

THE ROLE OF GENETIC COUNSELLING IN AMINO AND ORGANIC ACIDAEMIAS

Michael Urban

Division of Molecular Biology and Human Genetics

Stellenbosch University and Tygerberg Hospital



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Genetic counselling

- ..is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease
- Includes:
 - ▣ Assessment of chance of disease occurrence or recurrence
 - ▣ Education about inheritance, testing, management, prevention, resources and research
 - ▣ Counselling to promote informed choices and adaptation to the risk of the condition

Genetic counselling - some principles



- Trust:
 - ▣ Confidential, non-judgemental
- Information:
 - ▣ Full relevant information
- Decision-making:
 - ▣ Informed, autonomous, supported
- Sensitive to:
 - ▣ Psychosocial issues
 - ▣ Family issues
 - ▣ Cultural issues

Testing for metabolic disease



- Metabolite
- Enzyme assay
- Molecular genetic

- But:
 - ▣ All of these tests carry ‘genetic information’
 - ▣ The meaning of the information depends on the specific clinical context

Testing contexts

Context	Timing	Genetic counselling
CLINICAL TESTING		
Screening	Newborn	No
Diagnostic	When symptomatic	Yes
Prenatal diagnosis	Pregnancy	Yes
Carrier testing	Reproductive age	Yes
RESEARCH TESTING	?	?

Who provides genetic counselling?



- Genetic counsellors and nurses
- Medical geneticists
- Other health professionals

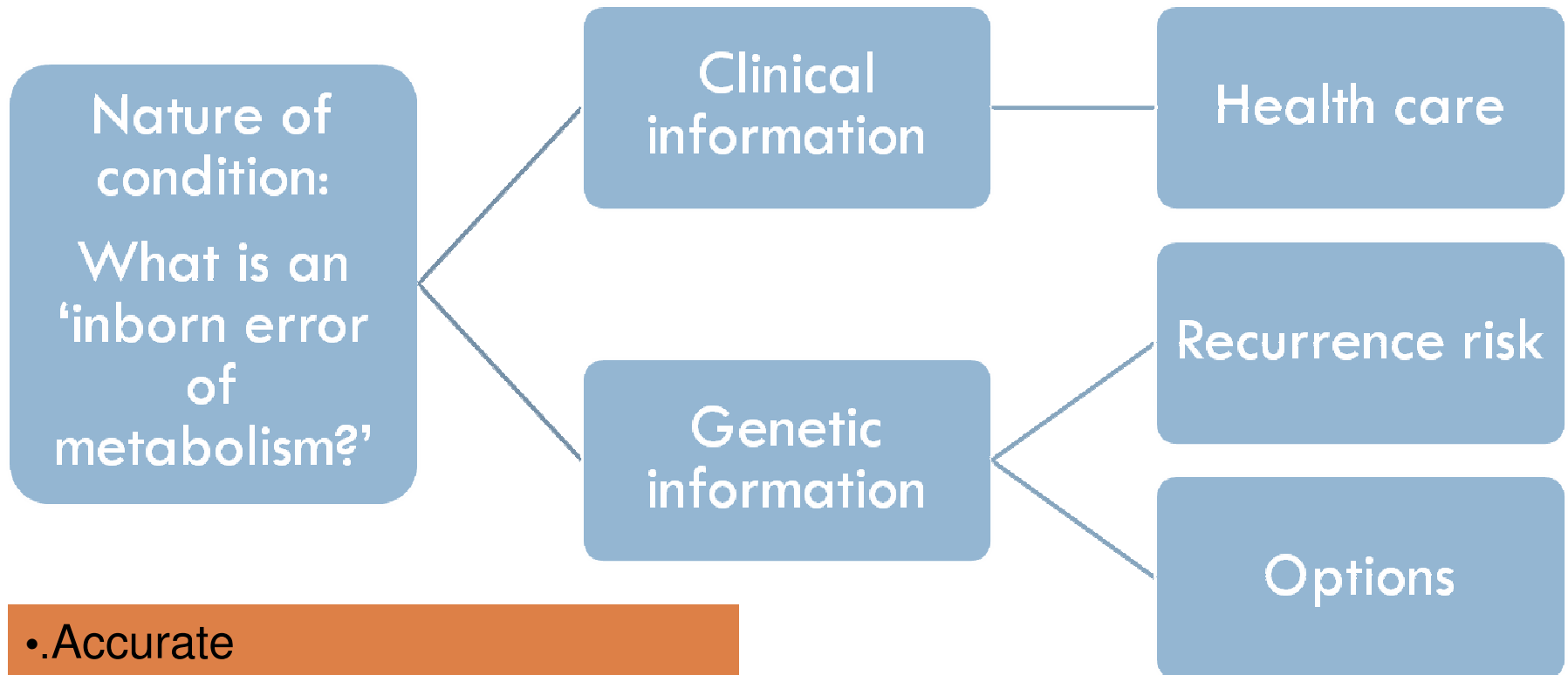
- Ideally, for IEMs the genetic counselling should be provided by a medical geneticist
- In the broader context of a team approach

