Kathmandu, Bir Hospital visit,
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Pathology North

Personalised medicine: Past, present and future

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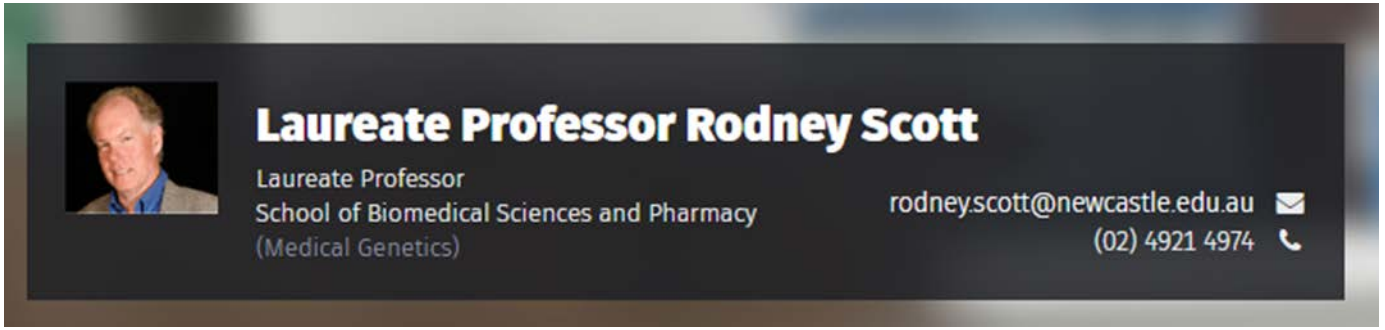
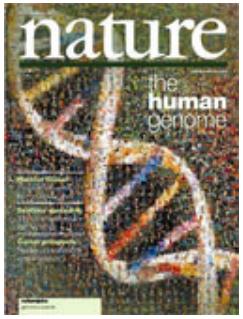


Current Medical Care Started Here

The systematic analysis of the human body, circa 1600



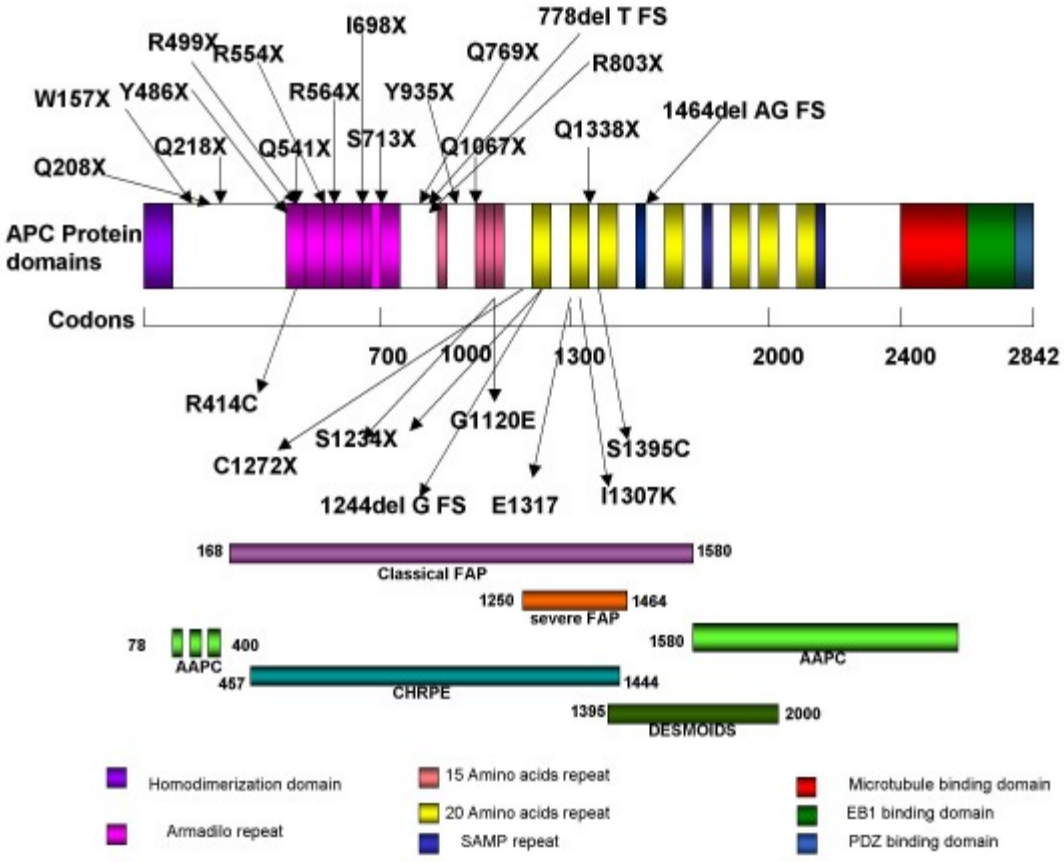
The Past

- >15 years since the official completion of the Human Genome Project
- Genomic Medicine first commonly used as a term in 1995
- Now a common place term
- Driven by changes and improvements in technology
- Ground breaking applications

Today

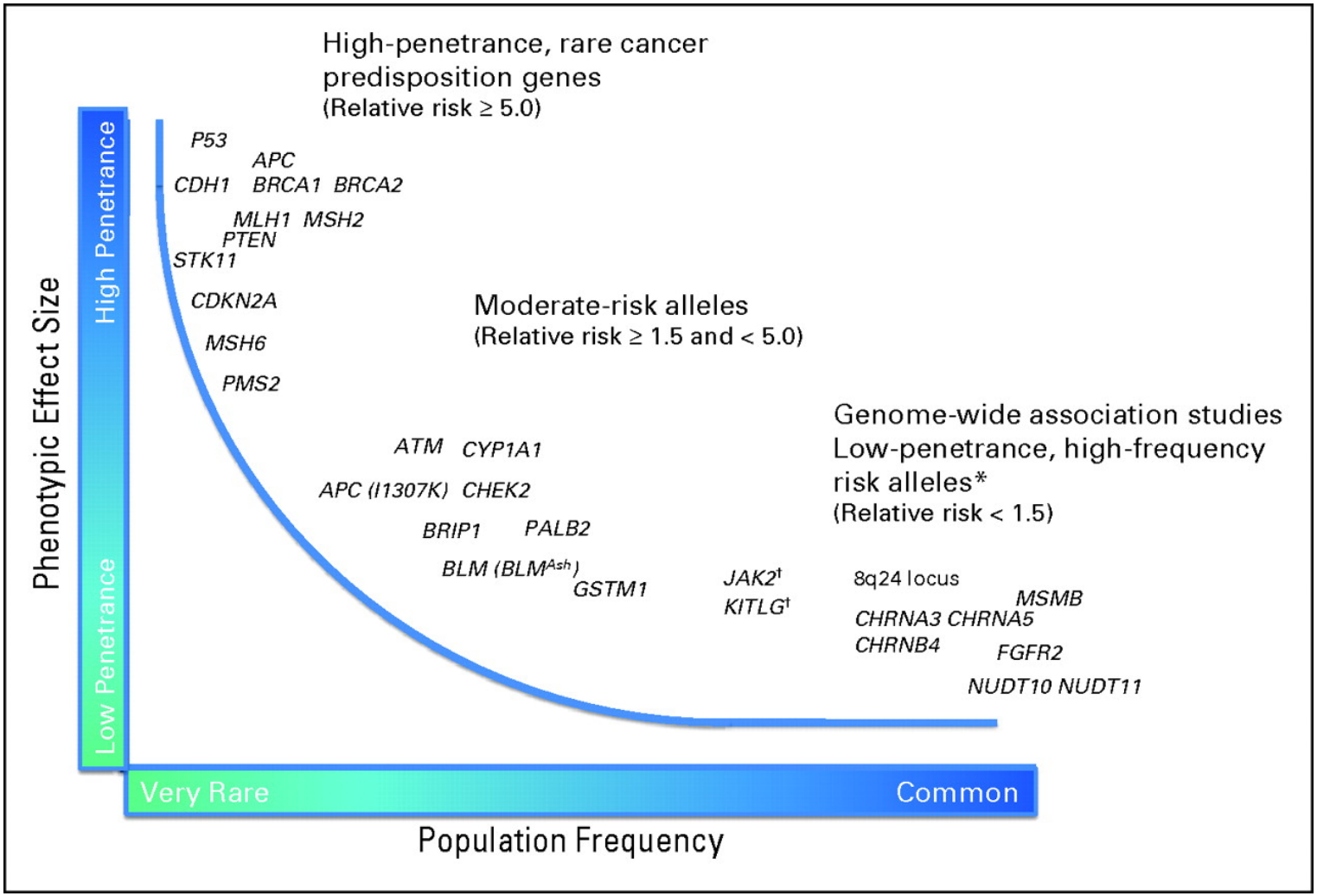
- Locus specific gene analysis
  - Started before 1990
  - Now occurring at an unprecedented pace
- Genome Wide Association Studies
  - Hypothesis free discovery: need to be careful what this information is used for
- Genome Wide Expression Studies
  - Many studies undertaken to identify gene expression profiles of disease
- Genome Wide Epigenetic Studies
  - Study numbers beginning to increase
- Exome Sequencing
  - Beginning to be common place
- Whole Genome Sequencing
  - Are we there yet?

