Presymptomatic Genetic Testing

David FitzPatrick

Genetic Testing Jan 2014

Principals of Clinical Ethics

- **Beneficence**
  - action should have a net benefit to the patient
- **Autonomy**
  - action should depend on an informed decision by the patient
- **Justice**
  - action should not be detrimental to society as a whole

Genetic Testing

- medical and non-medical reasons

A young man dies in a motor-cycle accident, his family are clear that he wished to donate his organs for transplantation.

BUT he explicitly wished that the donated organs were only to be used for treatment of “white” people.

Which component of clinical ethics is most clearly conflicting with this request?

The parents of a young girl with a rare untreatable genetic condition causing severe learning disability have requested that a paediatric surgeon performs an oophorectomy.

The purpose of the request is to keep the girl prepubertal to help with lifting and handling.

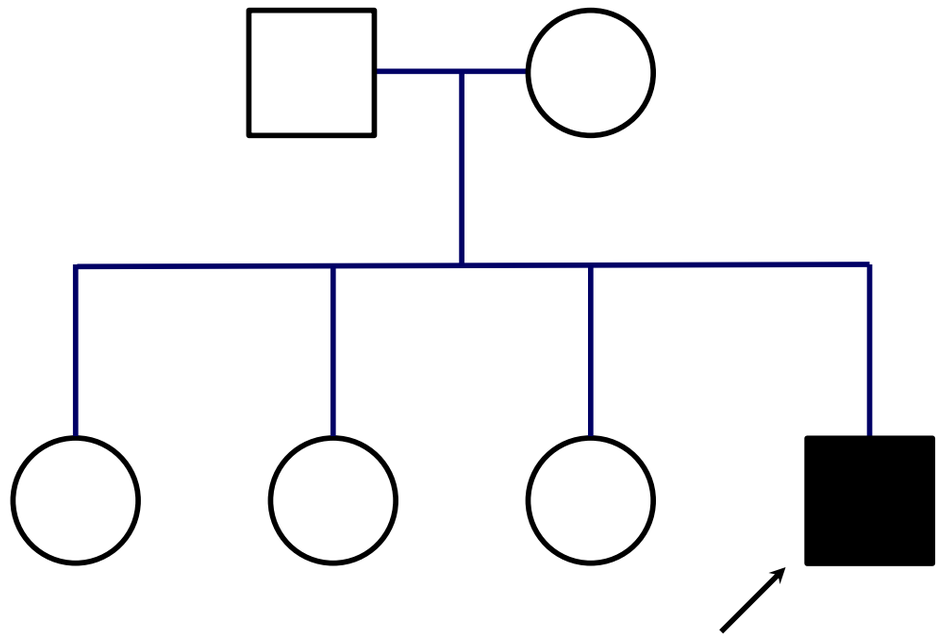
Which component of clinical ethics is most clearly conflicting with this request?

Genetic Testing and Screening

- population screening
- presymptomatic testing
  - for medical reasons
  - for non-medical reasons