Why do I make this point?



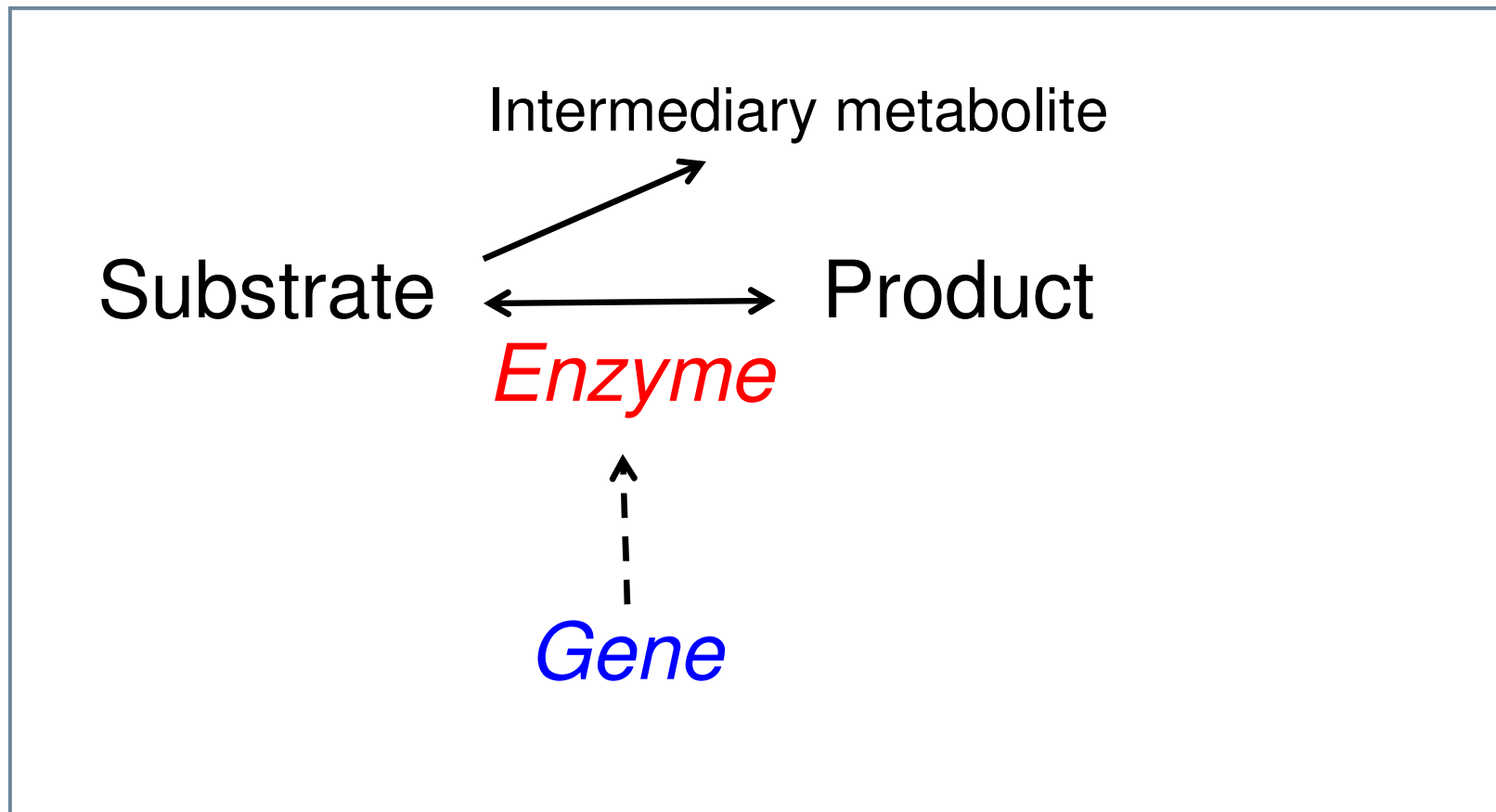
- Audit 2006 and 2010 (George v d Watt):
 - 48 IEM tested in the GSH/RXH area
 - 40% potentially treatable
- We counselled perhaps 5 of these