Locus Specific Gene Analysis (APC)



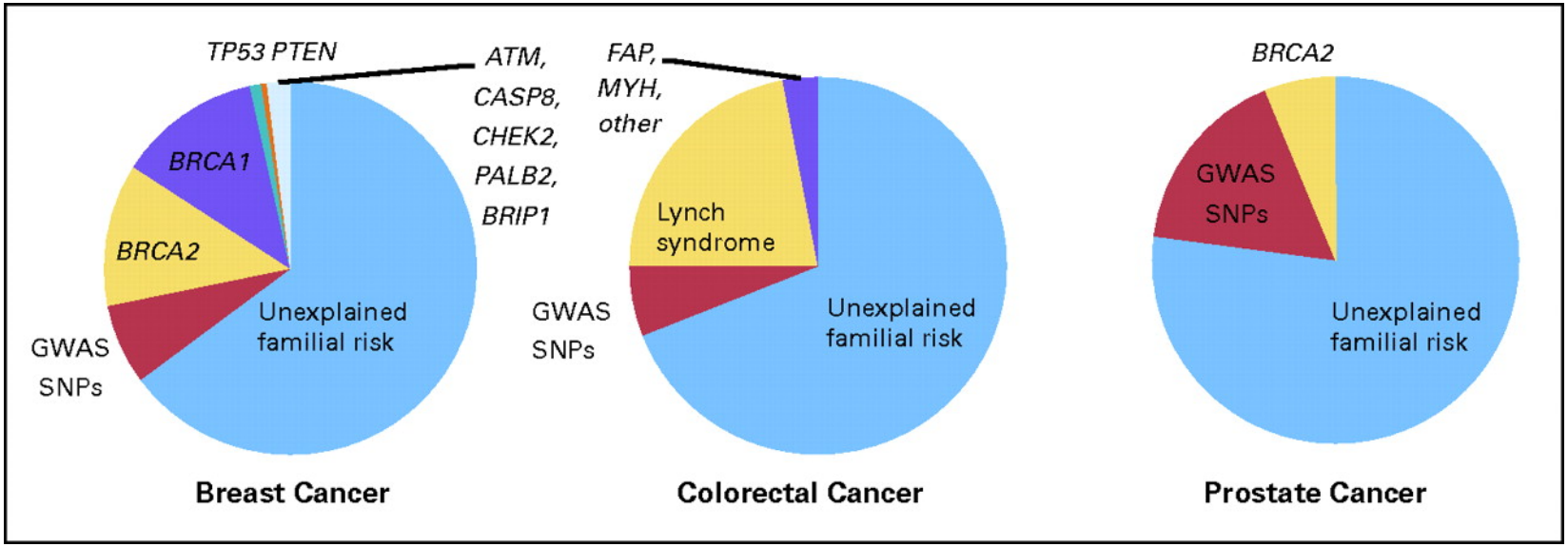
Genome wide Association Studies (→12/2012)

Phenotypic effect size and frequency of occurrence.



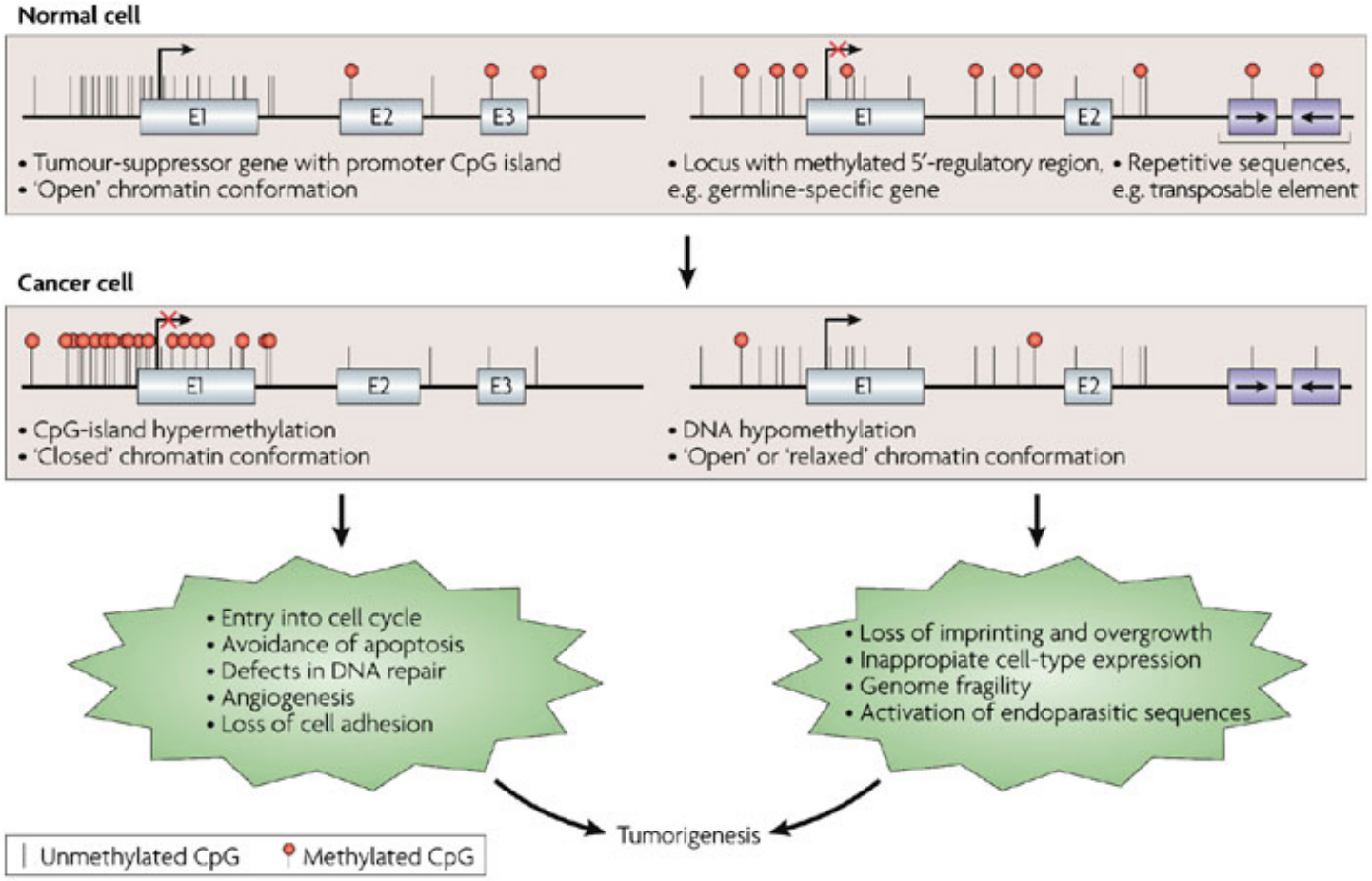
Stadler Z K et al. JCO 2010;28:4255-4267

Familial risk of common cancers.

