Genetics: National Changes and Impact on Clinical Care

NWNWIoM CHD ODN Study Day, Jan 2021

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Overview

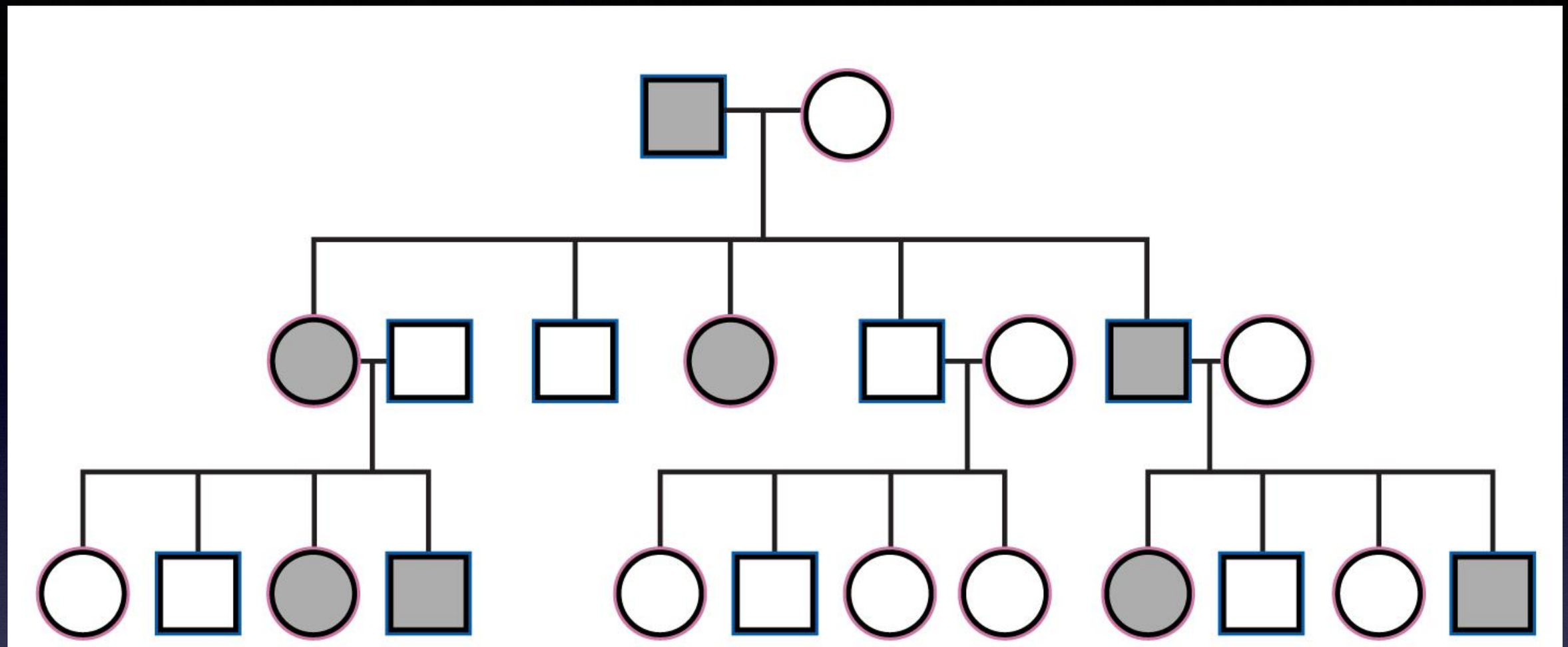
- 100,000 Genome Project Closure
- NW GMS-A
- NHS E Test Directory
- Clinical examples

