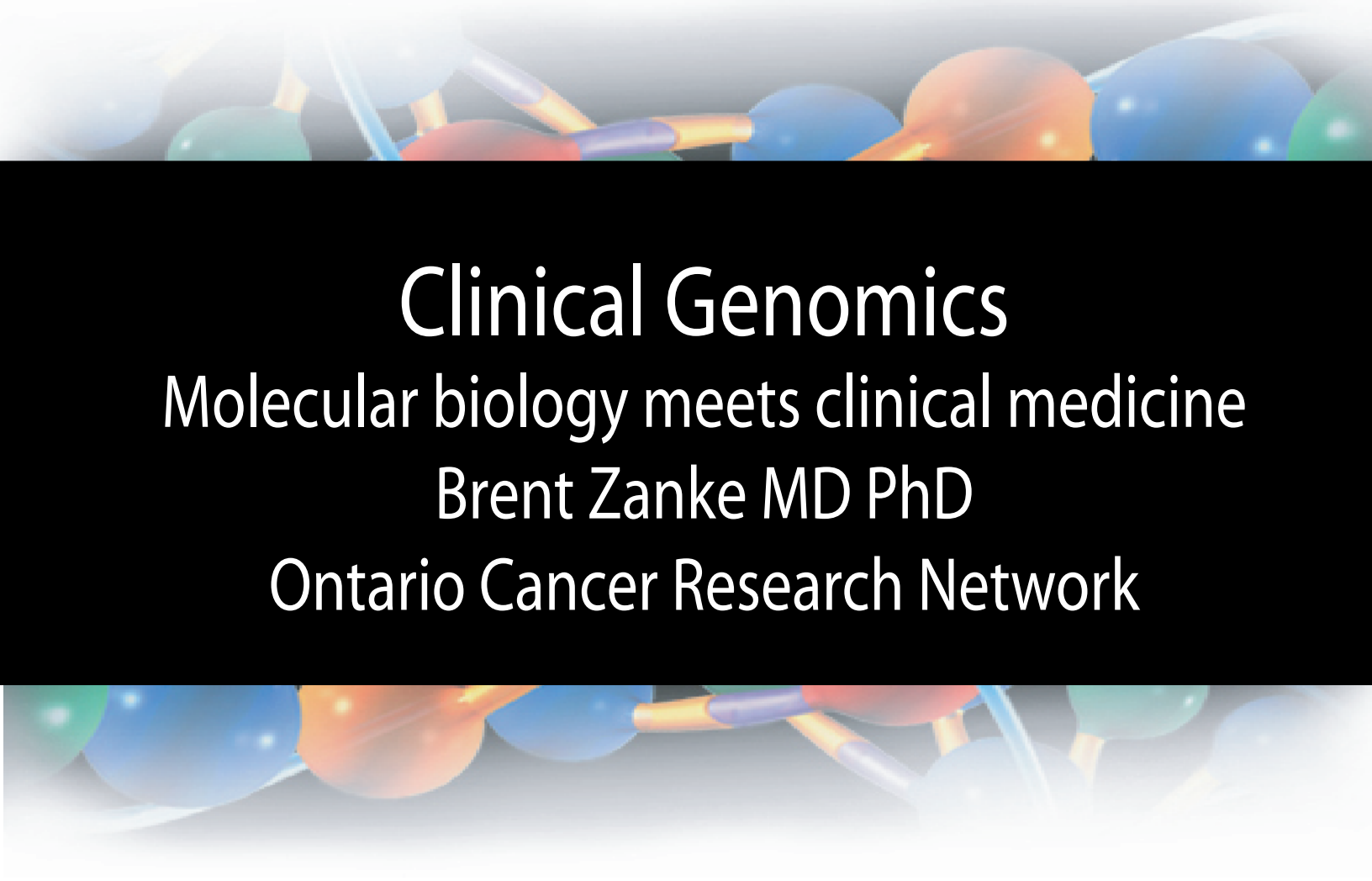
