A stress-free overview of Genetics

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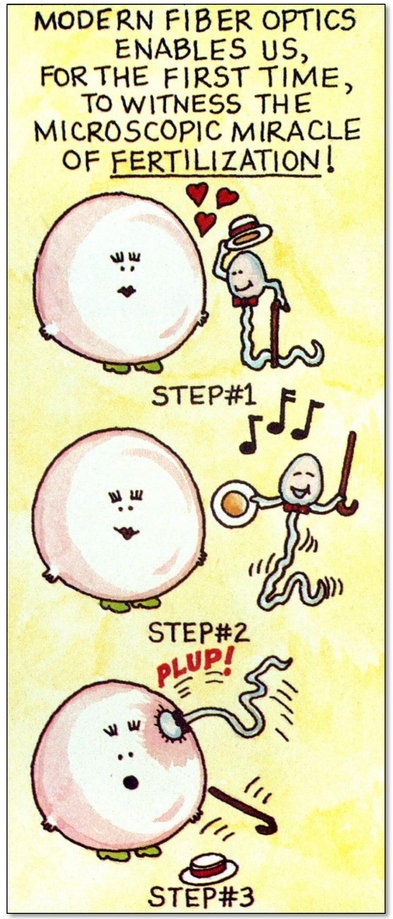
SONIC GENETICS

Genetics as the foundation: *the final chapter*

1500	structure	**anatomy**
1600	function	**physiology**
1800	chemistry	**clinical chemistry**
1850	microscopy	**histology**
1860	culture	**microbiology**
1950	proteins	**immunology**
2000	**genes**	***genetics***



Genetics as the foundation: *a test among many*

1500	structure	**anatomy**	*Mass in stomach*
1600	function	**physiology**	*Spread to lymph nodes*
1800	chemistry	**clinical chemistry**	*Blood in stool*
1850	microscopy	**histology**	*Different types of stomach cancer*
1860	culture	**microbiology**	*Chronic infection causing cancer*
1950	proteins	**immunology**	*Abnormal proteins as drug targets*
2000	genes	**genetic pathology**	*Genetic errors driving cancer*