David FitzPatrick
Genetic Testing Jan 2014

Newborn Screening in Scotland



phenylketonuria

hypothyroidism

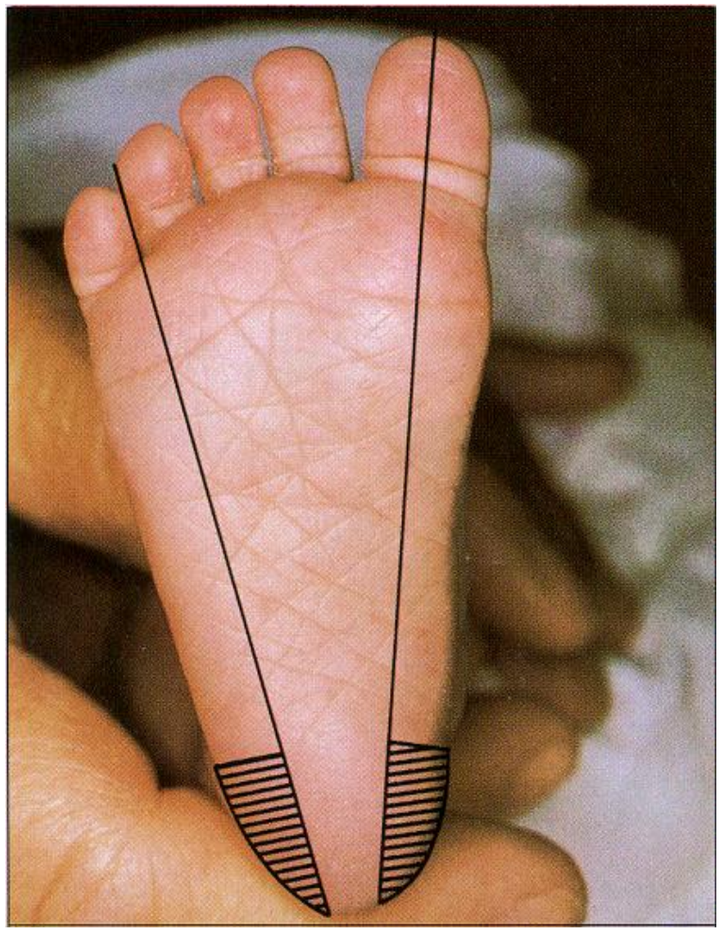
cystic fibrosis

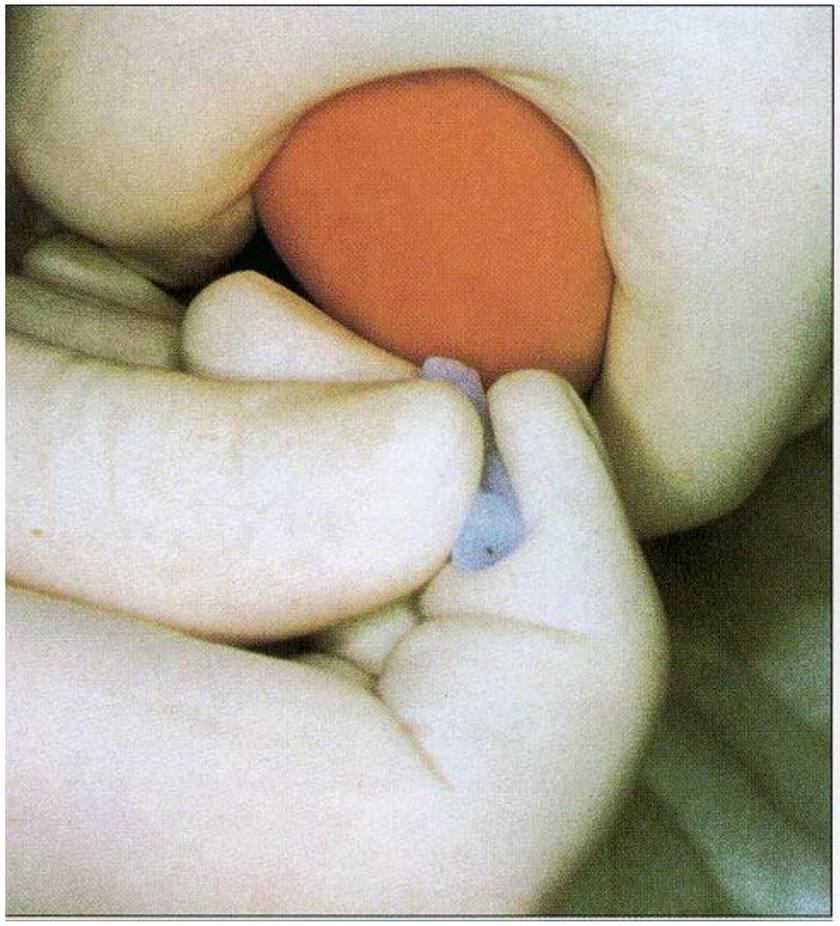
hearing loss

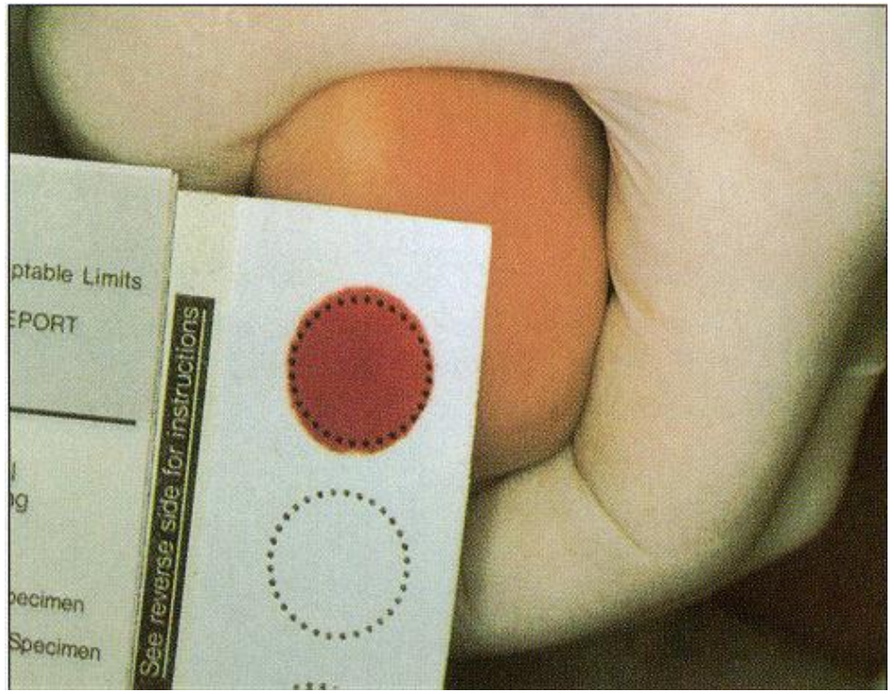
1916 - 1995

Dr Robert (Bob) Guthrie

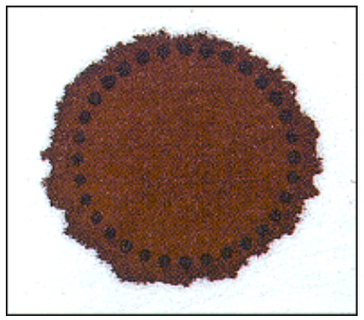
David FitzPatrick
Genetic Testing Jan 2014







