UNSW SYDNEY | Australia's Global University

BIOM9420

Clinical Laboratory Science

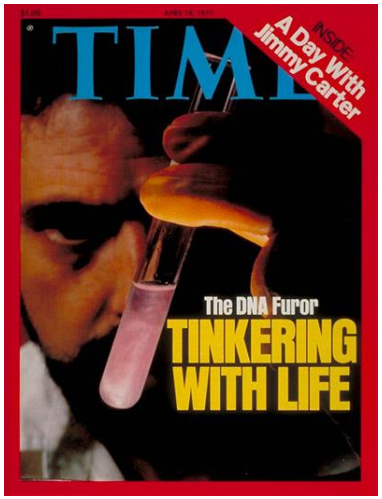
Term 1, 2019

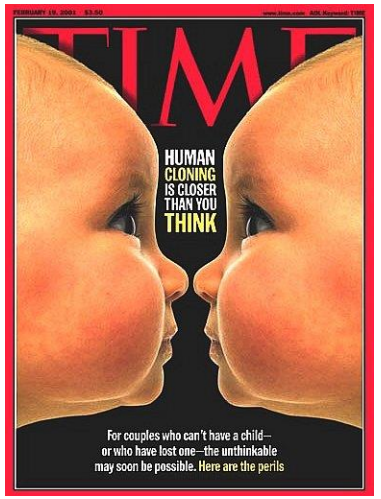
Week 5

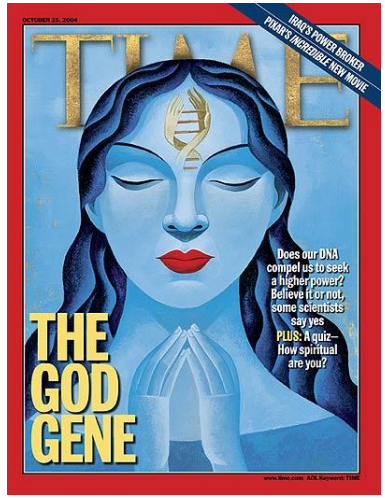
Genetic Testing

Dr Jelena Rnjak-Kovacina

Genes & Genetic Testing







Genetic testing: DNA as a tool

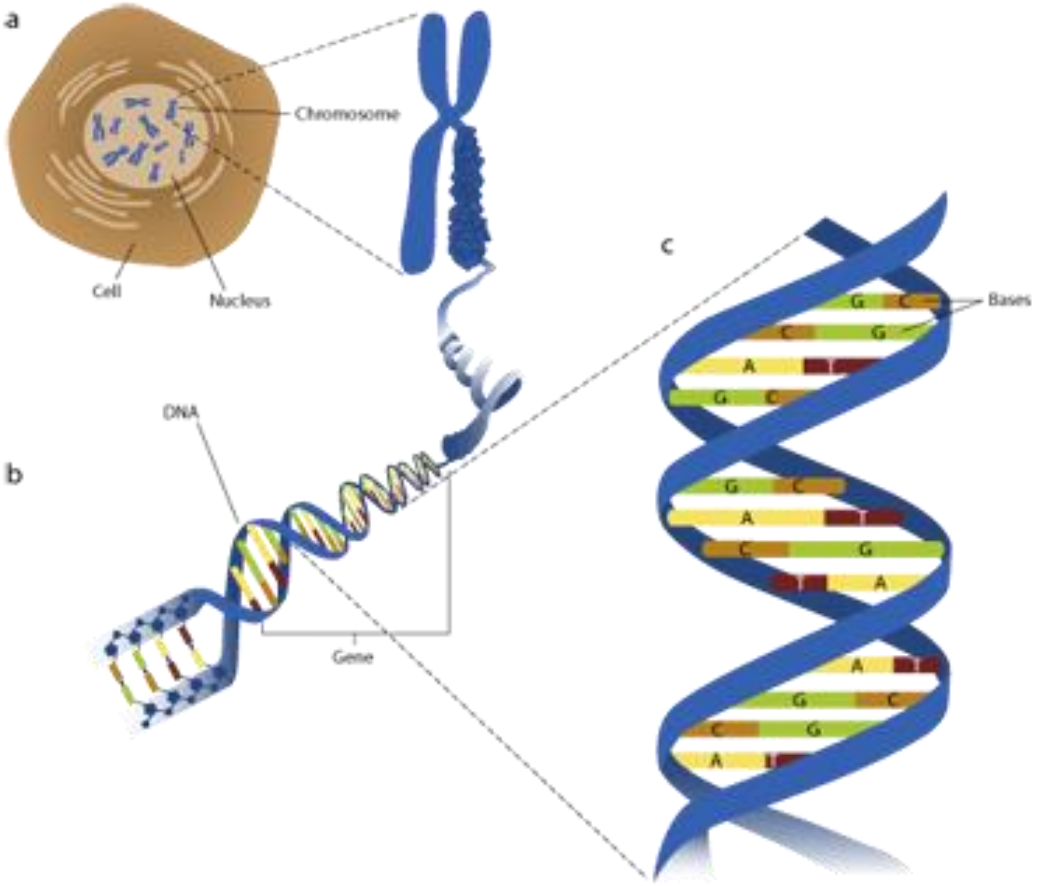
- DNA can be used as a diagnostic tool!
- Why does DNA make for a good diagnostic tool?

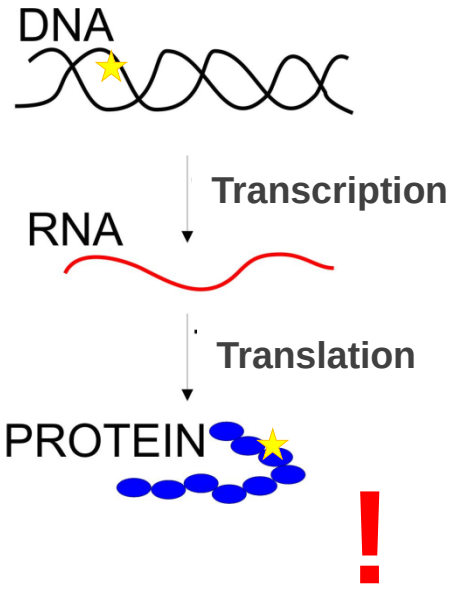
Genetic testing: DNA as a tool

- **DNA can be used as a diagnostic tool!**

- **Why does DNA make for a good diagnostic tool?**
  - In every cell in the body
  - Small samples needed
  - Minimally invasive
  - Predictive of future outcomes
  - ‘Unique’ to each individual

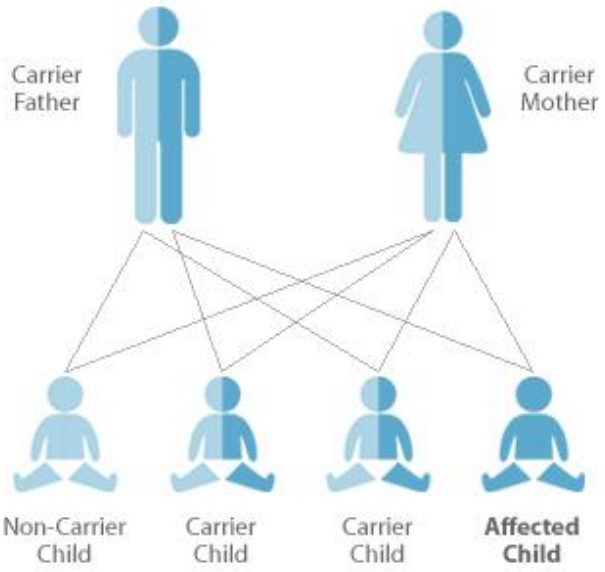
A few basics…


a
Chromosome
Cell
Nucleus
b
DNA
Gene
c
Bases


DNA
Transcription
RNA
Translation
PROTEIN
!