Information



- Accurate
- Up-to-date
- Comprehensive (not excessive)
- Relevant to family / situation

Information regarding nature of IEM



Genetic counselling at diagnosis



- Break news
- Give clinical information
- As a follow-up – inform parents of:
 - ▣ Inheritance pattern
 - ▣ Recurrence risk
 - ▣ Potential for prevention

- Medical information before genetic
- But health professionals tend to *under-estimate* importance to families of genetic information

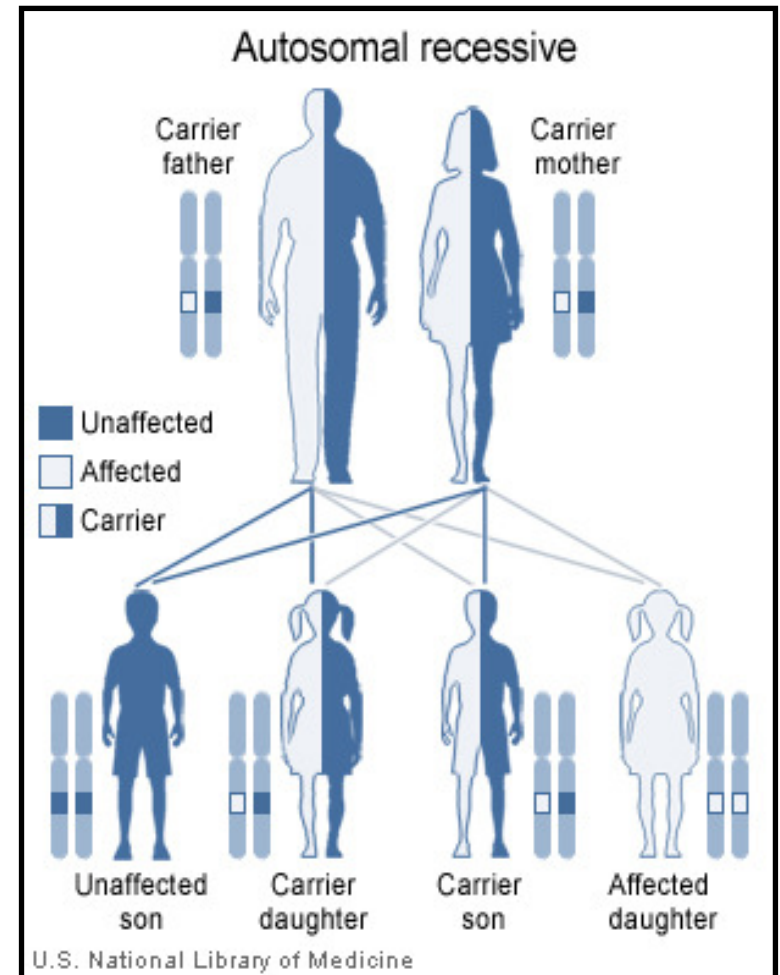
Inheritance of IEMs



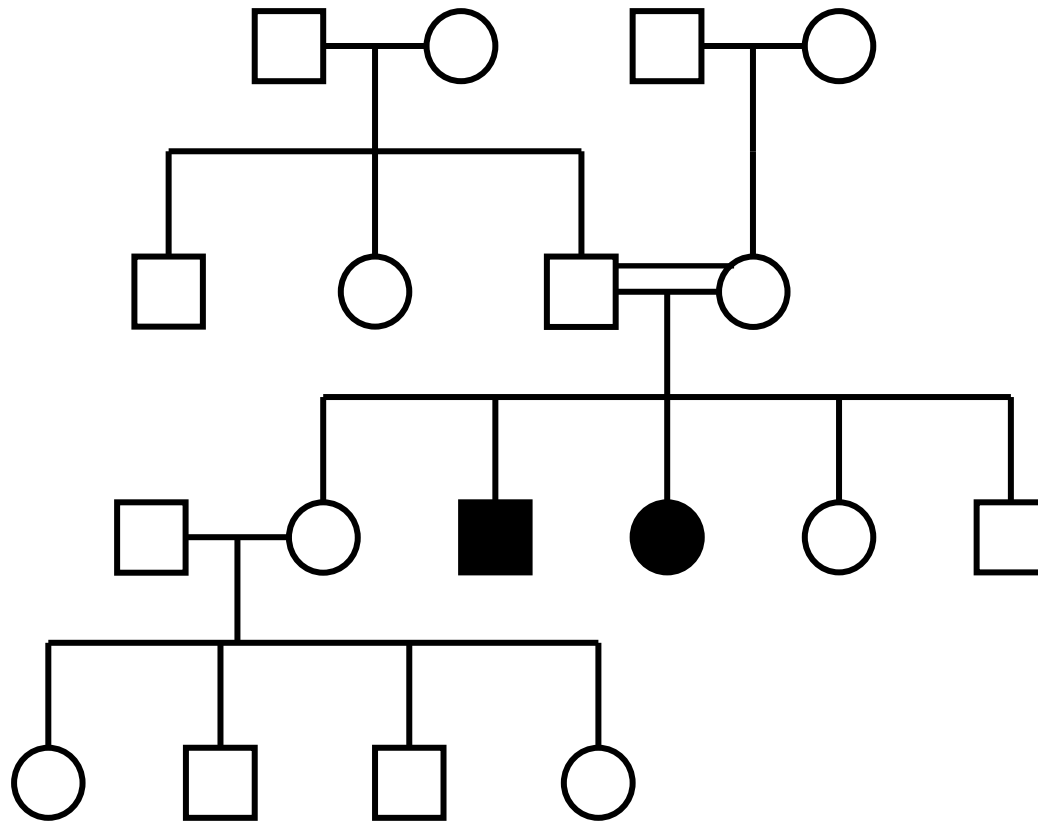
- Autosomal recessive:
 - Most IEMs
 - All of the AAs and OAs
- Autosomal dominant
- X-linked
- Mitochondrial

Autosomal recessive inheritance

- Biological parents are obligate carriers:
 - 'Horizontal pattern' – sibship
 - But often occurs for first time in proband
 - Remember consanguinity
- Future children of couple:
 - 1/2 chance of being affected
 - Unaffected child has 2/3 chance of being carrier
- AR conditions tend to run true in families (largely dependent on severity of less severe mutation)



Autosomal recessive inheritance



Consanguinity



- Strongly suggests AR inheritance
- Rarer condition = more likely is consanguinity
- Understand consanguinity as a social phenomenon:
 - ▣ Stigmatised in our society (difficulty getting history)
 - ▣ Common in some communities with good social reasons e.g. reduction of 'bride wealth' costs
 - ▣ May be multiple consanguinities within families – implications for recurrence