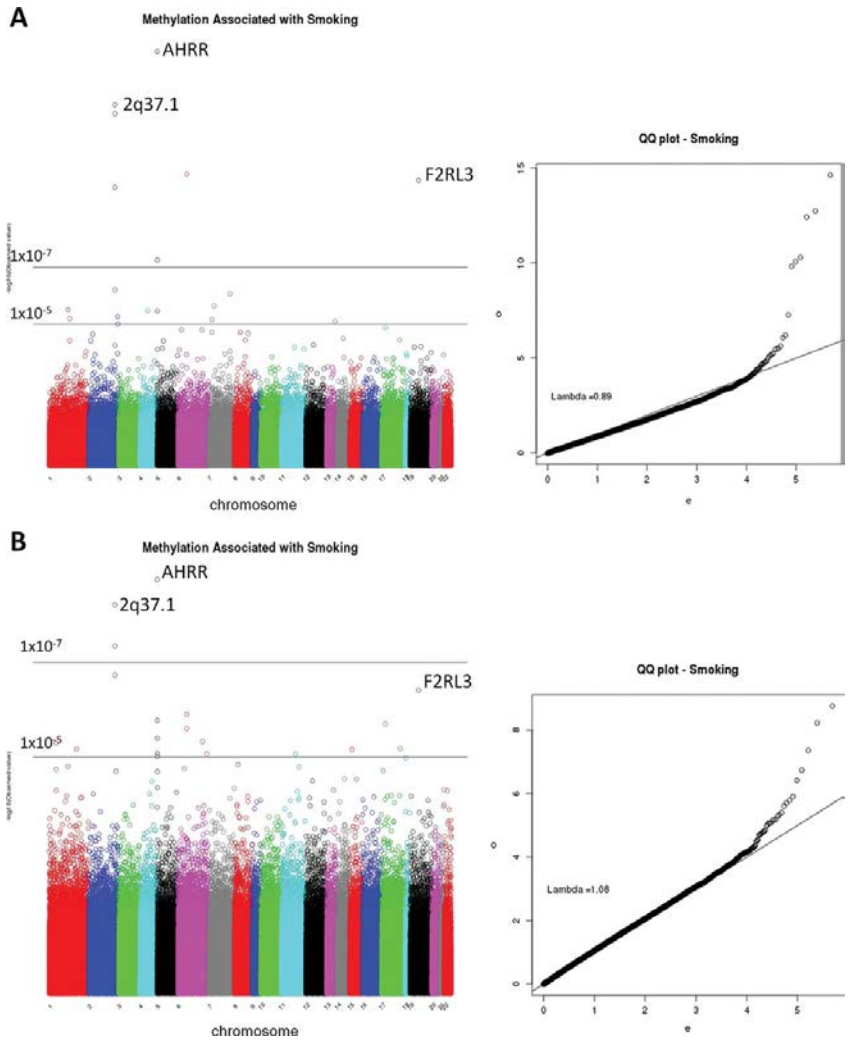


Stadler Z K et al. JCO 2010;28:4255-4267

Epigenetic Studies in Cancer



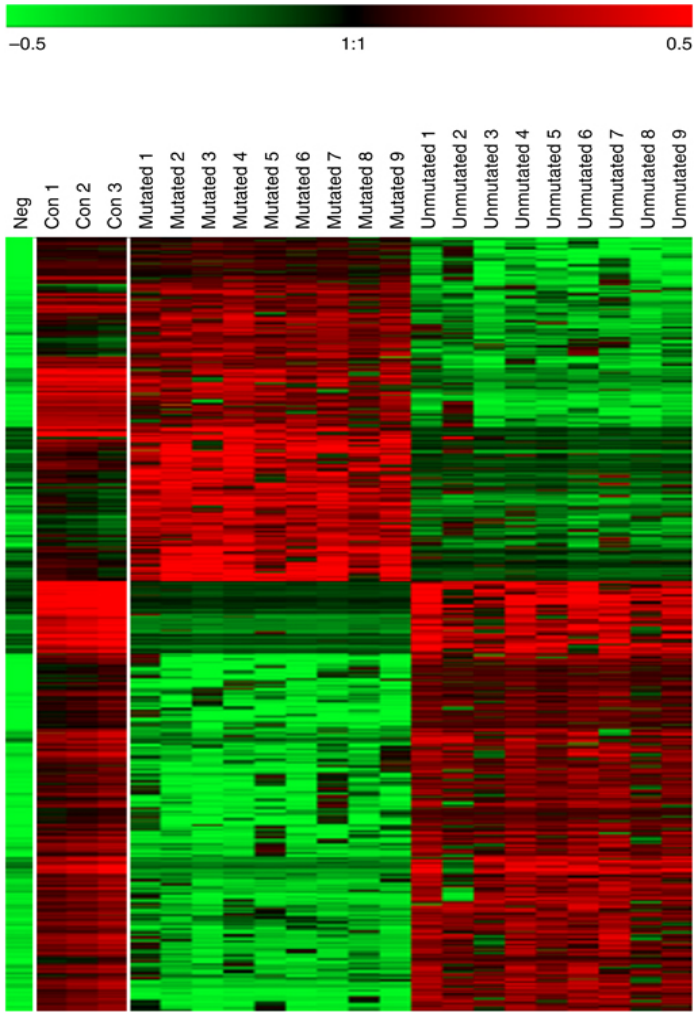
Manhattan plot and quantile–quantile (QQ) plot for EWAS results for smoking status in two case–control studies.



