NHS
West London
NHS Genomic Medicine Centre

Genomic results in the clinic

Dr Ellen Thomas
Locum Consultant in Genomic Medicine, ICHT
Clinical Lead for NHS Genomic Medicine, Genomics England

NHS
West London
NHS Genomic Medicine Centre

Overview

Why is a genetic/genomic diagnosis worth having?

How confident are we about genomic results?

Genomic reports – what you do (and don't) need to know

Case study: familial hypercholesterolaemia

Why make genetic diagnoses?

NHS
West London
NHS Genomic Medicine Centre

Clinical diagnosis allows:

- Treatment plan
- Prognosis
- Estimated recurrence risk
- Clinical screening for relatives
- Patient support groups

Genetic diagnosis allows:

- Treatment may be more specific
- Prognosis may be more specific
- Precise recurrence risk
- Reproductive testing
- Predictive / cascade testing for relatives
- Specific patient support groups

The Human Genome Project

Phase II: Interpretation

NHS
West London
NHS Genomic Medicine Centre

A genetic variant is a place in the genome where an individual has a different DNA base (or group of DNA bases) from the 'reference'

How many variants are present in the average human genome?

Genomic variation is common

NHS West London NHS Genomic Medicine Centre

- ~5 million variants in every genome

  ~500,000 rare variants

  ~72 de novo variants

- Exome = ~23,000 variants
  - 10,000-12,000 missense variants
  - 1,800 missense variants (MAF <1%)
  - 92 missense variants (MAF <0.1%)
  - 5 rare truncating variants (MAF <0.1%)
  - 0-2 de novo variants

NHS
West London
NHS Genomic Medicine Centre

Most genetic variants have no / minimal impact on health

How do we decide if a specific variant is likely to be disease causing or not?

Variant interpretation

NHS West London NHS Genomic Medicine Centre

1) Does the variant change the protein sequence?
2) Does the variant show the right inheritance pattern?
3) How common is the variant in the general population?
4) Has the variant been seen in other patients with the same condition?
5) What do we know about this gene already?
6) Can we predict *in silico* how the variant might affect the protein?
7) Has anyone done *in vitro* research into the effect of the variant on the protein?

	Benign		Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very strong**
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

ACMG Classification

NHS West London
NHS Genomic Medicine Centre

Pathogenic	(i) 1 Very strong (PVS1) *AND* (a) ≥1 Strong (PS1–PS4) *OR* (b) ≥2 Moderate (PM1–PM6) *OR* (c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) *OR* (d) ≥2 Supporting (PP1–PP5) (ii) ≥2 Strong (PS1–PS4) *OR* (iii) 1 Strong (PS1–PS4) *AND* (a)≥3 Moderate (PM1–PM6) *OR* (b)2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR* (c)1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Likely pathogenic	(i) 1 Very strong (PVS1) *AND* 1 moderate (PM1–PM6) *OR* (ii) 1 Strong (PS1–PS4) *AND* (PM1–PM6) *OR* (iii) 1 Strong (PS1–PS4) *AND* ≥2 supporting (PP1–PP5) *OR* (iv) ≥3 Moderate (PM1–PM6) *OR* (v) 2 Moderate (PM1–PM6) *AND* ≥2 supporting (PP1–PP5) *OR* (vi) 1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Benign	(i) 1 Stand-alone (BA1) *OR* (ii) ≥2 Strong (BS1–BS4)
Likely benign	(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR* (ii) ≥2 Supporting (BP1–BP7)
Uncertain significance	(i) Other criteria shown above are not met OR (ii) the criteria for benign and pathogenic are contradictory

Clinically actionable

Class 5	Pathogenic
Class 4	Likely pathogenic
Class 3	Uncertain
Class 2	Likely benign
Class 1	Benign

Difficult – but mainly ignore

Ignore for healthcare purposes

Clinical use of genomic data

NHS
West London
NHS Genomic Medicine Centre

- In the clinic, only two outcomes of data interpretation:
  - Alter clinical management on basis of data
  - Do not alter clinical management on basis of data
- The evidence presented must support the plan of action AT THE TIME
- Genomic data should be regularly re-evaluated
  - Who does this and when?
  - How do we manage the patient/family's expectations?
- Consent and ethical issues: generally very similar to other diagnostic tests, with minor additions, e.g:
  - Familial variants are considered familial data, not individual data
  - Trio tests may detect misattributed relationships e.g. paternity

Example report

NHS
West London
NHS Genomic Medicine Centre

- How would you advise a patient with this report?
- What would you say to the family of this patient?
- How would this result affect the patient's care?
- What else do the family need to know about this result?