Options for preventing recurrence



- 'Non-genetic':
 - Family planning
 - New partner
 - Adoption
 - ART (assisted reproductive technology):
 - Artificial insemination by donor
- 'Genetic'
 - PGD (preimplantation genetic diagnosis)
 - Prenatal diagnosis

Prenatal diagnosis



- Is prenatal diagnosis wanted and relevant?
 - Would couple consider TOP?
 - Careful information regarding prognosis
 - Will it have implications for early neonatal care?
- When should process be started?
 - 'Before pregnancy'
 - In fact, near time of diagnosis in proband
- Clear plan of action:
 - What method of testing will be used?
 - Any prior testing of proband required?
 - Should tissue or DNA from proband be banked?

Testing methods in different contexts

	Neonatal Screening	Diagnostic : 1 st line	Diagnostic: definitive	Carrier	Prenatal
Metabolite	++	++	++	-	++
Enzyme assay	-	-	++	+/-	++
Genetic	-	-	+	++	+++

Prenatal diagnosis methods

	Gestation	Test method	Sample
Amniocentesis	15-20 weeks	Metabolite Enzyme assay DNA	Supernatant Cell culture Cell culture (? Direct extraction)
Chorionic villous sample (CVS)	11-13 weeks	Enzyme assay DNA testing	Cell culture Direct extraction / culture

Prenatal diagnosis methods



- Metabolite testing:
 - ▣ Only useful for some of the AAs / OAs
 - ▣ Amniotic fluid standards / controls?
- Enzyme assay:
 - ▣ Specialised tests – may or may not be locally available locally for a particular AA or OA
 - ▣ Transport is expensive and difficult since need live cells