Shenker N S et al. Hum. Mol. Genet. 2013;22:843-851

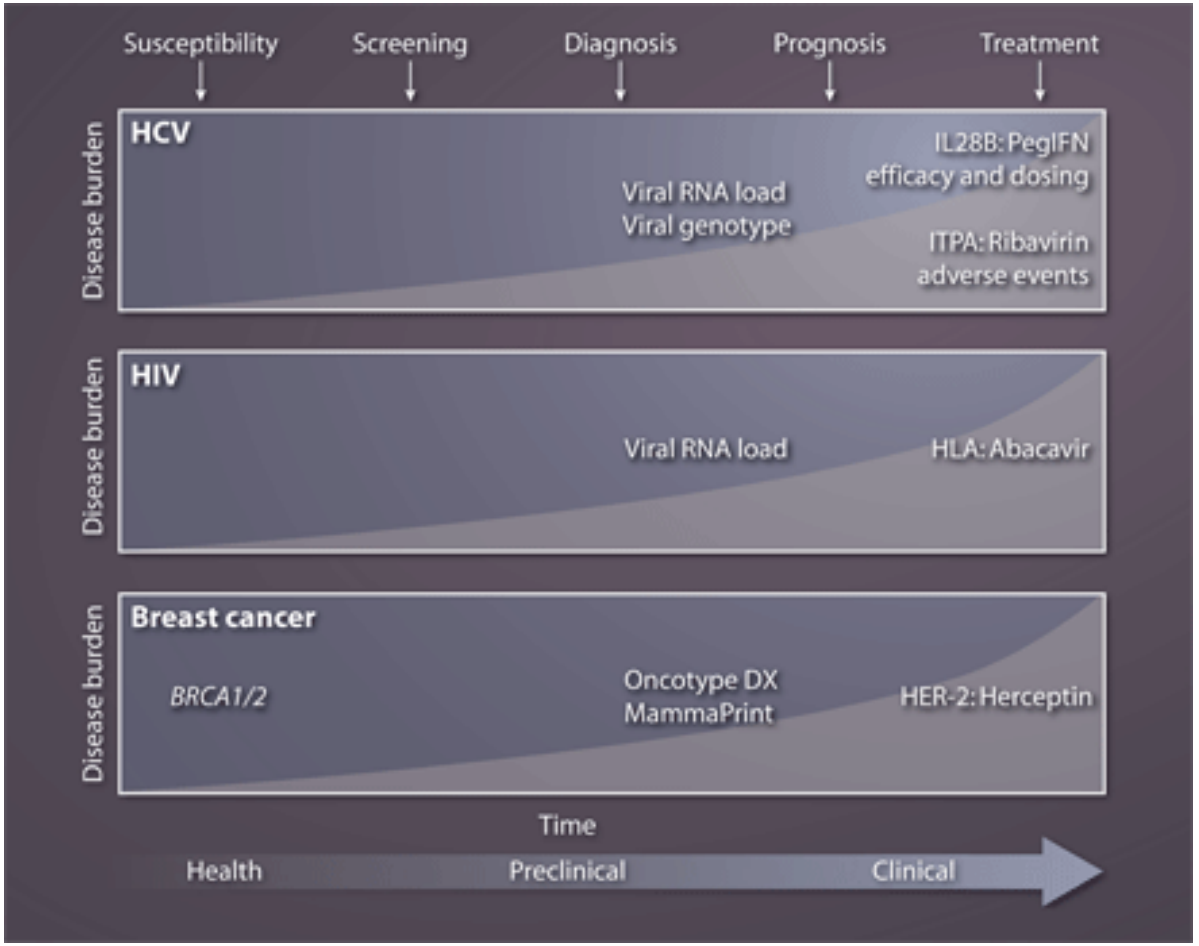
Human Molecular Genetics

Global Methylation Change is Relatively Stable over time



Cahill et al. Leukemia (2013) **27,** 150–158; doi:10.1038/leu.2012.245; published online 18 September 2012

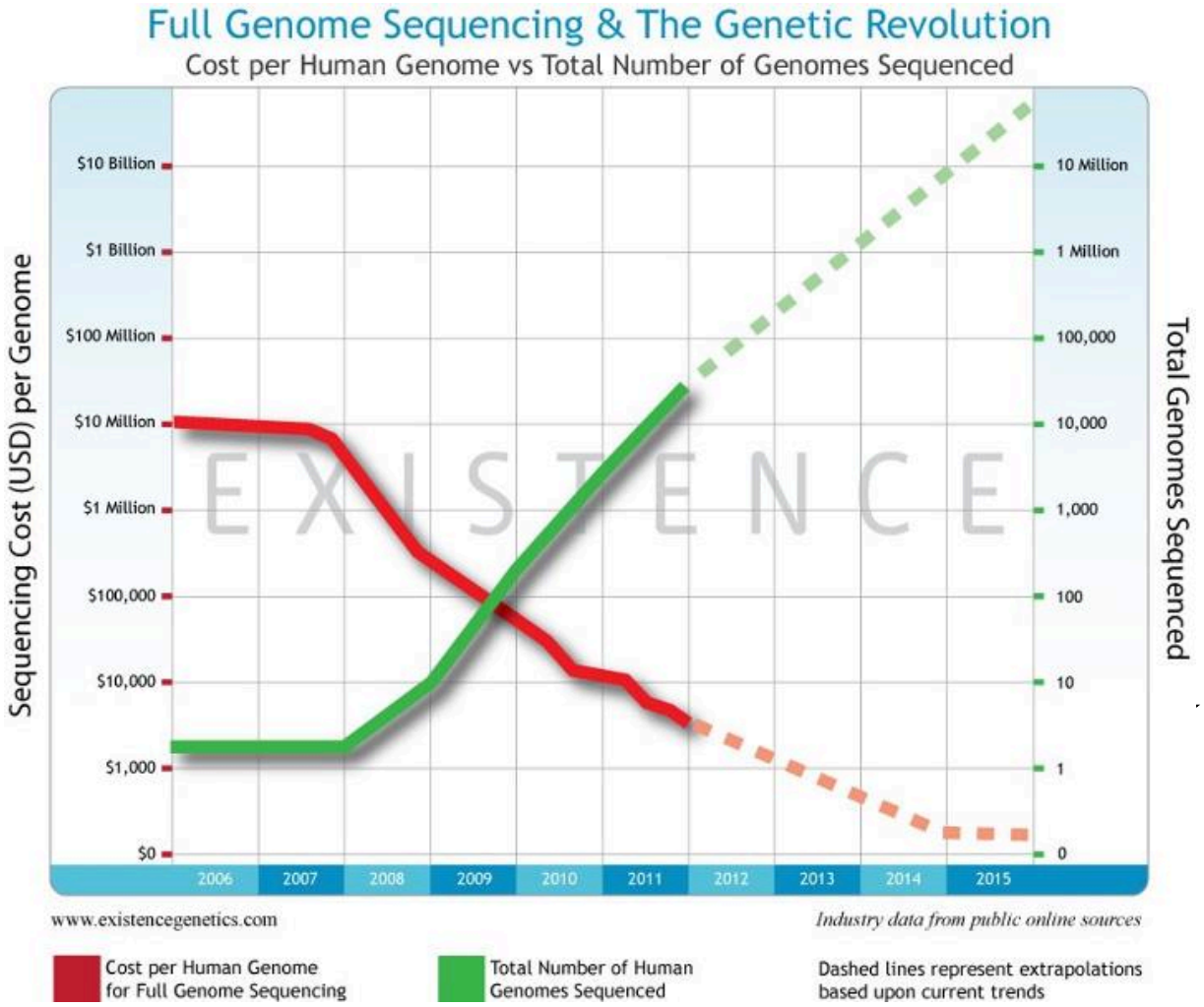
Some Significant Outcomes



The Present

- **Rapidly changing/evolving**
  - Technological developments have exceeded predictions
- Bioinformatic challenges
  - Becoming less so
- The Human Variome
  - Variant pathogenicity assessment – NOT EASY
- Data Storage problematic
  - Save data (is it worth it?) or re-assay?
- Ability to screen multiple genomes
  - Gene environment interaction analysis (e.g. gut microbiome & host genome
- RNA, miRNA, lncRNA analysis
  - Control of gene expression
- Epigenetic modification
  - Environmental effects on gene expression

