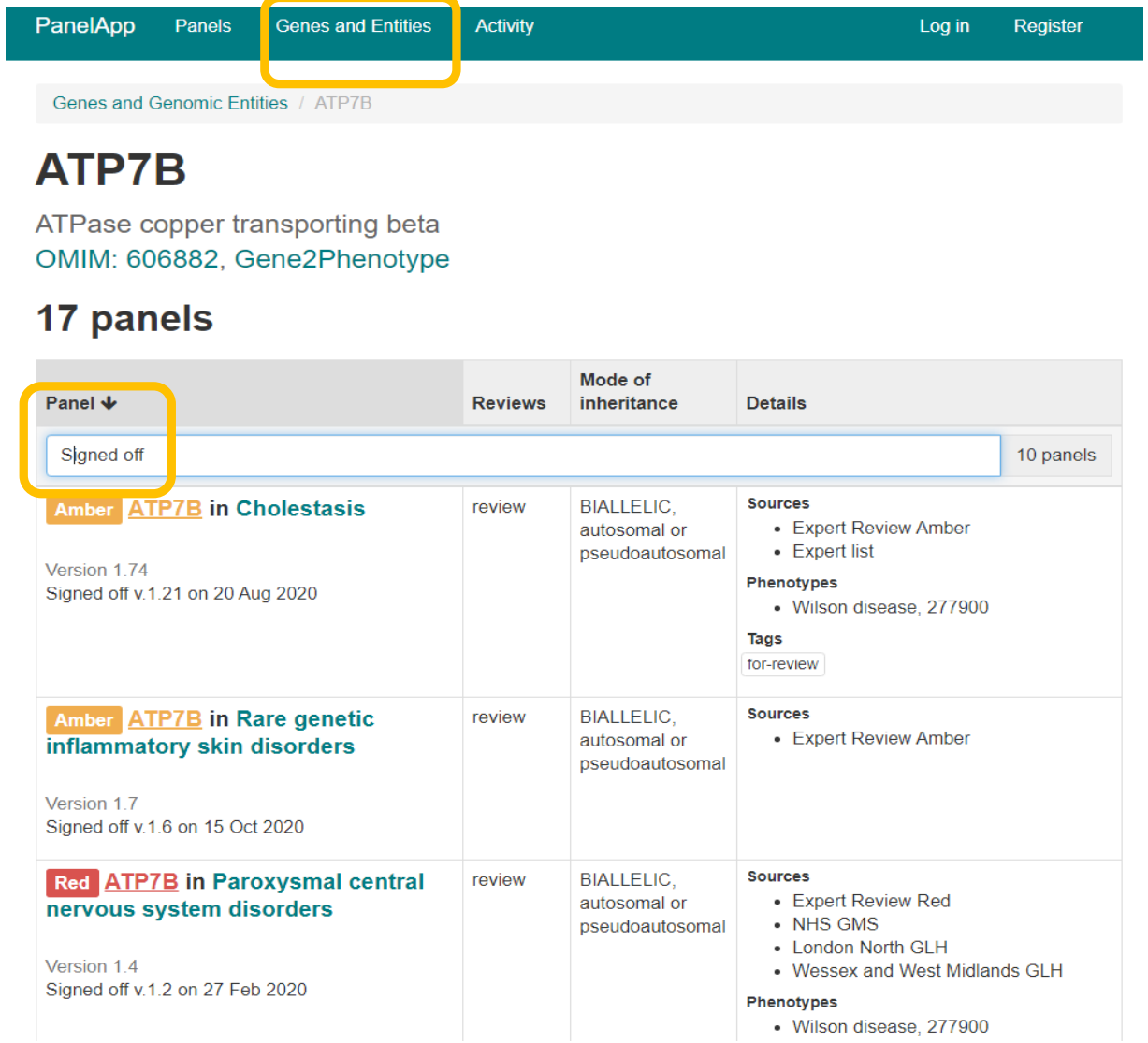
PanelApp



https://panelapp.genomicsengland.co.uk/

PanelApp

- Search by gene or panel
- Includes all 100K genome project panels
- Filter by “Signed off” for GMS panels
- RAG rated