NOTE: research reports may contain useful information for the patient, but should NOT be used for clinical care until checked in an NHS accredited diagnostic lab

Reason for testing

Diagnostic: to investigate the cause of Jean's developmental delay.

Result summary

Genetic diagnosis of *KAT6A*-related developmental delay

Result

Jean is heterozygous for a pathogenic *KAT6A* frameshift variant (details below). Monoallelic *KAT6A* variants cause intellectual disability, dysmorphic facial features, delayed psychomotor development and lack of speech (MIM616268). The *KAT6A* frameshift variant was not detected in her parents, Fred and Rosalind Helix, and is likely to have arisen *de novo*.

Implications of result

Each of this patient's offspring would be at 50% risk of inheriting this variant and also being affected with this disorder.

Date issued: 09/11/2017

TECHNICAL INFORMATION

Variant details

Gene	Zygosity	Inheritance	HGVS description	Location: GRCh37 (hg19)	*Classification
KAT6A	Heterozygous	*De novo*	NM_006766.4:c.3116_3117del p.(Ser1039Ter)	Chr8: g.41795009_41795010del	Pathogenic

Test methodology

Proband whole genome sequencing by the 100,000 Genomes Project with analysis of the Charcot-Marie-Tooth disease (version 1.12) gene panel followed by in-house Sanger sequencing confirmation. Please note that the sensitivity of this test is limited by the types of detectable pathogenic variants, regions of low read depth coverage and incomplete ascertainment of disease-gene associations. Further information including read depth coverage is available on request. *Variants are classified using the ACMG/AMP guidelines (Richards et al 2015 Genet Med).

Patient phenotype

Muscle weakness; Progressive muscle weakness; Motor axonal neuropathy; Distal upper limb muscle weakness; Proximal muscle weakness in lower limbs; Proximal muscle weakness in upper limbs; Distal lower limb muscle weakness.