100,000 Genomes Project

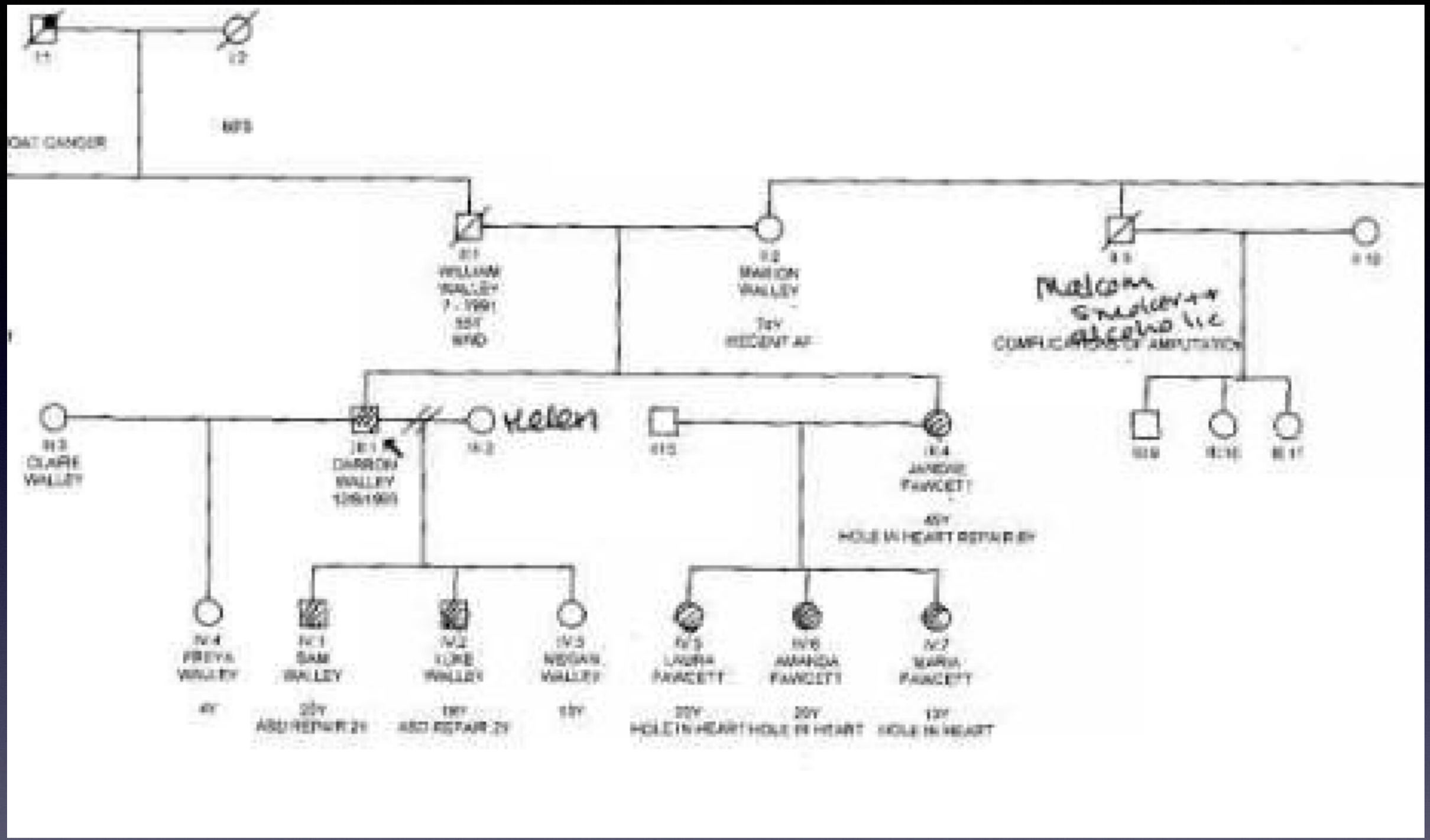
- Recruitment closed 2018
- Final few results being released in batches
- Additional findings have not been started:
    - Couple carrier testing eg for CF
    - Individual carrier testing eg for BRCA
    - Will be reported separately and later