Types of genetic testing

- **Diagnostic testing** - identifies a genetic condition or disease that is making or in the future will make a person ill. The results of diagnostic testing can help in treating and managing the disorder.
- **Predictive and pre-symptomatic genetic testing** - finds genetic variations that increase a person's chance of developing specific diseases. This type of genetic testing may help provide information about a person's risk of developing a disease, and can help in decisions about lifestyle and health care.
- **Carrier testing**–tells people if they "carry" a genetic change that can cause a disease. Carriers usually show no signs of the disorder; however, they can pass on the genetic variation to their children, who may develop the disorder or become carriers themselves.

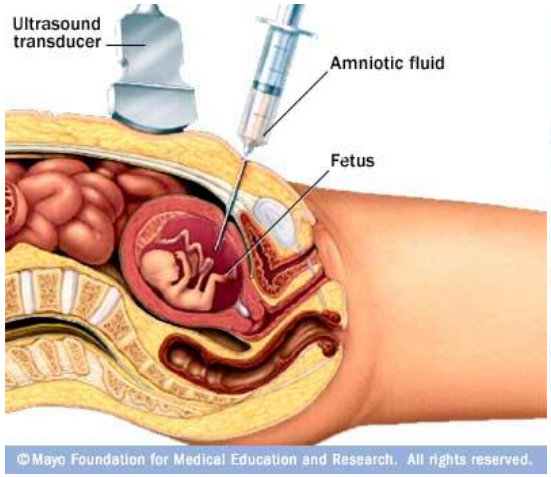


http://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=43

UNSW SYDNEY

Types of genetic testing

- **Prenatal testing** - is offered during pregnancy to help identify foetuses that have certain diseases.
- **Pre-implantation genetic testing** –is done in conjunction with *in vitro* fertilization to determine if embryos for implantation carry genes that could cause disease.
- **Newborn screening** - is used to test babies one or two days after birth to find out if they have certain diseases known to cause problems with health and development.



http://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=43

AMNIOCENTESIS	CHORIONIC VILLUS SAMPLING (CVS)	MATERNAL BLOOD TEST
1960s	1980s	2011
Identifies chromosomal abnormalities, inherited diseases and defects in the spinal column or brain. A needle through the belly extracts amniotic fluid, which contains fetal cells that are then analyzed	Identifies chromosomal abnormalities and inherited diseases. A needle through the belly or a catheter through the cervix suctions cells from the placenta. Placental tissue contains the same genetic material as the fetus	Allows doctors to assess the risk of chromosomal abnormalities. A blood sample is taken from the mother. Maternal blood contains fetal DNA, which passes through the placenta
15 to 20 weeks	10 to 13 weeks	10 weeks or later
Miscarriage occurs about 1 out of every 1,000 procedures	Miscarriage occurs about 1 out of every 500 procedures	Noninvasive
99%	98% to 99%	Detects 99% of Down-syndrome cases; up to 50% of positive tests are false positives

Types of genetic testing

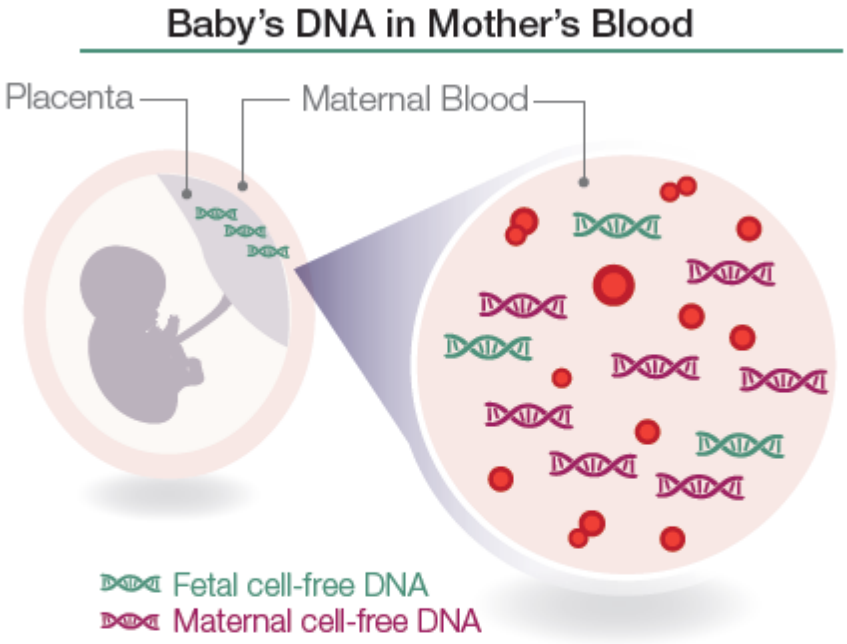


FIGURE 1: CELL-FREE FETAL DNA IN MATERNAL CIRCULATION

What Does Panorama Screen For?

Chromosomal Abnormalities

Trisomy 21 (Down syndrome)	Trisomy 18 (Edwards syndrome)	Trisomy 13 (Patau syndrome)	Triploidy

Babies with Down syndrome have three copies of chromosome 21 and have intellectual disabilities that range from mild to moderate. Children with Down syndrome will need extra medical care depending on the child's specific health problems. Early intervention has allowed many individuals with Down syndrome to lead healthy and productive lives. The presence of medical conditions, like heart defects, can affect the lifespan in these children and adults; however, most individuals with Down syndrome will live into their 60s. Miscarriage occurs in about 30% of pregnancies with Down syndrome while overall about 1 in 600 babies are born with Down syndrome.

Sex Chromosome Abnormalities

Monosomy X (Turner syndrome)	Klinefelter syndrome	Triple X syndrome	XYY syndrome

Babies with monosomy X are females who have one X chromosome instead of two. Unfortunately, a high proportion of pregnancies with monosomy X will result in a miscarriage in the first or second trimester of pregnancy. Babies with monosomy X that make it to term may have heart defects, learning difficulties, and infertility. In most cases, girls with monosomy X will need extra medical care including hormone therapies at various stages of life.

Microdeletions

22q11.2 deletion syndrome	Prader-Willi syndrome	Angelman syndrome	1p36 deletion syndrome	Cri-du-chat syndrome

The 22q11.2 deletion syndrome, also called DiGeorge syndrome or Velo-Cardio-Facial syndrome (VCFS), is caused by a missing piece of chromosome number 22. About one in every 2,000 babies is born with the 22q11.2 deletion syndrome. The majority of children with this disorder have heart defects, immune system problems, and specific facial features. Most children with 22q.11.2 deletion syndrome have mild-to-moderate intellectual disability and speech delays; some will also have low calcium levels, kidney problems, feeding problems and/or seizures. About one in five children with the 22q11.2 deletion syndrome have autism spectrum disorder; 1 in 4 adults with 22q11.2 deletion syndrome have a psychiatric illness, like schizophrenia.

What Types of Results Will I Receive From Panorama?

Although the majority of pregnancies result in deliveries of healthy babies, every woman has a background risk for having a baby with a chromosomal abnormality. The Panorama screening test can estimate your pregnancy-specific risk of having a baby with one of these conditions.