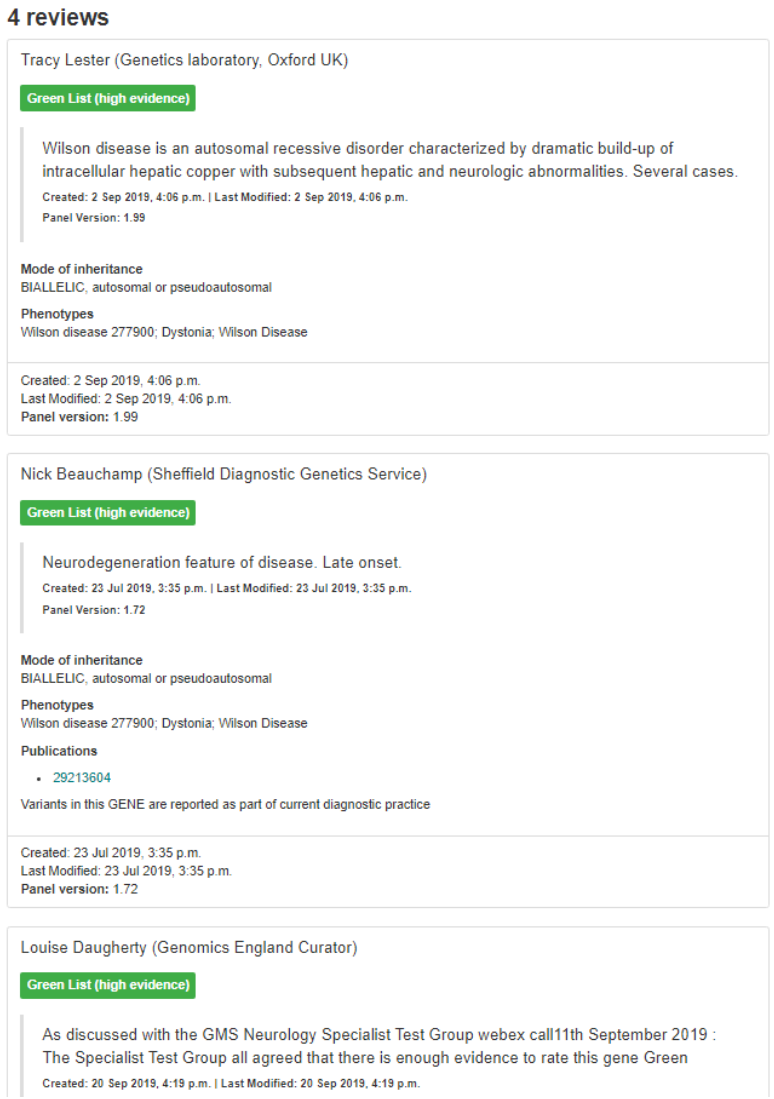


Green ATP7B in Iron metabolism disorders Version 1.4 Signed off v.1.2 on 3 Mar 2020 Haematology SS	review	BIALLELIC, autosomal or pseudoautosomal	Sources • Expert Review Green • North West GLH • Yorkshire and North East GLH • NHS GMS • Wessex and West Midlands GLH Phenotypes • 277900 WILSON DISEASE
Green ATP7B in Neurodegenerative disorders - adult onset Version 2.32 Signed off v.2.31 on 8 Oct 2020 Neurology SS	review	BIALLELIC, autosomal or pseudoautosomal	Sources • Wessex and West Midlands GLH • Yorkshire and North East GLH • NHS GMS • London North GLH • Expert Review Green Phenotypes • Wilson disease 277900 • Dystonia • Wilson Disease Tags treatable
Green ATP7B in Inborn errors of metabolism Version 2.32 Signed off v.2.3 on 17 Feb 2020 Component of the following Super Panels: • Hypotonic infant • Paediatric disorders • White matter disorders - childhood onset Metabolic SS	review	BIALLELIC, autosomal or pseudoautosomal	Sources • London North GLH • NHS GMS • Expert Review Green Phenotypes • Wilson disease
Red ATP7B in Intellectual disability Level 3: Neurodevelopmental disorders Level 2: Neurology and neurodevelopmental disorders Version 3.550 Signed off v.3.2 on 13 Feb 2020 Component of the following Super Panels: • Hypotonic infant • Paediatric disorders • White matter disorders - childhood onset	review	BIALLELIC, autosomal or pseudoautosomal	Sources • Expert Review Red • Expert Review Amber • BRIDGE study SPEED NEURO Tier1 Gene Phenotypes • Wilson disease 277900