Genetics as the foundation: *a recent phenomenon*

1500

1600

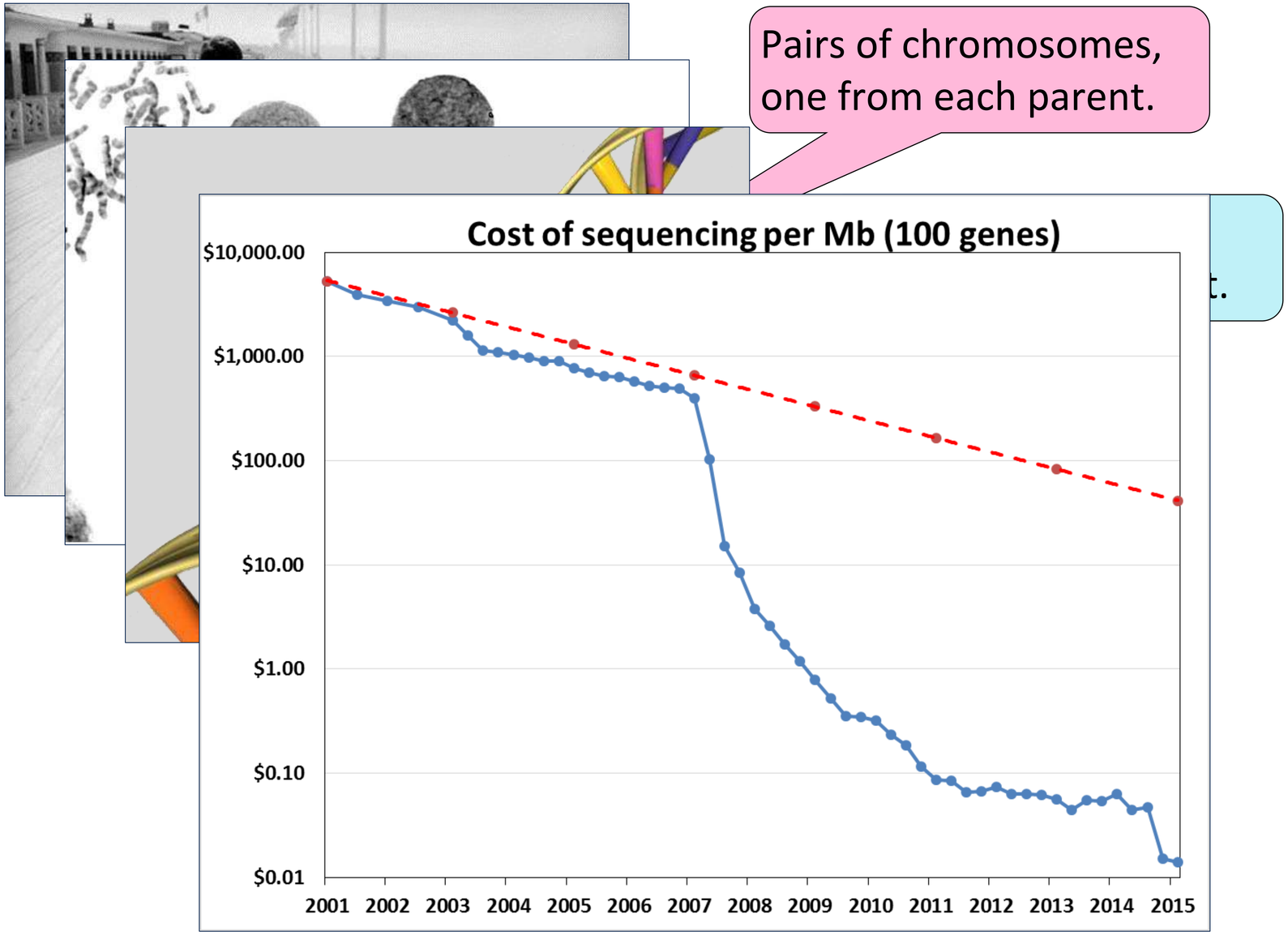
1800

1850 Discrete genes

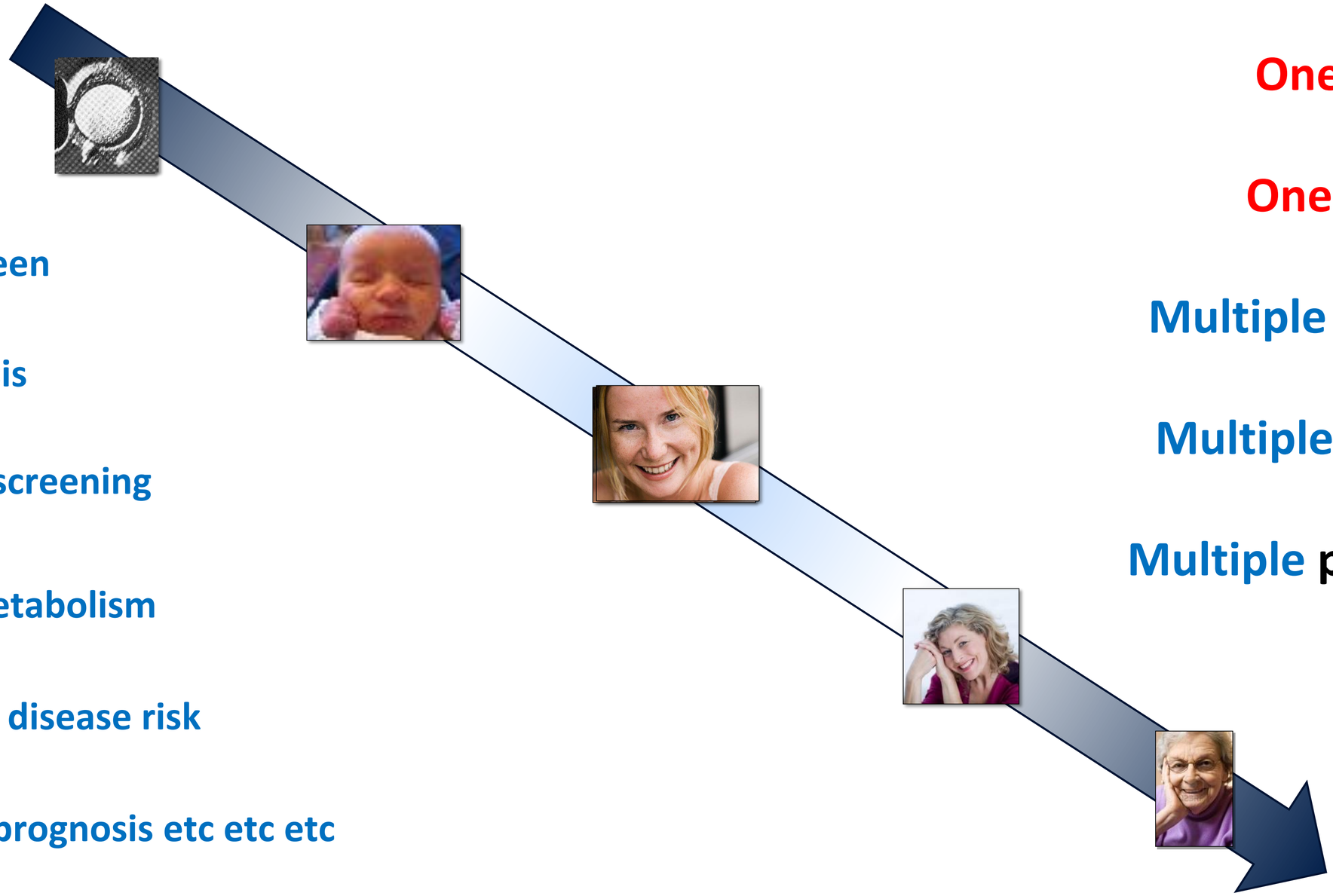
1900 chromosomes

1950 DNA

2007 genetics



Genetics as the foundation: *the scope of opportunity*



T21 screen

Diagnosis

Carrier screening

Drug metabolism

Familial disease risk

Cancer prognosis etc etc etc

One analyte

One method

Multiple samples

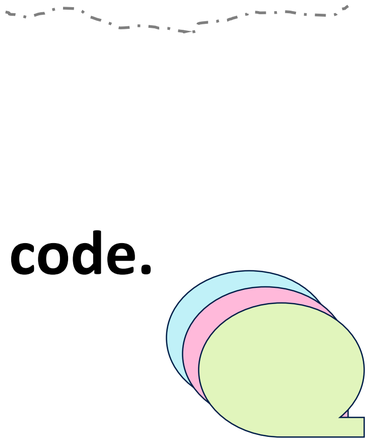
Multiple settings

Multiple purposes

Functional genetics: *DNA ➢ RNA ➢ protein ➢ action …*

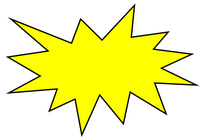
DNA is a stable string of information.

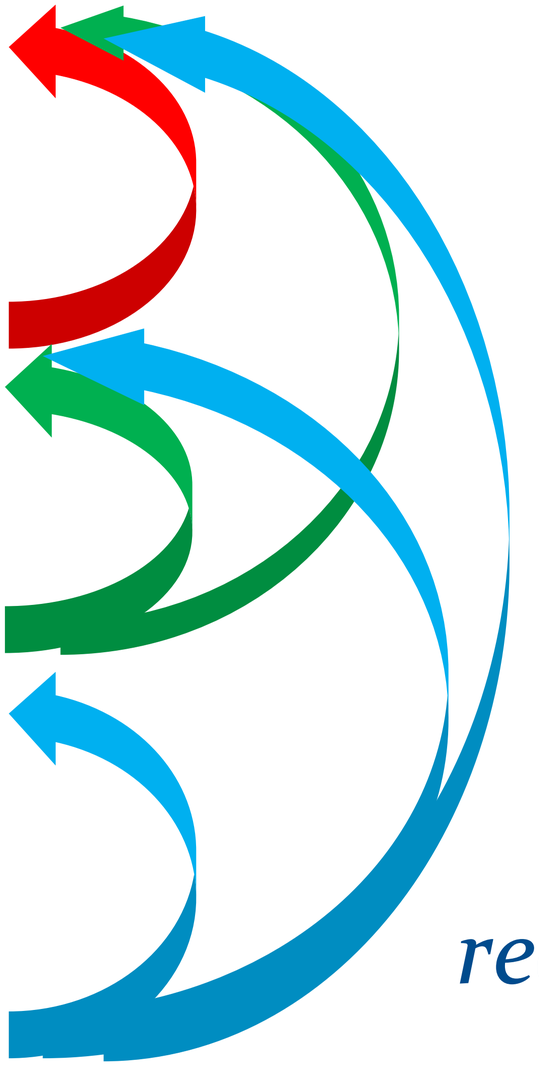
RNA is a transient copy of sections of DNA.



Proteins are built using the RNA code.

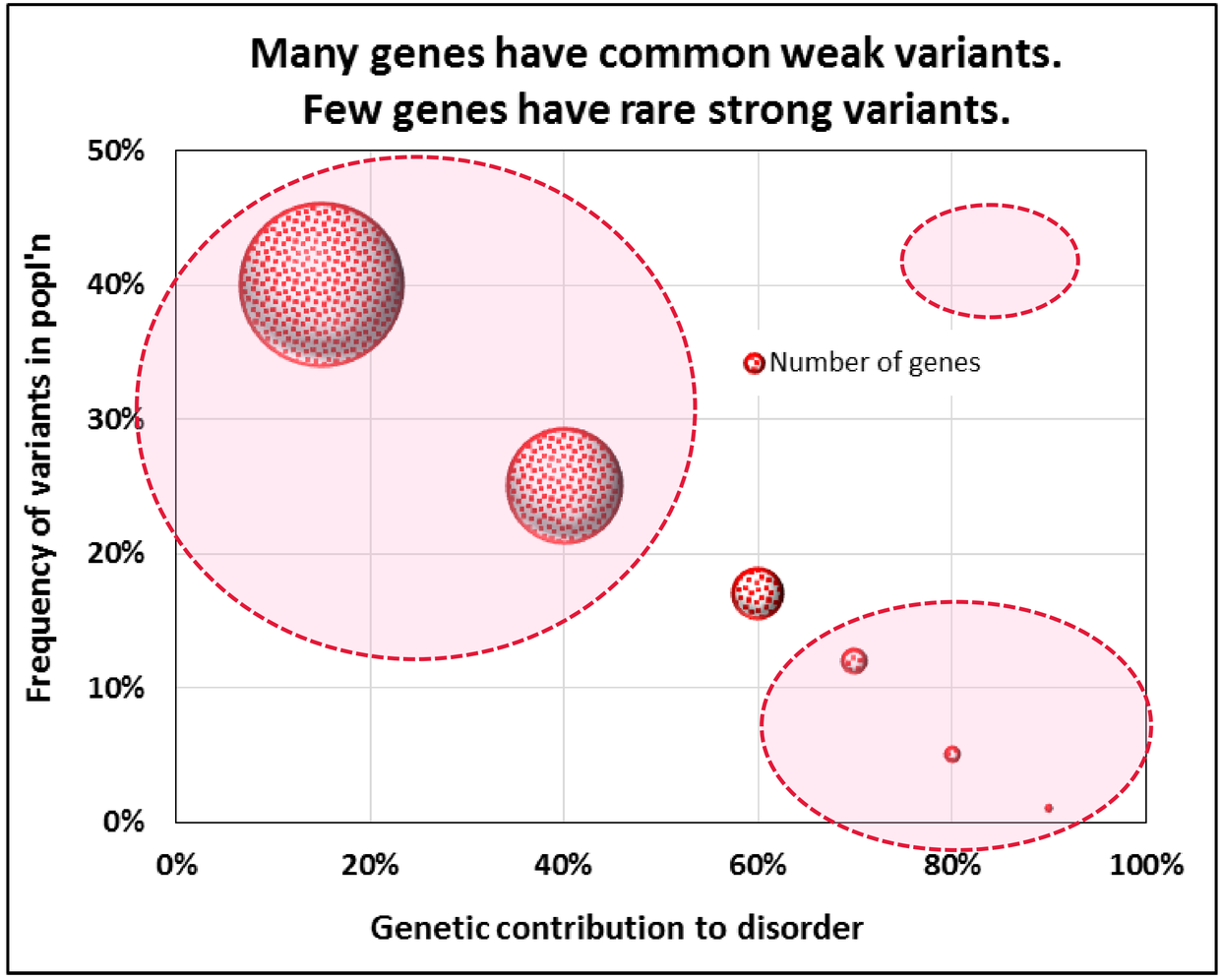
The work of cells is done by proteins.





… and reaction.

The spectrum of heritability



- Common disorders involve multiple "weak" genes.

  The risk from multiple weak genes is dispersed among relatives (may be "weakly familial").

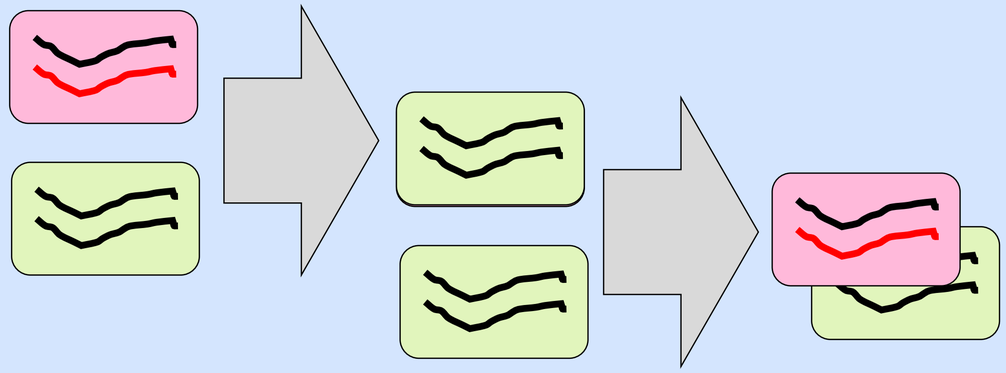
- Rare disorders involve few (one?) genes of strong effect.

  The risk from one strong gene is evident as the disorder among relatives ("strongly familial").

- Common strong genetic variants are normal *e.g. gender*.