When you get your Panorama results, your report may state the following:

Low Risk	High Risk	No Result

Foetal cell-free DNA (cfDNA) circulating in maternal plasma

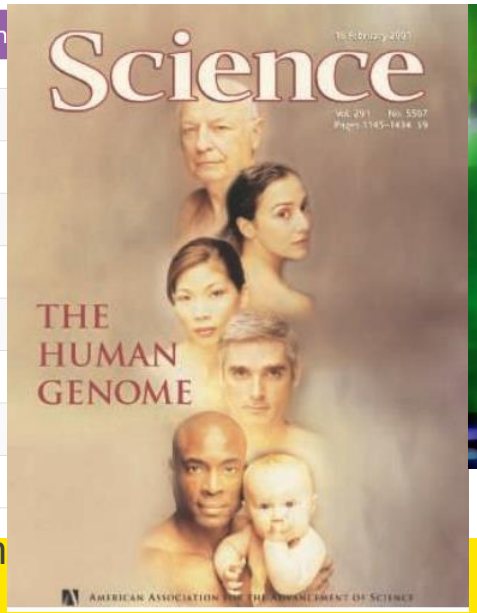
Types of genetic testing

- **Pharmacogenetic testing** - gives information about how certain medicines are processed in a person's body. This type of testing can help a healthcare provider choose the medicines that work best with a person's genetic makeup. For example, genetic testing is now available to guide treatments for certain cancers.
- **Research genetic testing** – helps scientists learn more about how genes contribute to health and disease, as well as develop gene-based treatments. Sometimes the results do not directly help the research participant, but they may benefit others in the future by helping researchers expand their understanding of the human body.
- **Forensic/identity testing**- used in paternity testing or crime scene investigation

The Medication DNA Insight™ genetic test reports on the following medication

Abacavir hypersensitivity	Methotrexate toxicity
Aminoglycoside antibiotics-induced hearing loss	Metoprolol metabolism
Beta-blockers	Phenytoin hypersensitivity
Beta-blockers, LVEF response	Phenytoin metabolism
Carbamazepine hypersensitivity	Proton pump inhibitors
Clopidogrel metabolism	Simvastatin-induced myopathy
Estrogen supplementation	Voriconazole metabolism
Interferon-alpha/ribavirin	Warfarin

http://report.nih.gov/nihfactsheets/ViewFactSh

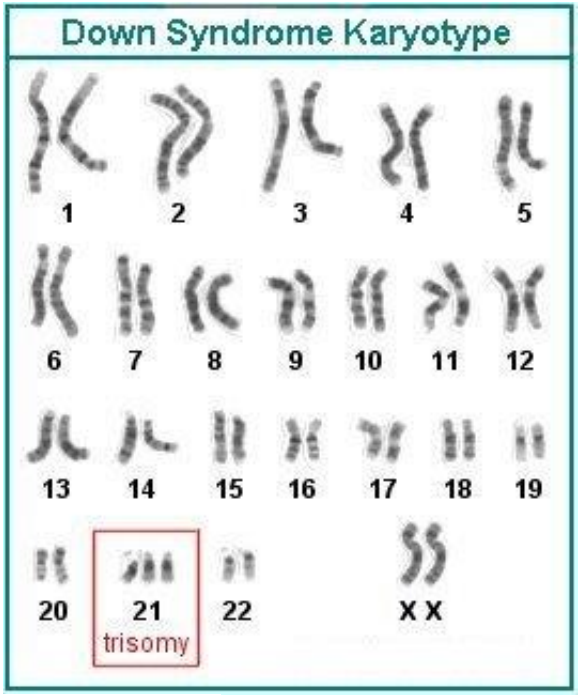


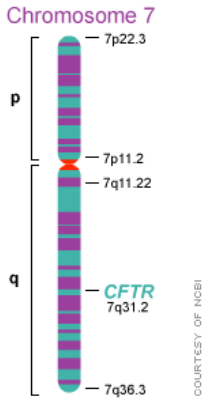
UNSW SYDNEY

Historical perspective

- **1960s- examination of chromosomes using light microscopy- Karyotype**
- Identification of disorders resulting from an incorrect number of chromosomes
- Eg. Down syndrome- extra chromosome 21, Klinefelter syndrome- extra chromosome X
- No info about individual genes

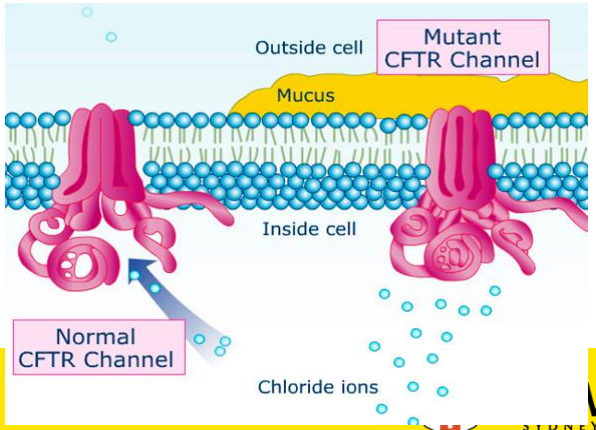
- **1970s- tests of individual genes**
- Tests where a mutation in a single gene (gene pair) causes the disorder
- Usually rare disorders
- Eg. sickle cell anaemia, cystic fibrosis, Huntington's disease



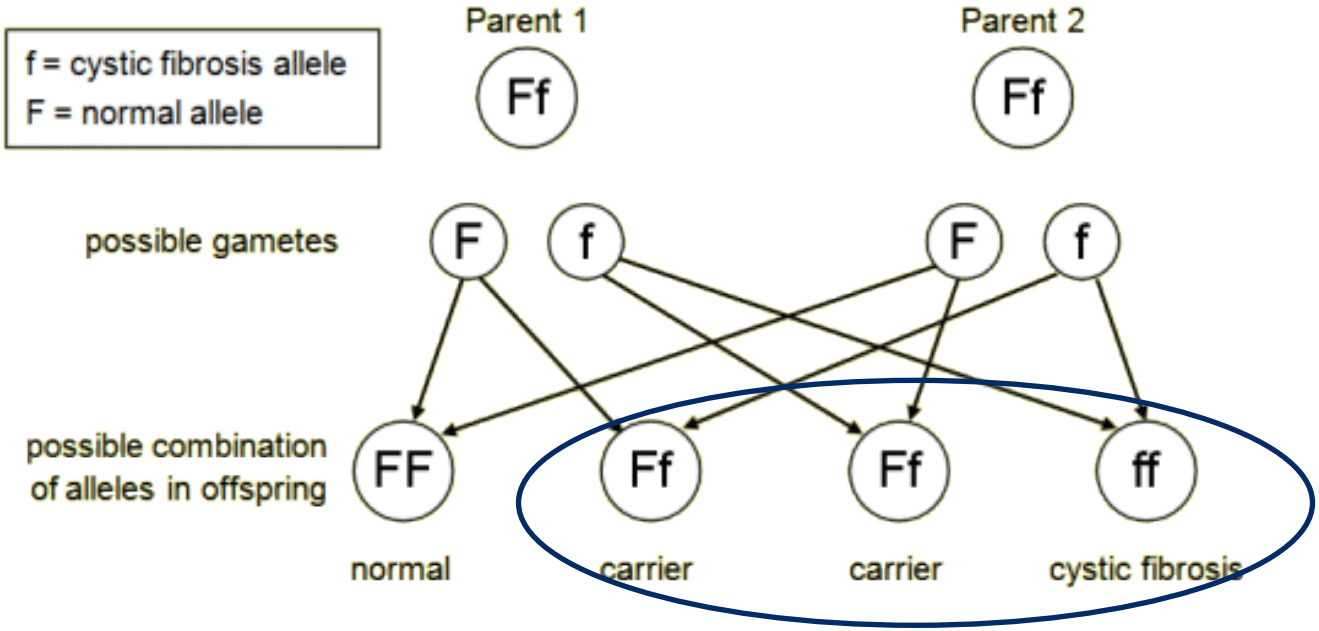


Screening an individual gene

- **Example disease:** Cystic fibrosis
  - Dysfunctional salt channels result in mucus build-up in multiple organs, in particular lungs & pancreas
  - Frequent lung infections, fibrosis & eventual lung transplant, poor food digestion (pancreas does not release necessary enzymes)
  - No cure, management of symptoms
- **Affected gene: c**ystic **f**ibrosis **t**ransmembrane conductance **r**egulator gene (CFTR)
- **Function of gene:** Transport of ions across epithelial membranes
- **Mutations:** >1000
- **Inheritance:** Autosomal recessive