Green ATP7B in Hereditary ataxia - adult onset Version 2.17 Signed off v.2.13 on 6 Oct 2020 Neurology SS	review	BIALLELIC, autosomal or pseudoautosomal	Sources • London North GLH • NHS GMS • Wessex and West Midlands GLH • Expert Review Green • Brain channelopathy v1.46 Phenotypes • Wilson disease 277900 • Wilson disease, 277900 Tags treatable
Green ATP7B in Adult onset movement disorder Version 1.15 Signed off v.1.14 on 15 Oct 2020 Neurology SS	review	BIALLELIC, autosomal or pseudoautosomal	Sources • NHS GMS • London North GLH • Expert Review Green Phenotypes • Wilson disease 277900 • Dystonia
Green ATP7B in Childhood onset dystonia or chorea or related movement disorder Version 1.62 Signed off v.1.58 on 6 Oct 2020 Neurology SS	review	BIALLELIC, autosomal or pseudoautosomal	Sources • PanelApp • Expert Review Green • London North GLH Phenotypes • Wilson disease 277900 • Dystonia

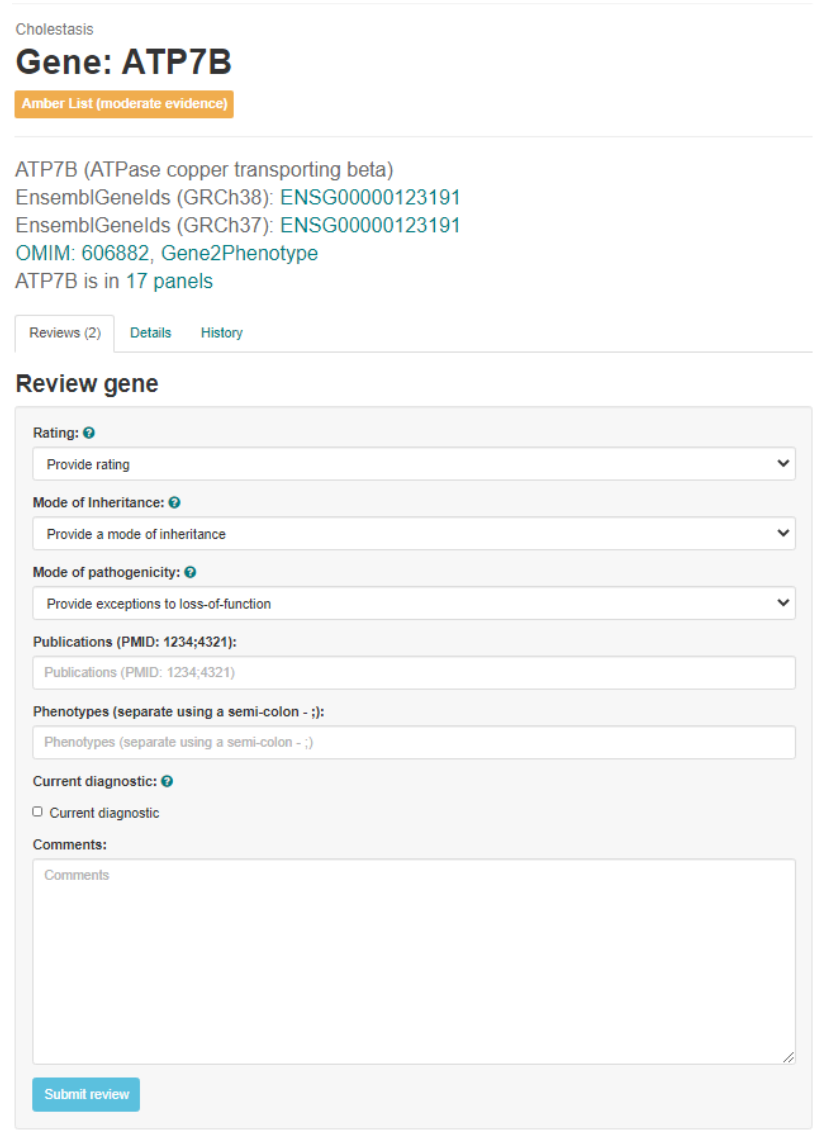
ATP7B is on 10 NHSE GMS panels (6 Green, 2 Amber & 2 Red) in addition to R172 Wilson disease single gene service