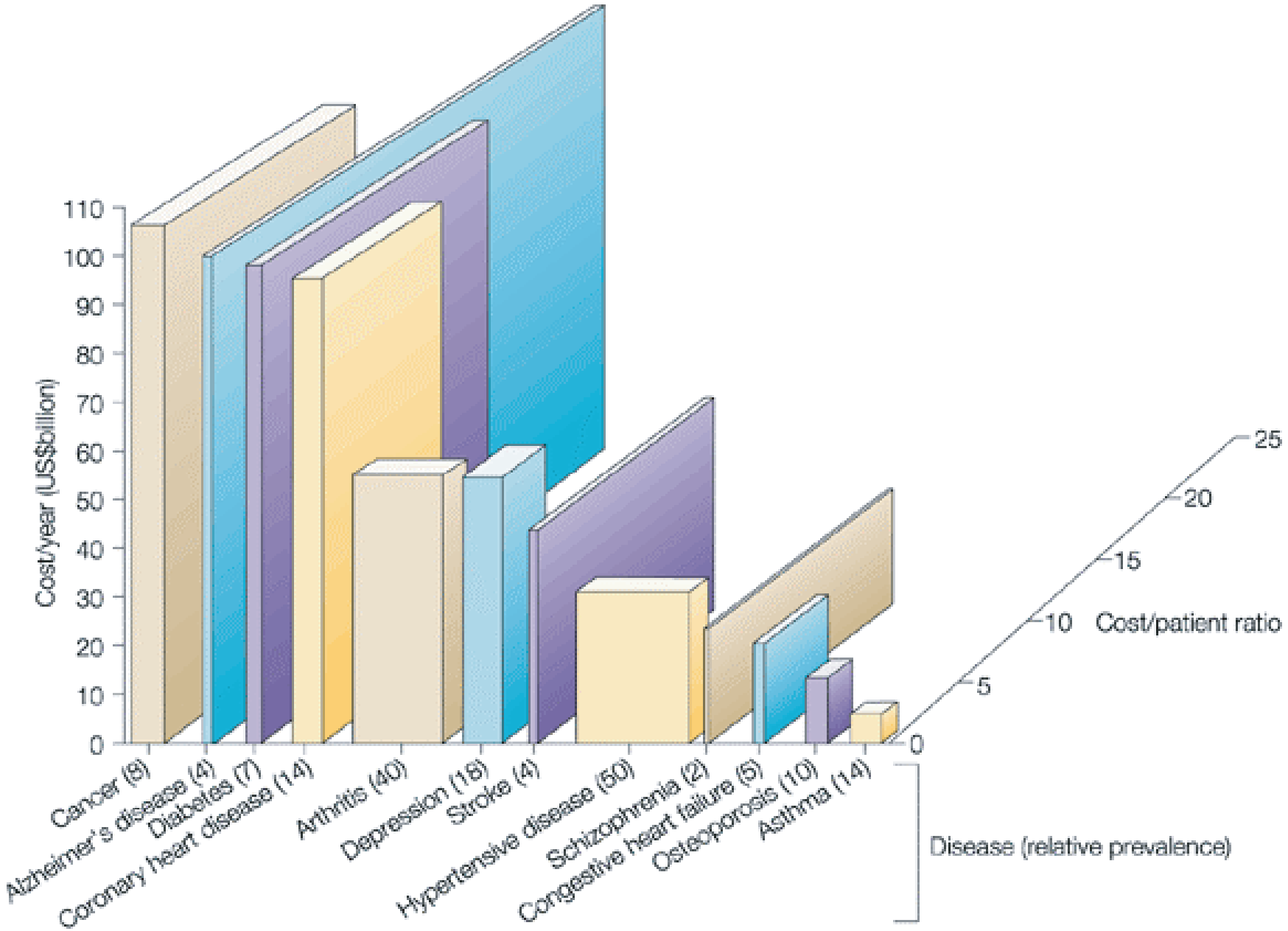