100KGP Results

- Results must go in patient notes/EPR and be communicated to patient:
    - Even if negative
- If you recruited, results will be sent directly to you
    - Genetics happy to help
- Happy to do joint consultations to give results
    - Joint video consultation Kabuki results
- Refer complex or non-cardiac patients results to Clinical Genetics for further discussion



Huge family with undefined cardiomyopathy
Very young onset
RBM20 Class 5 found in 100KGP
Accurately take kids in/out of follow up



Big family with multiple relatives with an ASD
Found Class 5 NKX2-5 in 100KGP
Unaffected relatives taken out of EP follow up

Progress Since 100KGP

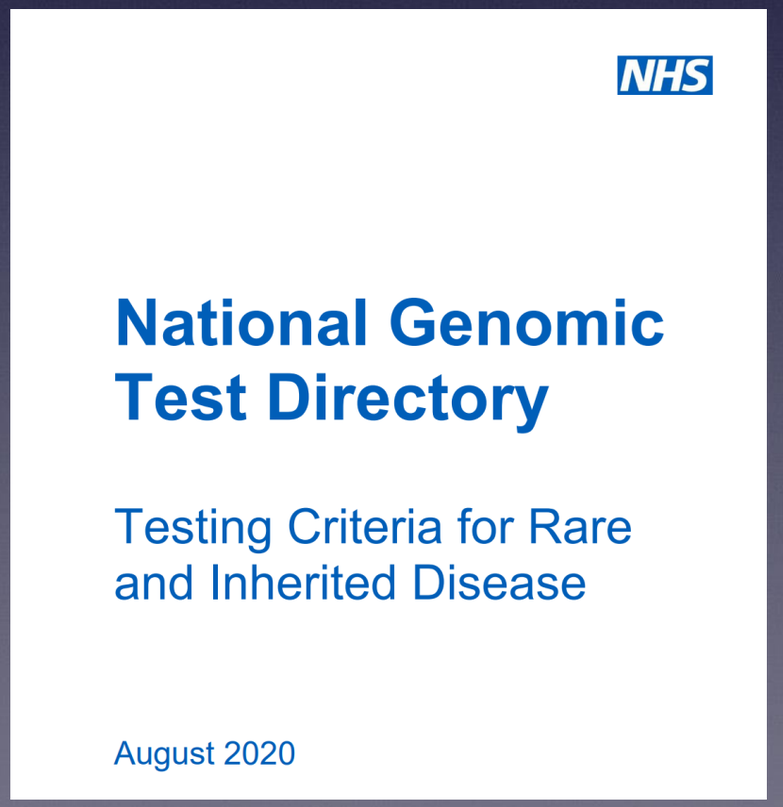
- 100KGP was run through Genomic Medicine Centres
- Now a single GMC across NW to close Project
- 7 Genomic Lab Hubs were then created, following 7 GMCs
    - NW GLH hosted by MFT, still a physical lab in LWH
    - One of their specialisms is Cardiovascular Genetics
- Now plan to create an integrated Genomic Medicine Service across England

NW GMSA

- December 2020 NW Genomic Medicine Service Alliance was created
- Number of partner organisations across NW
- Driving forward all things Genomic Medicine in North West
- Hosted by MFT
- Clinical Genetics Liverpool and Manchester will be one small part of GMSA
- Focus on integrating Genomic Medicine into other specialties

NHS E Test Directory

- NW GMSA has to deliver genetic testing in accordance with National Test Directory
- Clinical indications for testing national
- Windows to apply for changes
- Aim to standardise testing



Test Directory Aims

- Standardise:
    - When a genetic test is indicated
    - Which genes will be tested
    - How results will be reported
- Aim to open up testing to other clinicians

CHD Standards

- CHD Standards and Specifications 2016
- Level 1 centres must have “Working links to other specialist areas including … genetics…”
- “Genetics services must be able to provide advice and consultation by the following working day and … be experienced in patients with CHD”
- Recent ESC Consensus Document on Genetics[1]

