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National Health and Medical Research Council
NHMRC

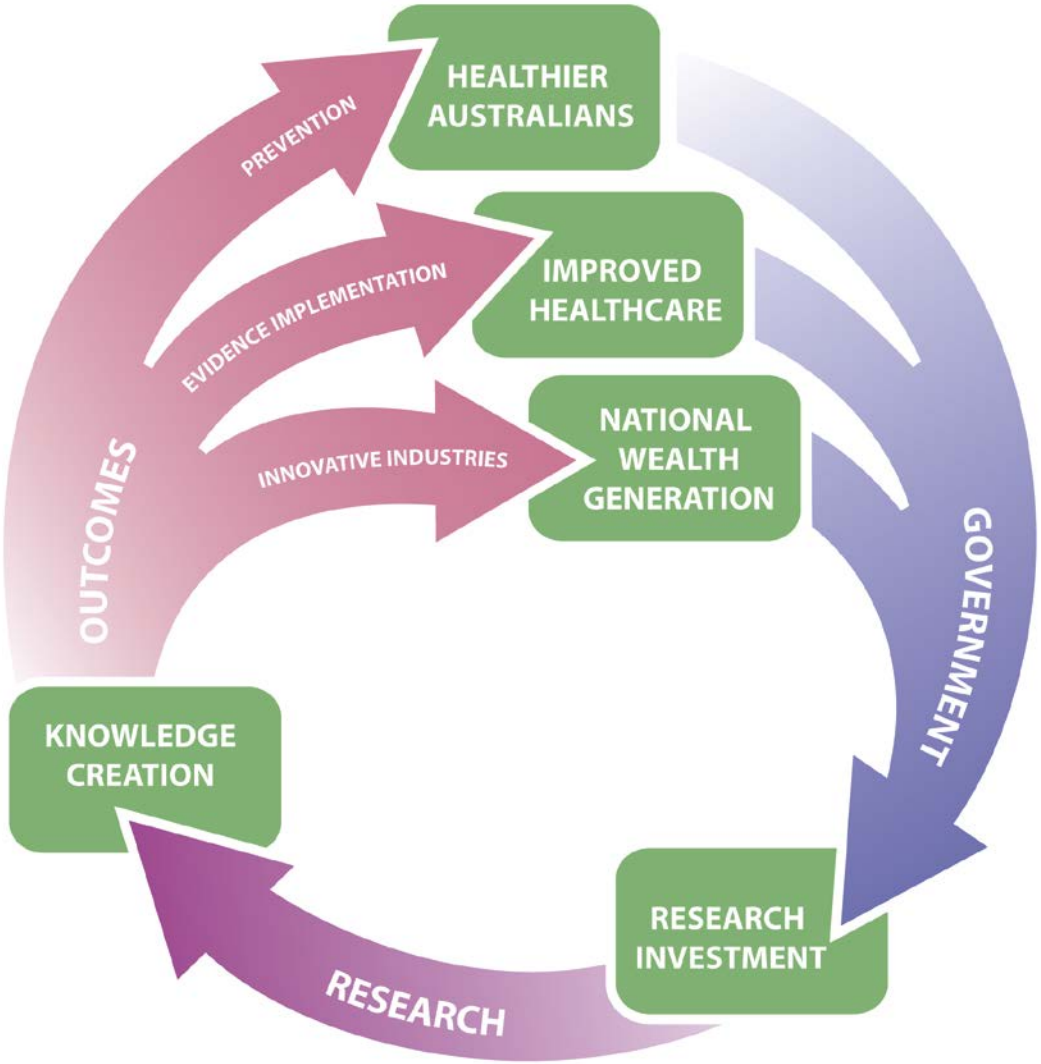
Genomics: The Coming Challenge to the Health System