Evidence for variant classification using ACMG/AMP guidelines

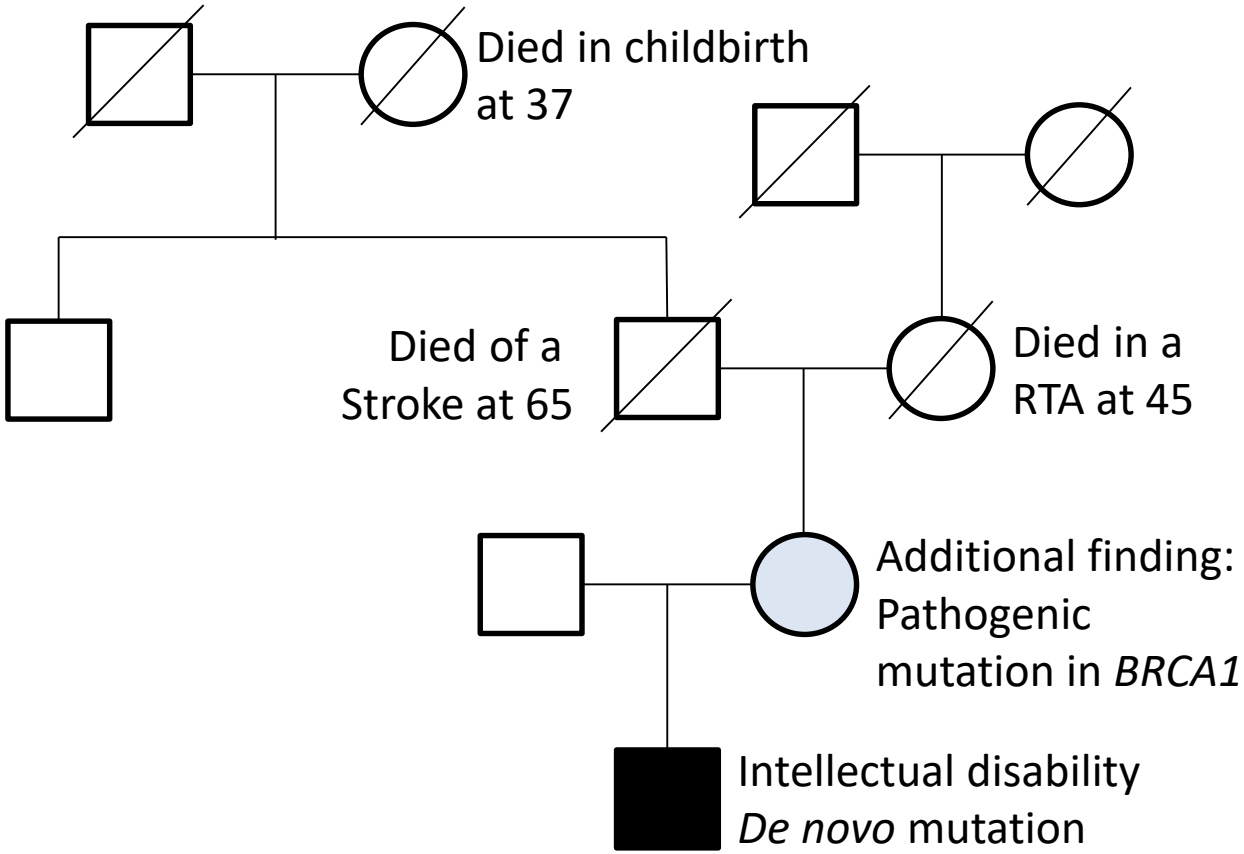
(Evidence code_ level) (Richards et al 2015 Genet Med)

- The p.(Asp96Asn) variant has been reported in 17 heterozygotes (12/9,434 East Asian, 2/15,391 South Asian, 1/12,892 Finnish, and 2/63,334 European (non-Finnish) individuals) in the Genome Aggregation database (http://gnomad.broadinstitute.org/). This raises the possibility that this is a low frequency non-pathogenic variant; however, the slow nerve conduction velocity phenotype associated with missense variants in this gene can be clinically asymptomatic (Verhoeven et al 2003 Am J Hum Genet 73(4):926-932, Gonzaga-Jauregui et al 2015 Cell Reg 12(7):1169-83).