Clinical Genomics

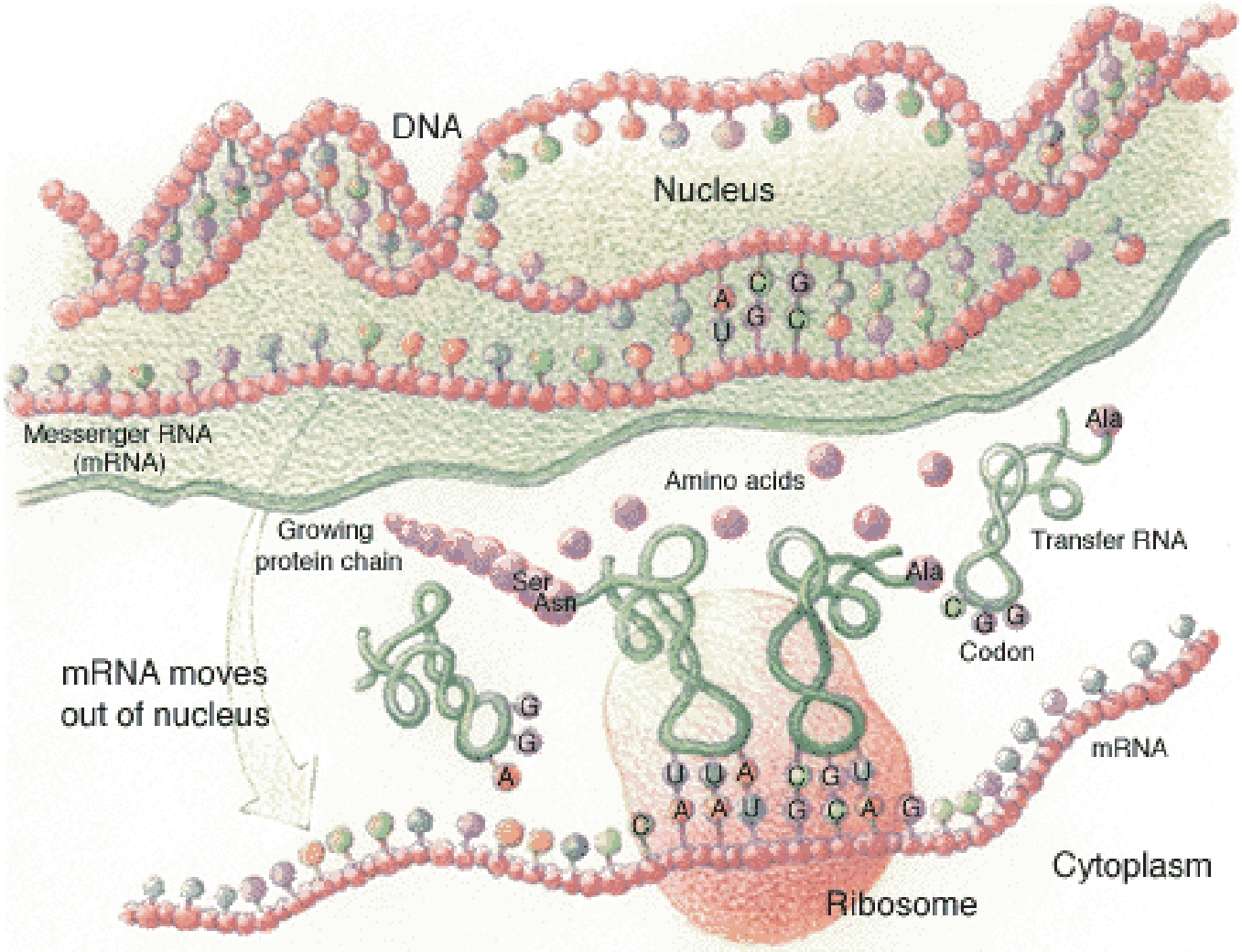
Molecular biology meets clinical medicine

