Unintended consequences; cautionary tales from a genomics approach to diagnostics

Dr Frances Elmslie
Consultant Clinical Geneticist
St George's, University of London
Chair, Clinical Genomics Clinical Reference Group

Audience participation

- Sigmoidoscopy for bowel screening
- MRI scan
- Whole Genome Sequencing

- NB DDD survey

The law of unintended consequences, often cited but rarely defined, is that actions of people—and especially of government—always have effects that are unanticipated or unintended. Economists and other social scientists have heeded its power for centuries; for just as long, politicians and popular opinion have largely ignored it.

The Concise Encyclopaedia of Economics 2nd Ed 2008: Rob Norton

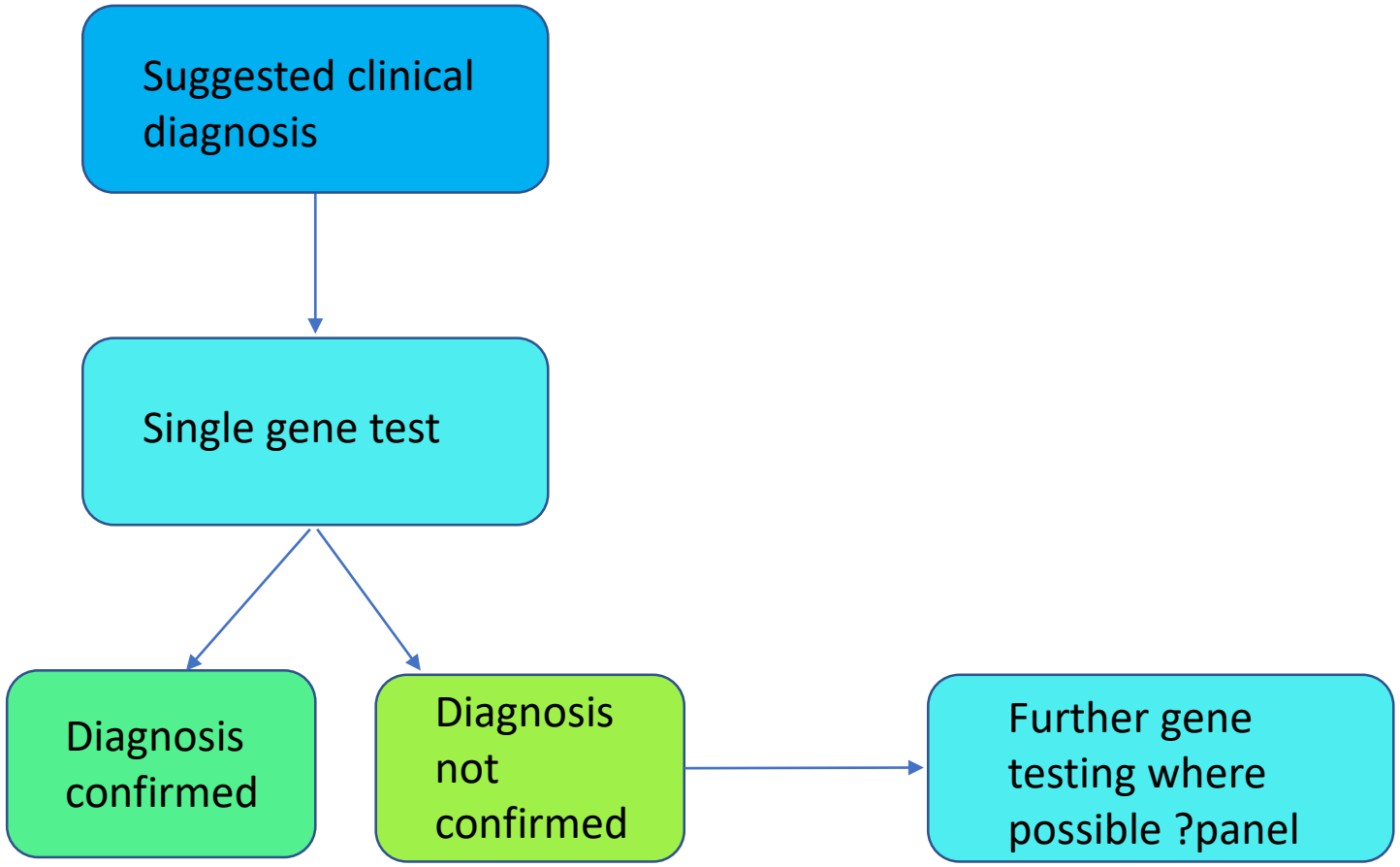
The potential for unintended consequences in genomic testing is not new.