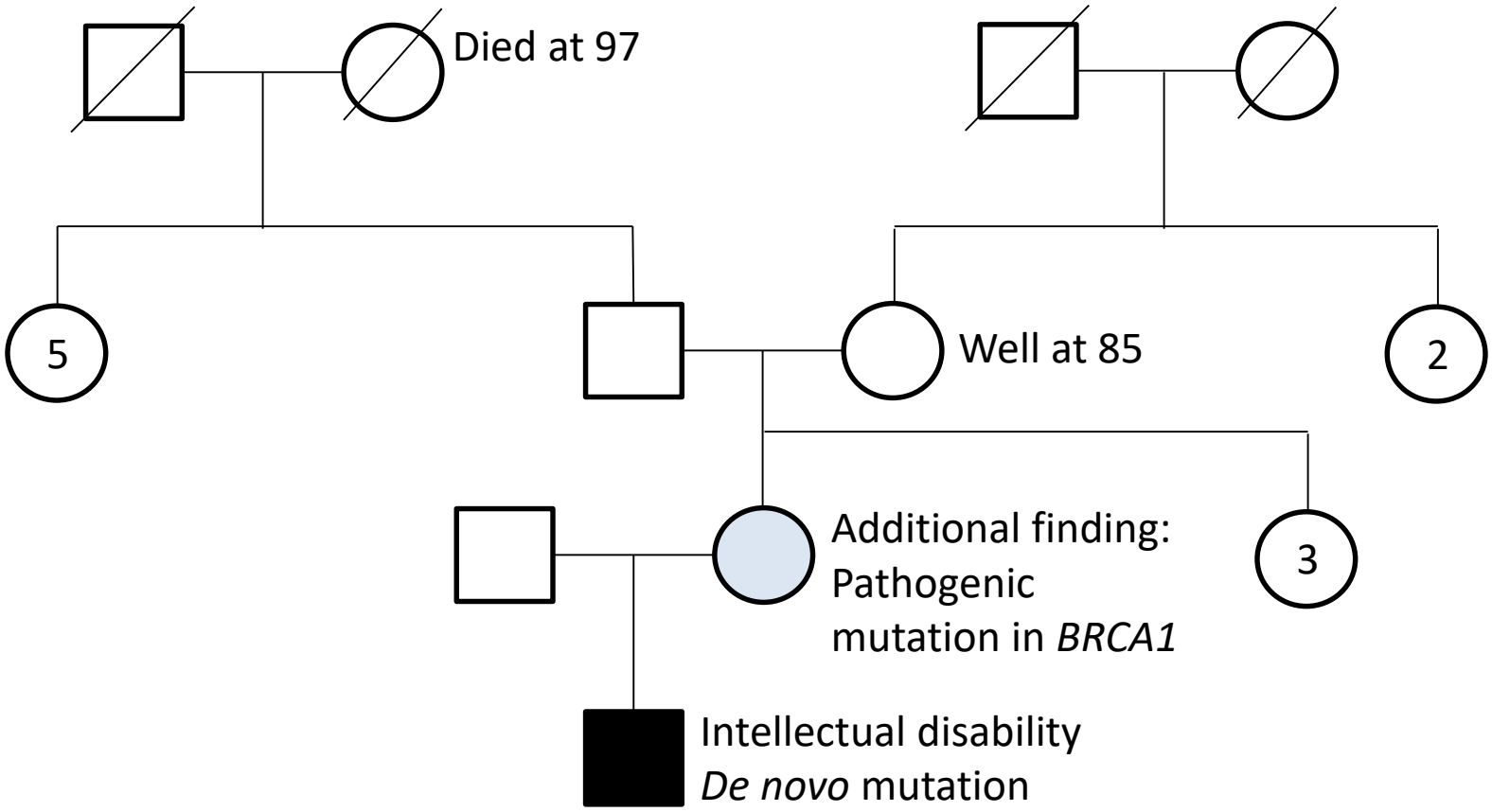
- The p.Asp96 residue is conserved in 6 out of 8 vertebrate species. The p.(Asp96Asn) variant is predicted to be tolerated by SIFT, to be benign by PolyPhen-2, and the Grantham score is 23, indicating a conservative substitution (Alamut Visual 2.10, Interactive Biosoftware) (BP4_Supporting).

Reports in family context

West London
NHS Genomic Medicine Centre



Reports in family context



NHS
National Institute for
Health and Clinical Excellence

Familial hypercholesterolaemia

Implementing NICE guidance

2nd. edition – January 2012

Clinical Guideline Implementation Tools

NICE clinical guideline 71

Simon Broome criteria

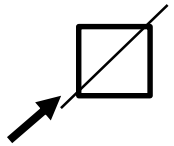
NHS West London NHS Genomic Medicine Centre

	Definite FH	Possible FH
	Total cholesterol >7.5mmol/l (adult) or >6.7mmol/l (child)	Total cholesterol >7.5mmol/l (adult) or >6.7mmol/l (child)
	LDL >4.9mmol/l (adult) or >4.0mmol/l (child)	LDL >4.9mmol/l (adult) or >4.0mmol/l (child)
OR	Tendon xanthomata in patient or first-degree relative	MI in FDR <60 MI in SDR <50
OR	Pathogenic mutation in *LDLR/APOB/PSCK9*	First or second degree relative meeting cholesterol/LDL criteria
	70% have a detectable mutation	**30% have a detectable mutation**

Impact of diagnosis

West London
NHS Genomic Medicine Centre

High cholesterol, but young and slim so still quite ‘low risk’



40
Total cholesterol 7.6
BMI 23

Management?