[1]EJPC 2020, Vol. 27(13) 1423–1435

Genetics in CHD

Why

Diagnosis
Management
Prognosis
Recurrence
Relatives

When

New diagnosis
Transition
Pre-conception
Noted to be untested

Who

ACHD Team
Paeds Cardio Team
Consultant Geneticist
Genetic Counsellors

How

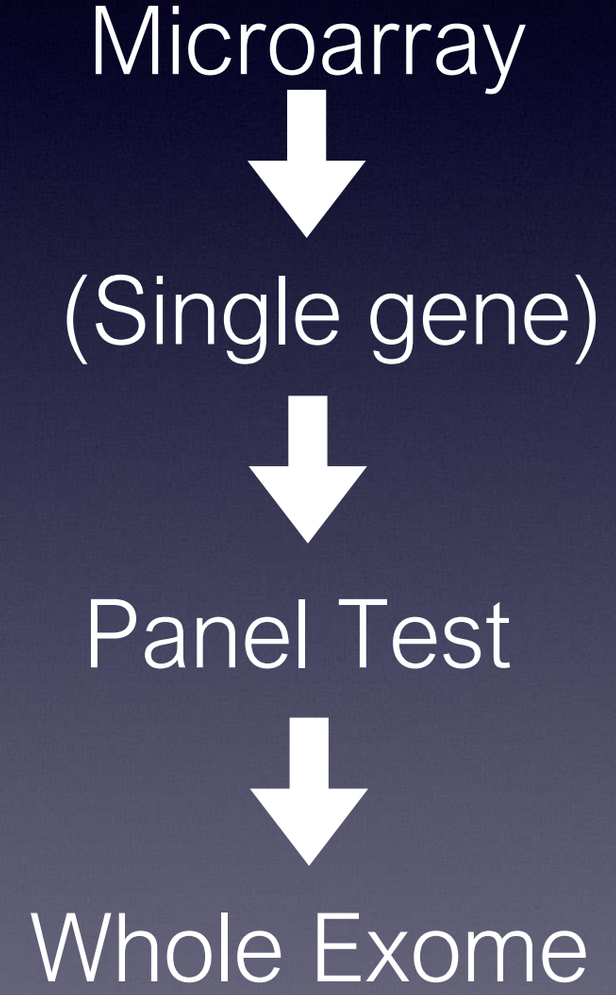
Array
Panel test
Whole exome

Always counselled first

Adapted from [1]EJPC 2020, Vol. 27(13) 1423–1435

Process of Genetic Testing

- Microarray first line in CHD
    - Usually even for eg DiGeorge, Turner
- Single gene testing rare
- Must be sure of phenotype if requesting panels
    - Requests for multiple panels may be rejected
- Whole exome has specific indications



Which Patients Need Genetics

- Phenotype of a recognisable chromosomal or genetic syndrome e.g DiGeorge
- Clinical features suggestive of an underlying, as-yet undiagnosed genetic syndrome
- Any congenital heart defect combined with
  - Facial dysmorphism or suspected dysmorphism
  - Skeletal defects e.g. limb abnormality
  - Other visceral organ malformations e.g. absent spleen
  - Growth delay e.g short stature
  - Developmental delay
  - Learning disability
  - Significant behavioural or psychiatric disorder
- Family history with one or more first-degree relatives with:
  - CHD
  - Multiple miscarriages
  - Siblings with birth defects