http://www.tdh.state.tx.us/newborn/newborn.htm

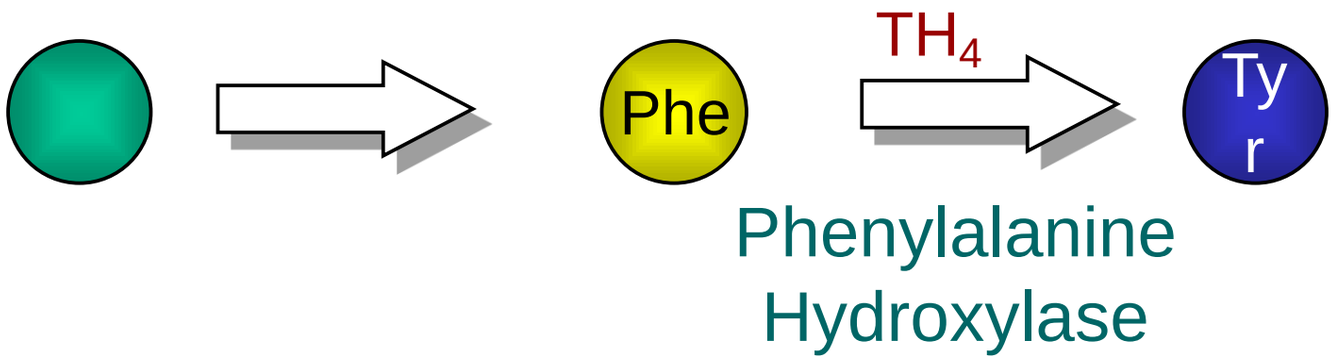


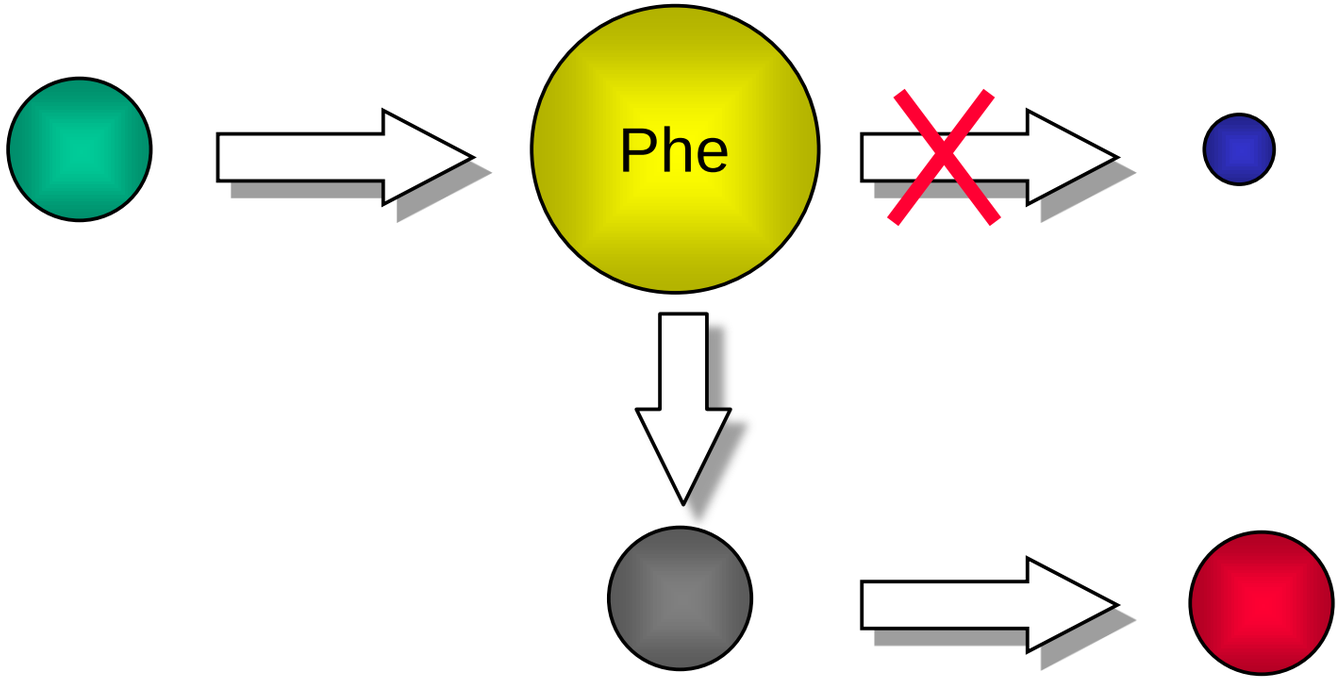
David FitzPatrick
Genetic Testing Jan 2014

Reporting and Recall Procedure for PKU

- <240μM ➡ Negative
- 240-600μM ➡ Repeat
- >600μM ➡ Refer to Metabolic Clinic

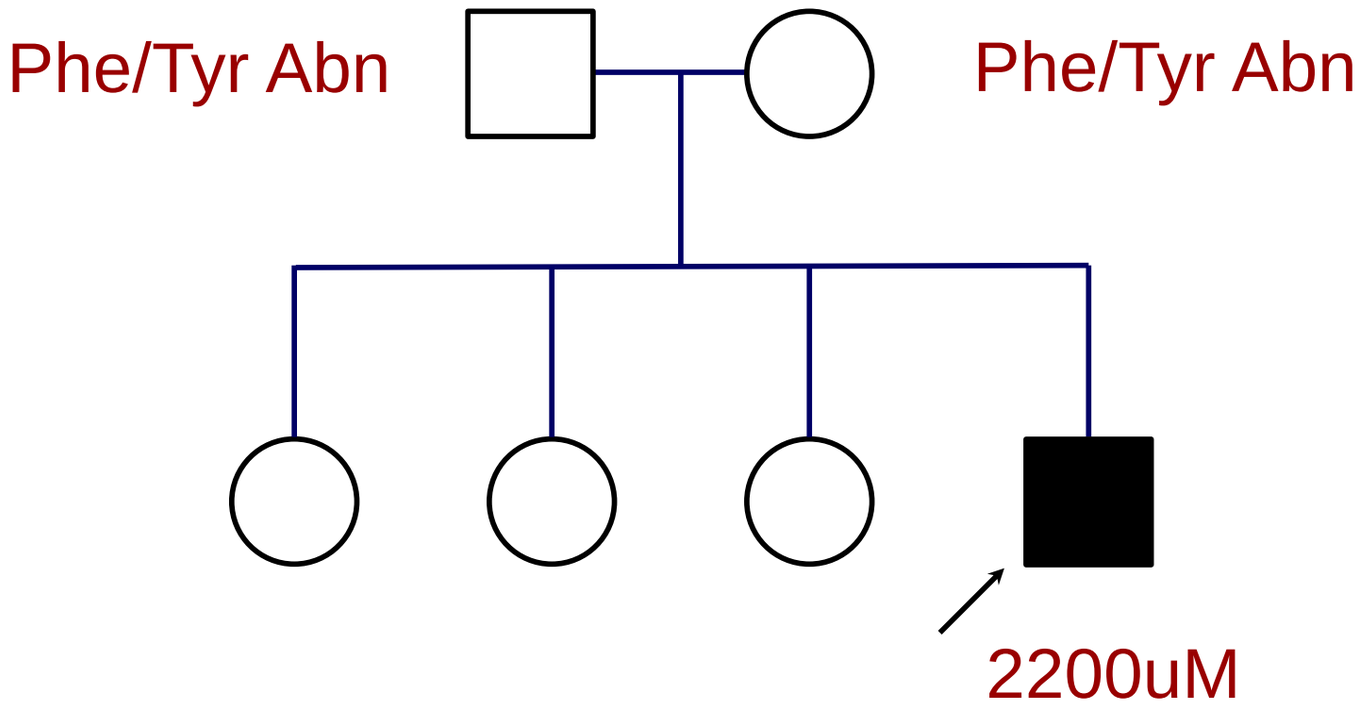
Inborn Errors of Metabolism





David FitzPatrick
Genetic Testing Jan 2014

Further Tests



- phenylalanine hydroxylase
- liver-specific enzyme
- rare malignant forms of PKU due to biopterin abnormalities