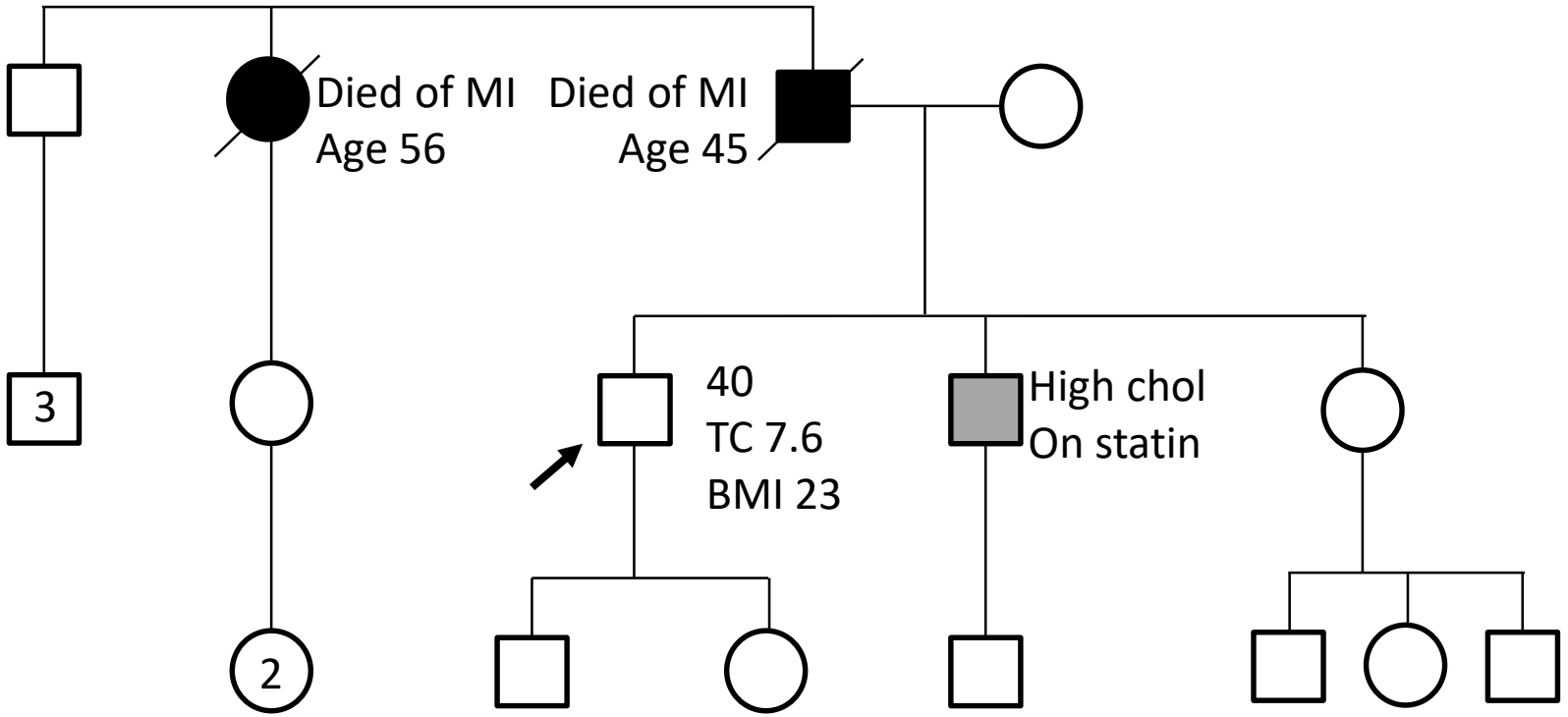
- Dietary advice
- Consider small dose of statin if no response to diet

Outcome?

- Patient at high risk of myocardial infarction in the near future

Impact of diagnosis

West London
NHS Genomic Medicine Centre



Diagnosis?