Department of Health & Social Care

The UK Rare Diseases Framework

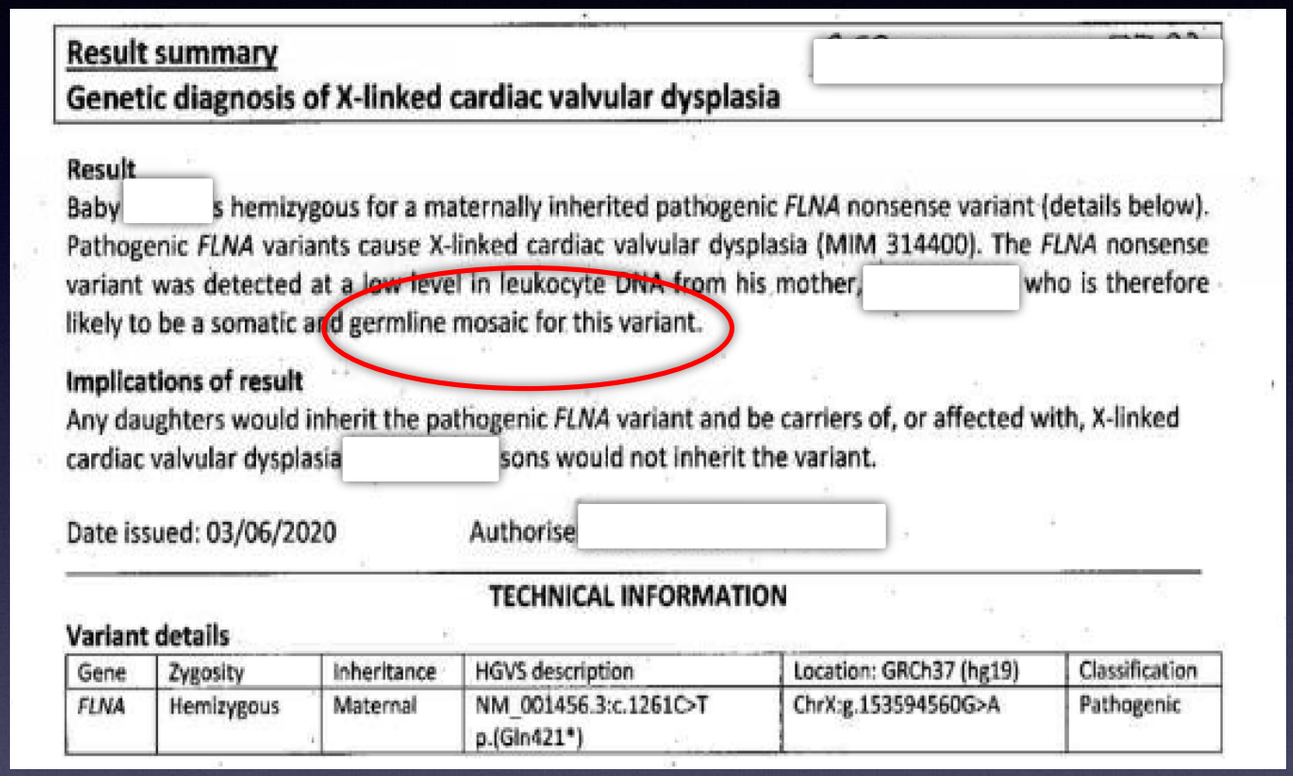
Published 9 January 2021

When to Consider Genetic Testing

- At first diagnosis
  - *Critically unwell neonate or child where genetic diagnosis would alter management*
- At transition
- With pregnancy and reproductive counselling
- If diagnosis would alter clinical decisions
  - Undiagnosed syndromic patient being surgically assessed
- For any adult patient not previously tested
  - Including those who's result is no longer accessible

Rapid Exome Sequencing

- Critically unwell neonate or child – NICU or PICU
- Management altered by genetic diagnosis
    - Including care withdrawal
- Can do video consults and photo review
- Requested on clinical genetics advice only



Result summary
Genetic diagnosis of X-linked cardiac valvular dysplasia

Result
Baby s hemizygous for a maternally inherited pathogenic *FLNA* nonsense variant (details below). Pathogenic *FLNA* variants cause X-linked cardiac valvular dysplasia (MIM 314400). The *FLNA* nonsense variant was detected at a low level in leukocyte DNA from his mother, who is therefore likely to be a somatic and germline mosaic for this variant.

Implications of result
Any daughters would inherit the pathogenic *FLNA* variant and be carriers of, or affected with, X-linked cardiac valvular dysplasia sons would not inherit the variant.