Professor Warwick Anderson

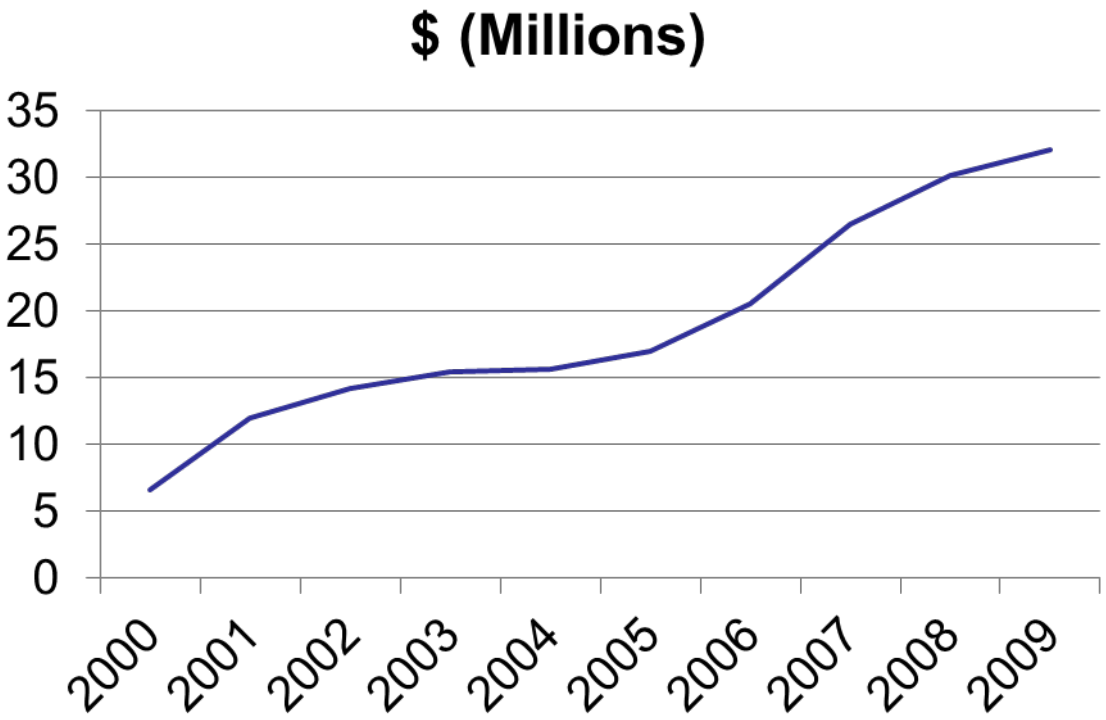
Chief Executive Officer

National Health and Medical Research Council

Virtuous Cycle



NHMRC funding - genomics research



NHMRC has invested over $190 million during the last ten years in genetics and genomics research.