Impact of diagnosis

West London
NHS Genomic Medicine Centre

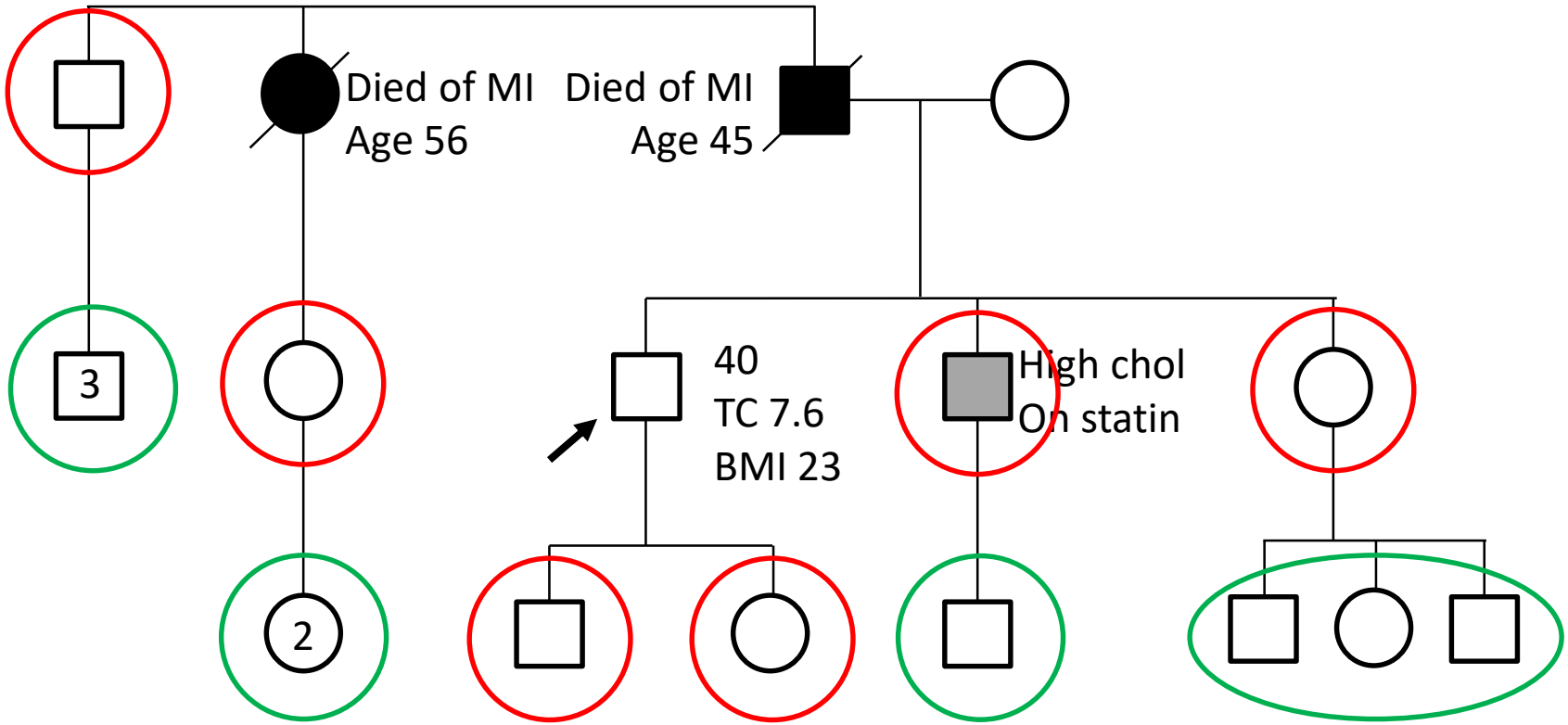
Management:

- Refer to lipid clinic
- High dose statin treatment
- Genetic testing

And other family members?