Prenatal diagnostic methods (cont)

□ Molecular testing:

□ Specialised, but:

- Transport and processing of DNA is relatively easy
- Often the best or only method

□ Has its own issues:

- For most genetic disorders one cannot detect 100% of mutations
- Therefore a negative result is only meaningful if you know the mutations in proband
- In addition, targeted mutation analysis is much simpler than sequencing and therefore preferable in prenatal diagnosis

□ Need to know the mutations you are looking for :

- Test proband – prior to pregnancy (if at all possible)
- Consider DNA banking (especially if concerns that proband might die)

Difficult prenatal diagnosis situations



- Limited time
- Lack of a definitive diagnosis
- Proband is deceased
- Test itself e.g. enzyme assays

Case study 1

- Boy born in 2000 to non-consanguineous parents
- Encephalopathic at 3 months:
 - Metabolites = likely B12 responsive methylmalonic acidemia (MMA)
 - Treated with vitamin B12 – uncertain response. Continued vitamin 12, folate
 - TB meningitis also suspected and treated
- Medical Genetics – seen at school outreach in 2008:
 - Severe intellectual disability, autistic-like, unusual movements and epilepsy
 - Normal growth, no progressive deterioration or acute episodes
 - Follow-up metabolite testing normal (on vitamin B12)
 - Older sister with developmental delay: normal metabolite profile (?phenocopy)
 - Younger sister hadn't been tested
- Mother pregnant in 2009

Case 1: Methylmalonic acidemia

- MMA:
 - ▣ Variable severity, age of onset
 - ▣ Onset in infancy with predominant encephalopathy is consistent with the diagnosis
 - ▣ Some cases are vitamin B12 responsive
- Biochemical basis:
 - ▣ Deficient functioning of methylmalonyl-CoA mutase (MUT)
 - ▣ Dependent on cofactor cobalamin (vitamin B12)
- Genetic basis:
 - ▣ At least 3 genes: MUT, MMAA, MMAB
 - ▣ Genetic testing is not fully established

Case study 1



- Mother interested in prenatal diagnosis:
 - Would only consider TOP on a definitive prenatal result
 - Did not get this on metabolite testing
- Unproven diagnosis in proband:
 - Skin biopsy for fibroblast culture
 - Testing in Europe: enzyme assay etc, still awaiting results (?research basis)
- Already 36 weeks pregnant:
 - Plan for neonatal period

Case study 2



- Boy born in 2009
- Definite diagnosis of glutaric aciduria type 1 made at ~6 months age
- Following initial diagnosis referred for genetic counselling
- Parents clear that they would want further children and prenatal diagnosis:
 - ▣ Molecular testing appropriate
 - ▣ Mutations detected in proband
 - ▣ Firm basis for future prenatal diagnosis

Carrier testing

- Biological parents are obligate carriers
- So who might want to know carrier status?
 - Siblings of proband
 - Potentially also other family members...
- When?
 - Carrier status relevant only for reproduction
 - At 'reproductive age'
- Genetic counselling
 - Would s/he want to know carrier status?
 - If not a carrier, may be reassuring
 - If carrier:
 - What is recurrence risks for children?
 - Can partner's carrier status be established?

Carrier testing methods



- In general, is based on molecular genetic testing (other methods unreliable for AAs and OAs)
- Molecular testing usually does not detect 100% of mutations
 - Best started by testing the proband

Summary



- Genetic counselling information is:
 - Important to parents
 - Should be provided relatively early
- In particular, prenatal diagnosis allows:
 - Prevention
 - Early treatment
- Strengthen link between labs and clinical genetics
- Ideally we need a 'Rare Diseases Plan'

Archibald Garrod



Fig. 1 Archibald Garrod, circa 1910 (from Harris 1963)

- Classic paper 1902 on alkaptonuria and Croonian lectures in 2008...
- Coined the term inborn errors of metabolism
- Understood these as faults in individual enzymes involved in metabolic pathways
- Described autosomal recessive inheritance in humans / disease
- Aminoacidurias (AAs) and organic acidurias (OAs) have since been found to fit this model

The view is daily gaining ground that each successive step in the building up and breaking down ... of proteins, carbohydrates, and fats ... is the work of special enzymes set apart for each particular purpose If any one step in the process fail the intermediate product in being at the point of arrest will escape further change.... In