Brent Zanke MD PhD
Ontario Cancer Research Network

The Burden to Health Care Expenditure



The Three Dimensions of Nucleic Acid Diagnostic Inquiry

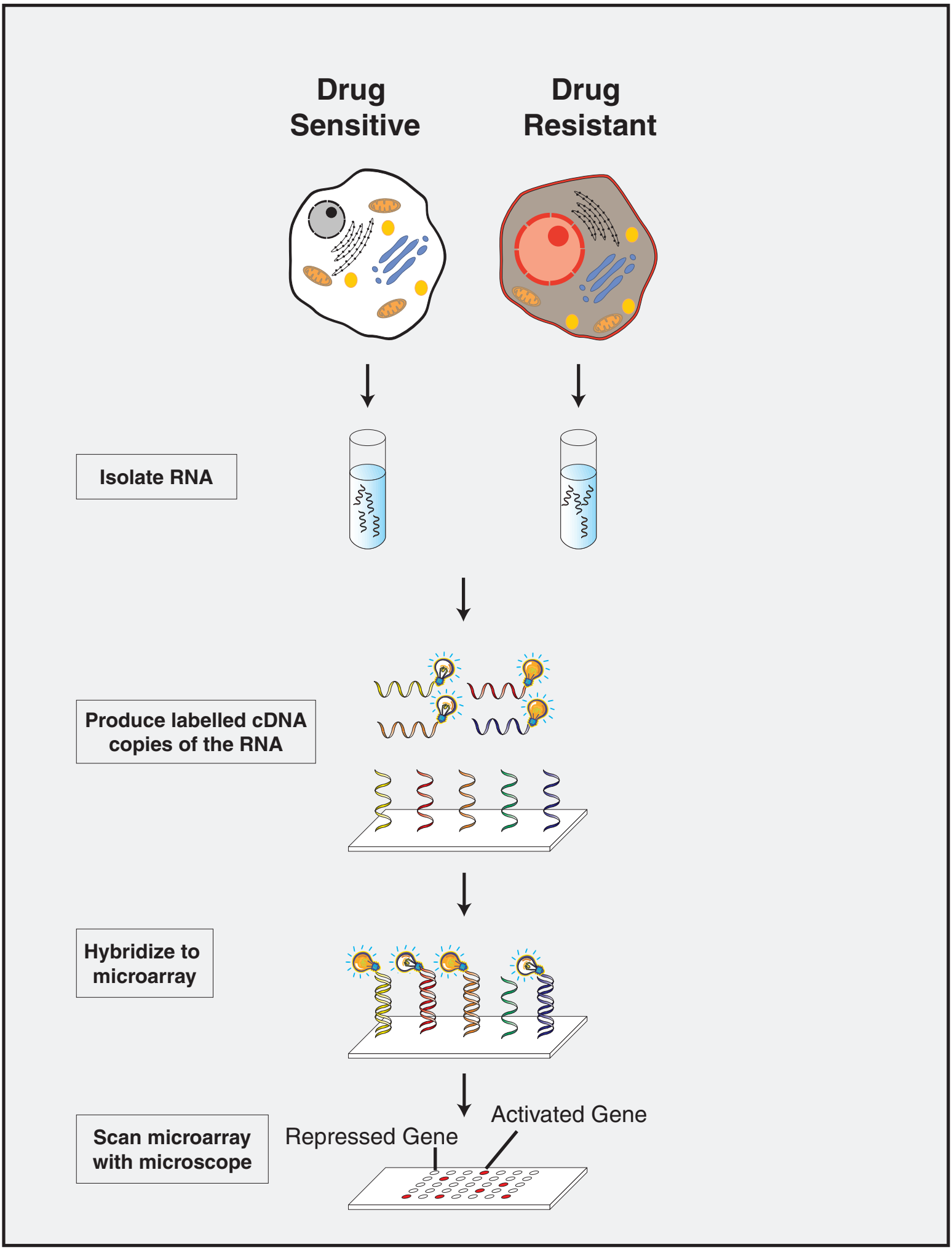


Genome
(Genotyping)
SNPs

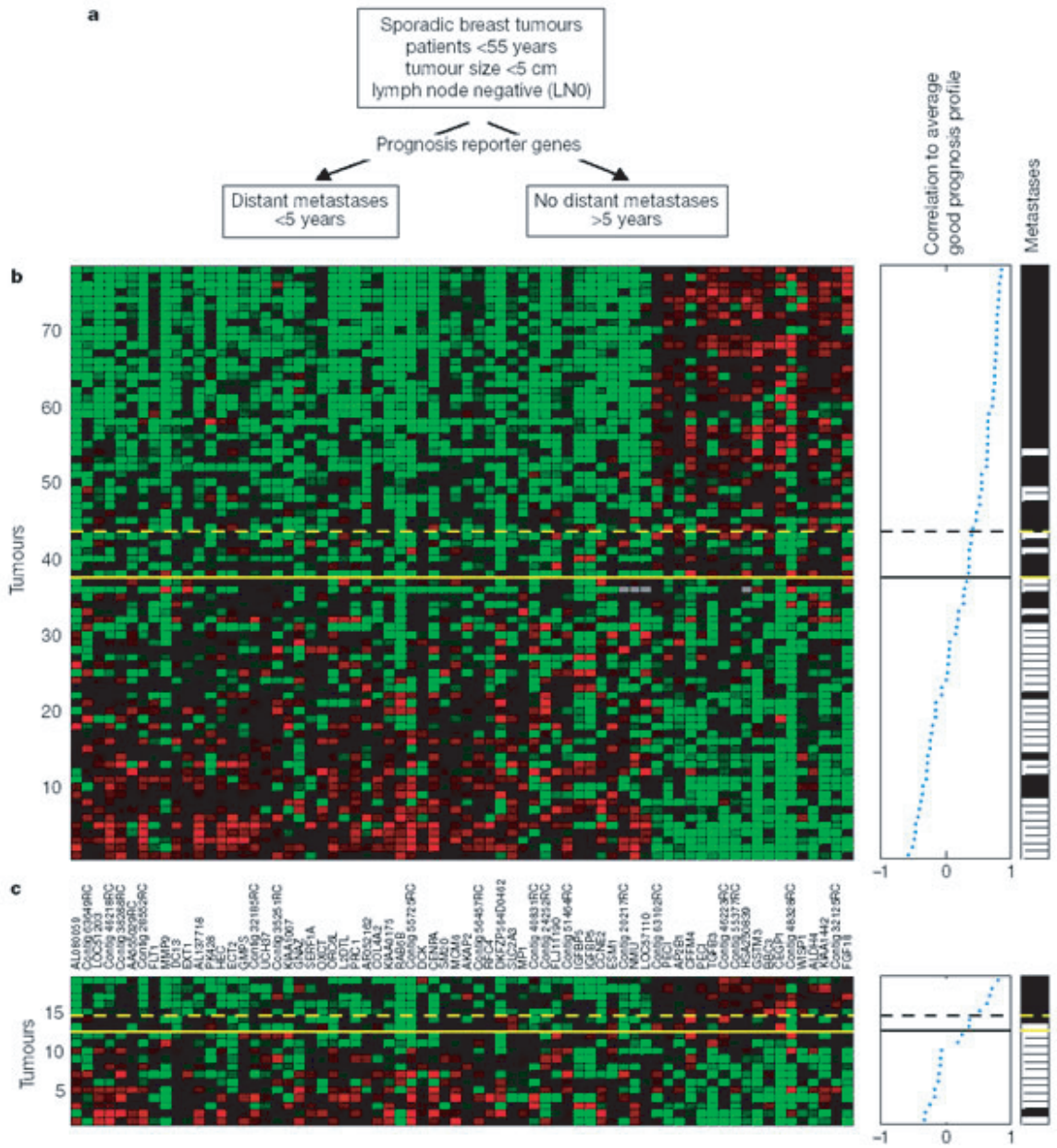
Transcriptome
Expression (mRNA)
profiling
Ribotyping

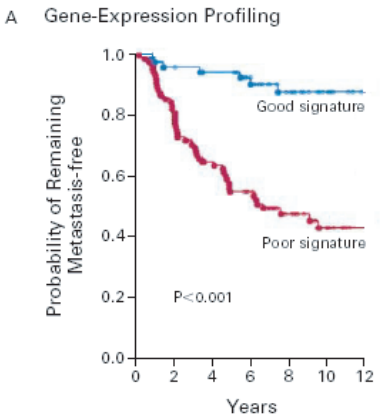
Genomic tools:

* RNA expression analysis: micro array.
* Single nucleotide polymorphism (SNP) determination.
* Array-based DNA methylation studies.
* Proteomic evaluation using MS or gels.
* Metabonomic studies using NMR spectroscopy.