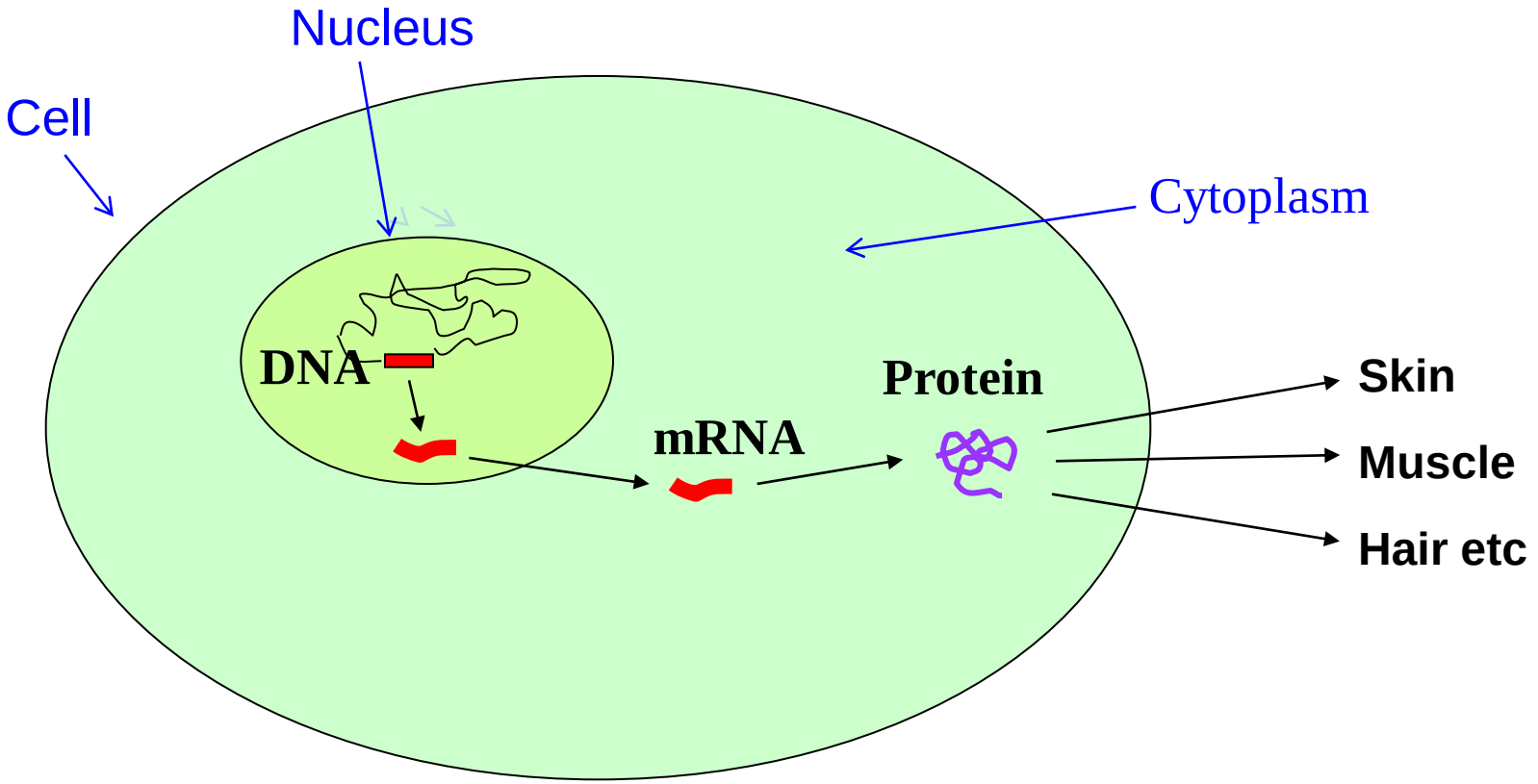
Most biomedical research now involves a genomics component.

Topics funded vary from genomic profiling of high risk acute lymphoblastic leukaemia to the development of personalised medicine decision support tools.

International Cancer Genomics Consortium(ICGC)

- Investigate the genetic basis of up to 50 types of cancer (25,000 tumors)
- 24 countries will share tissue samples, data and information
- Australia's focus is on ovarian and pancreatic cancer
- NHMRC is committing ~$25m over 5 years
- Pancreatic cancer
  - very heterogenous
  - routinely sequence tumor for mutations
  - Treatment optimisation - *Individualised Molecular Pancreatic Cancer Therapy* (QIMB, Garvan Institute)

DNA - What does it do?



DNA ’ mRNA ’ Protein

The Human Genome

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46 chromosomes (23 pairs) – 22 autosomal pairs
plus
– XX ♀ or XY ♂

DNA – double stranded helix; four bases – A C G T (A-T, C-G)

Human Genome Project

- public and private consortia in US
- sequencing completed in 2003 – many gaps
- approx. 3 billion base pairs
- approx. 20,000 genes, but functions of many genes yet to be fully determined

Types of Genetic Disorders

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1. Somatic cell defects (not heritable)

Acquired, not inherited, no implications for family.

Cancer tissue testing. Helps in guiding therapy e.g. *HER2*

2. Mendelian genetic defects (heritable)

Inherited = risks for family members.