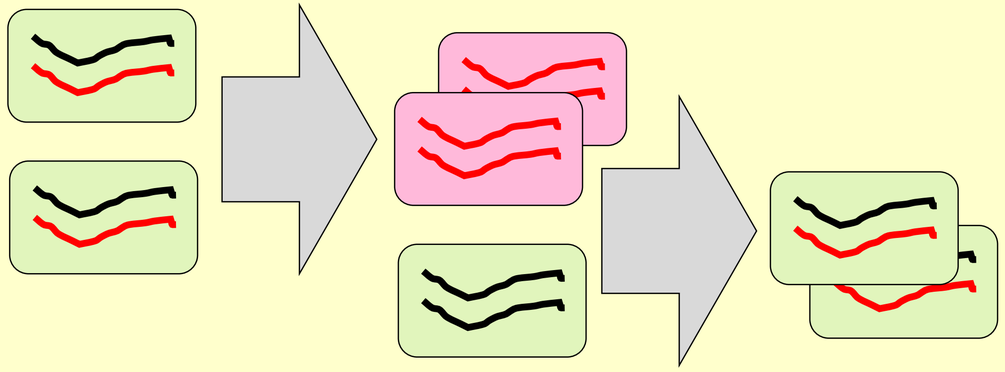
Heritability is a continuum.

The spectrum of heritability: *single gene disorders*

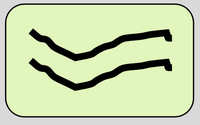


Genetic information comes in pairs.

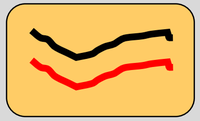
- An error in **one copy** can cause a disorder.
- The error came from **one** parent.
- The error can be passed to a child.
- The disorder recurs over **generations**.



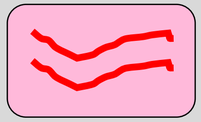
- An error in **both copies** of a gene can cause a disorder.
- An error came from **each** unaffected parent.
- The error - but not the disorder – is passed to children.
- The disorder recurs among **siblings**.



Normal genes
No disease



One abnormal gene
Mild disease



Two abnormal genes
Severe disease

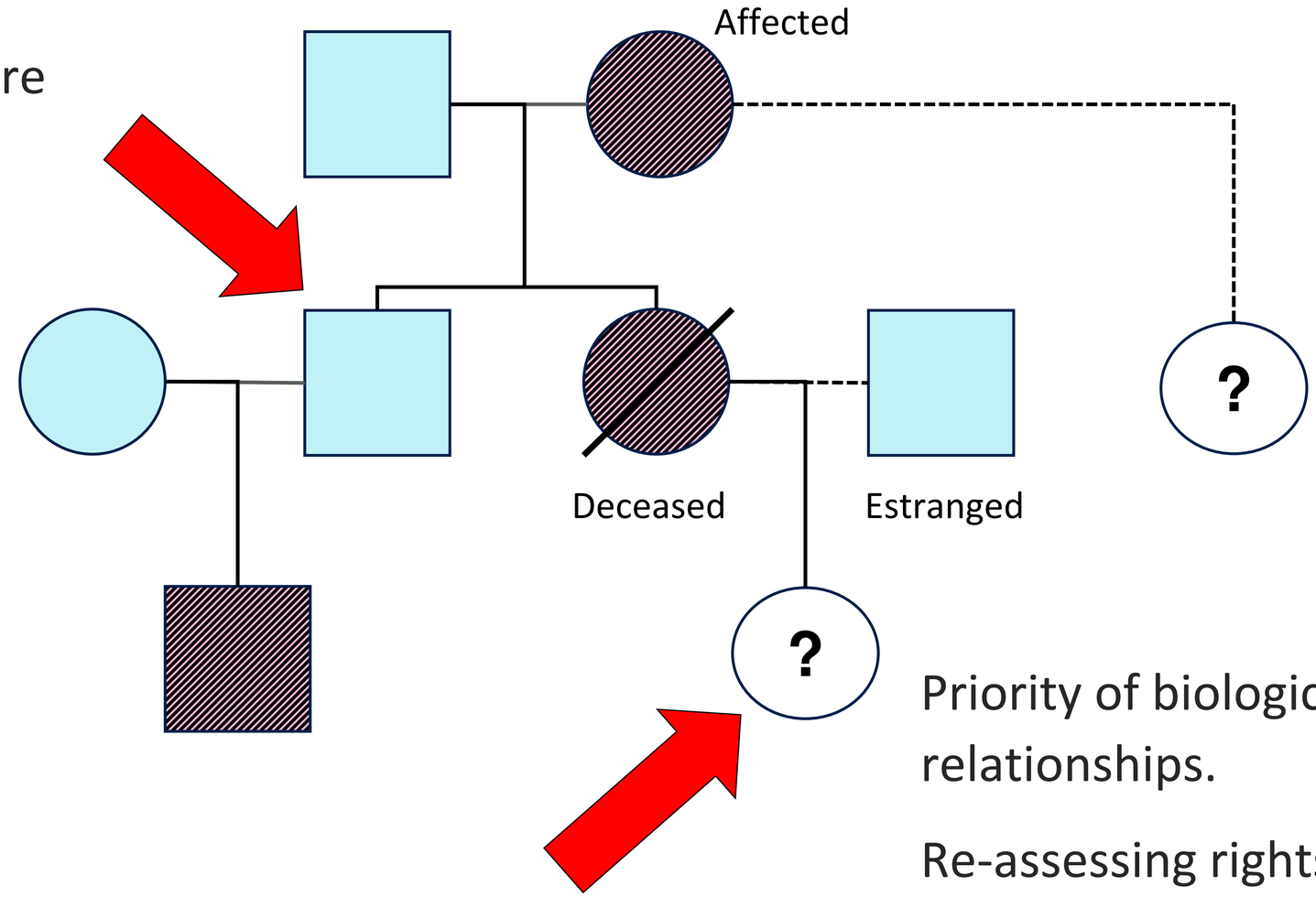
Variations are possible….

Ethics and heritability: *single gene disorders*

Age of onset and effects are variable.

Potential impact of environmental factors.

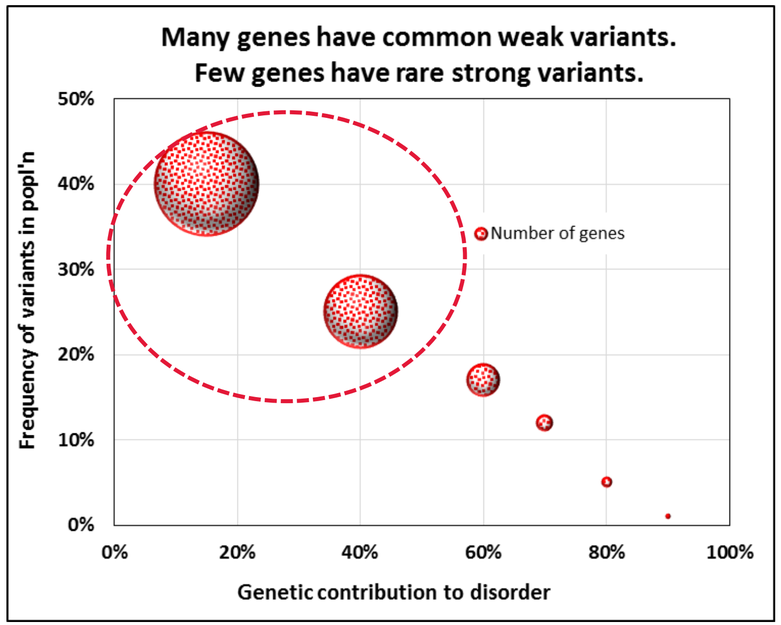
Abnormal gene does not equal “affected”.

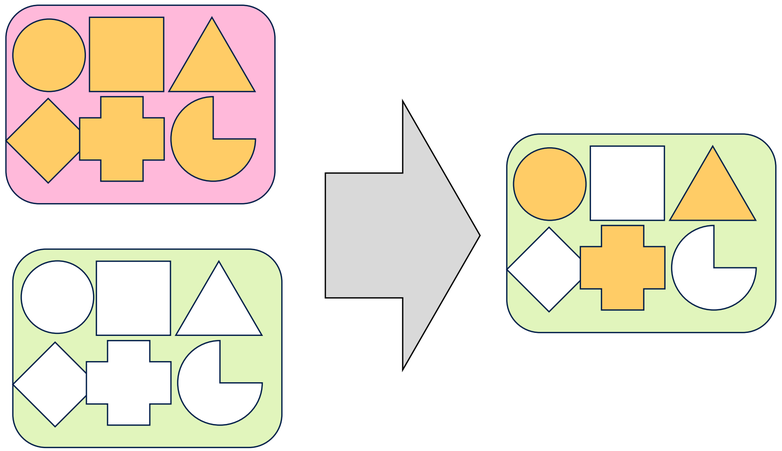


Priority of biological *vs* legal relationships.

Re-assessing rights and obligations in the light of new information.