Screening an individual gene



f is the cystic fibrosis allele		mother	
		F	**F**
father	**F**	FF	FF
	f	Ff	Ff

0% CF

50% carrier

f is the cystic fibrosis allele		mother	
		F	**f**
father	**F**	FF	Ff
	f	Ff	ff

25% CF

50% carrier

f is the cystic fibrosis allele		mother	
		f	**f**
father	**F**	Ff	Ff
	F	Ff	Ff

0% CF

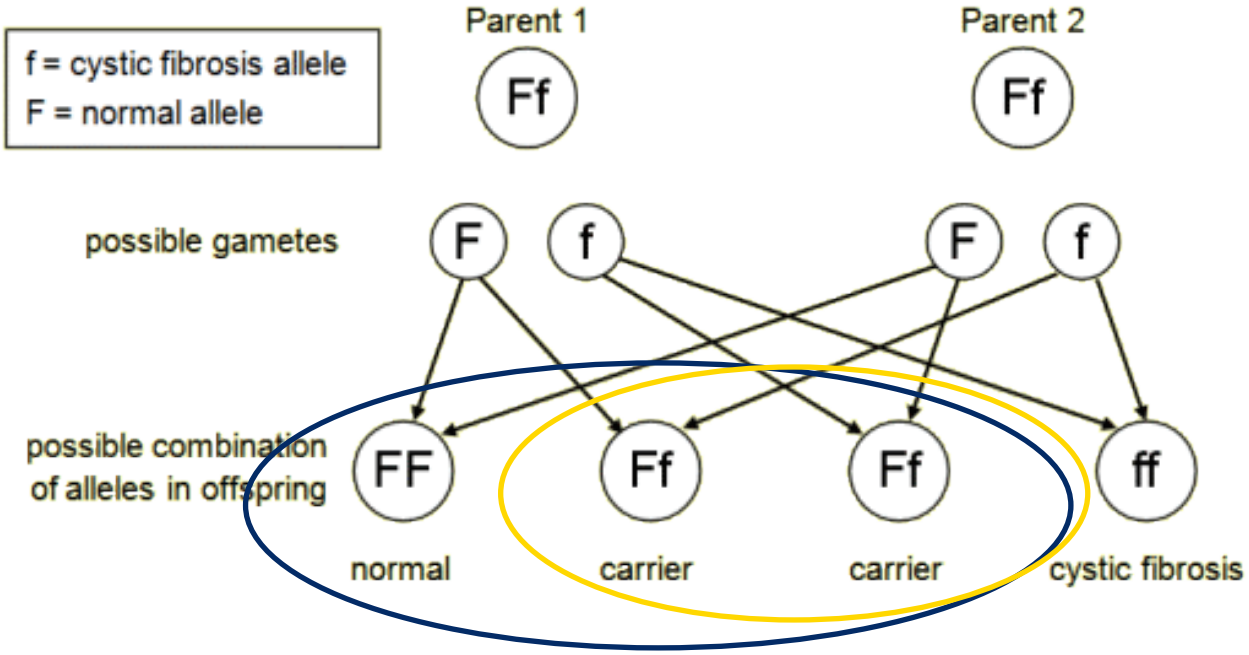
100% carrier

f is the cystic fibrosis allele		mother	
		f	**f**
father	**F**	Ff	Ff
	f	ff	ff

50% CF

50% carrier

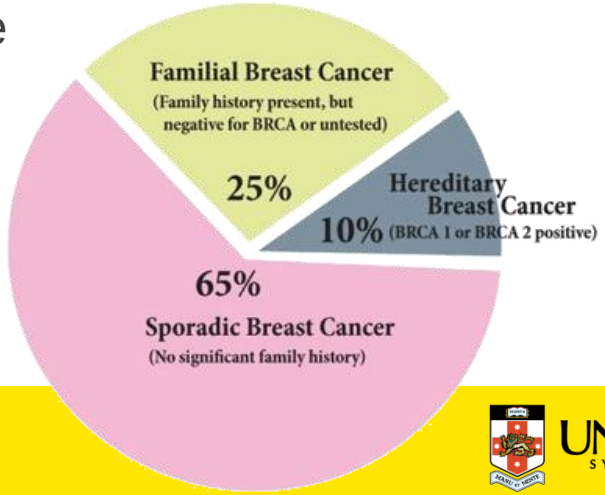
Screening an individual gene



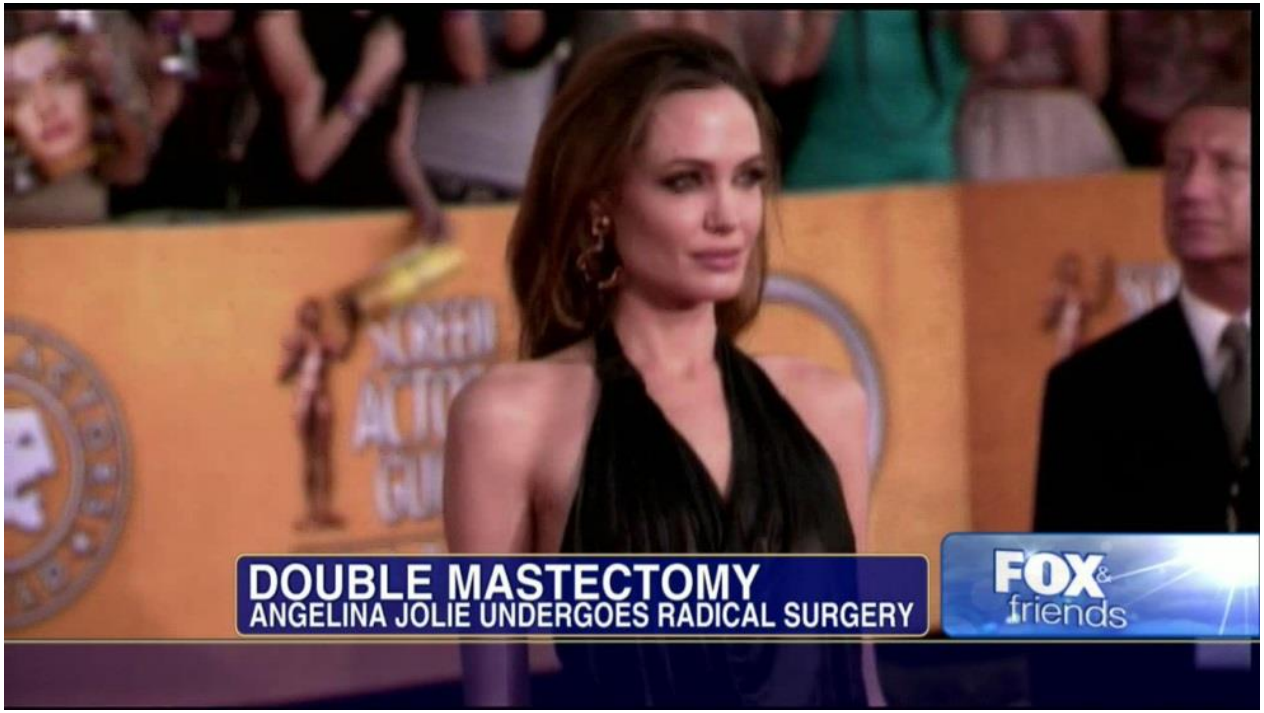
What is the carrier risk of a person with two carrier parents who does not present with the disease?