There has always been a need to correlate genetic findings with phenotype, and to determine whether a genetic variant is causative of the condition.

What is new…

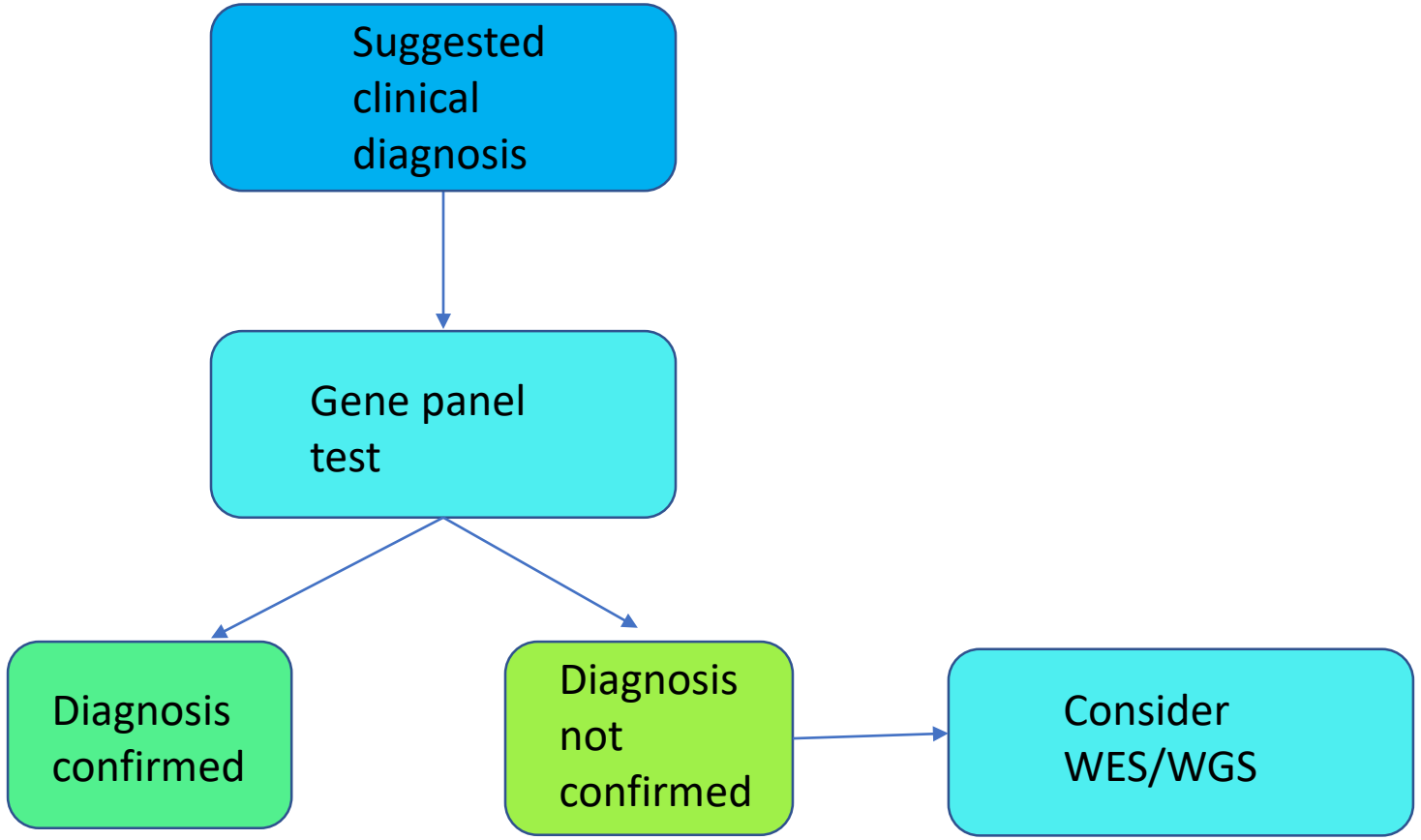
- Is the scale and the complexity
  - Variants in genes where a clinical diagnosis is non-specific
  - Phenotype is not what is expected for a variant in that gene
  - Wider availability of genomic testing for health professionals and patients
  - Dilution in scientific expertise for diagnostic testing of known genes
  - Patients may choose to have access to whole genome data