Strong gene effects so can draw family trees

e.g. cystic fibrosis

3. Complex genetic disorders (heritable)

Gene (G) + environment (E). Difficult to understand due to G x E and other interactions.

Familial risk but not quantifiable. Twin studies confirm heritability e.g. Type 2 diabetes

DNA testing – Huntington Disease

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attgccccgg tgctgagcgg cgccgcgagt cggcccgagg cctccgggga ctgccgtgcc
gggcgggaga ccgccatggc gaccctggaa aagctgatga aggccttcga gtccctcaag
tccttccagc agcagcagca gcagcagcag cagcagcagc agcagcagca gcagcagcag
cagcagcagc aacagccgcc accgccgccg ccgccgccgc cgcctcctca gcttcctcag
ccgccgccgc aggcacagcc gctgctgcct cagccgcagc cgcccccgcc gccgcccccg
gctaccaaga aagaccgtgt gaatcattgt ctgacaatat gtgaaaacat ag ……..

- Number CAG repeats up to 26 = NORMAL
- Number e 40 = Huntington Disease
- Number = 27-39, more complicated to explain significance

Applications: Diagnostic ---- Predictive ---- Prenatal

Whole Genome Sequencing – the $1,000 genome sequence

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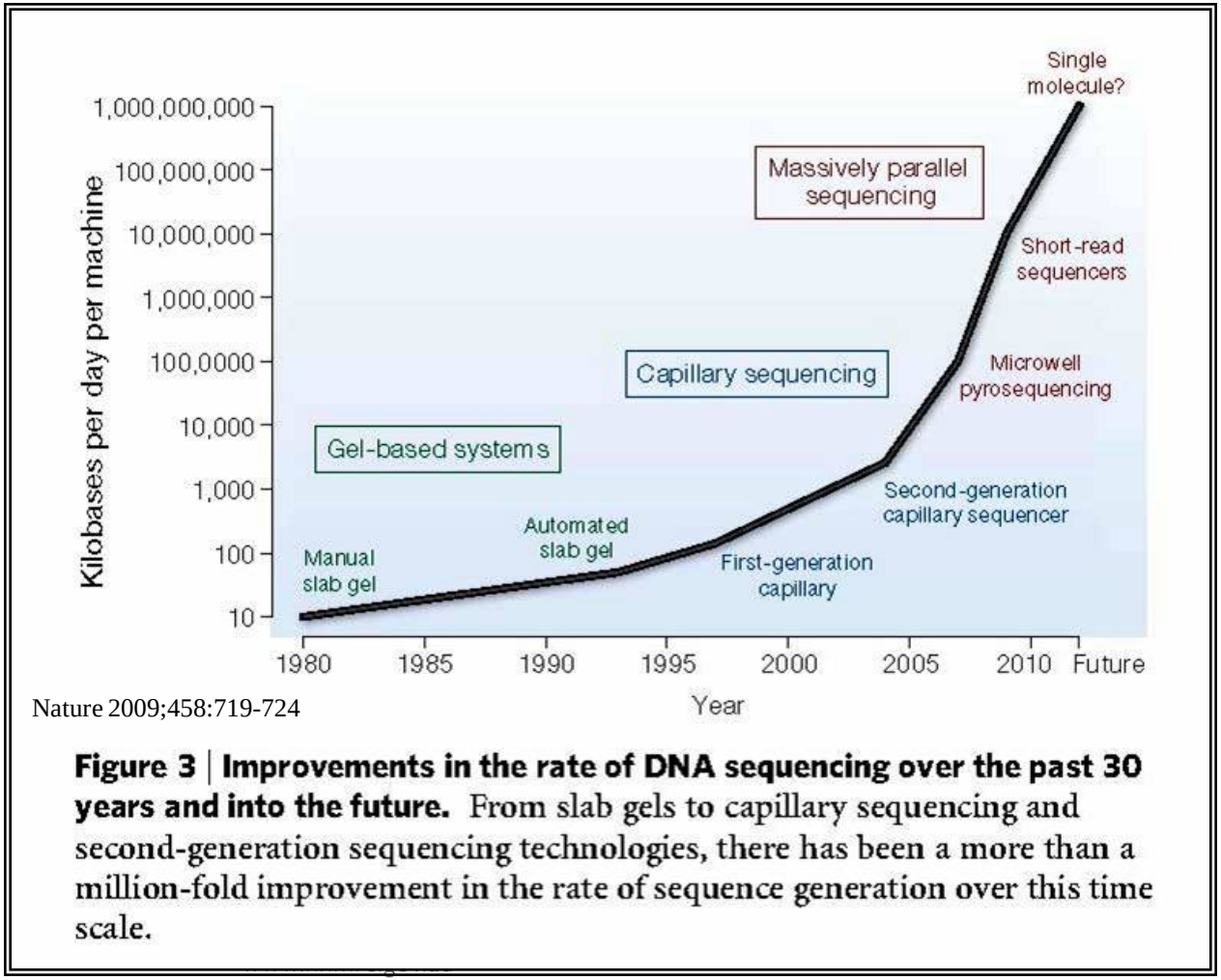
Paradigm shift in DNA Testing:

Diagnostic to Screening



Nature 2009;458:719-724

Figure 3 | Improvements in the rate of DNA sequencing over the past 30 years and into the future. From slab gels to capillary sequencing and second-generation sequencing technologies, there has been a more than a million-fold improvement in the rate of sequence generation over this time scale.

DNA sequencing – reading the ATGCs

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- WGS is well established in research
- Automation, including greater use of robotics
- Technology has become the driver
- Chemical sequencing – since early 1990s
- **Now** massively parallel sequencing (AKA Next Generation sequencing)
- 3rd gen sequencing underway (in future, medical professionals may have DNA sequencers in their surgeries)

Costs of Sequencing

Targeted gene sequencing	→	Exome sequencing	→	Whole Genome sequencing
e.g.BRCA1,2		All 20,000 Genes		The Lot
$2,500		$999 now		$3billion in 2003 →$1,000

❖ **Costs for interpretation NOT included**

WGS paradigm shift - Personalised medicine

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Personalised medicine is defined as:

'the capacity to predict disease development and influence decisions about lifestyle choices or to tailor medical practice to an individual'.

Personalised medicine can be split into *predictive medicine* and *treatment optimisation*.

Personalised Medicine

Predictive Medicine

Using a DNA test to PREDICT a disease will develop in the future

Treatment Optimisation

Using a DNA test to SELECT a drug or dosage or assess risk of TOXICITY to a drug

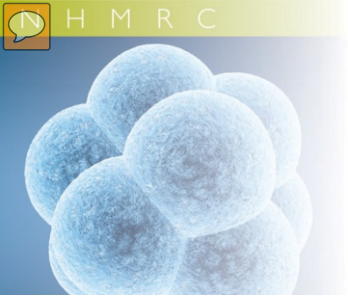
- ✓ Improved patient outcomes
- ✓ Reduced adverse events
- ✓ Cost effective use of health care resources

Predictive Medicine

Genetic information can inform prediction of risk of:

- developing a disease
- disease progression
- severity of symptoms

This can be used to tailor prevention and treatment and make informed choices relating to lifestyle, reproductive matters, screening and preventative treatments.



Predictive Medicine: Familial Adenomatous Polyposis

An example of predictive medicine in practice:

- Presence of adenomatous polyposis coli gene mutation confers almost 100% penetrance for FAP
- Individuals with a family history of FAP undergo extensive surveillance which is expensive, invasive and can have side effects
- Negative test result removes the need for surveillance

Treatment Optimisation

Absorption, kinetics, metabolism, effectiveness and risks of drugs vary between patient, due to genetic factors.