The spectrum of heritability: *polygenic disorders*





- Many common disorders involve multiple “weak” genes.
- Thousands of common weak variants have been found.
- The load of variants increases risk/severity in a patient.
- A child inherits ~half of a patient’s load of weak variants.
- Common disorders exhibit
  - weak familial tendency
  - variability, and
  - non-genetic influences.

i.e. the influence of

genes

environment

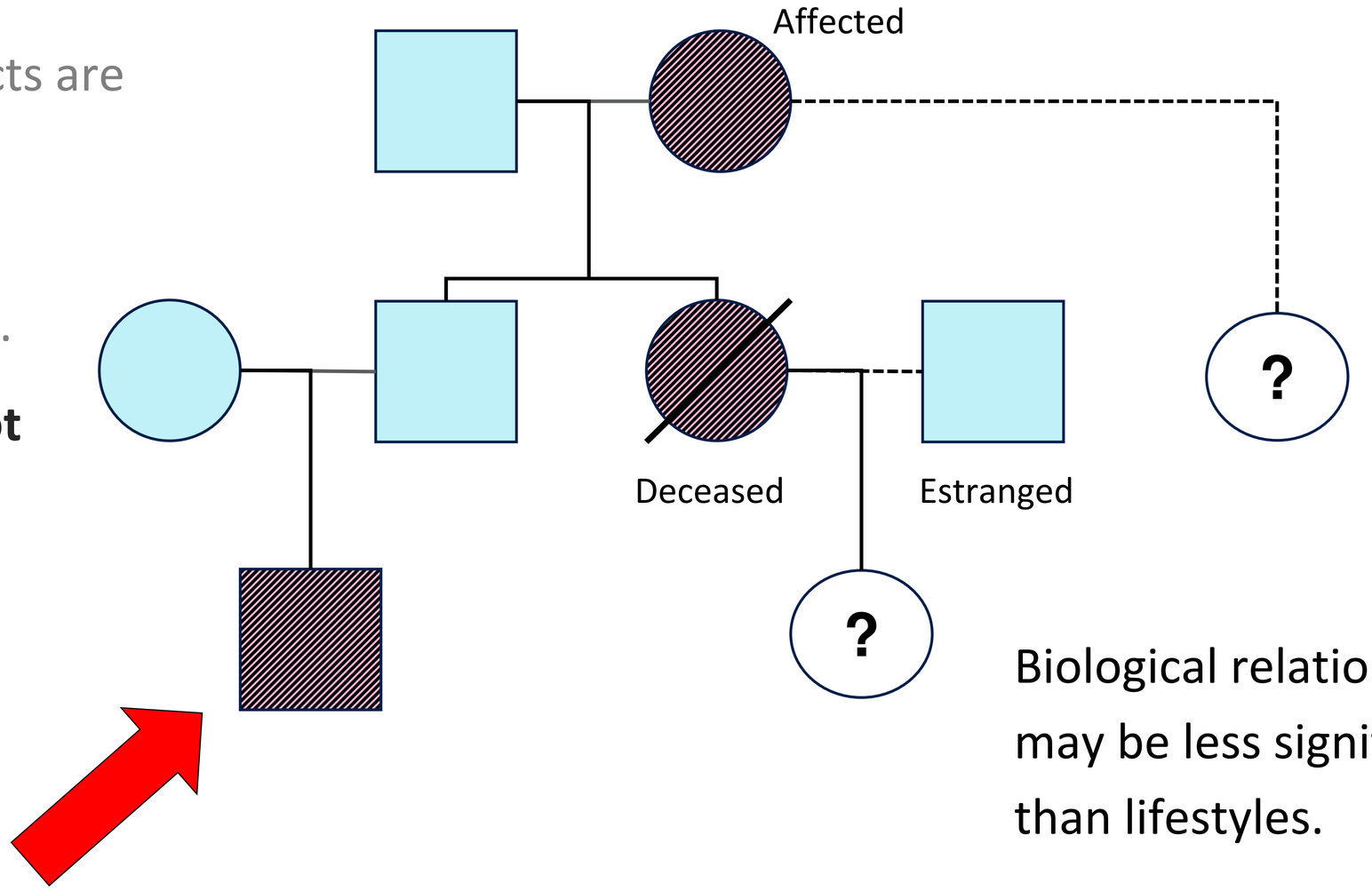
chance

Ethics and heritability: *polygenic disorders*

Age of onset and effects are variable.

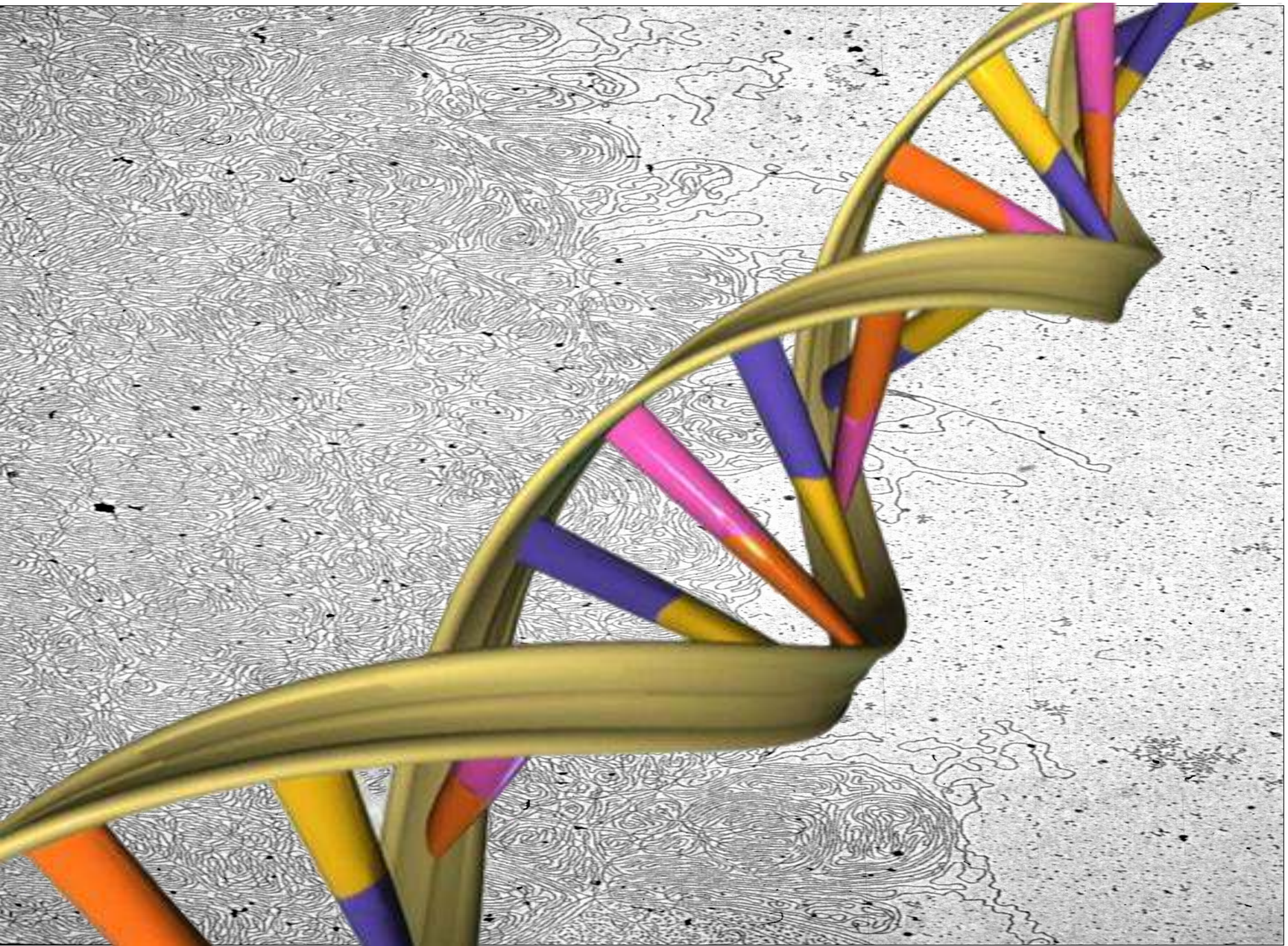
Potential impact of environmental factors.

Same disease does not mean same abnormal genes.



Biological relationships may be less significant than lifestyles.

Beyond heritability: *the decay of the genetic code*



There is 1 metre of DNA in each sperm and ovum.