Drug Sensitive
Drug Resistant
Isolate RNA
Produce labelled cDNA copies of the RNA
Hybridize to microarray
Scan microarray with microscope
Repressed Gene
Activated Gene

Gene Expression Profiling Predicts Metastatic Breast Cancer



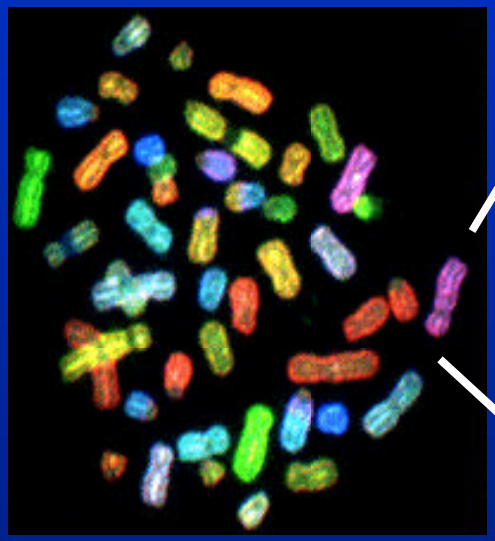


Current clinicalhistopathological prognostic criteria

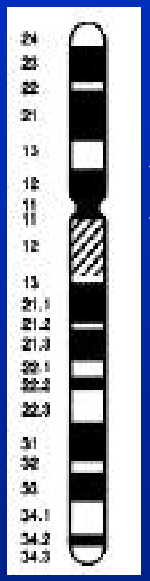
High grade	OR 6.4
Tumor > 2 cm	OR 4.4
Angioinvasion	OR 4.2
Age <40 (OR	OR 3.7
ER negative	OR 2.4

Multivariate model model indicates independent of classical prognostic factors
OR 18

Genome sequence: a comprehensive encyclopedia of human genes



Genome



23 Chromosomes

stSG35361	ESTs, Highly similar to NEUR
stSG4144	Human mRNA for KIAA0377 gene
sts-U04209	Human associated microfibril
sts-N35229	ESTs
WI-6562	Unknown
sts-R01211	Human associated microfibril
stSG8159	Human mitochondrial creatine
WI-15193	ESTs, Highly similar to CREA
stSG43153	Microtubule-associated prote
sts-F15934	ESTs, Weakly similar to deve
stSG4897	Human clone 53BP1 p53-bindin

100,000 Genes

```
BASE COUNT    101 a   118 c   111 g    96 t
  1 ttttttttt tttttttttg aaaaagtcat ggagttgagc agggaagtac
 61 agccagctga tcgtagtcct cagggccaaa gggcgcatcc catctgaaca
121 ccgagccttc acccggtgct ggcagctgct caaggaatcc ccatcgctgt
181 attcatgttg gcactcttca ccatttgcac caaaatgggt gtcagctccc
241 cagaaggccc ttggcgaagg cagcagcagt catctgaaca gagacgaagc
301 gatcttgaga tcgtggcgga aagtgctatg gagacgaagc gcagcgaaaa
361 agcatagtca ccctgtcctc cagggtacat gcagcgaaaa tcgtggcgga
421 ctgaac
//
```