Treatment optimisation refers to pharmacogenetics/ pharmacogenomics:

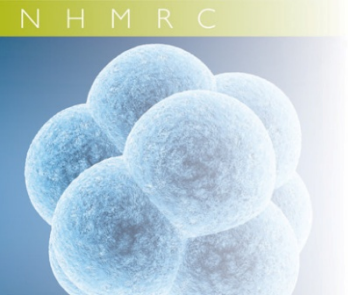
- Pharmacogenomics aims to match the best available drug or dose to the individual's genomic profile
- Genetic differences can give rise to differing responses to a given drug
- Genetic tests can inform drug and dose selection improving drug efficacy and reducing side effects.

Treatment Optimisation: Tamoxifen

Treatment optimisation in practice:

- Tamoxifen is used to treat oestrogen-receptor positive breast cancer
  - *CYP2D6 is involved in metabolising tamoxifen*
  - *About 1/3 of women relapse*
  - *There is considerable variation in response including side effects*
- Warfarin,
  - *CYP2C9 and VKORC1 influence responses*

Clinical utility of genetic testing to determine the dose and predict the response to tamoxifen remains to be determined.



International Cancer Genomics Consortium(ICGC)

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Pancreatic cancer

- very heterogenous
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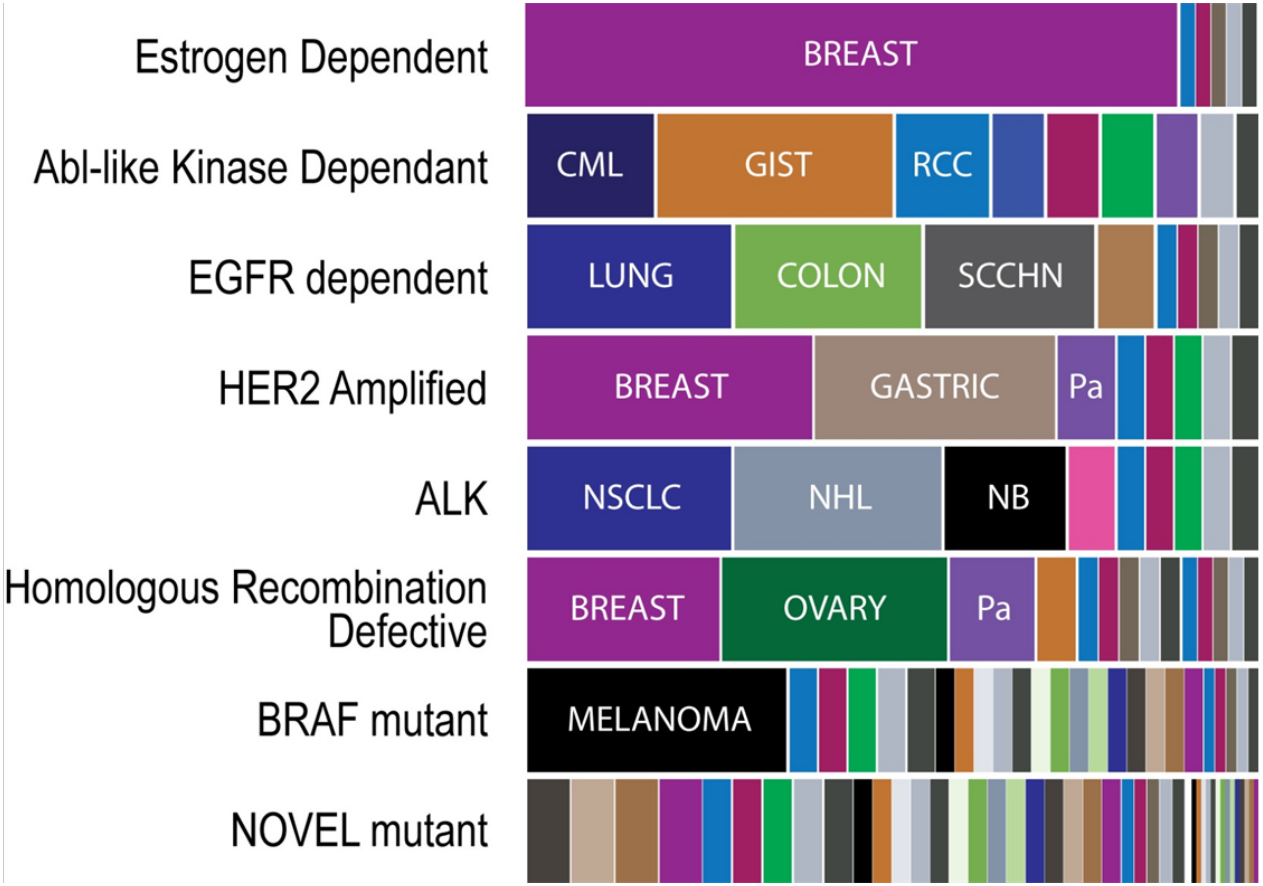
Molecular taxonomy - Cancer biotypes (Classified by mutations, not source tissue)