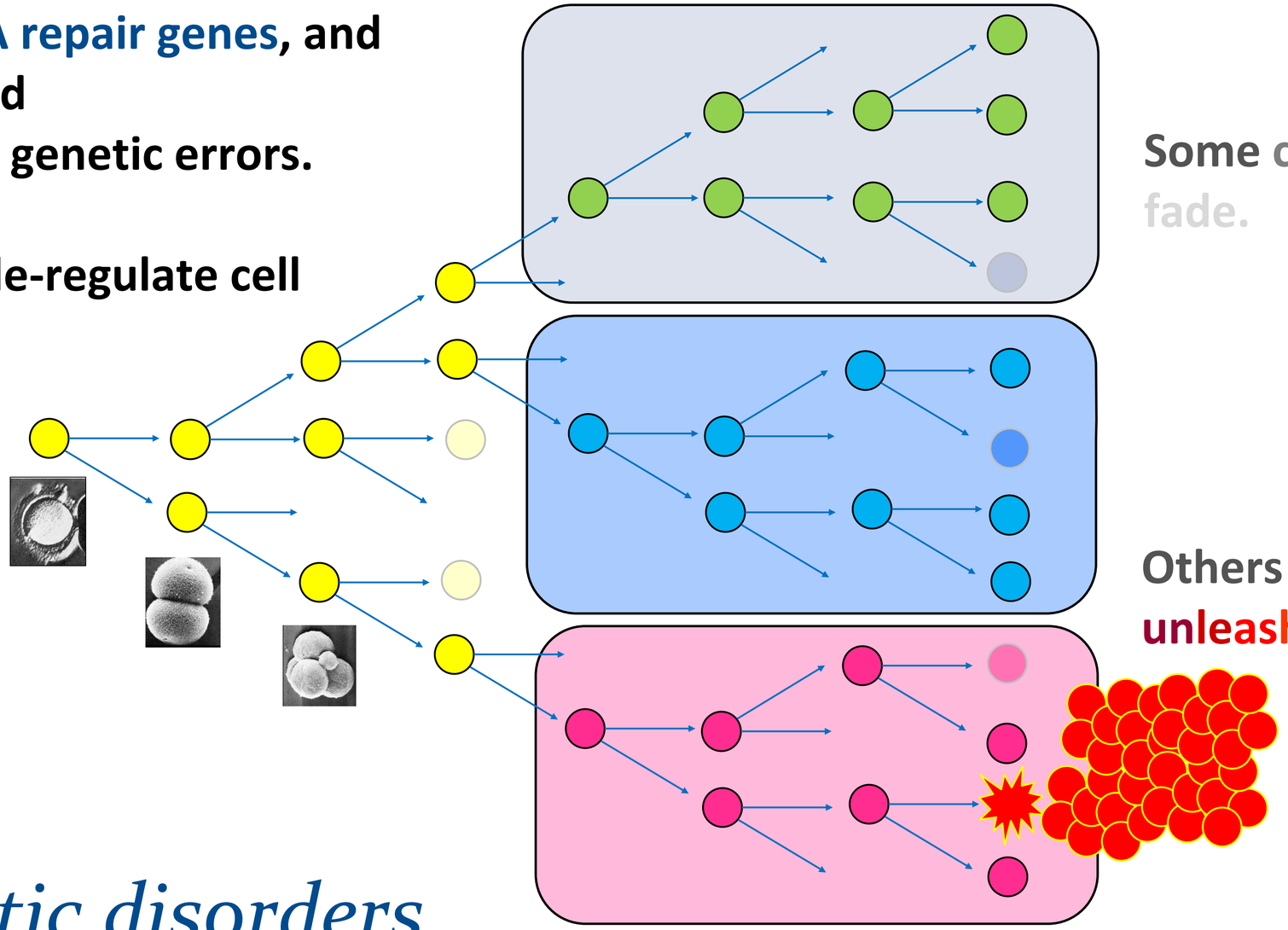
- **2 metres of DNA in every cell.**
- **10^6 km synthesised per day during gestation.**
- **10 light-days of DNA in an adult.**
- **Hundreds of genes maintain DNA repair.**
- **Nonetheless, errors accumulate in making and maintaining this length of DNA.**

Beyond heritability: *the disorders of ageing*

Inherited variation in DNA repair genes, and environmental factors, and chance cause non-familial genetic errors.

The accumulating errors de-regulate cell function …

… and cell division …



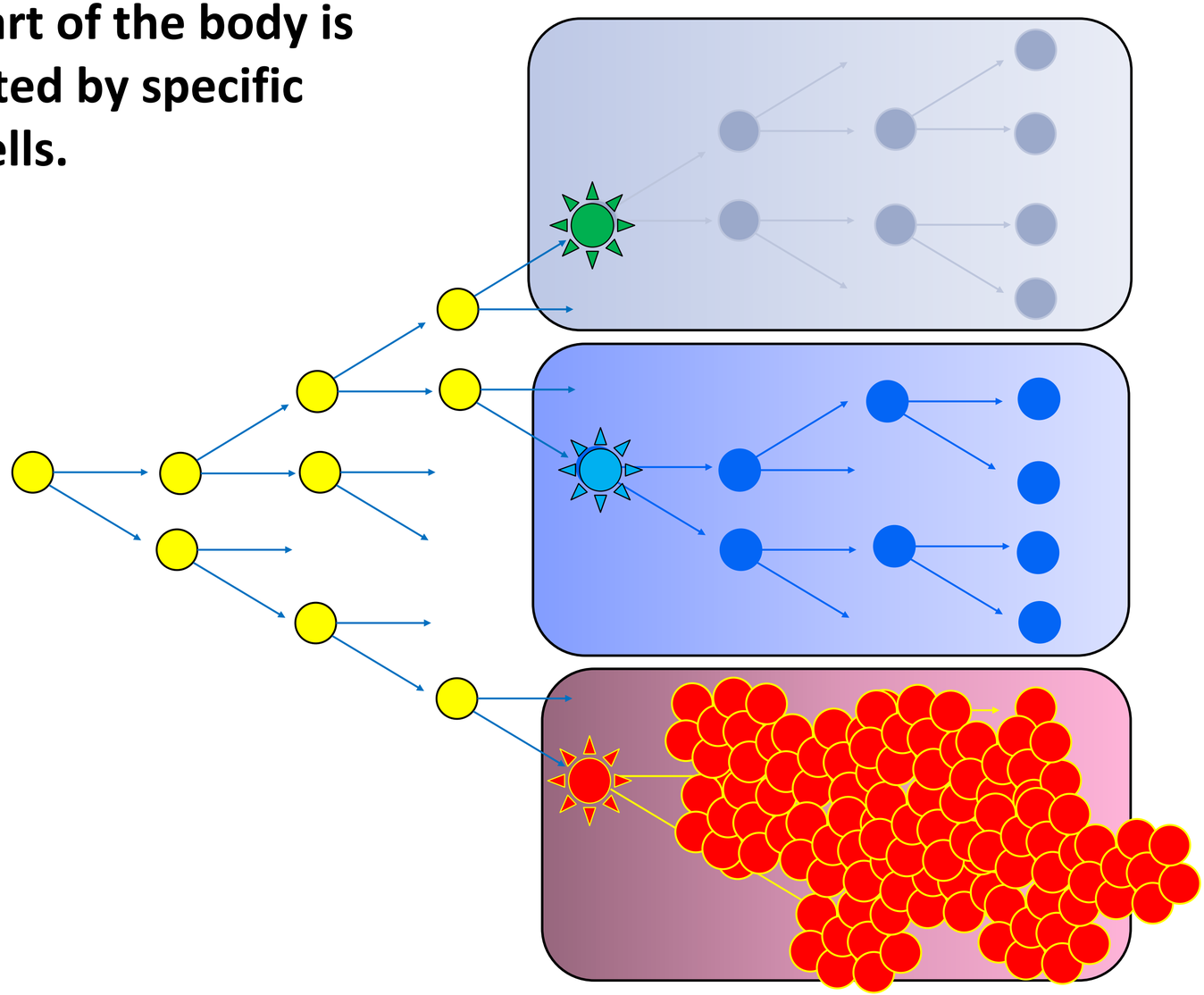
Some cells fade.

Others are unleashed.

… causing “acquired” genetic disorders

Stem cells: *stemming the decay*

Each part of the body is populated by specific stem cells.



“Daughter” cells can divide and die without penalty.

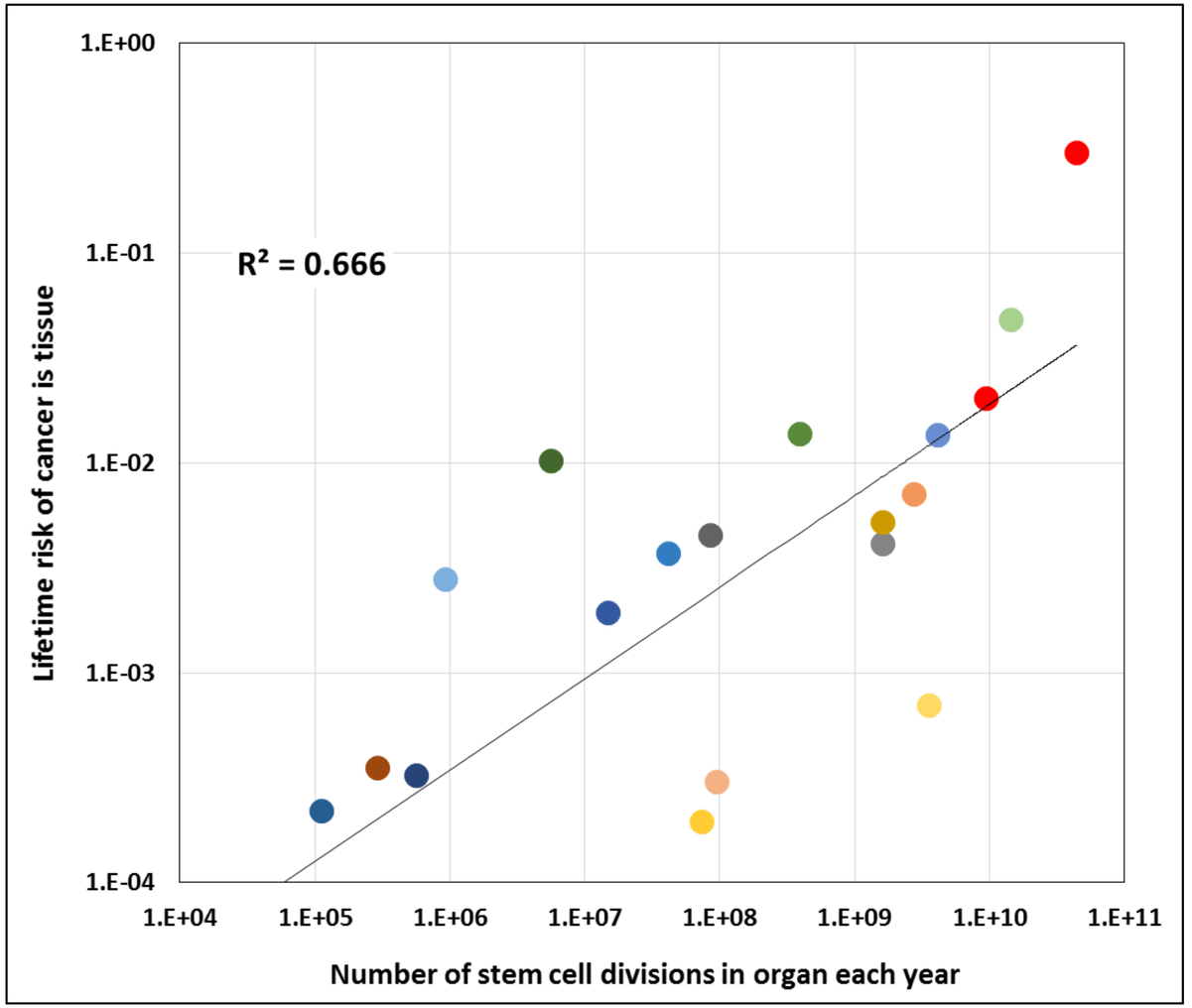
Stem cells replenish tissues to replace fading cells ... for a while.