Approaches to genetic testing (1)



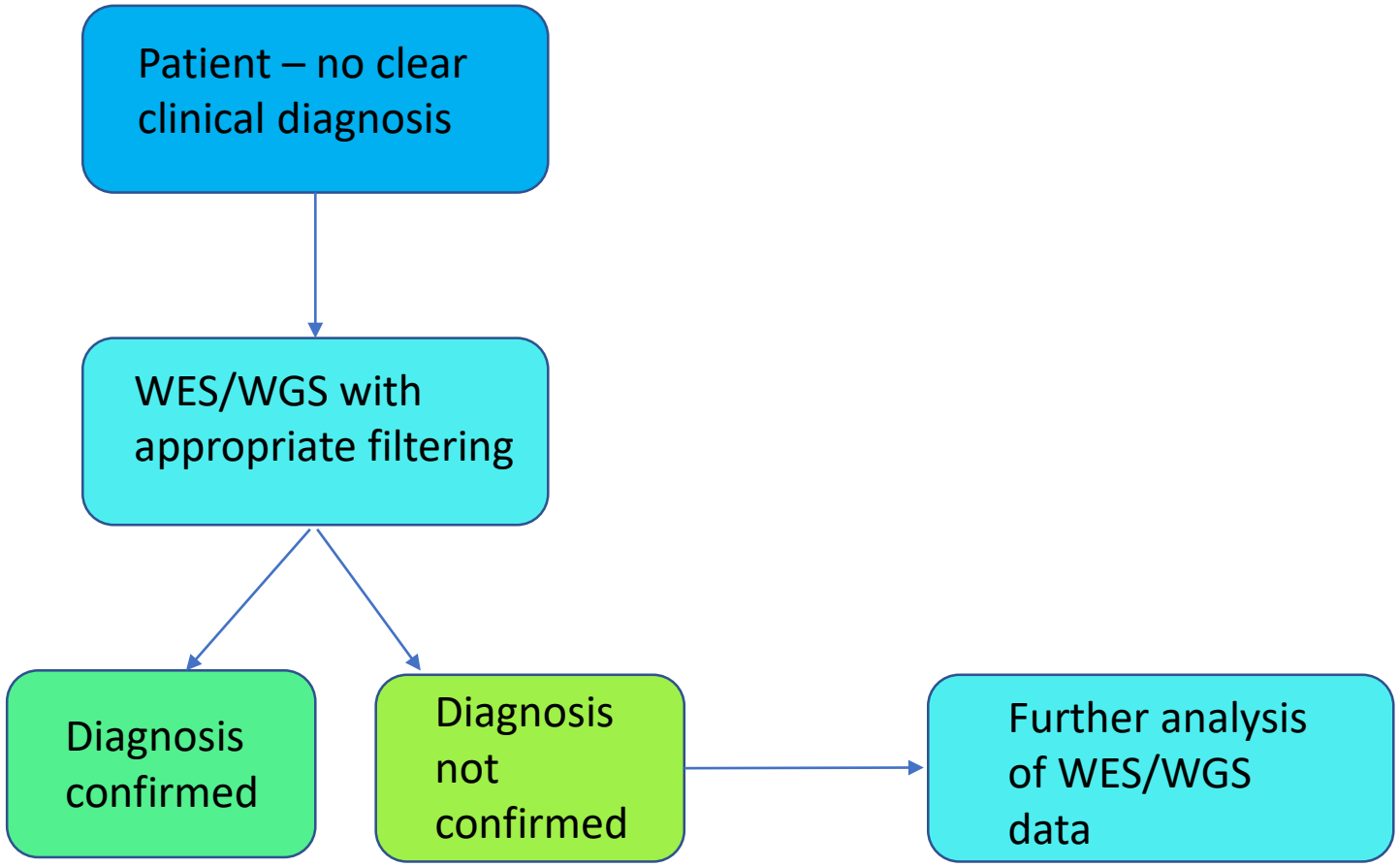
For example:
Huntington's disease
HMSN type 1A
PKD1/2
TSC1/2