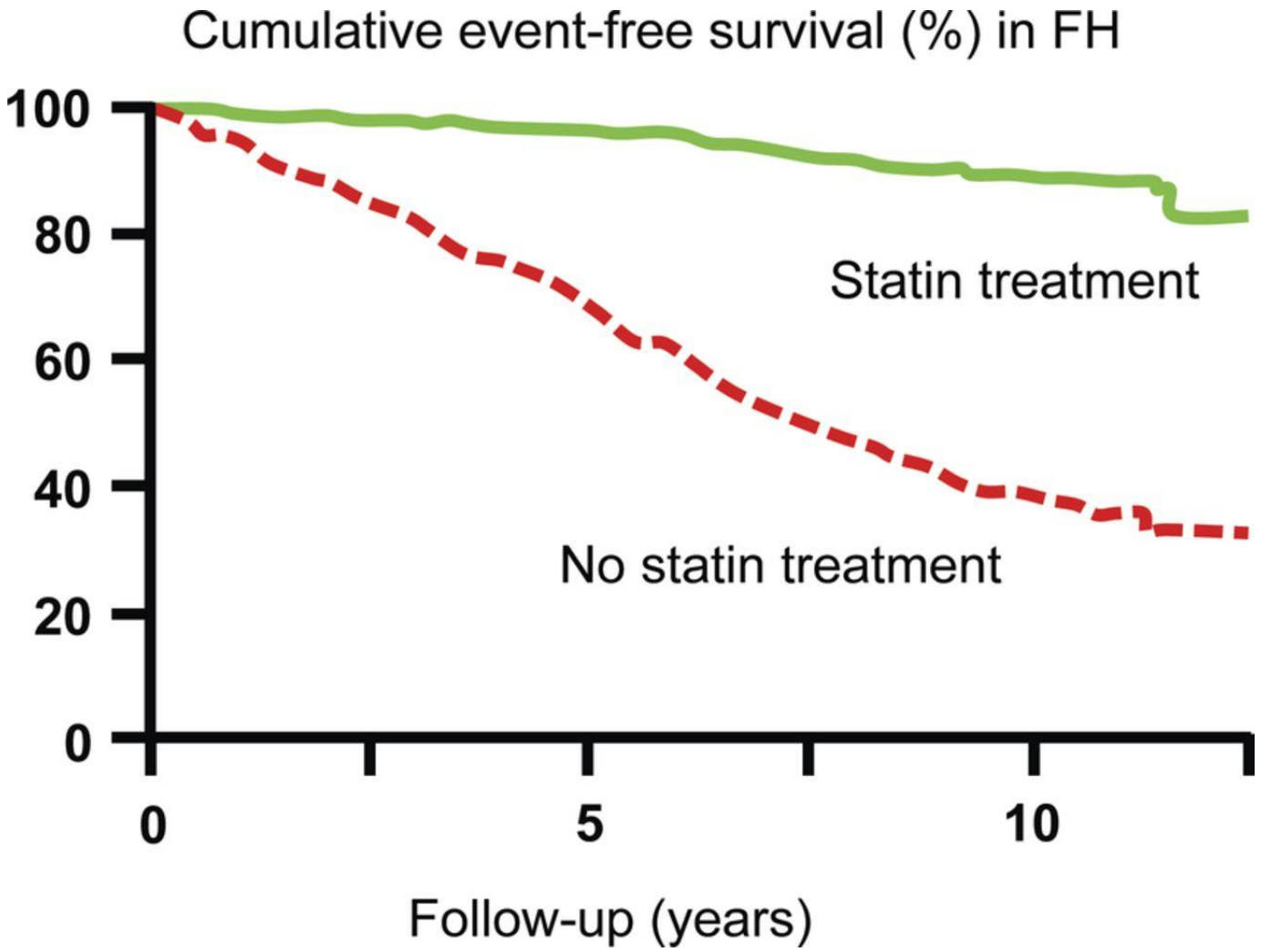
Impact of diagnosis

NHS
West London
NHS Genomic Medicine Centre



Family testing for FH using the genetic diagnosis

Kaplan–Meier curve estimates of cumulative CHD-free survival among individuals with familial hypercholesterolaemia according to statin treatment (P < 0.001 for difference).