Sequencing Technology Costs - There getting better

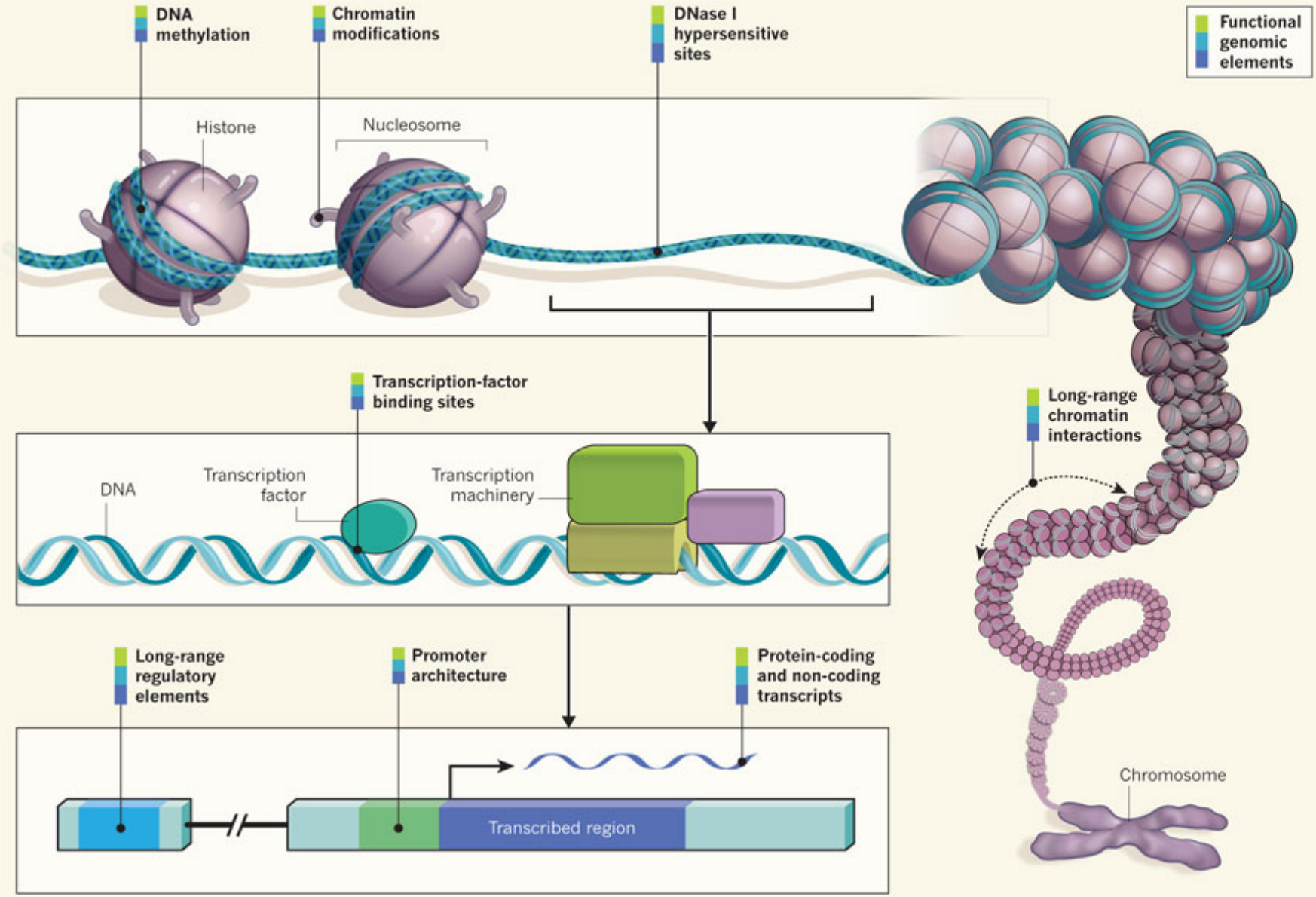


Current State-Of-The-Art

Whole Genome Sequencing: Where Are the Problems

- Coverage is low - errors rates high!
- Where is the evidence that it can be used for prediction
- Many different variants to assess
- Number of samples/tumour type is currently small
- None of the assays have been validated – still in the discovery phase
- Little if any quality assurance
- **Knowledge about the genome is limited**

ENCODE - **Encyclopedia of DNA Elements**



Which approach?

- **What type of sample**
  - Constitutional DNA
    - Affected family members
    - Individual patients with specific tumour characteristics

- **Whole Genome**
    - Bioinformatic challenges

- **Exomes**
  - Easily achievable approach to identifying “new” genes
  - Only ~ 3% encodes a translatable product

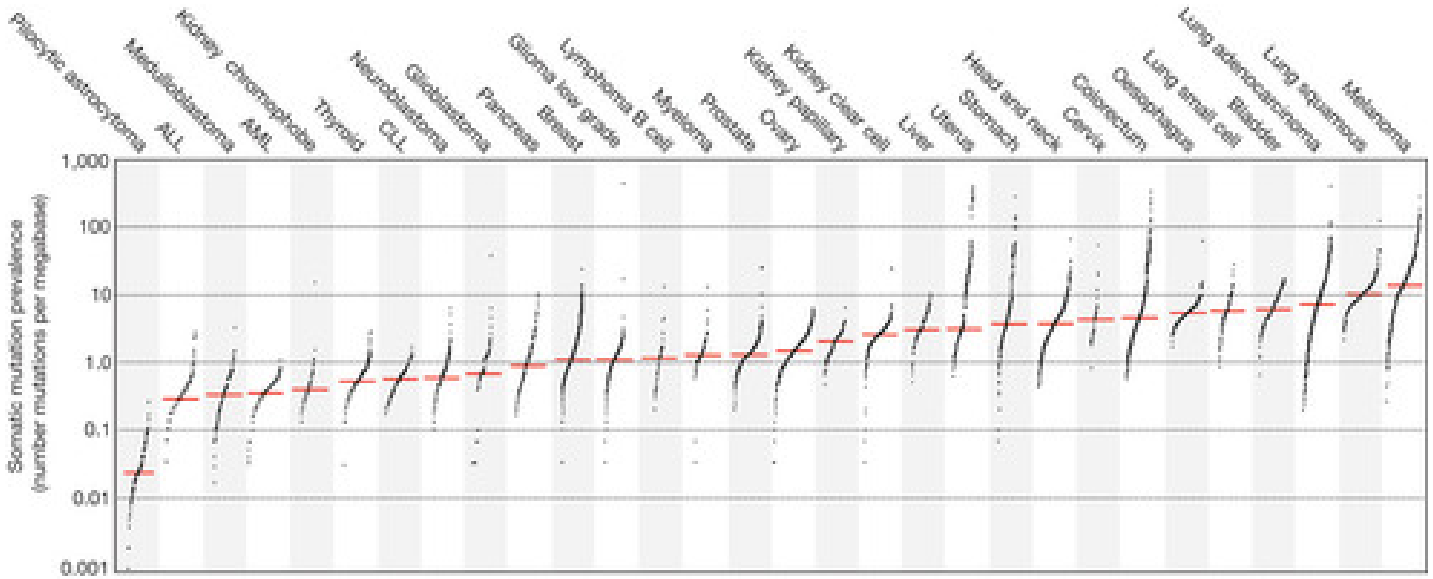
    - Penetrance, disease associations etc. difficult to determine → poor clinical acceptance

- ***<u>Targeted Sequencing & Re-sequencing</u>***
  - *Screening large numbers of suspected patients*
  - *Re-analysis of known genes could reveal unsearched for associations*

Tumour Analysis leading the Field:

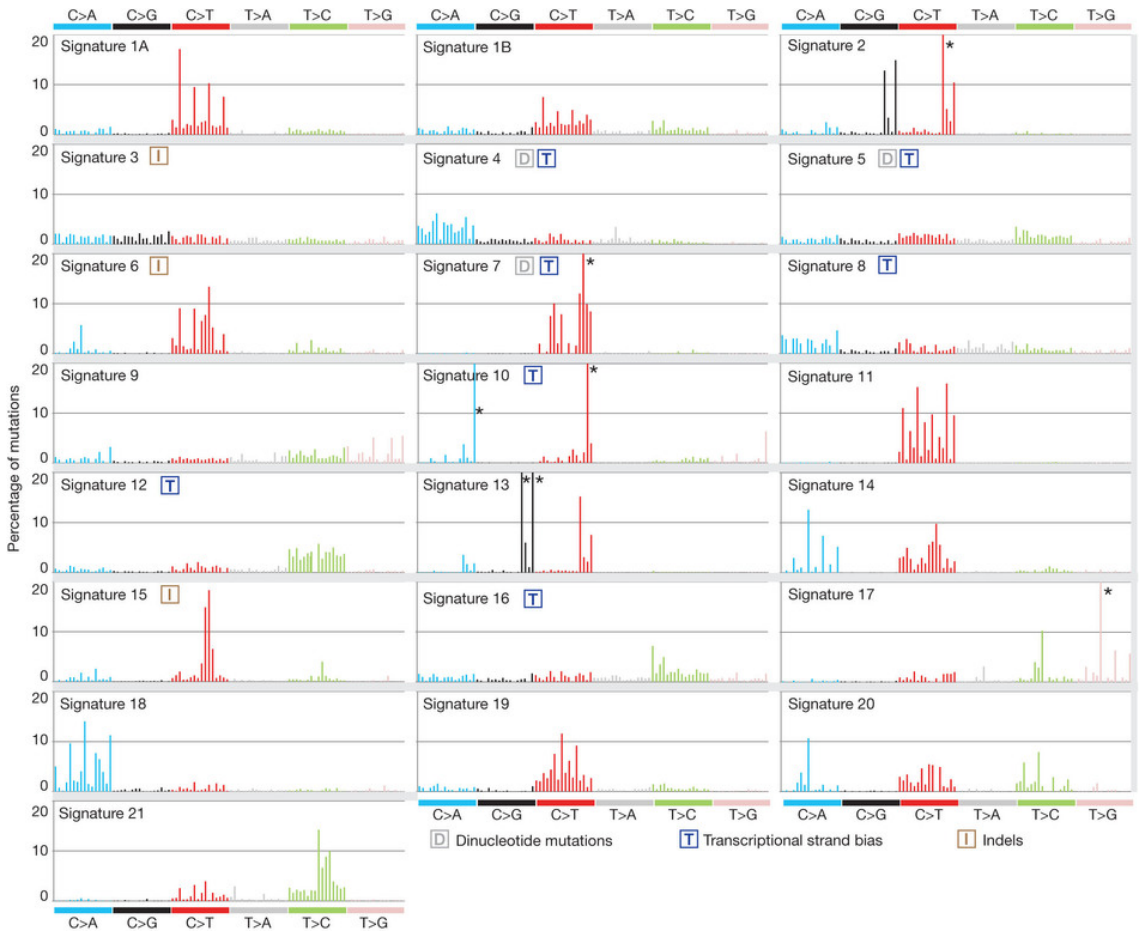
- Copy Number Variants
- Tumour genomes – The Cancer Gene Anatomy Project
- Epigenome
- Targeted Therapies
  - HER2, EGFR, KRAS, BRAF, PI3K,
- Circulating tumour markers
  - Prognostic information

The Prevalence of Somatic Mutations Across Human Cancer Types



Taken from Alexandrov et al (2013) Nature doi:10.1038/nature12477

Validated mutational signatures found in human cancer



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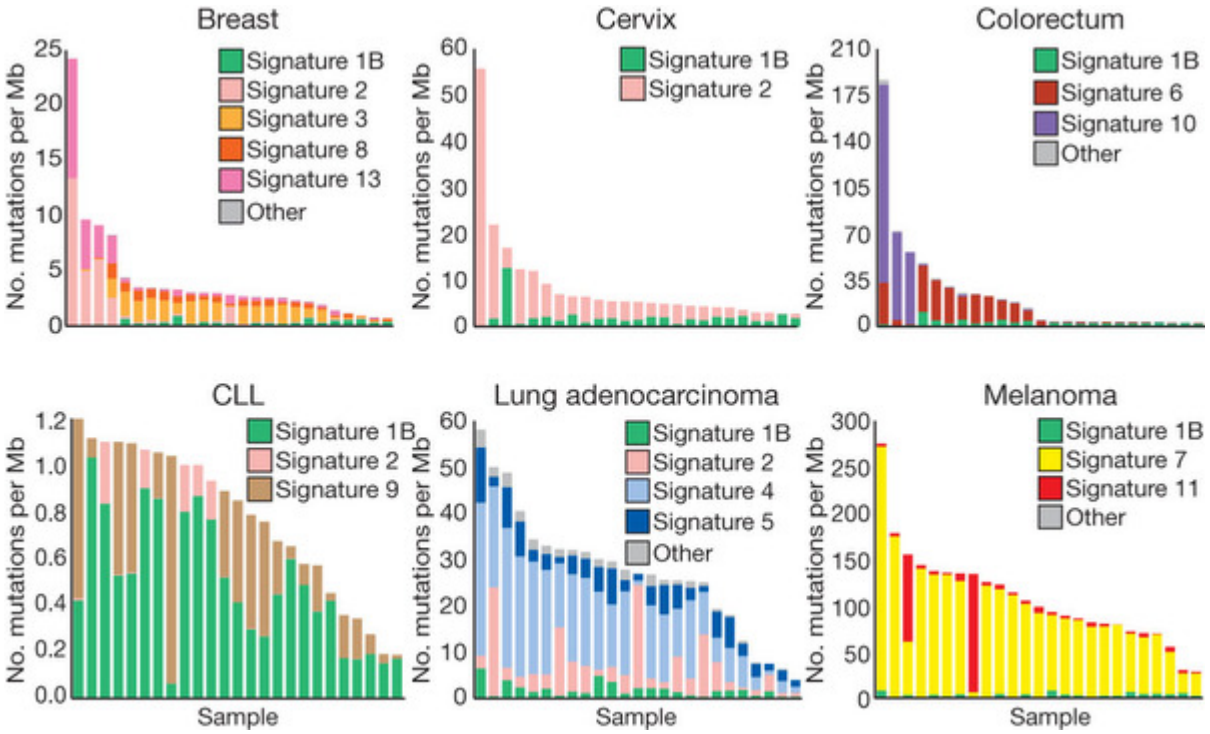
The contributions of mutational signatures to individual cancers of selected cancer types