Approaches to genetic testing (2)



For example:
Noonan syndrome
Marfan and related disorders
Epilepsy
HMSN
Ataxia

Approaches to genetic testing (3)



For example:
Severe intellectual disability +/- other features..
And many more in the future

What are the unintended consequences of whole genome approach?

1. Unintended benefit…for example..
2. Requirement for additional investigations to prove or refute diagnosis
3. Misdiagnosis – potential for litigation
4. Effect on further management of proband and family
5. Secondary findings
6. Incidental findings

Three illustrative cases

Case 1:

- 2 year old child referred by paediatric neurologist to specialist tuberous sclerosis service
- Child had presented age 9 months with seizure-like episodes
- Fully investigated – EEG/MRI brain/metabolic bloods/epilepsy gene panel test
- EEG initially inconclusive but on repeat reported as normal
- Episodes settled
- On re-evaluation felt not to be seizures – child discharged by neurologist

However……

- Some months later….
- Gene panel result
  - Missense variant in TSC1 identified

- Referred to specialist TSC clinic at St George’s for further evaluation

TSC Diagnosis: Major Criteria

- Facial angiofibromas or forehead plaque[1]
- Nontraumatic ungual/ periungual fibroma[2]
- Hypomelanotic macules (> 3)[3]
- Shagreen patch (connective tissue naevus)[3]
- Multiple retinal nodular harmartomas[3]
- Cortical tuber[a4]

[a]Co-occurrence of cerebral cortical dysplasia and CWMRML = 1 major feature.
All figures used with permission.

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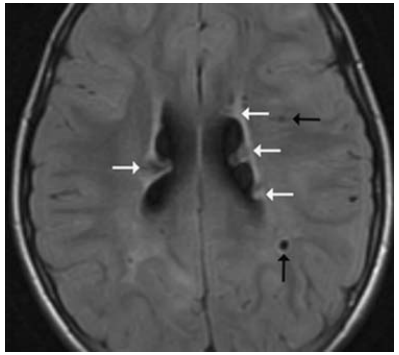
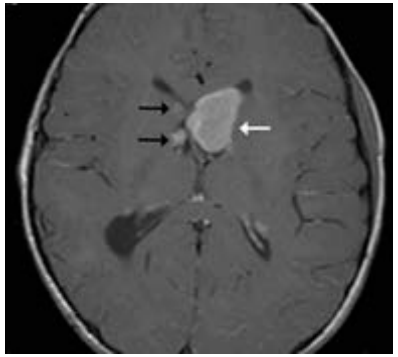
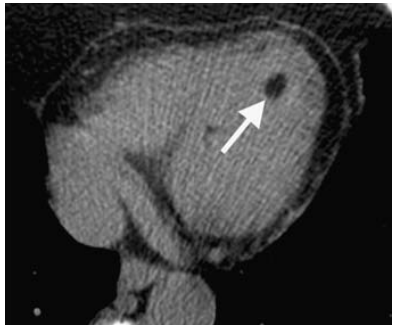
TSC Diagnosis: Major Criteria