Date issued: 03/06/2020 Authorise

TECHNICAL INFORMATION

Variant details

Gene	Zygosity	Inheritance	HGVS description	Location: GRCh37 (hg19)	Classification
FLNA	Hemizygous	Maternal	NM_001456.3:c.1261C>T p.(Gln421*)	ChrX:g.153594560G>A	Pathogenic

Refer to Genetics

- Suspected syndromic diagnosis with normal array for consideration of additional testing
- Complex array result requiring further testing or genetics input
- Complex family history of CHD and/or other congenital anomalies, including heterotaxy
- Any patient or at patient or clinician request

Whole Exome/Genome Sequencing

- For patients with unexplained Intellectual Disability
    - Do WGS but analyse against an ID panel
- Expected April 2020
- Pilot started Dec 2020 – very limited numbers
- Financial envelope restricted
- Cap on numbers likely to remain
- Where likely to get a monogenic diagnosis that impacts clinical management

Test Indications

Part II. Cardiology

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

R140 Elastin-related phenotypes

Testing Criteria

1. Congenital heart disease of a type associated with Elastin mutations, with an autosomal dominant pattern of inheritance in at least 3 family members, OR
2. Supravalvular aortic stenosis characteristic of Elastin mutations

Overlapping indications

- R28 Congenital malformation and dysmorphism syndromes – microarray only should be used for patients with clinical features strongly suggestive of Williams syndrome
- R27 Congenital malformation and dysmorphism syndromes - likely monogenic test should be used for individuals with syndromic forms of cutis laxa

R125 Thoracic aortic aneurysm or dissection test should be used for individuals with primarily aortic/large arterial involvement, with some features of cutis laxa

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

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R140.1	ELN Single gene sequencing	Singleton	Small variants	Single gene(s)	ELN	Single gene sequencing >=10 amplicons

Specific Issues for CHD

- Currently Manchester GLH unable to offer paediatric/syndromic cardiomyopathy panel
    - Work in progress
- Test directory does not have a Noonan/RAS-MAPK panel
    - Need to do Whole Exome at present
- Some panels not provided by Manchester
    - Laterality and isomerism; unclear if will be provided
- No CHD panel – 100KGP suggests not clinically useful

Genomics England Panel App

- Current panel gene content
- Archived panels and clinical/scientific reasons for changes
    - Includes old 100KGP panels, eg CHD
- Search by panel name, R number or gene
- Any genes that are green will be reported if clinically actionable variant reported
    - Class 4 and 5 and any ‘hot’ Class 3s

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

panelapp.genomicsengland.co.uk/panels/749/

Bloodhound - MSoft EDMS Growth Charts ICE Login LWH

Version 1.4 of this panel was signed-off for the GMS. The current version, shown here, may differ from the signed-off version.

Cardiomyopathies - including childhood onset (Version 1.18)

Relevant disorders: Paediatric or syndromic cardiomyopathy, R135
Panel types: GMS Rare Disease Virtual, GMS Rare Disease, GMS signed-off
Panel version 1.4 has been signed off on 19 Feb 2020

Download Signed-Off Version

Description

This panel will be routinely applied for clinical indication “R135 Paediatric or syndromic cardiomyopathy” and can also be used as part of the analysis of a broader phenotype, where relevant, using genome or exome data in the NHS Genomic Medicine Service.