Historical perspective

- **2000s- tests of ‘susceptibility genes’**
  - 2003- Human Genome Project completed - Drove advances in genetic testing
  - Trying to understand common disorders-eg. cancer, heart disease, Alzheimer’s disease
  - Caused by many different genes interacting in complicated ways with a variety of environmental factors
  - **Testing of heightened susceptibility to develop a certain disorder**
  - Still not well understood
  - Mutations may increase the chance of the disorder developing, but no certainty, environmental factors play a big role
  - Potential of disease/disorder prevention



Screening ‘susceptibility genes’



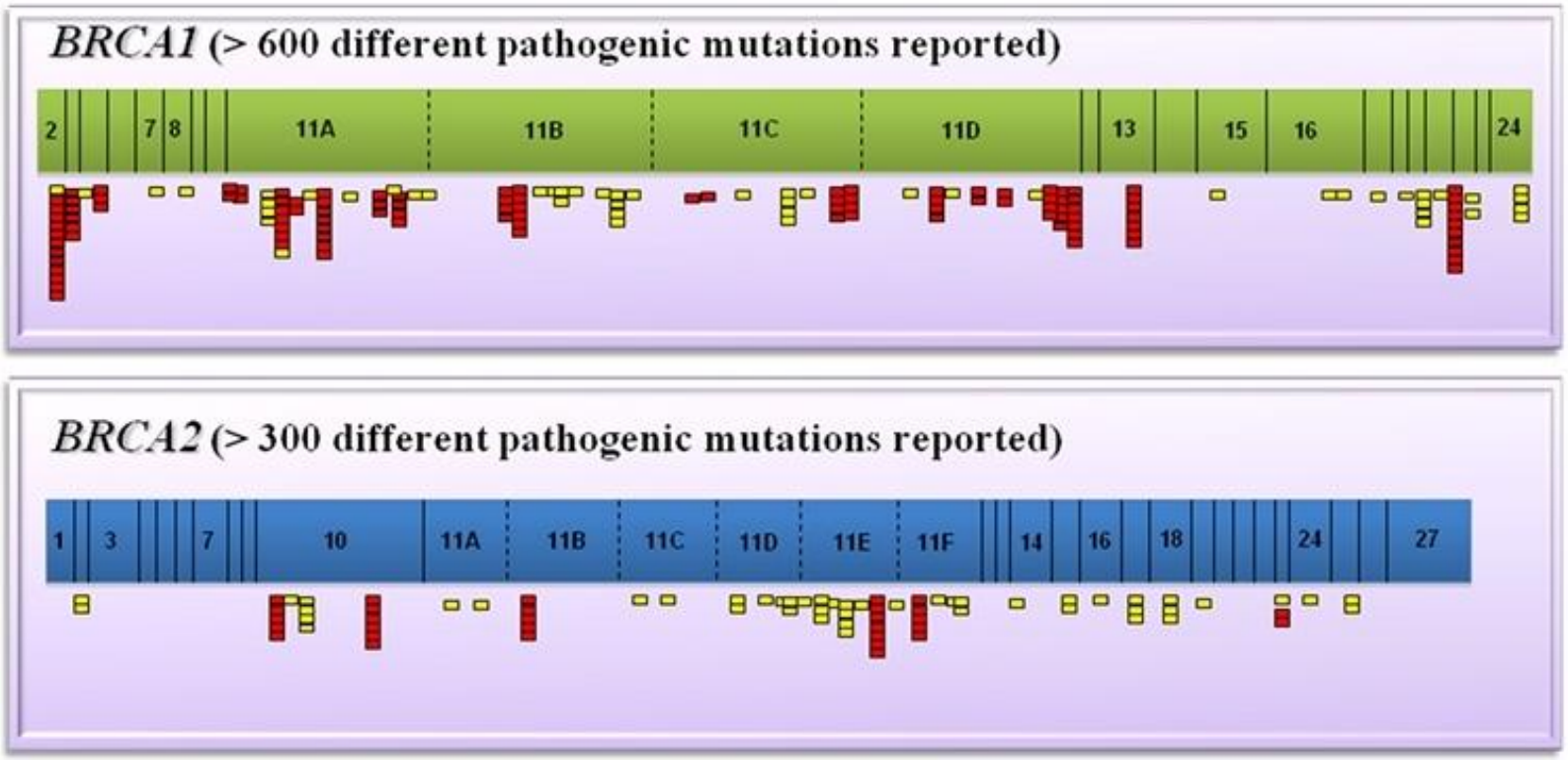
Screening ‘susceptibility genes’

- **Example disease:** Breast/Ovarian cancer
- **Known susceptibility genes:** BRCA1 and BRCA2
- **Function of genes:** Regulation cellular proliferation / tumour inhibition, DNA damage repair
- **Mutations:** Many, some occur more frequently in certain heritage, ethnic or geographic groups (eg. Ashkenazi Jewish, Norwegian, Dutch & Icelandic peoples have a higher incidence of specific, harmful BRCA1/2 mutations)
- **Known environmental factors:** menstruation age, first pregnancy age, menopause age, hormone replacement therapy
- **Susceptibility:**

Breast cancer- ~12% of women, 55-65% of women with a harmful BRCA1 and ~45% of women with a harmful BRCA2 mutation will develop breast cancer by the age of 70

Ovarian cancer- ~1.4% of women, ~39% of women with a harmful BRCA1 and 11-17% of women with a harmful BRCA2 mutation will develop ovarian cancer by the age of 70

Screening ‘susceptibility genes’



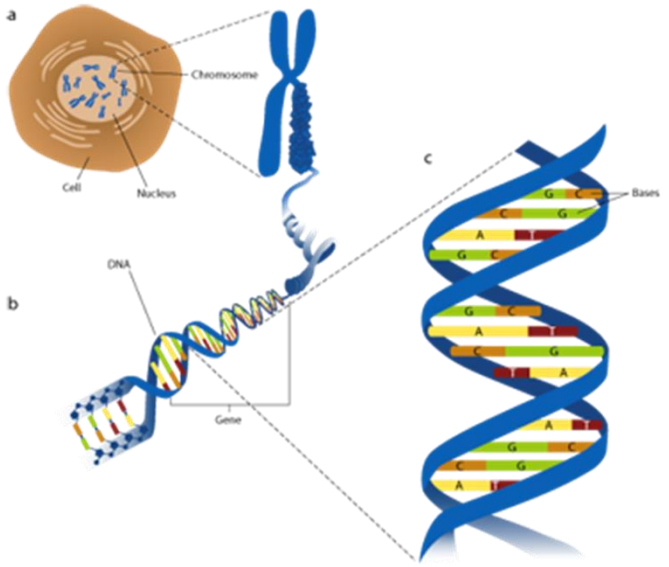
The science behind genetic testing

In order to analyse genes, we need to be able to do one or more of these:

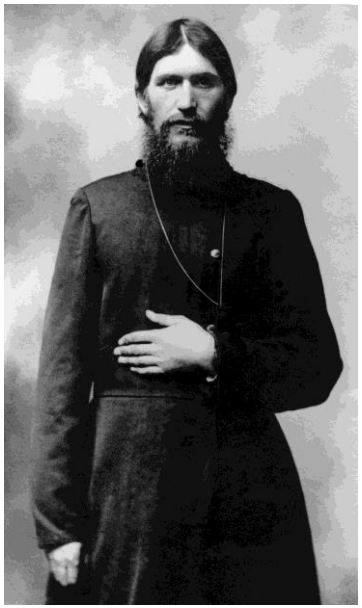
- Isolate DNA
- Cut DNA
- Amplify DNA
- Visualise DNA
- Sequence DNA