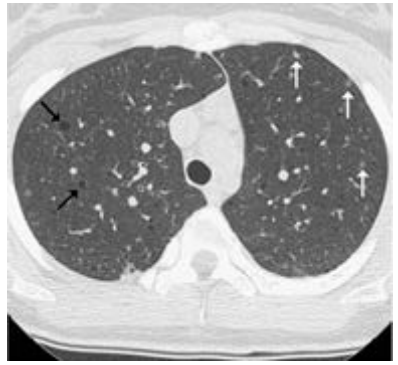
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma: single or multiple

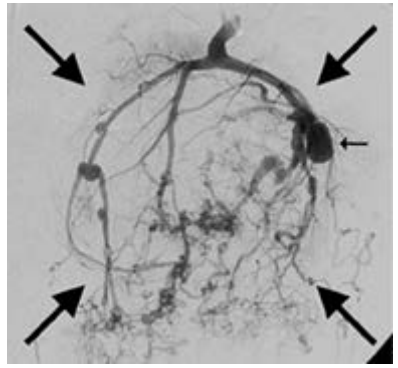






- Lymphangio-myomatosis (LAM)[a]
- Renal angio-myolipoma (AML)[a]





[a]In patients with both LAM and AML, another feature must be identified before a *definite* diagnosis is assigned.
Figures from Baskin. *Pediatr Radiol*. 2008;38:936-952, with permission.

Further assessment

- Clinical examination – no features of TSC
- MRI review – normal
- Echocardiogram - normal
- Renal US - normal
- Mother found to carry TSC1 variant – no features of TSC
- Reassured – variants in TSC1/2 common
- Mother remained very anxious and requested further follow up for her child

Unintended consequence - 2

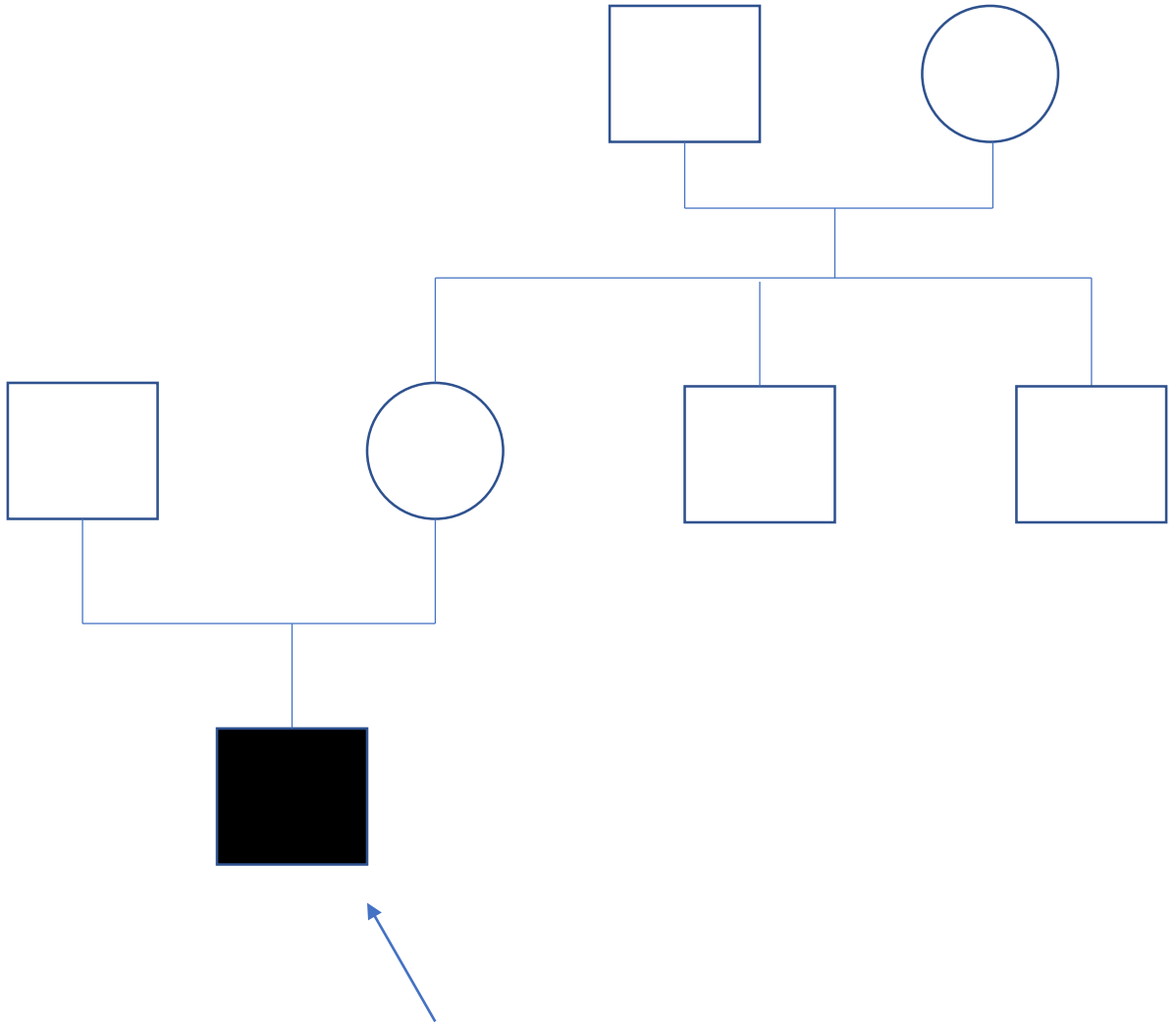
- Child subjected to further evaluation to disprove a suggested diagnosis
- Avoided unintended consequence -3 - misdiagnosis – label of TSC applied and consequent life-long surveillance