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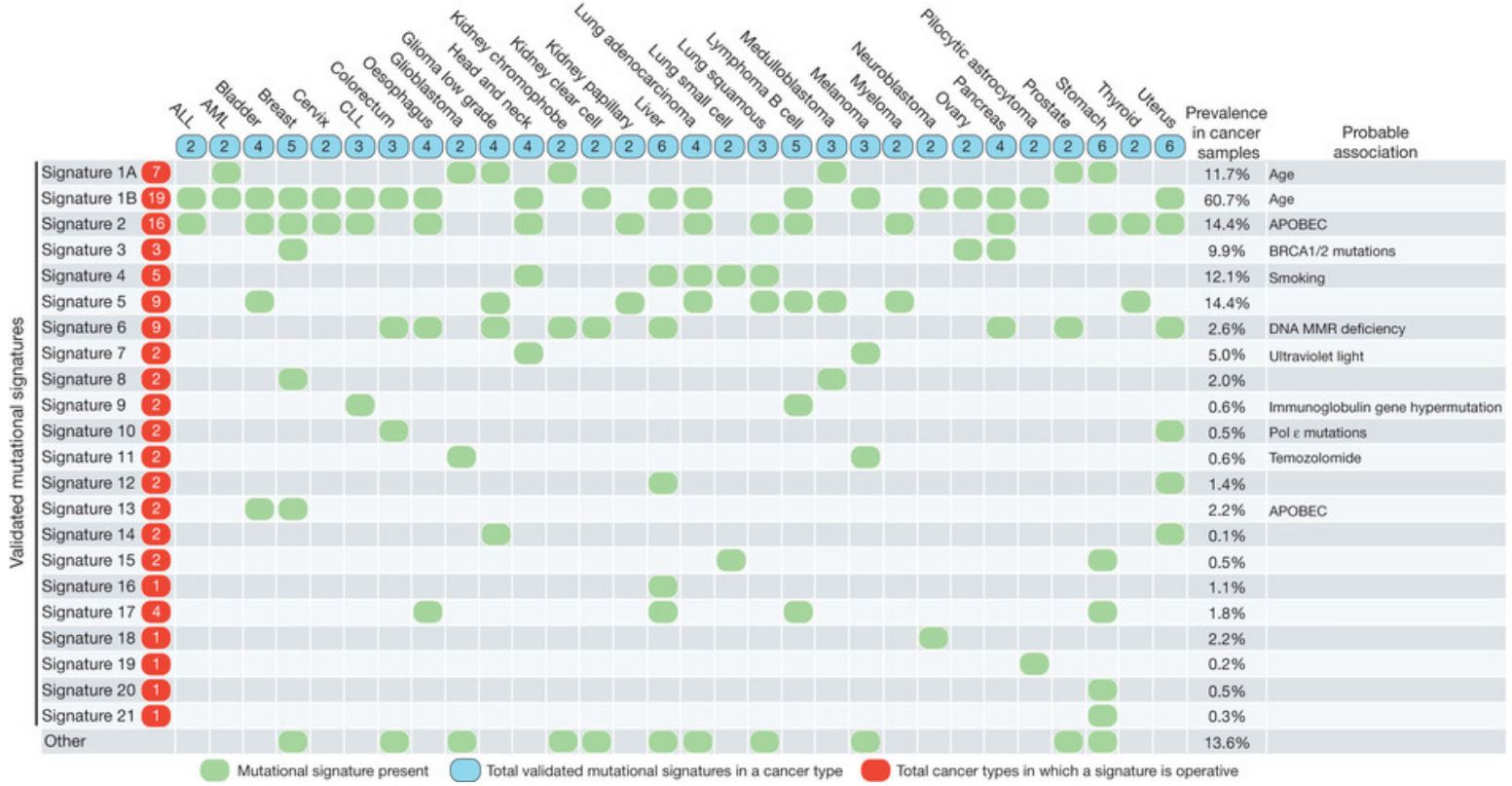
The presence of mutational signatures across human cancer types



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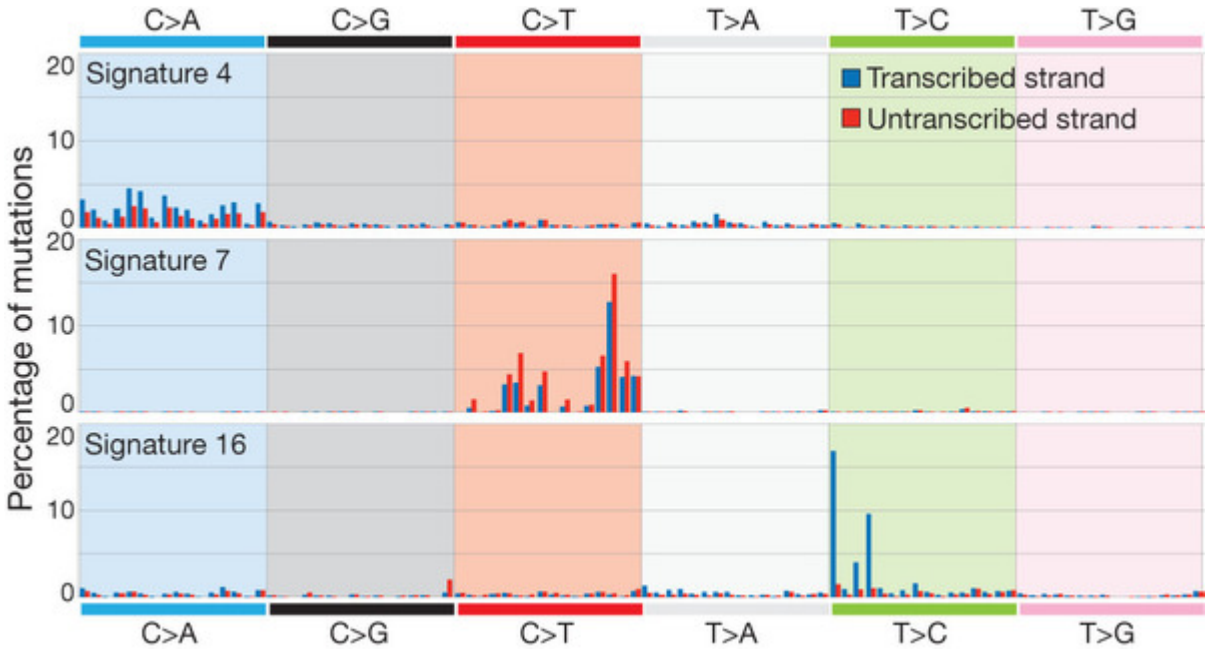
Selected mutational signatures with strong transcriptional strand bias



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Mutation Spectrum

- Tumour signatures beginning to appear
- Much to learn about genomic change and what it means to cellular physiology
- Encode project suggests most of the genome is associated with the control of gene expression
- Pairing of tumour types by mutation spectrum
  - More rationale treatment decisions

Cancer Pharmacogenomics

- GWAS have been used successfully in pharmacogenomics research
  - Efficacy, Adverse Events, dosing

- Companion Diagnostics

  BCR-ABL (Imatinib), KRAS (Erbitux), BRAF (Vermurafenib), EGFR (Gefitinib), HER2 (Trastuzimab), ALK (Crizotinib)

- Uptake has been variable
  - HLA-B*5701 & abacavir (HIV)
  - HLA-B*1502 & carbamazepine (epilepsy)

Diagnostic Genetic Testing

Colorectal Cancer

- AXIN
- APC
- PTEN
- SMAD4
- STKII
- MUTYH
- POLD1…

Breast Cancer

- BRCA1
- BRCA2
- TP53
- PALB2
- ATM
- CHEK2
- BRIP1
- RAD51C
- RAD51D…
- OncoType DX 21 gene sign.
- Mammaprint 70 gene sign.

Clinical Dilemmas

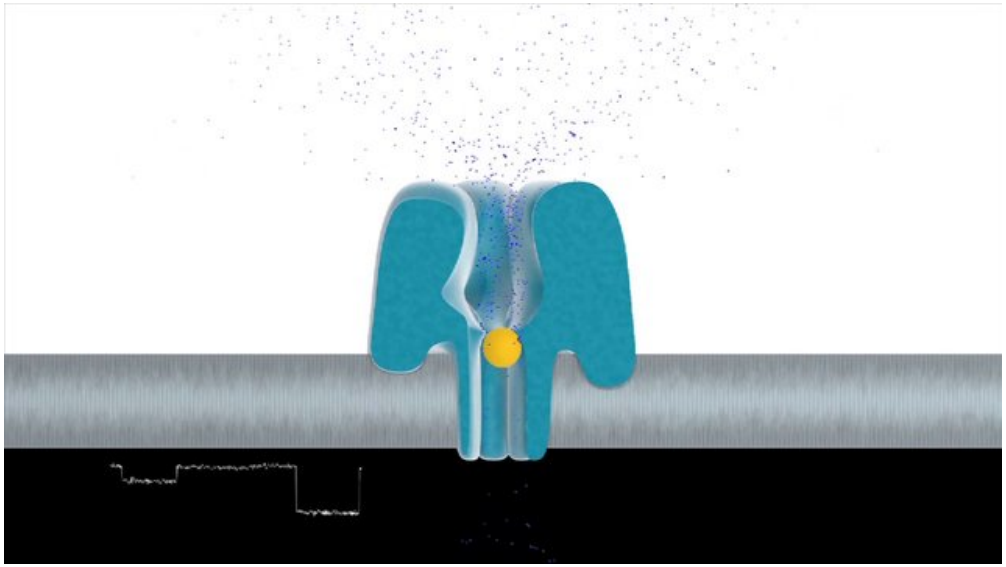
- Evidence Framework for acceptance in to clinical practice
- Diffusion of knowledge into Healthcare
- Clinical Implementation
- Regulation of Genomic Tests
- Population coverage and reimbursement
- Ethical Legal and Social Issues
- Continuing Education