Clinical Features: Phenylketonuria [PKU]

- clinically silent in first months
- eczema
- hypopigmentation
- severe developmental delay
- “mousey” smell to urine

Treatment: Phenylketonuria [PKU]

- phenylalanine-restricted diet
- started <21days
- continue diet for life
- normal outcome in most children

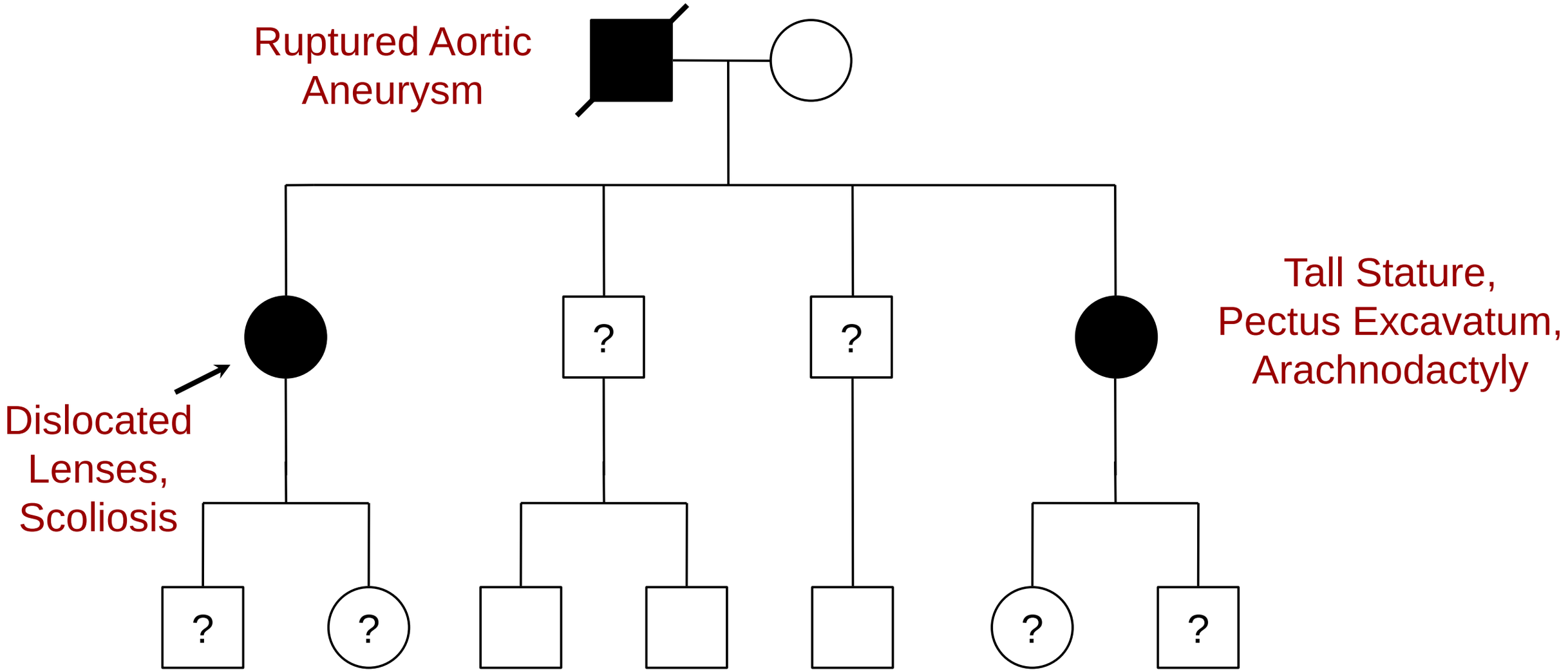
Wilson and Jungner (WHO, 1968)

- well-defined disorder ☑
- known incidence ☑
- significant morbidity or mortality ☑
- effective treatment available ☑
- period before onset during which intervention improves outcome ☑
- ethical, safe, simple and robust screening test ☑
- cost-effect ☑

Genetic Testing and Screening

- population screening
- presymptomatic testing
  - for medical reasons
  - for non-medical reasons

Marfan Syndrome



David FitzPatrick
Genetic Testing Jan 2014

Marfan Syndrome

autosomal dominant

mutations in FBN1 gene (15q)