- Panel test requested early in diagnostic pathway – likely to become more routine practice in future

Case 2

- Boy, now aged 5
- Learning disability – no diagnosis
- Recruited to DDD study
- PGK1 missense variant identified by WES – classed as variant of uncertain significance

Case 2



PGK1

- Mutations in PGK1 cause X-linked recessive disorder phosphoglycerate kinase deficiency
- Associated with haemolytic anaemia in 60% of patients, myopathy, rhabdomyolysis but also learning disability

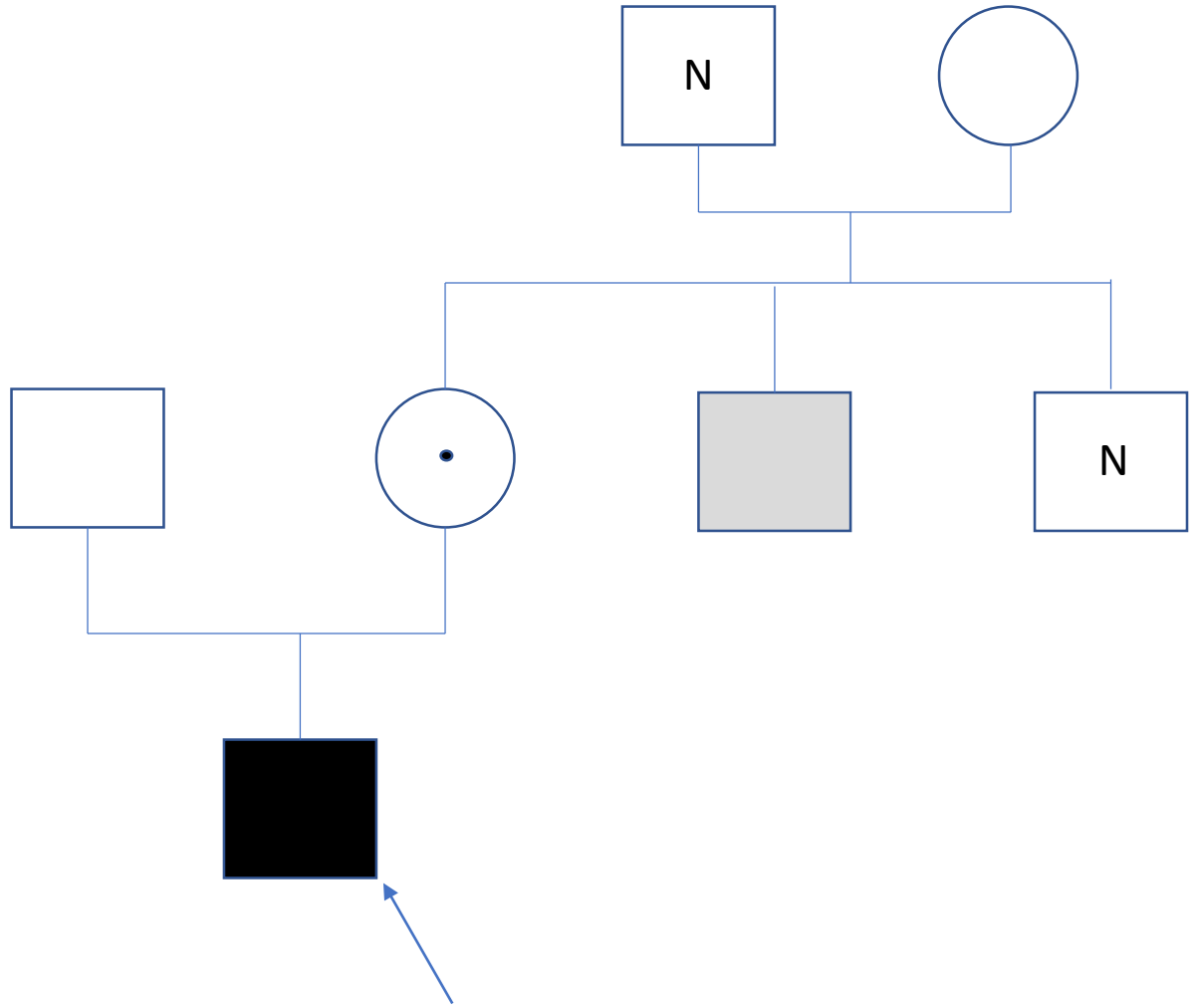
- Further tests requested in child:
  - FBC and film
  - LFT
  - Phosphoglycerate kinase levels

Case 2

- Routine bloods normal BUT phosphoglycerate kinase levels ↓
- So variant is likely pathogenic, but is it causing his learning disability?

Case 2

- Further testing showed that his mother carried variant.
- Her brothers consented to testing – one carried the variant and had reduced phosphoglycerate kinase levels but no learning disability.



Case 2 – further results

- De novo heterozygous variant in a novel gene identified in DDD.
- Several other cases around the world of children with variants in this gene.

- Therefore this mutation is likely cause of learning disability.

- But what about phosphoglycerate kinase deficiency?
- Implications for family – unintended consequence 4 and 5

Case 3

- 43 year old gentleman
- Fit and well
- Decided to have whole genome sequencing ‘for fun’
- Pathogenic variant in MYBPC3 identified
- Sought advice from GP who referred to genetics

MYBPC3

- Homozygous or heterozygous mutations in MYBPC3 are associated with hypertrophic cardiomyopathy of variable age of onset
- Shows incomplete penetrance

MYBPC3

- Family history uninformative – father deceased but not of cardiac cause.
- Cardiac investigations all normal including cardiac MRI..
- Variant confirmed in diagnostic lab – classified as likely pathogenic.

- What do we do now?
- Unintended consequence - 6

What can be done to mitigate against unintended consequences?

- That is.. to ensure that they are in fact intended?

- Appropriate consent
  - Consider secondary/incidental findings
  - Potential need for additional investigations
- Consider the family at instigation of genomic testing
- Work with clinical geneticists/scientific colleagues

Conclusions

- Unintended consequences are not all bad – may have positive health benefits
- We just need to consider them and use whole genome technology wisely