Large panel TAT = 12 weeks



- Click to read reviews

- Register & log in to add your own evidence e.g. new publication



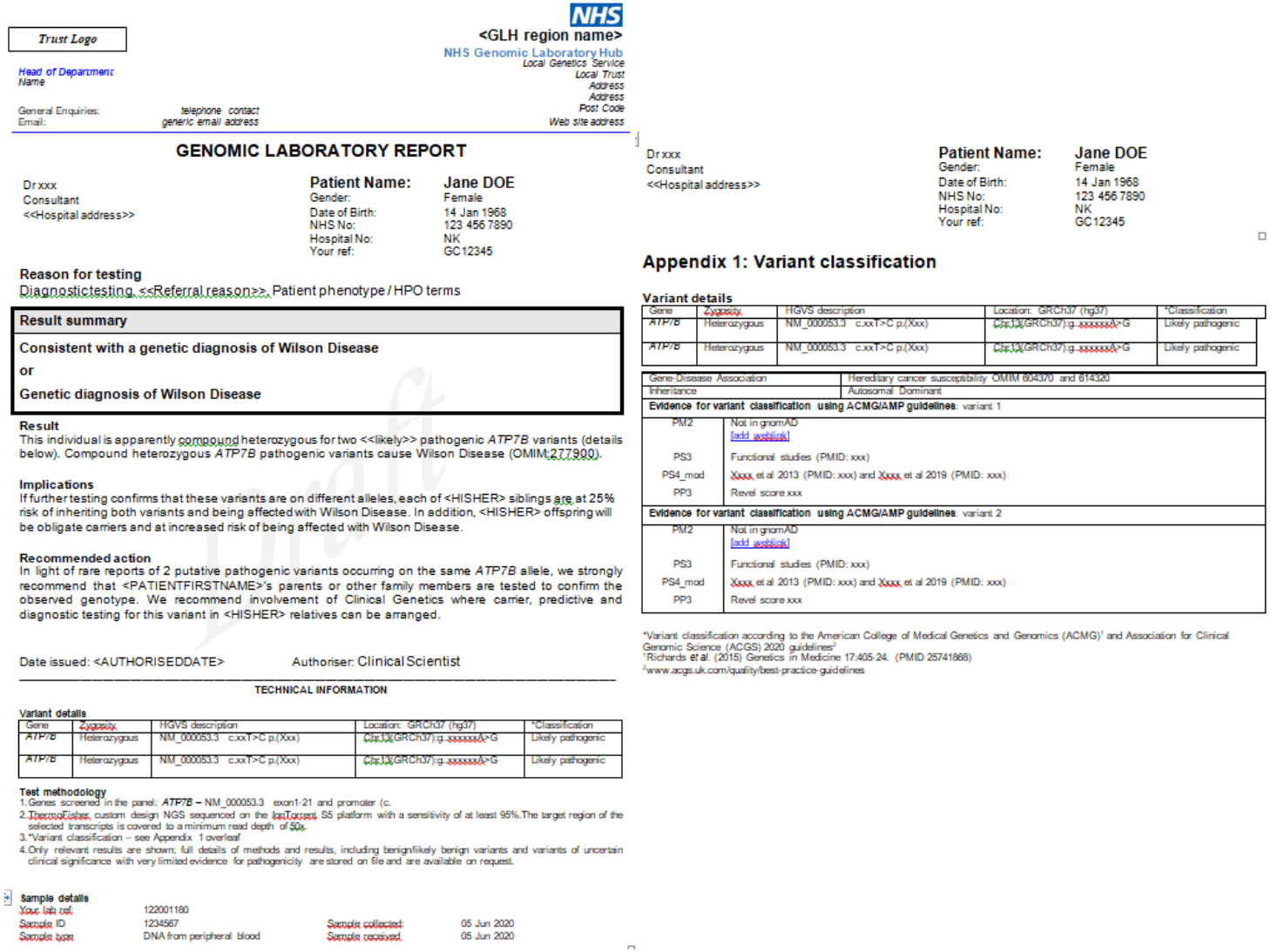
Where we are now…

- 1st April 2020 start delayed due to Covid-19
- 96% of new tests ready
- Awaiting finance sign off
- WD service is continuing as usual ☺
- Some new services operating, others waiting for finance
- Refer samples via your local genetics centre
- WGS to start soon

Where we are going…

- Nationally agreed report templates
- Increased collaboration
- Increased research opportunities
- Please get in touch ☺

- Any questions?