Ultimately accumulating errors in stem cells de-regulate growth, and cause cancer.

Stem cells: *the cause (and cure) of acquired genetic disease*

The number of stem cells per organ, and the frequency of stem cell divisions, vary **a lot** throughout the body.

The rate stem cell divisions in an organ correlates with the lifetime risk of cancer.



Science 347 (6217): 78-81, 2015

Ethics and non-heritability: *clear, and not so clear*

1. Non-familial mutations require no special “genetic” consideration.

2. A familial mutation may only be relevant on exposure to a specific environment.

3. It may not be clear whether a mutation in cancer is acquired or familial.

Test for a non-familial mutation in cancer

A familial mutation in a gene places a

Test ovarian cancer for mutation indicating responsive to chemo.

Of the responsive cancers, ~1/3 have a non-familial mutation i.e. not in blood.

- ✓ treatment decision
- ✓ no significance for relatives

~2/3 have a familial mutation i.e. in blood.

- ✓ treatment decision
- X **very significant for relatives.**

Balance issues for patient & family.

Controlling genes: *gene switches*

Men and women have the same set of genes.
Why are we different?

Men and mice have almost the same set of genes.
What happened to our tails?

The same genes are used to guide embryonic development – and cancer.
What goes wrong?

Genes are switched off *(and on)* by adding *(and removing)* small molecules from the beginning of a gene.

The genetic code is not altered; this is **epigenetics**.

Controlling genes: *epigenetics is HUGE*

Epigenetics is normal.

- Gene activity is dynamically regulated by epigenetics.

Epigenetic patterns are re-set at conception

- Epigenetics can switch the paternal (or maternal) copy of a gene off for a lifetime.

Epigenetics can <u>mask</u> an abnormality.

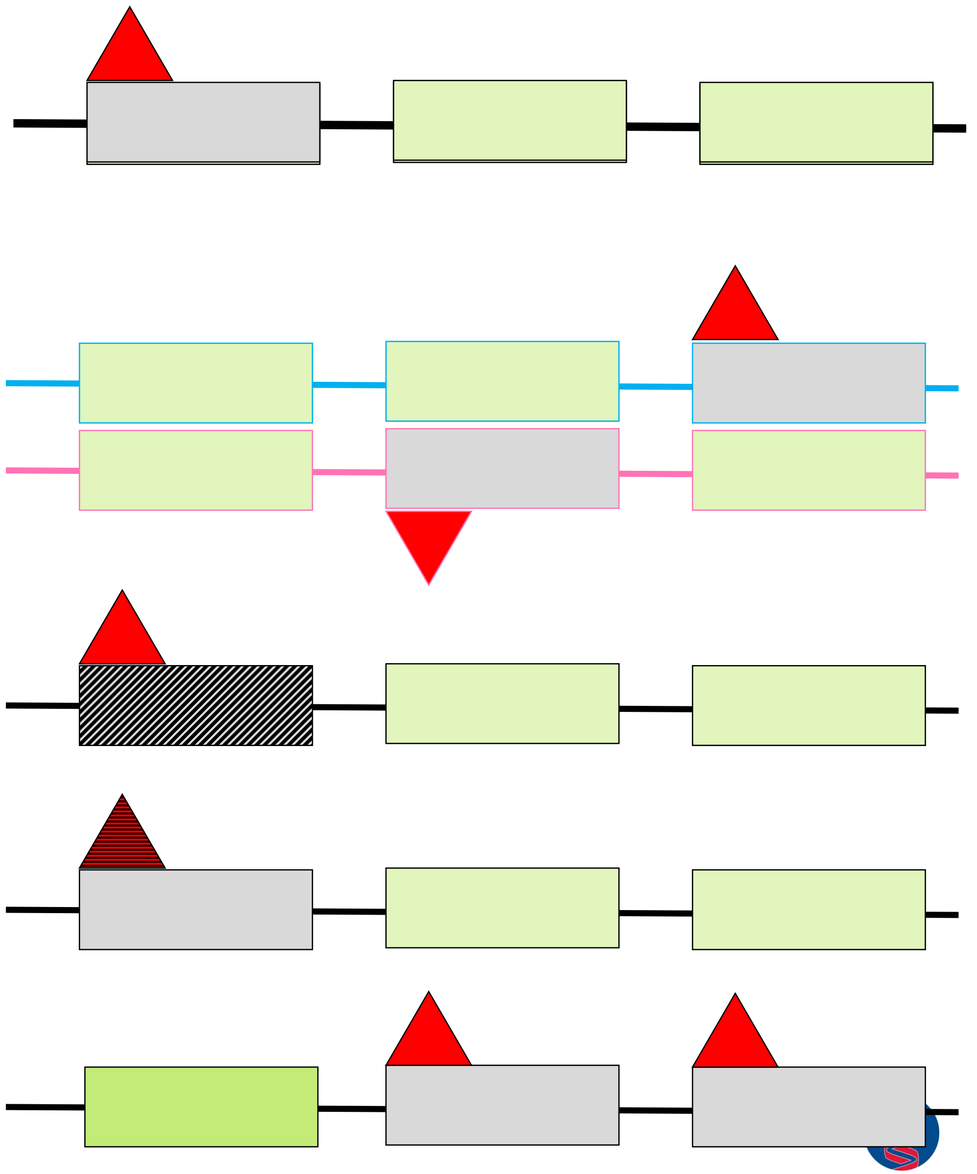
- A mutation has no impact on an inactivated gene.

Epigenetics can <u>be</u> the abnormality.

- A normal gene can be inappropriately inactivated.

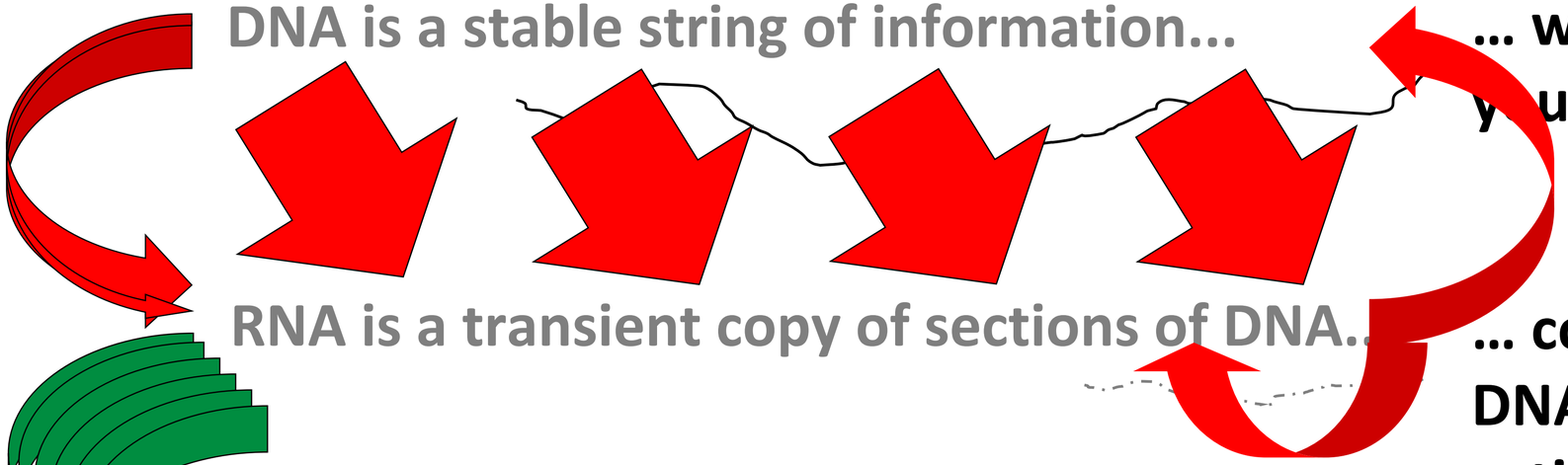
Epigenetic regulation is lost in cancer tissue.