Factoids:

- **Human genome-3.2 billion base pairs**
- **>20,000 identified genes**

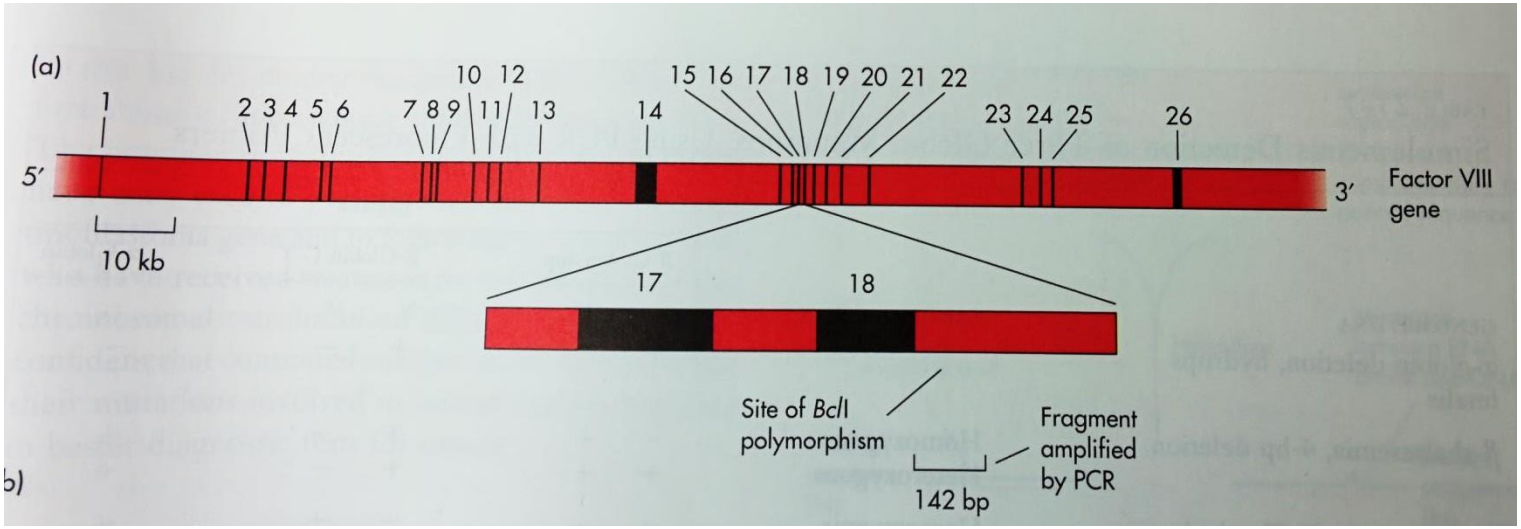


An example: prenatal diagnosis of haemophilia

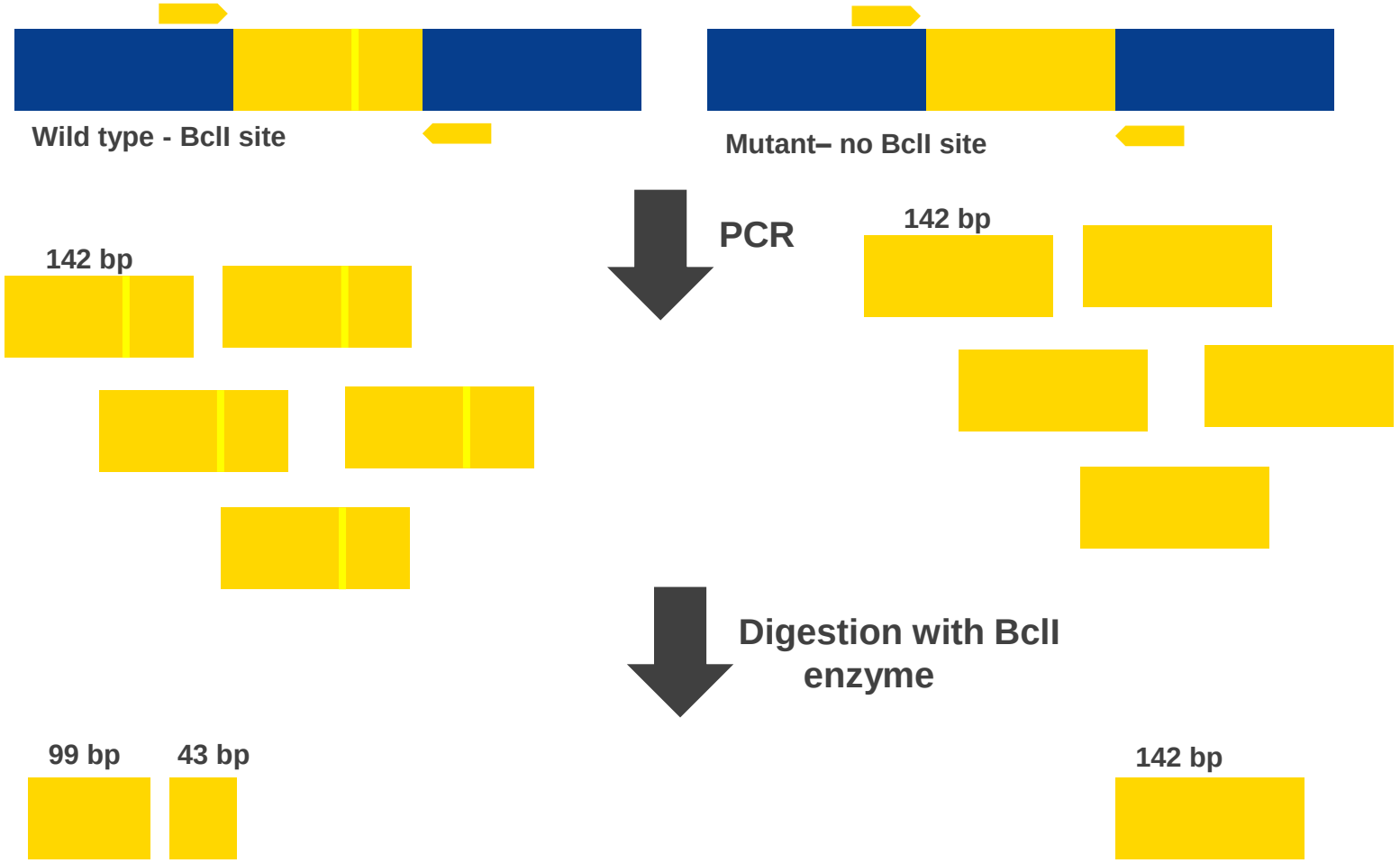


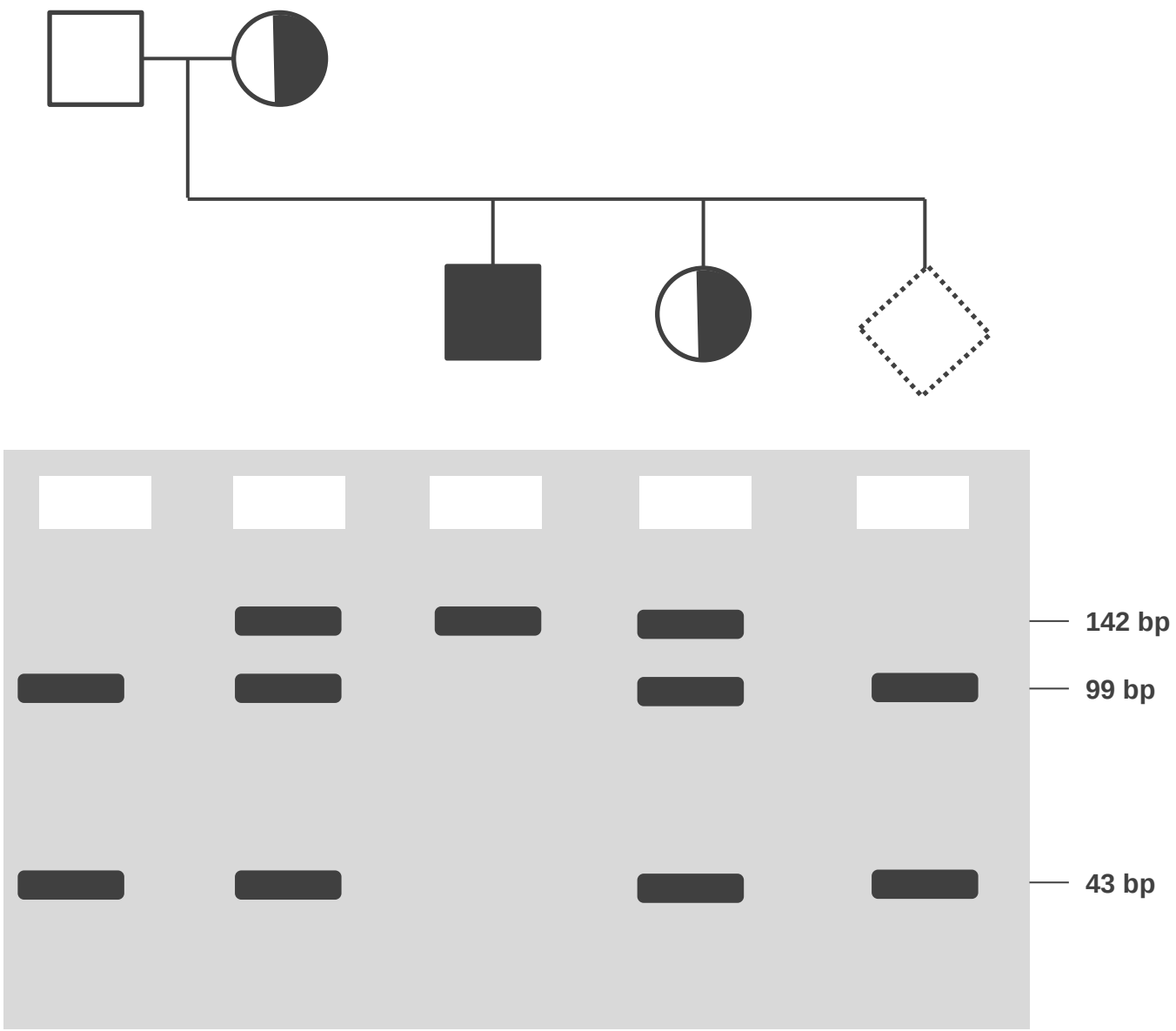
An example: prenatal diagnosis of haemophilia

- Group of hereditary genetic disorders that impair the body's ability to control blood clotting
- Haemophilia A- deficiency in clotting factor VIII

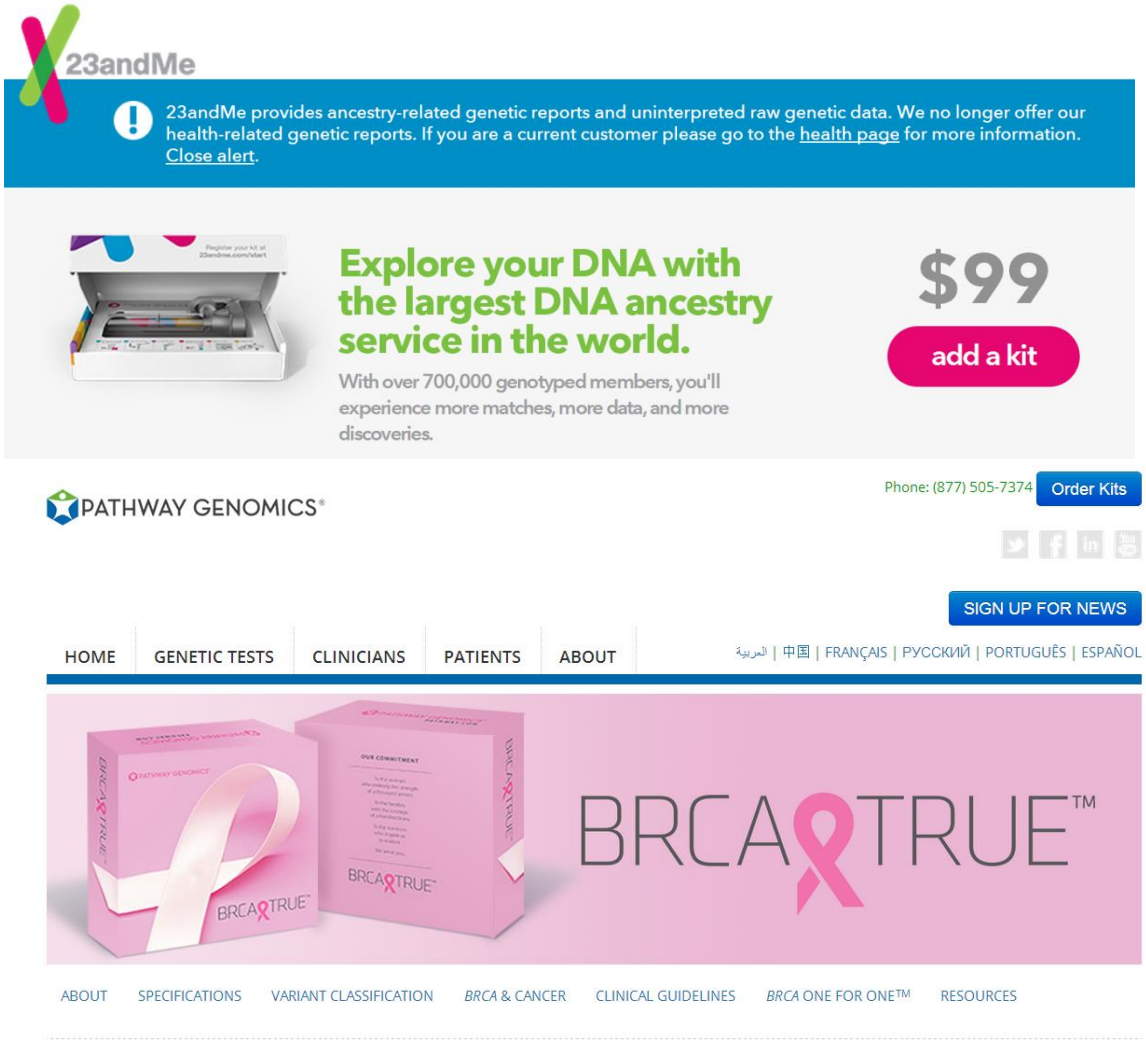


Prenatal diagnosis of haemophilia




142 bp
99 bp
43 bp

Genetic testing widely available



In 2013 the US Food and Drug Administration (FDA) ordered 23andMe to discontinue marketing its personal genome service as the company had not obtained the legally required regulatory approval resulting in concerns about the potential consequences of customers receiving inaccurate health results. The company still sells a personal genome test without health-related results.