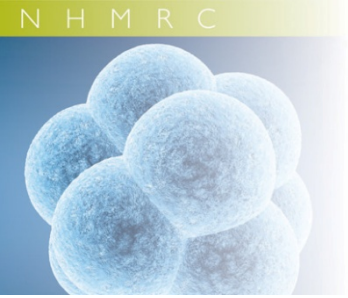
Andrew Biankin and Sean Grimmond, APGI

Benefits of Personalised Medicine

- Improved patient outcomes
- Reduced adverse events
- Cost effective use of health care resources - the cost of genetic testing may be offset by:
  - avoiding expensive treatments when they are unlikely to be efficacious
  - avoiding additional treatment for side effects which are less likely to occur

Challenges

- The development of drugs that are beneficial for only a small cohort of patients is often more expensive and pharmaceutical companies may not be interested in developing them
- The potential to tailor drug treatments may go unfulfilled due to a lack of resources, funding and take up by pharmaceutical companies
- The process for assessing the clinical utility of genetic tests is not as well developed as for drugs.



Direct to Consumer DNA testing Lumigenix

By looking very closely at your genome using the latest genotyping technology, we can determine whether you have the SNP associated with an increased risk of a particular disease. This is then linked to current scientific research about that particular SNP to give you your report.

We currently test for 81 diseases in our Comprehensive kit.

Brain and nerves
- Cerebral aneurysm
- Cluster headache
- Creutzfeldt-Jakob disease
- Multiple Sclerosis
- Parkinson's disease
- Progressive supranuclear palsy
- Essential tremor
- Restless legs syndrome
- Lou Gehrig's disease
- Narcolepsy (with cataplexy)

Cancers
- Aerodigestive cancer
- Basal cell carcinoma
- Bladder cancer
- Breast cancer
- Colon cancer
- Gastric cancer (diffuse-type)
- Diffuse large B-cell lymphoma
- Follicular lymphoma
- Lung cancer
- Lymphocytic leukemia (acute)
- Lymphocytic leukemia (chronic)
- Melanoma
- Nasopharynx cancer