- The epigenetic pattern is scrambled…



Controlling genes: *genetics is more RNA than DNA*

DNA is a stable string of information...

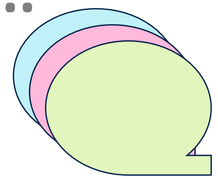


… with genes being only 1-2% of your DNA.

RNA is a transient copy of sections of DNA...

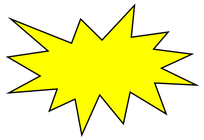
… coming mostly from non-coding DNA, and regulating DNA activation and RNA formation.

Proteins are built using the RNA code...



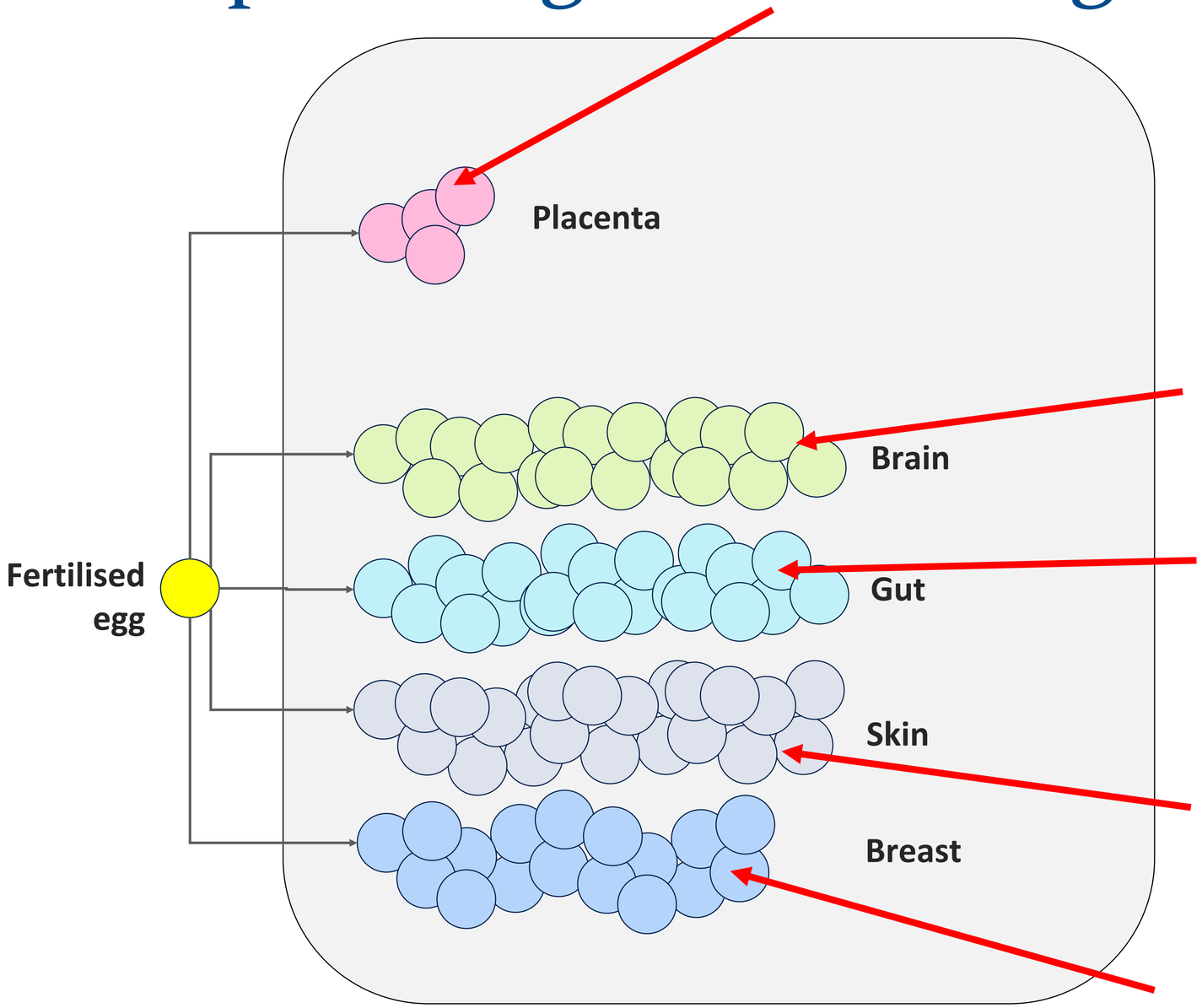
… with an average of 5 different proteins from each gene, due to impact of RNA regulation.

The work of cells is done by proteins...



… but it is <u>controlled</u> by non-coding RNA.

Samples for genetic testing: *a universal tool*

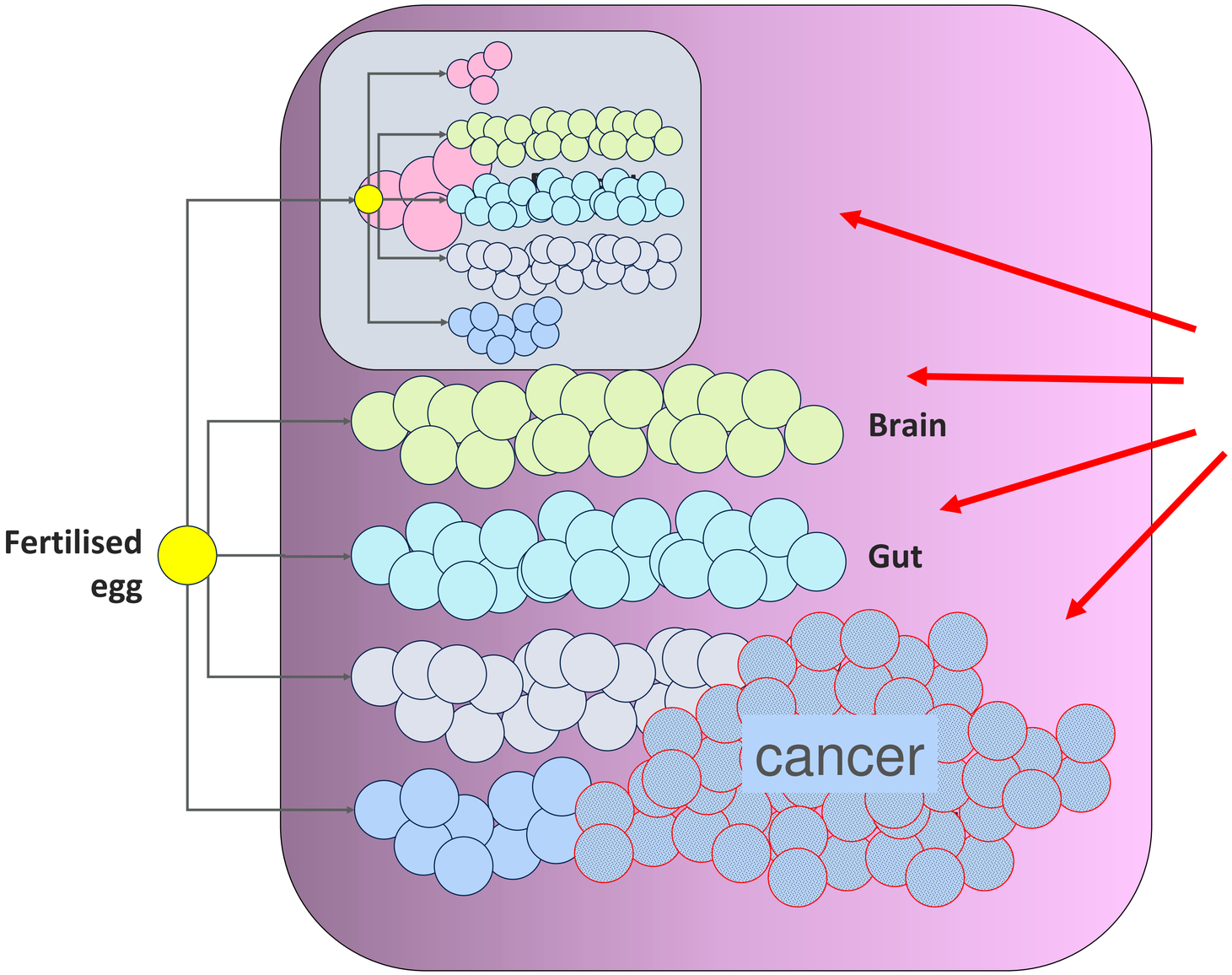


A genetic test can be done on

- any organ
- at any time
- using any sample.

