Choosing the right genetic test

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Sonic Genetics
Clinpath Pathology

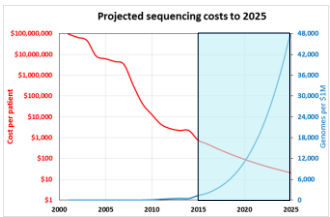
Disclosures

I am an employee and shareholder of Sonic Healthcare.

Sonic Healthcare provides a variety of medical genetic assays.

I do not receive any direct or indirect benefits from other companies.

Genetic testing goes mainstream



- The cost of genetic sequencing has dropped in 15 years.
- The cost of computing has dropped only 100-fold in this period.
- The drop in price has driven industrialisation in medical research.
- Pathology laboratories are now implementing "industrial" level genetic testing.
- **What does this mean for the practice of pathology?**

A common view of medical genetic tests …

Learning points about medical genetic tests

The difference between **data information knowledge wisdom.**

General principles

1. A disease is a sequence of discrete diagnoses (genetic, metabolic, clinical etc).
2. Different tests make different diagnoses (genetic test <> clinical diagnosis).
3. Different diagnoses require different management (prevention vs intervention).
4. One genetic diagnosis may need multiple genetic tests ("single gene disorder" with multiple possibilities).
5. One genetic test may make multiple genetic diagnoses (both in and out of scope).

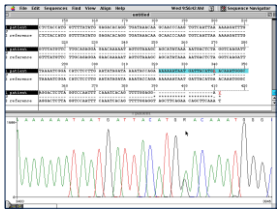
Doing it

6. Know why you are testing (clear utility, balance of risks and benefits).
7. The power of "panels" of gene tests (realising the genomic revolution).
8. Power comes with responsibility (pre- and post-test counselling).
9. Resources.

A genetic test begins with data

This is the role of technicians, not clinicians

Genetic data is interpreted to create information

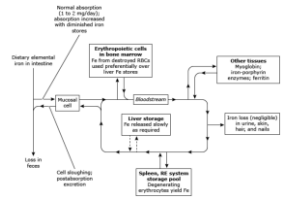


Haemochromatosis gene
Protein has cys282tyr
Causes haemochromatosis

HFE: c.845G>A

This is the role of scientists, not clinicians

Genetic information plus context = knowledge



Raised ferritin x3
Type 2 diabetes

Haemochromatosis gene
Protein has CYS282TYR
Causes haemochromatosis

HFE: c.845G>A

This is pathology: what clinicians know.

Genetic knowledge informs wise decisions

Investigations
Interventions
Risks for relatives

Raised ferritin x3
Type 2 diabetes

Haemochromatosis gene
Protein has CYS282TYR
Causes haemochromatosis

HFE: c.845G>A

And this is what clinicians do.

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Varieties of diagnostic tests – and diagnoses

LDLR mutation	Raised cholesterol	Coronary A. stenosis	Myocardial ischaemia	Cardiac arrest
Genetic test	Serum chemistry	Vascular imaging	Clinical features	Light microscopy
Genetic diagnosis	Biochemical diagnosis	Radiological diagnosis	Clinical diagnosis	The end game

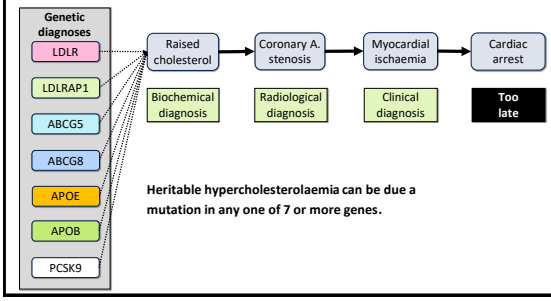
The consequences of different diagnoses

LDLR mutation	Raised cholesterol	Coronary A. stenosis	Myocardial ischaemia	Cardiac arrest
Genetic diagnosis	Biochemical diagnosis	Radiological diagnosis	Clinical diagnosis	Too late
Targeted advice	Lifestyle & medication	Invasive precautions	Crisis care	

Potential for intervention

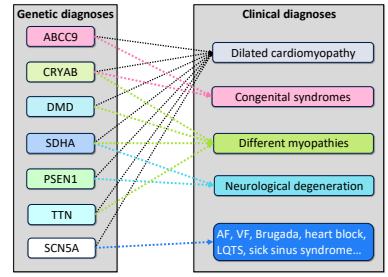
Immediate consequences

There may be many potential genetic diagnoses



Heritable hypercholesterolaemia can be due a mutation in any one of 7 or more genes.

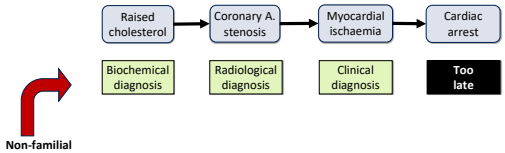
There may be many potential clinical diagnoses



There are no "single-gene" disorders ...

... and no "single-disorder" genes.

And genetics is not everything ...



Many diagnoses of cardiac disease are not familial.