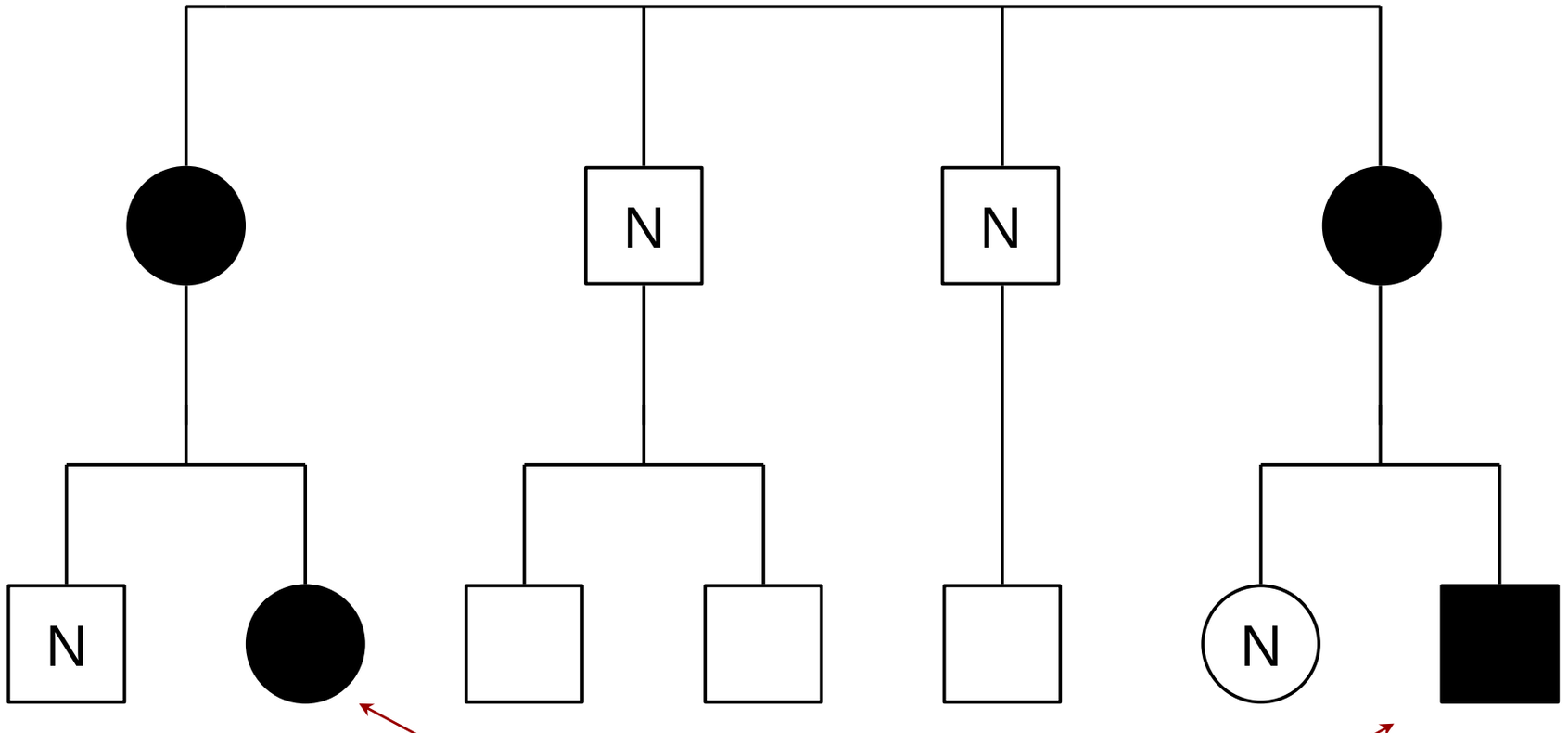
connective tissue disorder

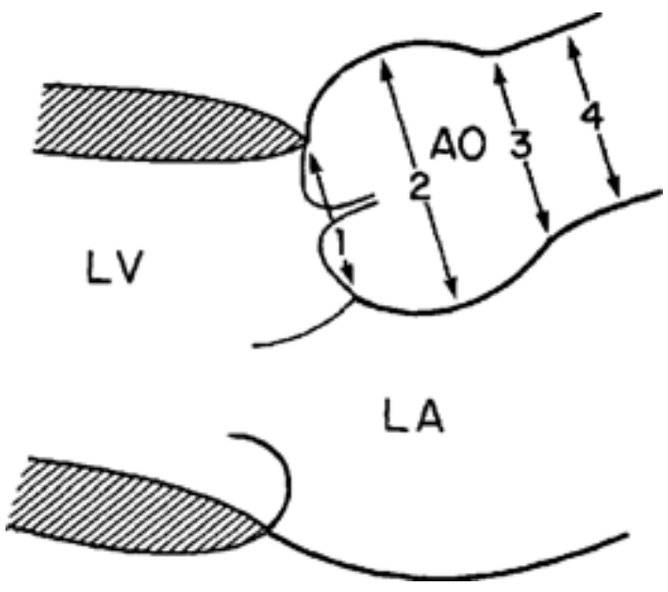
Skeletal Complications

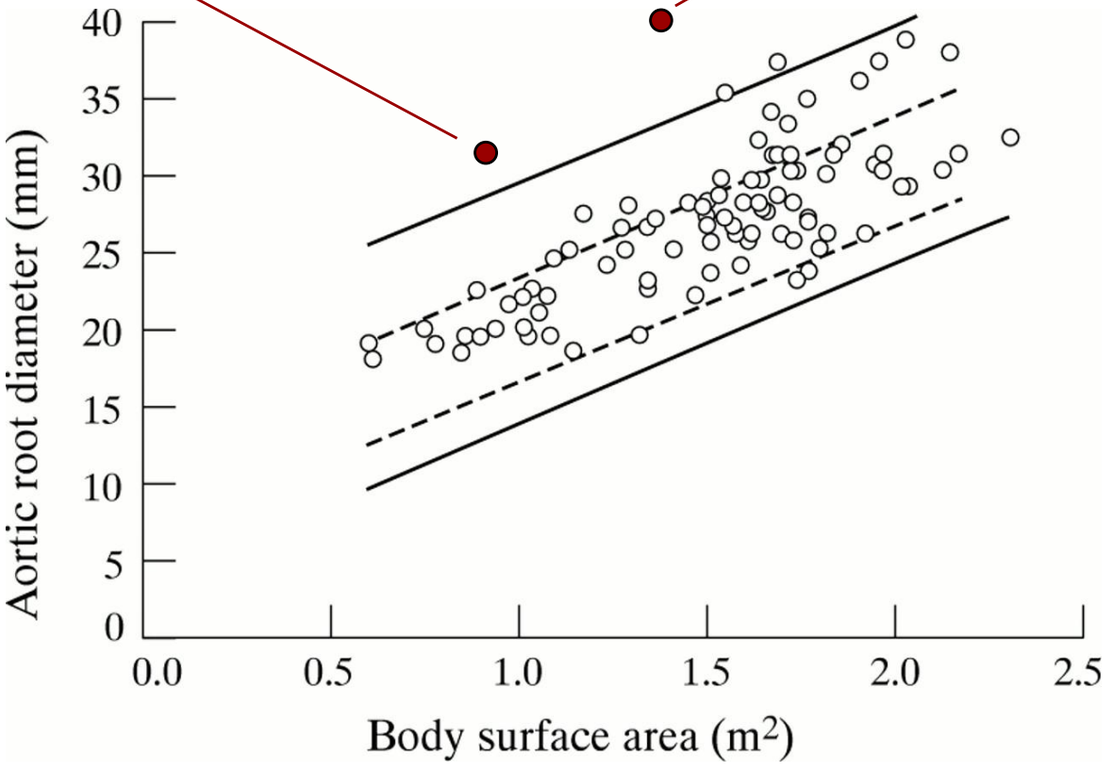
Ophthalmological Complications

Cardiac Complications

David FitzPatrick
Genetic Testing Jan 2014


N
N
N
N


AO
1
2
3
4
LV
LA


Aortic root diameter (mm)
0
5
10
15
20
25
30
35
40
0.0
0.5
1.0
1.5
2.0
2.5
Body surface area (m²)

Presymptomatic Genetic Testing

- does not always require DNA test
  - clinical examination
  - investigations
- if done for medical reasons