A genetic test is defined by the organ, timing, and sample – not by the method

Samples for genetic testing: *cell-free DNA*

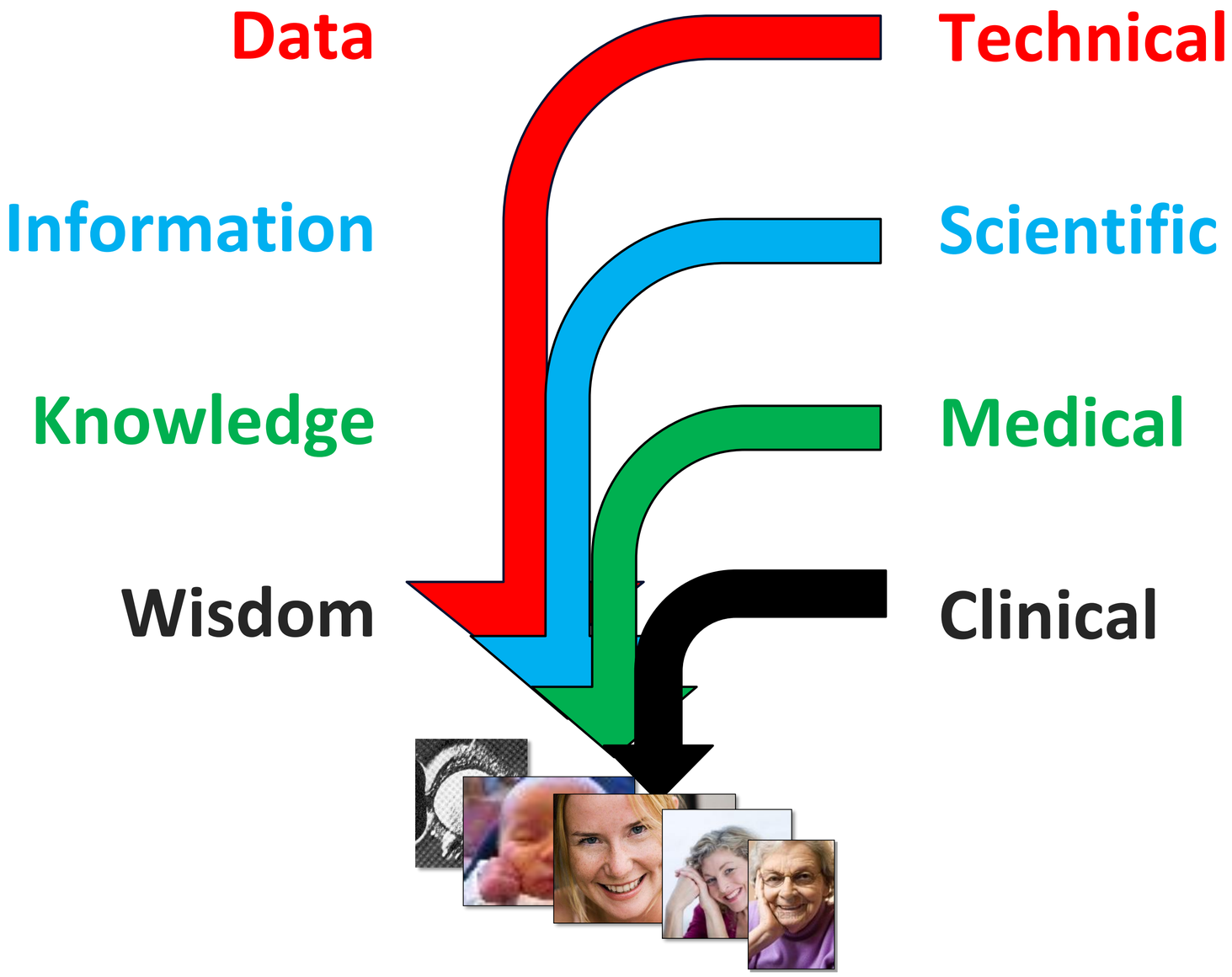


Blood carries traces of free-floating DNA from every organ – and cancer.

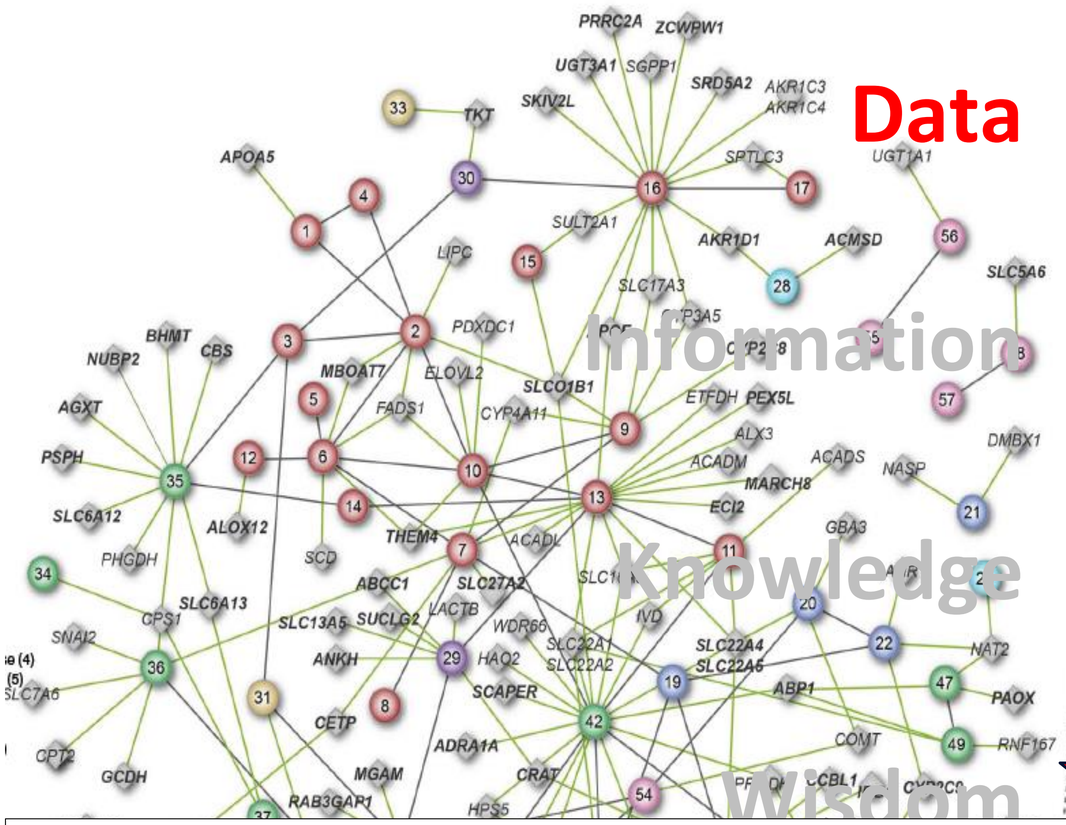
Each tissue has its own epigenetic "signature", and identifies the source of "free DNA".

Cell-free DNA already provides an accurate test for fetal mutations; cancer tests are coming.

Managing genetics: *just another a test*



Managing genetics: *the illusion of data*



Data → **Technical**

Information → Scientific

Knowledge → Medical

Wisdom → Clinical

Where is the Life we have lost in living?
Where is the wisdom we have lost in knowledge?
Where is the knowledge we have lost in information?

TS Eliot. Choruses from The Rock (1934).

Managing genetics: *the science must be disciplined*

Actor Jeff Goldblum

Dr Ian Malcolm (in *Jurassic Park* by Michael Crichton.)

"Most kinds of power require a substantial sacrifice by whoever wants the power. There is an apprenticeship, a discipline lasting many years …

"But scientific power is like inherited wealth: attained without discipline. You read what others have done, and you take the next step. You can do it very young. You can make progress very fast ...

Reputation Eater

"You don't even know exactly what you have done, but already you have reported it; patented it, and sold it. And **the buyer will have even less discipline than you**."

Managing genetics: *Demanding clarity of purpose*

Height is highly familial.

By 2008, 54 genes were implicated in determining height.

A study estimated height by

- genes *(odds of being correct 2:1)*
- average height of parents *(odds 5:1).*

Methodologically useful.
Practically useless.

Genes influence the age at which you lose your virginity, study shows.

theguardian

"We were able to calculate for the first time that there is a familial component to age at first sex,

and the heritability is about 25%, so one quarter nature, three quarters nurture," said an expert at Cambridge.

I have no idea what this means.

Managing genetics: *what do you expect of genetics?*

From a judicial inquiry into the jailing of an innocent man in Victoria in 2010.

"….. the DNA evidence had been perceived as being so powerful by all involved in the case that none of the filters upon which our system of criminal justice depends to minimise the risk of a miscarriage of justice, operated effectively at any stage until a matter of weeks before [the man's] appeal was expected to be heard."

Vincent FHR. Victorian Government Printer, 2010. PP No 301:Session 2006e10.

What have we covered …

1. Genetics is the foundation of medical science.
2. Genetic basics: *string of DNA bundled as chromosomes producing RNA & proteins*
3. Spectrum of heritability: *one or many familial mutations, acquired mutations*
4. Ethics and heritability: *a spectrum of implications, with blurry margins*
5. The degradation of the genetic code: *genes, environment, chance*
6. Stem cells: *a temporary reprieve*
7. Controlling genes: *universal epigenetics, the primacy of RNA*
8. Samples for genetics: *any tissue, any time – with cell-free DNA as a surrogate.*
9. Managing genetics: *a clear purpose, discipline, challenging expectations.*

Thank you.

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