Opportunities

- Develop creative partnerships and increase consumer-driven genomic research
- Re-define disease taxonomy
  - Better disease definition based on molecular signatures
- Pre-emptive medicine
  - Medicine is transitioning from a reactive profession to a predictive one
- Point-of-care diagnostics
  - Are we ready for this?
- Third party genomic information brokers
  - Genomic interpretive services

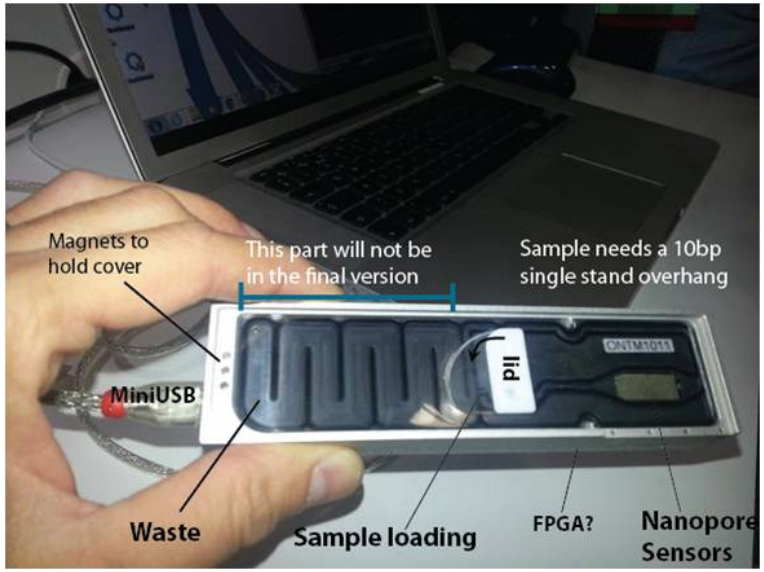
Future Expectations – Its All In The Technology

Nanopore Technology – Oxford Nanopore



GRIDION

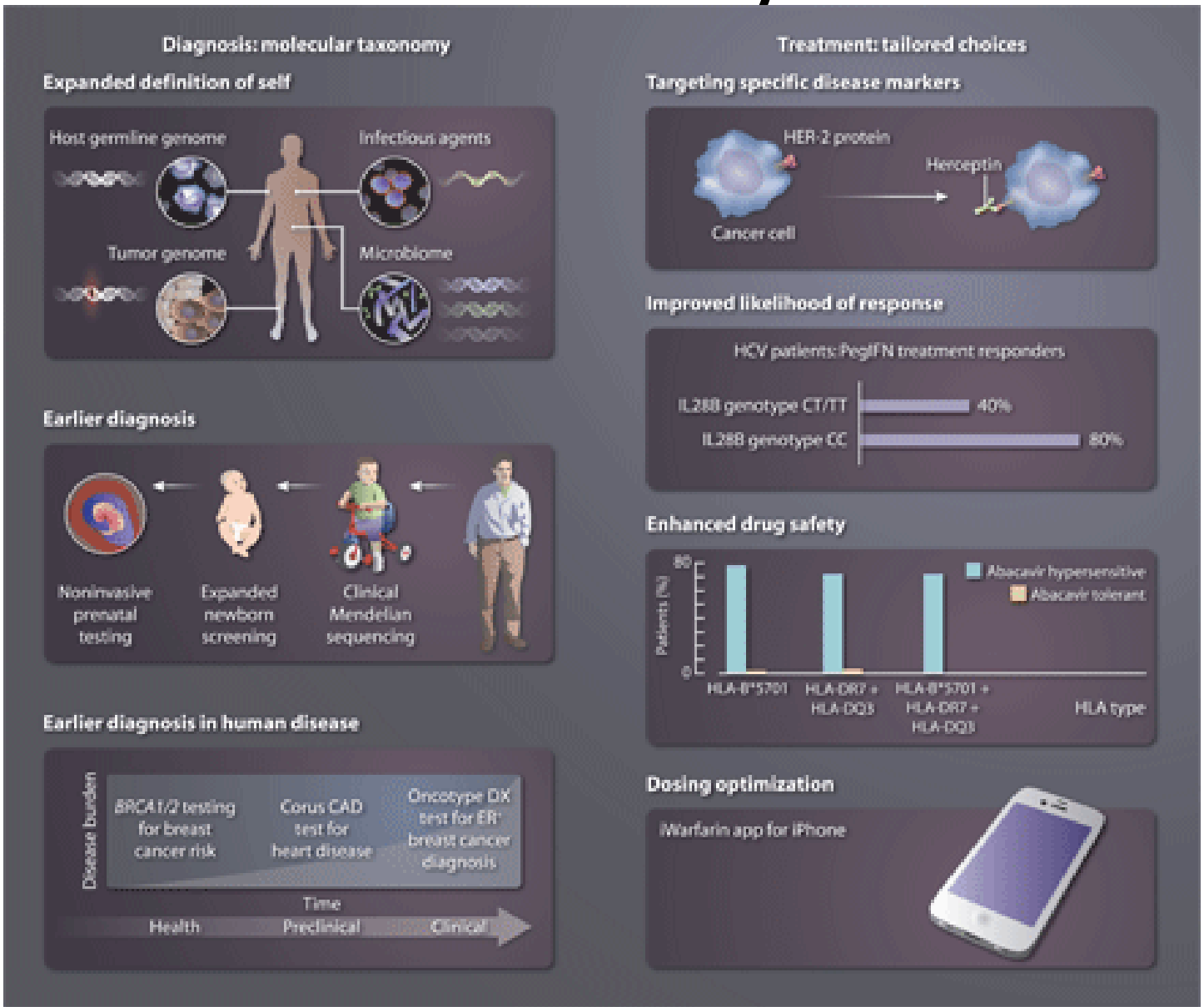
MINION



Conclusion

- Genomic Medicine WAS an aspiration NOW becoming a reality
- Technology relentlessly moving towards inexpensive individualised assays – will cause problems of acceptance etc.
- Can the medical profession meet the challenge?
- Has genomic medicine the capacity to radically alter health outcomes?
- **Do create undue expectations of what genomice medicine is capable of – BE REALISTIC**

Summary


Diagnosis: molecular taxonomy
Expanded definition of self
Host germline genome
Infectious agents
Tumor genome
Microbiome
Earlier diagnosis
Noninvasive prenatal testing
Expanded newborn screening
Clinical Mendelian sequencing
Earlier diagnosis in human disease
Disease burden
BRCA1/2 testing for breast cancer risk
Corus CAD test for heart disease
Oncotype DX test for ER+ breast cancer diagnosis
Time
Health
Preclinical
Clinical
Treatment: tailored choices
Targeting specific disease markers
HER-2 protein
Herceptin
Cancer cell
Improved likelihood of response
HCV patients: PegIFN treatment responders
IL28B genotype CT/TT
40%
IL28B genotype CC
80%
Enhanced drug safety
Patients (%)
80
0
Abacavir hypersensitive
Abacavir tolerant
HLA-B*5701
HLA-DR7 + HLA-DQ3
HLA-B*5701 + HLA-DR7 + HLA-DQ3
HLA type
Dosing optimization
iWarfarin app for iPhone


HMRI