  - should result in a preventative intervention
  - family implications need to be considered
- testing of children is appropriate if intervention starts in childhood

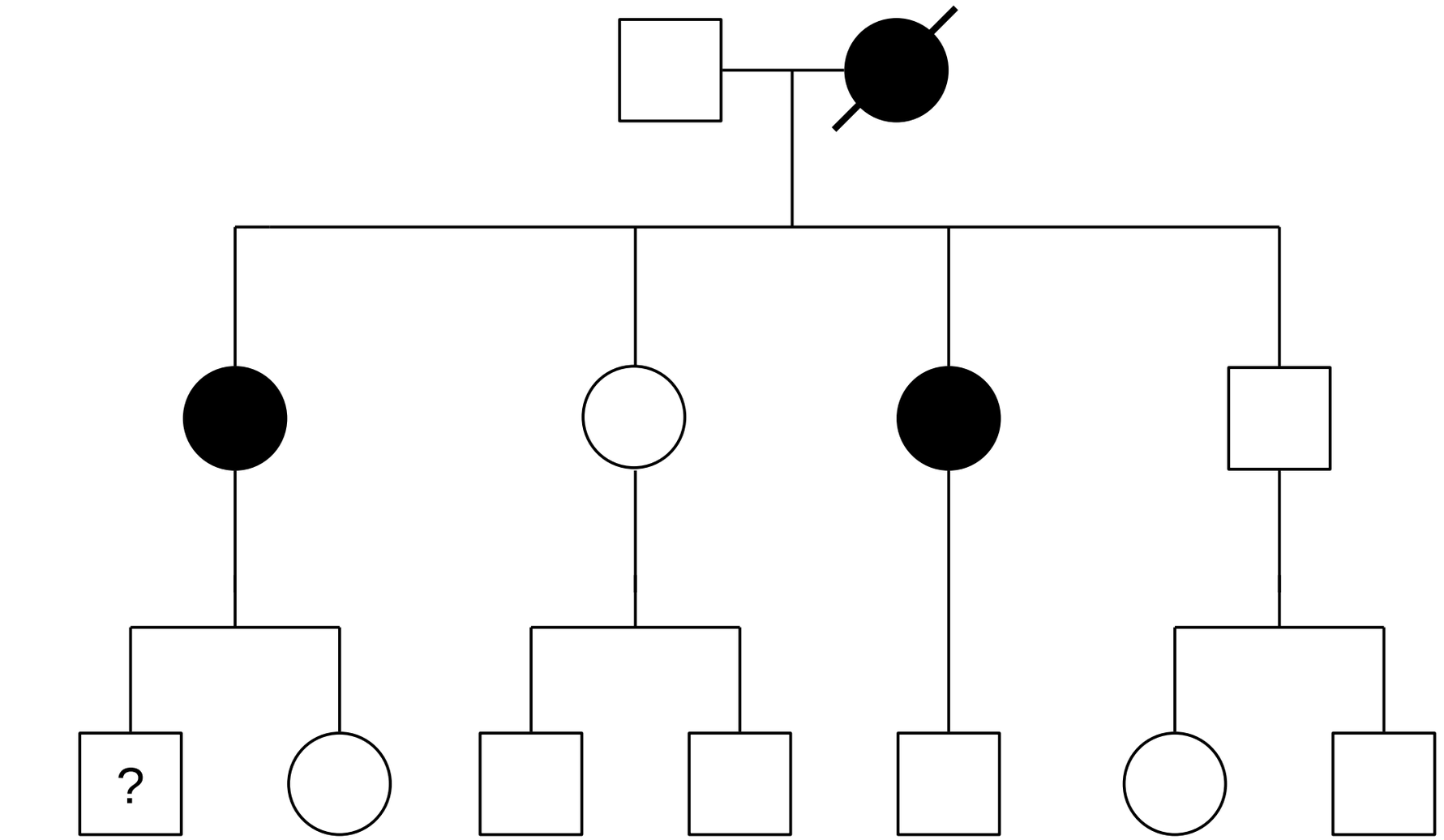
Presymptomatic Genetic Testing

- many genetic conditions with interventions
  - familial cancer syndromes
    - BRCA1/2
    - von Hippel Lindau etc.
  - genodermatosis
    - neurofibromatosis
    - tuberous sclerosis
  - cardiac genetics
    - long QT syndrome
    - HOCM
  - specific dysmorphic syndromes
    - Beckwith Weidemann syndrome
    - simpson-golabi-behmel etc.