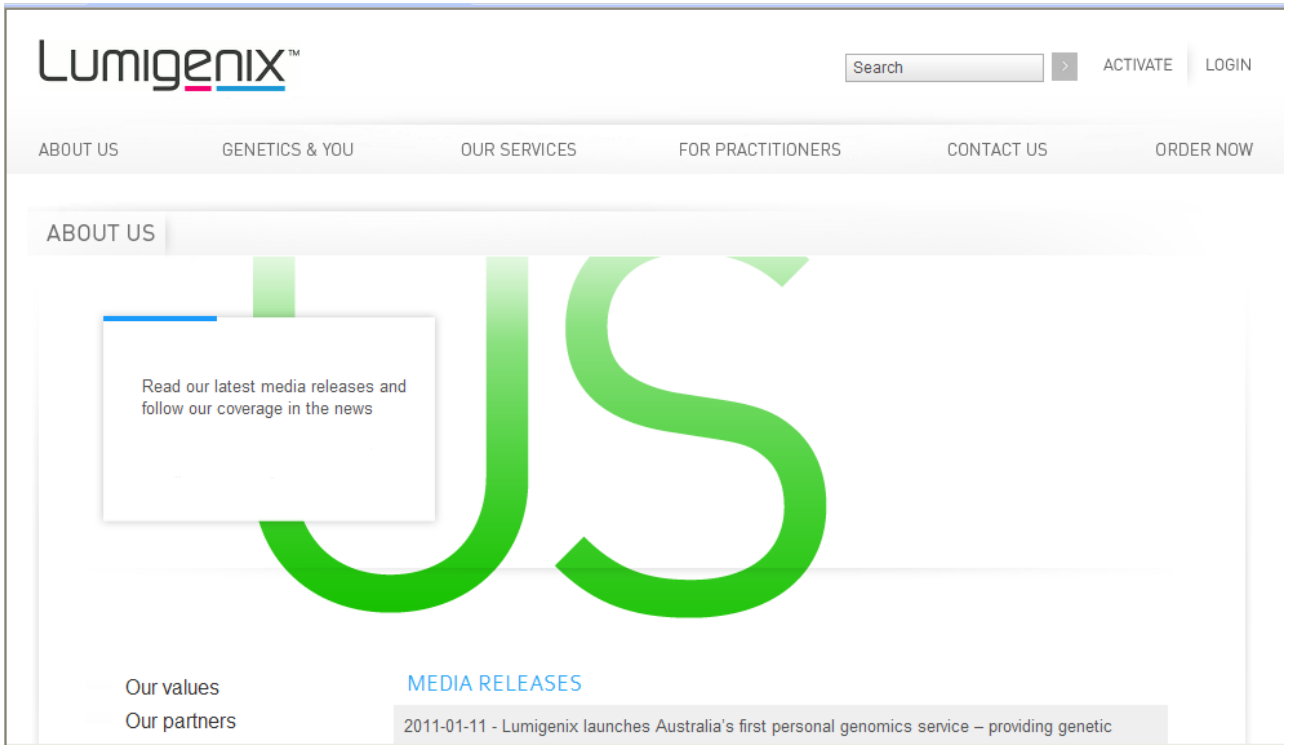
Lungs and breathing
- Asthma
- Nicotine dependence
- Tuberculosis

Kidneys and urinary system
- Chronic kidney disease

Psychological
- Bipolar disorder
- Schizophrenia
- Tourette's syndrome
- Alcohol dependence
- Developmental dyslexia
- Autism

Reproduction
- Endometriosis
- Gestational diabetes
- Male infertility
- Placental abruption
- Preeclampsia
- Premature birth
- Uterine fibroids

Continued…



DISCLAIMER: This service is not a test or kit designed to diagnose, treat or prevent a disease or medical condition and is not intended to be medical advice. This service has not been approved by the TGA or FDA for diagnostic use.

Challenges to the health system - Summary

- Bioinformatics… what does it all mean?
  The $1,000 genome, the $100,000 analysis? (Genome Medicine Nov 2010)
- Data storage; electronic health records
- Workforce – shift from lab to computer; need for new type of health professional (medical informatics)
- DTC DNA testing – challenge for GPs
- Personalised medicine – challenge is coordinating test/treatment (co-dependent technology)
- Ethical, legal and social issues, e.g. implications for family members, access in rural and remote regions, intellectual property

Relevant NHMRC publications (www.nhmrc.gov.au)

- *Medical Genetic Testing: Information for health professionals*
- *Clinical Utility of Personalised medicine*
- *Genetics in Family Medicine: Australian handbook for General Practitioners*

Coming soon…

- *DNA genetic testing in the Australian Context: A statement from NHMRC*
- *Medical Genetic Testing: Health information for you and your family*
- *Direct-To-Consumer DNA genetic Testing: An information resource for consumers*

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