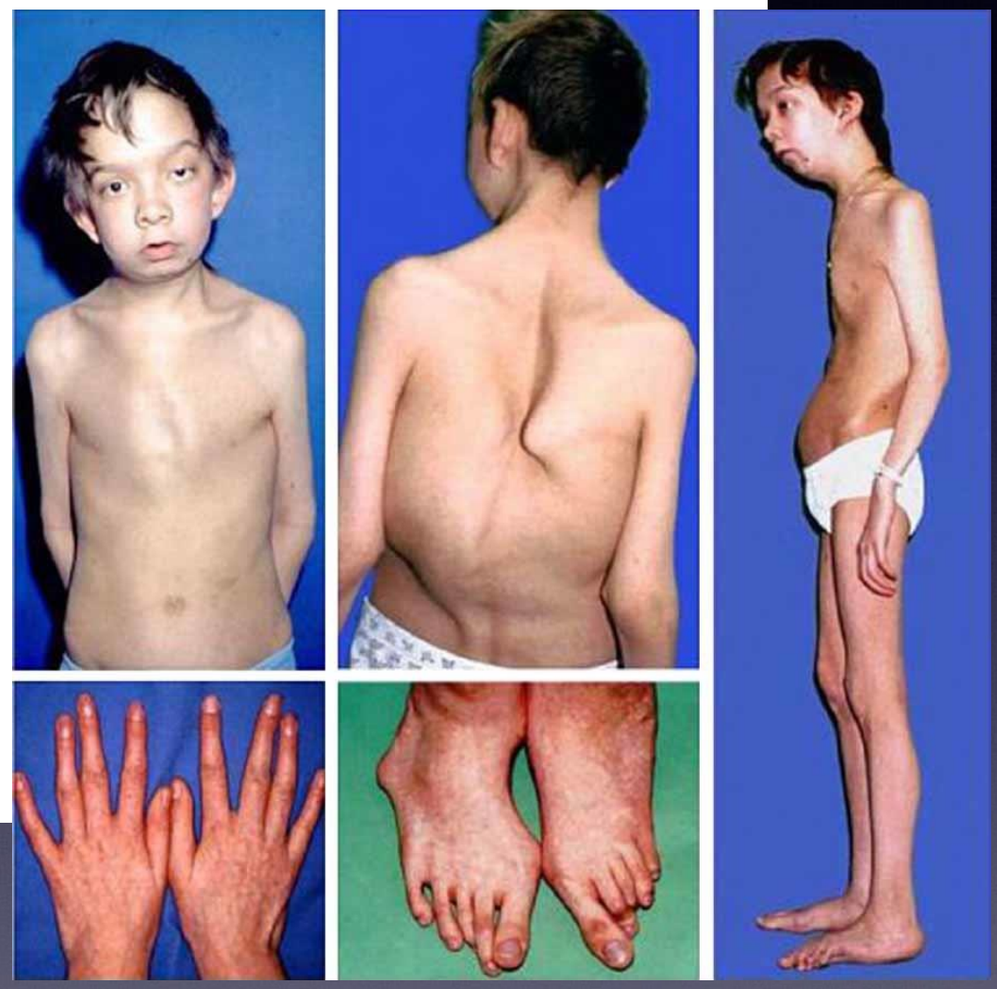
Further information on the testing criteria and any overlapping clinical indications can be found within (https://www.england.nhs.uk/publication/national-genomic-test-directories/) under 'R135 Paediatric or syndromic cardiomyopathy'.

Version 1.2 of this panel was signed-off for the GMS. The current version, shown here, may differ from the signed-off version.

Thoracic aortic aneurysm and dissection (Version 1.3)

Relevant disorders: R125
Panel types: GMS Rare Disease Virtual, GMS signed-off
Panel version 1.2 has been signed off on 19 Feb 2020

Download Signed-Off Version



Description

This panel is used as a virtual panel to analyse genome or exome data in the NHS Genomic Medicine Service; the panel will routinely be applied for clinical indication 'R125 Thoracic aortic aneurysm or dissection' but can also be used as part of the analysis for a broader clinical presentation, where relevant.

Further information on the testing criteria and any overlapping clinical indications can be found within (https://www.england.nhs.uk/publication/national-genomic-test-directories/) under 'R125 Thoracic aortic aneurysm or dissection'.

- 10 genes → 32 genes
- Much more accurate for ‘Marfanoid’ children
- Implications for surgical thresholds

Summary

- New testing indications
- New tests
- Faster tests
- Not perfect yet and still some issues
- Genetics always happy to advise or consult
    - Joint consults or hybrid with video

Any questions?

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