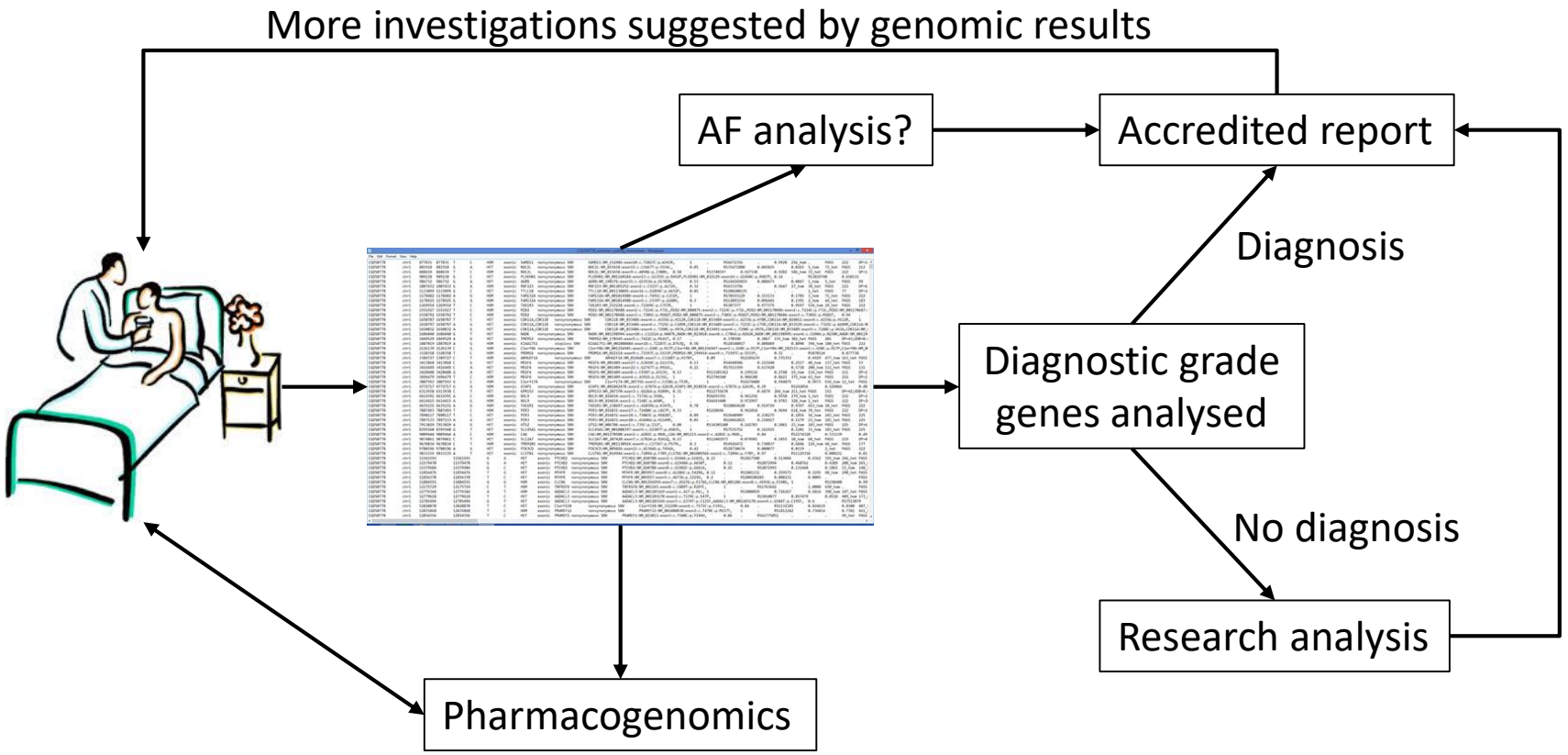


Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273

European Heart Journal

Use of genomics in healthcare

NHS
West London
NHS Genomic Medicine Centre



Conclusions

NHS West London NHS Genomic Medicine Centre

- Good quality advice depends on detailed, accurate information (the test report)
- Interpretation of genomic variation in the clinical context is a highly skilled art as well as a science
- Getting it wrong can have major clinical implications
- Results must be interpreted in the context of the clinical situation and family history
- A negative genetic test rarely ‘rules out’ a diagnosis
- Genetic and genomic testing is a fantastic diagnostic tool, but like other diagnostic tools has false positive and negative outcomes; these may change over time
- Genomic data is (currently) better at explaining existing phenotypes than predicting future disease