Presymptomatic Genetic Testing
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
Newborn Screening in Scotland

- phenylketonuria
- hypothyroidism
- cystic fibrosis
- hearing loss
1916 - 1995
Dr Robert (Bob) Guthrie
http://www.tdh.state.tx.us/newborn/newborn.htm
Reporting and Recall Procedure for PKU

• <240μM ➔ Negative
• 240-600μM ➔ Repeat
• >600μM ➔ Refer to Metabolic Clinic
Inborn Errors of Metabolism

Phenylalanine Hydroxylase

Phe $\rightarrow$ TH$_4$ $\rightarrow$ Tyr

Phe $\xrightarrow{\text{X}}$ 

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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 <21 days
- 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-effectiveness

Wilson and Jungner (WHO, 1968)
Genetic Testing and Screening

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

Ruptured Aortic Aneurysm

Dislocated Lenses, Scoliosis

Tall Stature, Pectus Excavatum, Arachnodactyly
Marfan Syndrome

autosomal dominant

mutations in FBN1 gene (15q)

connective tissue disorder

Skeletal Complications

Ophthalmological Complications

Cardiac Complications
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

[Genetic tree diagram]

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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

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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

semi-structured questionnaire

~1 month

coping strategies appointment

~1 month

blood sample and consent

~1 month

result

~2 weeks

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

Lauren 15 yrs