Genetic Testing and Screening

- population screening
- presymptomatic testing
  - for medical reasons
  - for non-medical reasons

Adult-Onset Neurodegenerative Disorders



David FitzPatrick
Genetic Testing Jan 2014

Adult-Onset Neurodegenerative Disorders

- autosomal dominant
- DNA diagnosis available
- no effective treatment
- no accurate prediction of age of onset

Huntington Disease

Neuropathology

Caudate & Basal Ganglia

Atrophy

Cortical Atrophy

Clinical Features

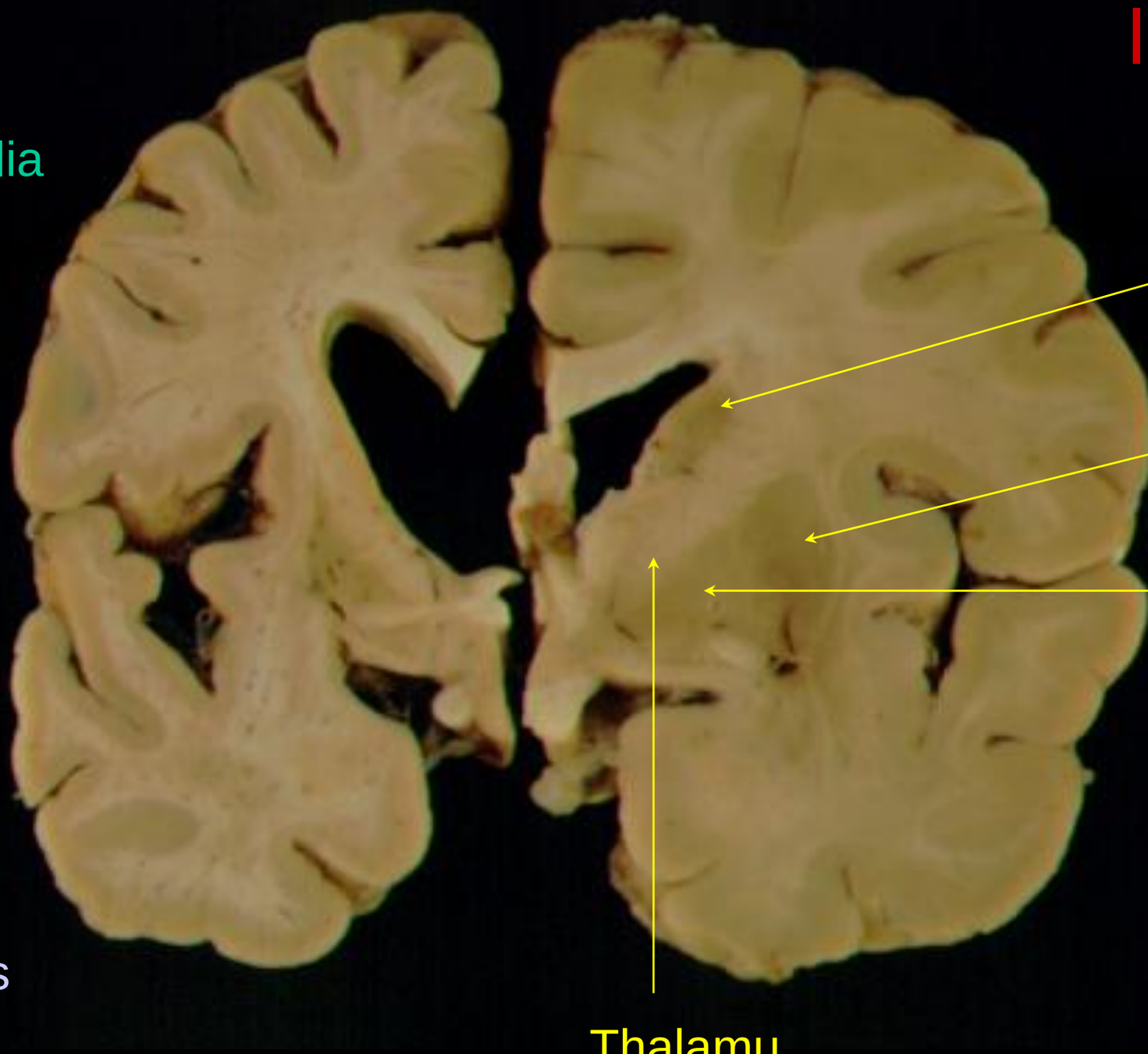
Psychiatric

depression
dementia
psychosis
addiction
impulse control
suicide

Movement Disorder

involuntary movements
ataxia
dystonia
dysarthria

Normal



David FitzPatrick
Genetic Testing Jan 2014

Presymptomatic Testing: Problems

- no medical benefit
- side-effects unknown
- many people request test to confirm they do not have the condition
- insurance/mortgage problems