Gene panels for certain cardiac disorders

- **Aortopathy** (13 genes)
  - Ehlers-Danlos syndrome type 4
  - familial thoracic aortic aneurysm
  - Lois-Dietz syndrome
  - Marfan syndrome
- **Hypercholesterolaemia** (7 genes)
  - familial combined hyperlipidaemia
  - familial defective apo B-100
  - familial hypercholesterolaemia
  - lipaemic splenomegaly
  - sitosterolaemia
- **Hypertriglyceridaemia** (7 genes)
  - apolipoprotein C-III deficiency
  - combined lipase deficiency
  - familial combined hyperlipidaemia.
  - hyperchylomicronaemia
  - hyperlipoproteinemia (type 1d)
  - hyperlipoproteinemia (type Ib)
  - infantile hypertriglyceridaemia
  - lipoprotein lipase deficiency
- **Pulmonary hypertension** (8 genes)
  - hereditary haemorrhagic telangiectasia
  - primary pulmonary hypertension
  - pulmonary veno-occlusive disease
- **Vasculopathy panel** (8 genes)
  - Adams-Oliver syndrome
  - adult polycystic kidney disease
  - arterial tortuosity syndrome
  - cutis laxa (type 1b)
  - familial aortic valve disease
  - familial tortuosity of retinal arteries
  - hereditary haemorrhagic telangiectasia

Mutations can be found in 3-90% of patients with each disorder.

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Know why you test

A genetic test is neither necessary nor sufficient to make a clinical diagnosis.

*A genetic diagnosis **can***

- *explain what has already happened*
- *predict what is likely to happen.*

*A genetic diagnosis **cannot***

- *create a clinical diagnosis*
- *negate a clinical diagnosis*

A genetic test is only as useful as the question you ask.

If a mutation were found, ...

... would this inform your management?

i.e. utility for the patient

... and would this be useful to relatives?

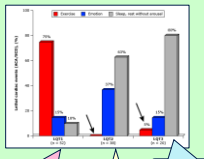
i.e. utility for the family

... and is the payer willing to pay?

i.e. utility for the payer

For example: utility for the patient

Triggers for cardiac events in long QT syndrome are related to genotype.



KCNQ1
- Avoid strenuous exercise
- Use ß-blockers

SCN5A
- Avoid ß-blockers
- Consider cardiac pacing

KCNH2
- Avoid abrupt arousal
- ? spironolactone

Circulation 2001; 103:89
UpToDate 2018

Familial **primary pulmonary hypertension** and **pulmonary veno-occlusive disease** may be clinical indistinguishable.

The disorders have different management strategies.

Genetic testing may be necessary to **differentiate the diagnoses and guide management**.

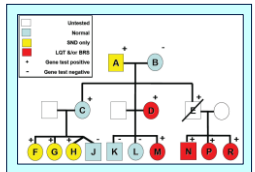
For example: utility for the family

Dilated cardiomyopathy (DCM) can have
- dominant
- recessive, or
- X-linked inheritance.

Asymptomatic relatives may have DCM on echocardiography – or be yet to develop signs.

Genetic testing identifies unaffected carriers and allows for targeted surveillance.

Early diagnosis and intervention are associated with better outcomes.



Sudden death in (E) led to **diagnoses in 9 relatives** of Brugada syndrome, LQTS, or sinus node dysfunction.

Genet Med 12:665-667, 2010
SCN5A Foundation 2008

For example: utility for the payer

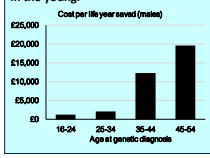
In familial HCM, identification of the causative gene directs management to carriers who need it.

In an Australian study,
- genetic testing added $305 per clinic patient
- the incremental benefit was 0.389 QALYS per patient
- the **ICER was <$1,000.**

Case finding in FH by family tracing is effective …

… but young carriers are harder to detect (cholesterol may be normal).

Genetic diagnosis is more cost-effective in the young.



Heart 2012;98:625e630
BMJ 324_1_JUNE 2002

Pre-test issues for requesting doctor

Understand the purpose of the test.
- The clearer your question, the clearer the answer will be.
- Understand what is **not** being asked of the test.

Should every patient have genetic testing?
- The test should only be done if it will provide useable information that is not already available.
- If doctor and the patient cannot identify a clear "use" (medical, psychological, familial), don't do the test.

And if the test result is ABNormal …
- This possibility must be discussed and the plan agreed BEFORE the test is requested.
- The management plan must include
  Patient management (consider referral, MDT)
  Family management (clinical genetics referral)

Pre-test issues for affected patients

What does the patient want to know?
- A genetic test does not test for every possible abnormality.
- A normal result does not exclude a clinical diagnosis.
- The test may reveal unexpected risks for other disorders.

What will the patient do with the result?
- The identification of a mutation carries important medical consequences for relatives; they should be informed.
- Relatives should also be informed of the clinical diagnosis, even if a mutation is not found.

Does the patient understand the process?
- The test requires a fresh blood sample.
- The cost is usually not rebated.
- The turnaround time is 6-8 weeks.

Genetic counselling considerations

1. **Genetic counselling is not mandated for testing an affected patient.**
   Pre- and post-test genetic counselling is bundled with some of Sonic's genetic tests.
2. Counselling considerations are similar to those required for any test for a familial disorder.
   - Possible outcomes discussed.
   - Inform relatives.
   - Inform other clinicians.
   - Life insurance.
   - Emotional sequelae.
   - Disclosure without consent.
3. Issues that are more "genetic" include
   - Distant *versus* immediate risk.
   - Potential for incidental findings.
   - Result interpretation may change.
   - Insurance implications for unaffected relatives.
   - Testing may reveal unacknowledged relationships e.g. non-paternity.
4. **Genetic counselling is mandated for testing unaffected relatives** *(not in scope)*.

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