Trust Logo

Head of Department
Name

General Enquiries: telephone contact
Email: generic email address

NHS
<GLH region name>
NHS Genomic Laboratory Hub
Local Genetics Service
Local Trust
Address
Address
Post Code
Web site address

GENOMIC LABORATORY REPORT

Dr xxx
Consultant
<<Hospital address>>

Patient Name: Jane DOE
Gender: Female
Date of Birth: 14 Jan 1968
NHS No: 123 456 7890
Hospital No: NK
Your ref: GC12345

Reason for testing
Diagnostictesting, <<Referral reason>>, Patient phenotype / HPO terms

Result summary

Consistent with a genetic diagnosis of Wilson Disease
or
Genetic diagnosis of Wilson Disease

Result
This individual is apparently compound heterozygous for two <<likely>> pathogenic *ATP7B* variants (details below). Compound heterozygous *ATP7B* pathogenic variants cause Wilson Disease (OMIM:277900).

Implications
If further testing confirms that these variants are on different alleles, each of <HISHER> siblings are at 25% risk of inheriting both variants and being affected with Wilson Disease. In addition, <HISHER> offspring will be obligate carriers and at increased risk of being affected with Wilson Disease.

Recommended action
In light of rare reports of 2 putative pathogenic variants occurring on the same *ATP7B* allele, we strongly recommend that <PATIENTFIRSTNAME>'s parents or other family members are tested to confirm the observed genotype. We recommend involvement of Clinical Genetics where carrier, predictive and diagnostic testing for this variant in <HISHER> relatives can be arranged.

Date issued: <AUTHORISEDDATE> Authoriser: Clinical Scientist

TECHNICAL INFORMATION

Variant details

Gene	Zygosity	HGVS description	Location: GRCh37 (hg37)	*Classification
ATP7B	Heterozygous	NM_000053.3 c.xxT>C p.(Xxx)	Chr13(GRCh37):g.xxxxxxxA>G	Likely pathogenic
ATP7B	Heterozygous	NM_000053.3 c.xxT>C p.(Xxx)	Chr13(GRCh37):g.xxxxxxxA>G	Likely pathogenic

Test methodology
1. Genes screened in the panel: *ATP7B* – NM_000053.3 exon1-21 and promoter (c.
2. ThermoFisher custom design NGS sequenced on the IonTorrent S5 platform with a sensitivity of at least 95%. The target region of the selected transcripts is covered to a minimum read depth of 50x.
3. *Variant classification – see Appendix 1 overleaf
4. Only relevant results are shown; full details of methods and results, including benign/likely benign variants and variants of uncertain clinical significance with very limited evidence for pathogenicity are stored on file and are available on request.

Sample details

Your lab ref:	122001180		
Sample ID	1234567	Sample collected:	05 Jun 2020
Sample type	DNA from peripheral blood	Sample received	05 Jun 2020

Dr xxx
Consultant
<<Hospital address>>

Patient Name: Jane DOE
Gender: Female
Date of Birth: 14 Jan 1968
NHS No: 123 456 7890
Hospital No: NK
Your ref: GC12345

Appendix 1: Variant classification

Variant details

Gene	Zygosity	HGVS description	Location: GRCh37 (hg37)	*Classification
ATP7B	Heterozygous	NM_000053.3 c.xxT>C p.(Xxx)	Chr13(GRCh37):g.xxxxxxxA>G	Likely pathogenic
ATP7B	Heterozygous	NM_000053.3 c.xxT>C p.(Xxx)	Chr13(GRCh37):g.xxxxxxxA>G	Likely pathogenic

Gene-Disease Association	Hereditary cancer susceptibility OMIM 604370 and 614320
Inheritance	Autosomal Dominant
Evidence for variant classification using ACMG/AMP guidelines: variant 1	
PM2	Not in gnomAD [add weblink]
PS3	Functional studies (PMID: xxx)
PS4_mod	Xxxx et al 2013 (PMID: xxx) and Xxxx et al 2019 (PMID: xxx)
PP3	Revel score xxx
Evidence for variant classification using ACMG/AMP guidelines: variant 2	
PM2	Not in gnomAD [add weblink]
PS3	Functional studies (PMID: xxx)
PS4_mod	Xxxx et al 2013 (PMID: xxx) and Xxxx et al 2019 (PMID: xxx)
PP3	Revel score xxx

*Variant classification according to the American College of Medical Genetics and Genomics (ACMG)[1] and Association for Clinical Genomic Science (ACGS) 2020 guidelines[2]
[1] Richards et al. (2015) Genetics in Medicine 17:405-24. (PMID 25741868)
[2] www.acgs.uk.com/quality/best-practice-guidelines