Presymptomatic Testing: Benefits

- removes uncertainty
- clarifies reproductive risks
- career/lifestyle choices

information visit

~1 month

semi-structured questionnaire

~1 month

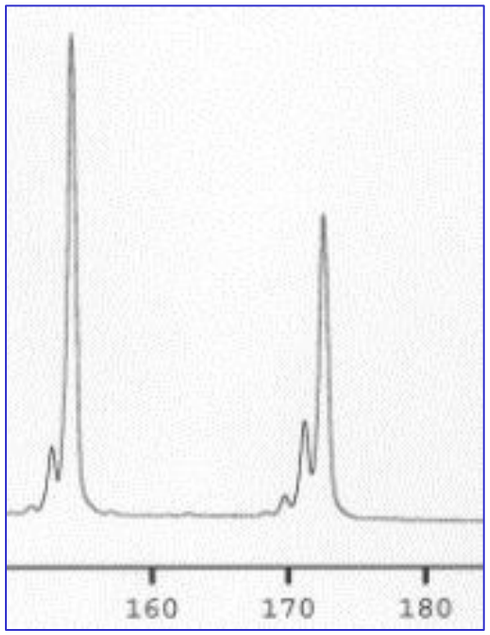
coping strategies appointment

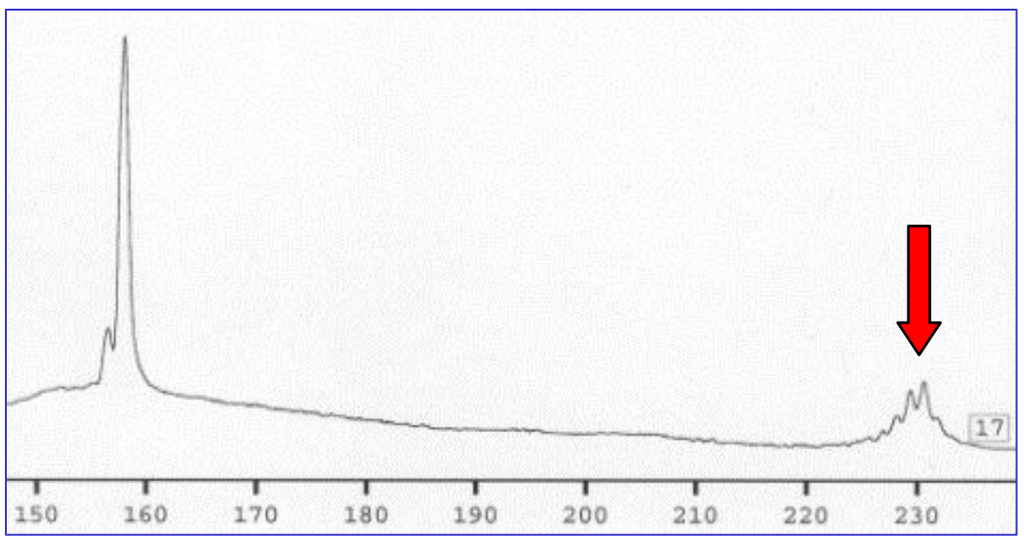
~1 month

blood sample and consent

~2 weeks

resul t





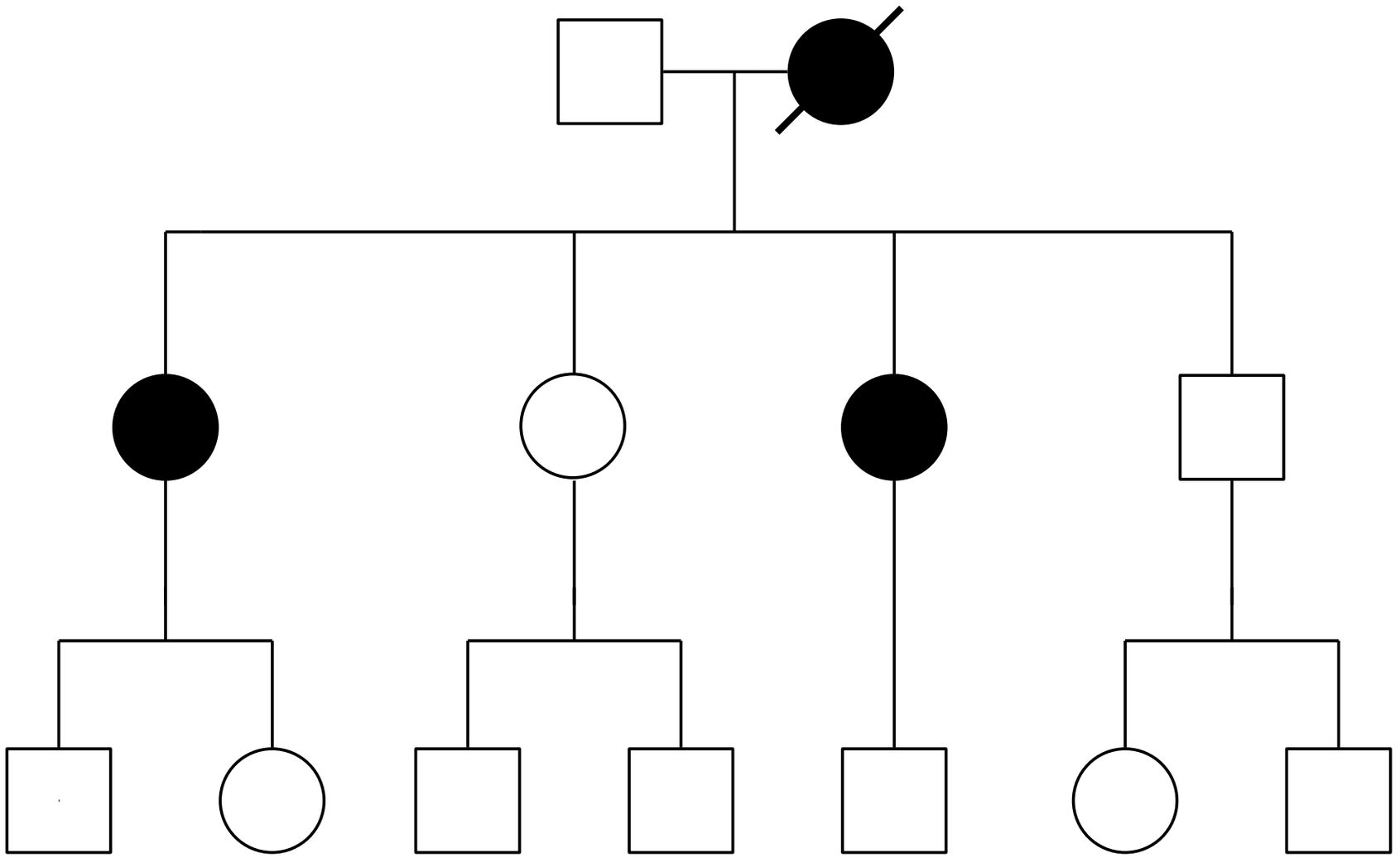
follow-up appointments

1 week,
1 month,
3 months etc.

Presymptomatic Genetic Testing

- for non-genetic reasons
  - performed only in specialist units
  - restricted to adults
  - obligate carriers are a problem
  - may be done for reproductive reasons alone
  - should become rarer

Adult-Onset Neurodegenerative Disorders



David FitzPatrick
Genetic Testing Jan 2014