UNSW SYDNEY

SIGN UP FOR NEWS

HOME | GENETIC TESTS | CLINICIANS | PATIENTS | ABOUT

العربية | 中国 | FRANÇAIS | РУССКИЙ | PORTUGUÊS | ESPAÑOL

Home › Genetic Tests / Mental Health DNA Insight™

Genetic Tests

Cancer

- *BRCA*True™
- ColoTrue™
- Familial Studies Program
- CancerFit™

Cardiac

- Cardiac DNA Insight™
- Cardiac Healthy Weight DNA Insight™

Carrier Screening

- Carrier Status DNA Insight™

Medication

- Mental Health DNA Insight™
- Pain Medication DNA Insight™
- Medication DNA Insight™

Mental Health DNA Insight™

Mental Health DNA Insight™ analyzes a patient's DNA to identify genetic variants that affect the metabolism and efficacy of psychiatric medications. Genetic research suggests that categorizing individuals based on genotypes will make the pharmacologic treatment of psychiatric illnesses more predictable and effective. Mental Health DNA Insight can help a physician predict a patient's response to more than 40 common antidepressants, mood stabilizers and antipsychotic medications. The report provides outcomes in a clear color-coded chart.

Mental Health DNA Insight™

- A **green** light indicates to prescribe the drug as directed in the product insert.
- An **orange** light signals caution. For medications in this category, the outcome may indicate that dosing levels need to be lowered or increased, or that the drug's side effects may cause an adverse reaction for this patient.
- Medications in the **red** light category should be used with caution and with more frequent monitoring, due to risk of severe adverse reaction or lack of therapeutic

s DNA Insight™

th DNA Insight™

tion DNA Insight™

)NA Insight™

The Health Conditions DNA Insight™ genetic test reports on the following conditions:

Age-related macular degeneration	Lung cancer
Alzheimer's disease, late onset	Melanoma
Amyotrophic lateral sclerosis (sporadic)	Multiple sclerosis
Asthma	Myocardial infarction
Atrial fibrillation	Obesity
Breast cancer (females only)	Osteoarthritis
Colorectal cancer	Parkinson's disease
Coronary artery disease	Peripheral arterial disease
Diabetes, type 1	Prostate cancer (males only)
Diabetes, type 2	Psoriasis
Exfoliation glaucoma	Rheumatoid arthritis
Hypertension	Systemic lupus erythematosus
Leukemia, chronic lymphocytic	Ulcerative colitis

Phone: (877) 505-7374 Order Kits

SIGN UP FOR NEWS

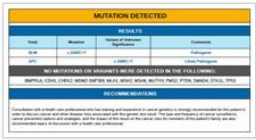
NICIANS | PATIENTS | ABOUT

العربية | 中国 | FRANÇAIS | РУССКИЙ | PORTUGUÊS | ESPAÑOL

ColoTrue™

Approximately 25 percent of all cases of colorectal cancers can be attributed to heritable genetic changes.* Based on a saliva or blood sample, Pathway Genomics' ColoTrue™ uses **next-generation sequencing (NGS) technology** to identify genetic changes that increase a patient's risk of developing certain types of cancer.

Understanding what genetic risk factors a patient possesses can help create personalized risk-reducing strategies and guide preventive measures.
Pathway Genomics can help to **understand a patient's cancer risk,** facilitate genetic and medical counseling, as well as assist physicians in making informed health care decisions.



UNSW SYDNEY

Genetic testing widely available

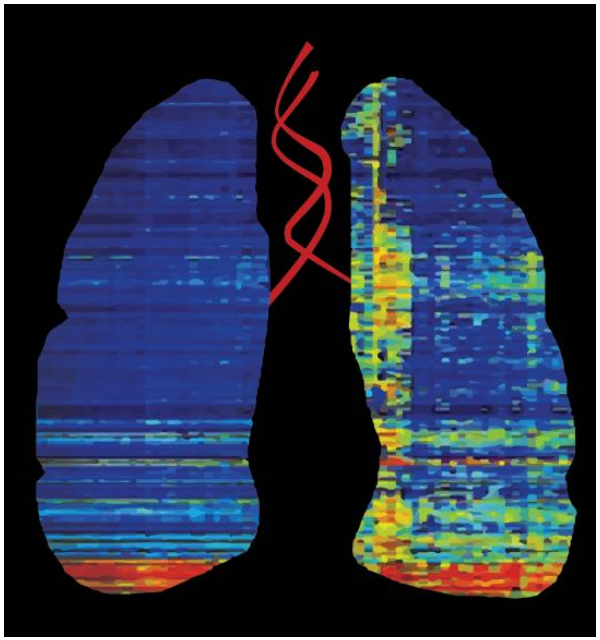
Examples of genetic tests available online

Company (Web site)	Sample	Conditions	Price
deCODE genetics (**www.decodeme.com**)	Cheek swab	Carrier status for disorders, disease risk, drug metabolism, ancestry	$2000 for complete panel; $500 each, cancer or heart panel. Genetic counseling included in price.
23andMe, Inc. (**www.23andme.com**)	Saliva	Carrier status for disorders, disease risk, drug metabolism, ancestry	$429 for health panel (carrier status, disease risk, drug metabolism); $399 for ancestry; $499 for both. Genetic counseling available for additional fee.
Pathway Genomics* (**www.pathway.com**)	Saliva	Carrier status for pregnancy planning, disease risk, drug metabolism, ancestry	$399 for disease risk panel; $249 each for ancestry, pregnancy planning, drug metabolism. Genetic counseling included in price.
Interleukin Genetics (**www.ilgenetics.com**)	Cheek swab	Obesity, heart attack, B vitamin metabolism, bone loss	$149 each; discounted prices for two or more. Genetic counseling and consultation included in price.

*Disclosure: Harvard Health Publications, publishers of *Harvard Women's Health Watch*, has a licensing agreement with Pathway Genomics unrelated to this article.

Ethical considerations of genetic testing

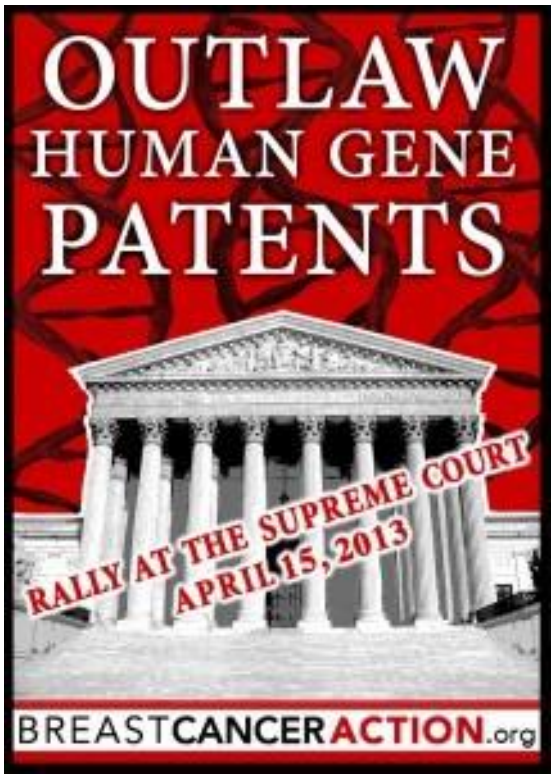
- **The shared nature and ownership of genetic information**
  - Family issues
- **Limitations of genetic testing**
  - Genetic tests find mutations, not diseases (or cures)
  - Are we defined only by our genes? Nature vs Nurture? Environmental factors? Epigenetics?



http://www.genetics.edu.au/Genetic-conditions-support-groups/Understanding-Genetic-Testing

Ethical considerations of genetic testing

- **Inappropriate applications of genetic testing**
  - Sex determination? Designer babies?
- **Setting boundaries in applications of the genetics technology**
- **The potential for discrimination**
  - Insurance providers, employers, eugenics
- **Forensic DNA databanks**
  - Privacy issues, misuse
- **Patenting of genes**



http://www.genetics.edu.au/Genetic-conditions-support-groups/Understanding-Genetic-Testing