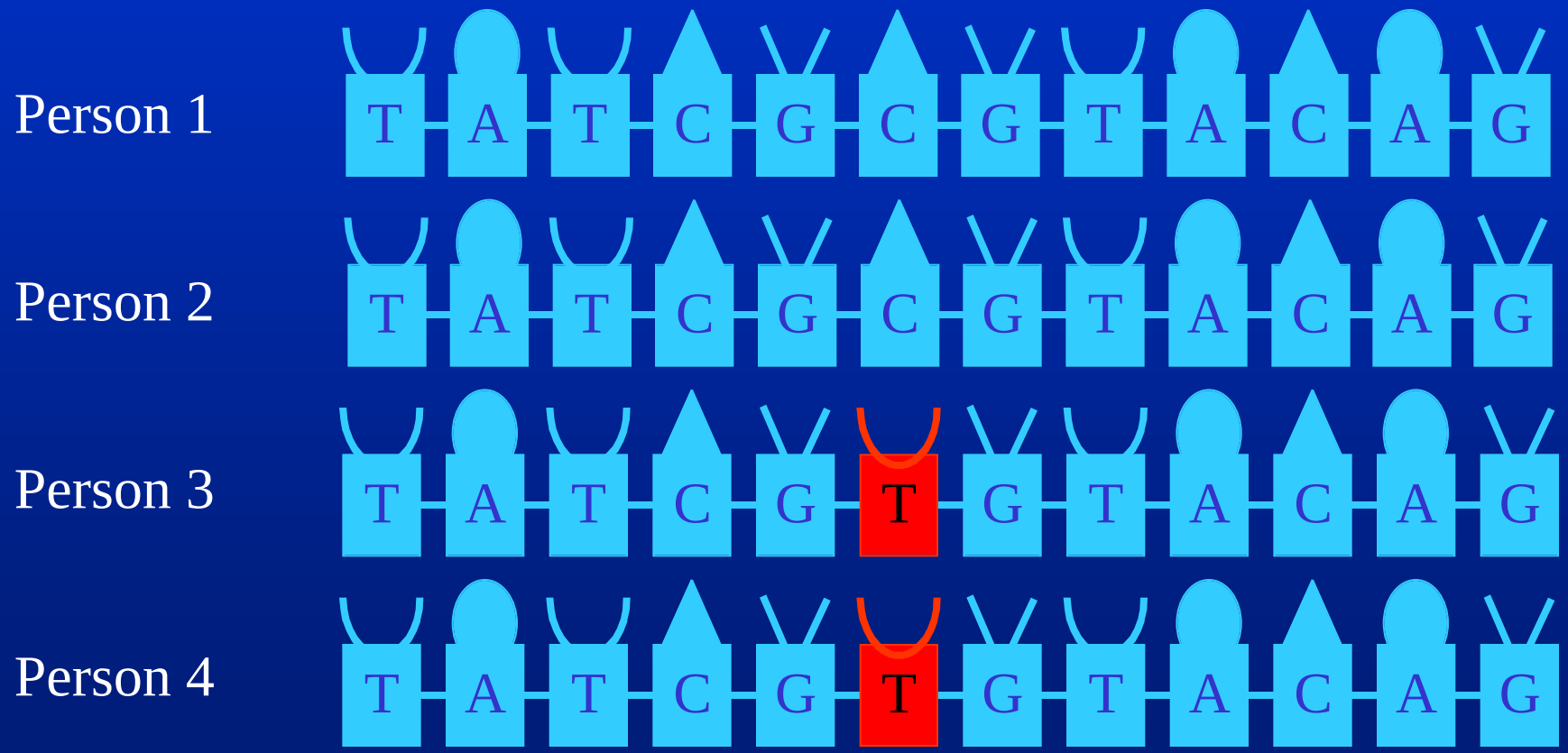
3,000,000,000 base pairs

“working draft” in 2000

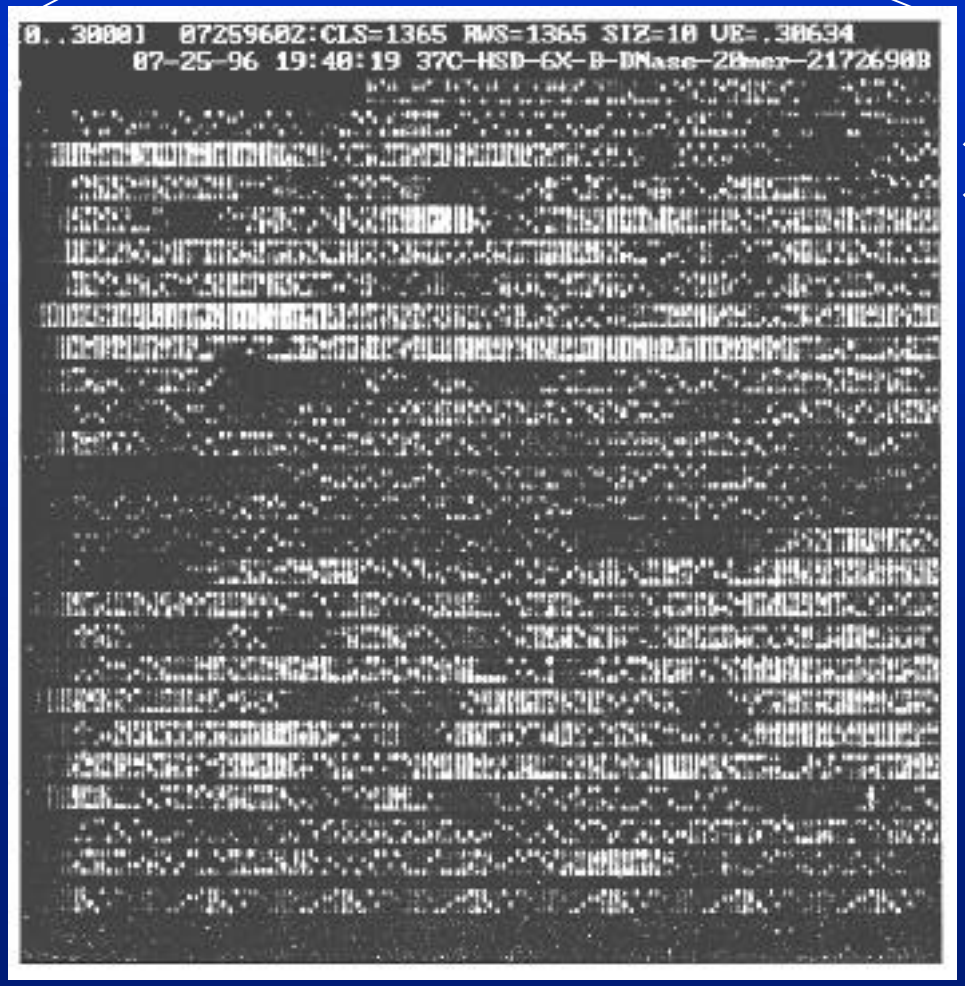
Associating inherited (DNA) variation with biological variation

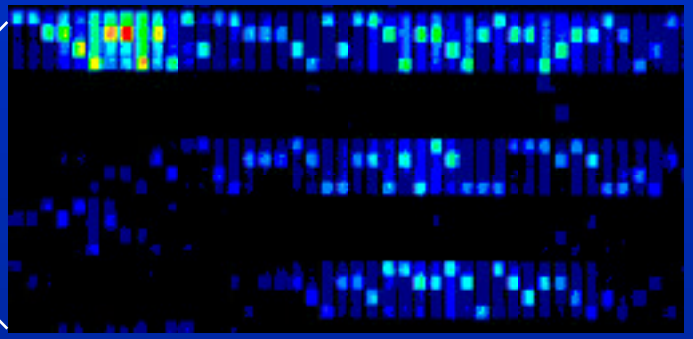
- Each person's genome is slightly different
- Some differences alter biological function
- Questions:
  - How much variation exists?
  - Which differences matter?

Most variants change a single DNA letter: single nucleotide polymorphism ("SNP")



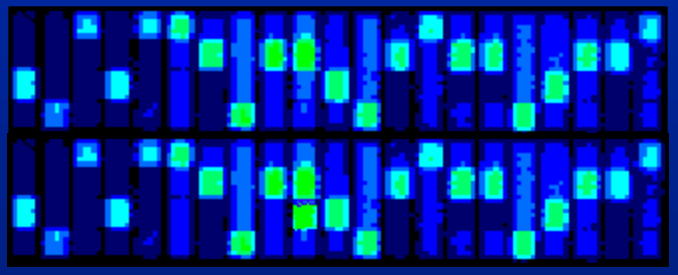
Gene chip image





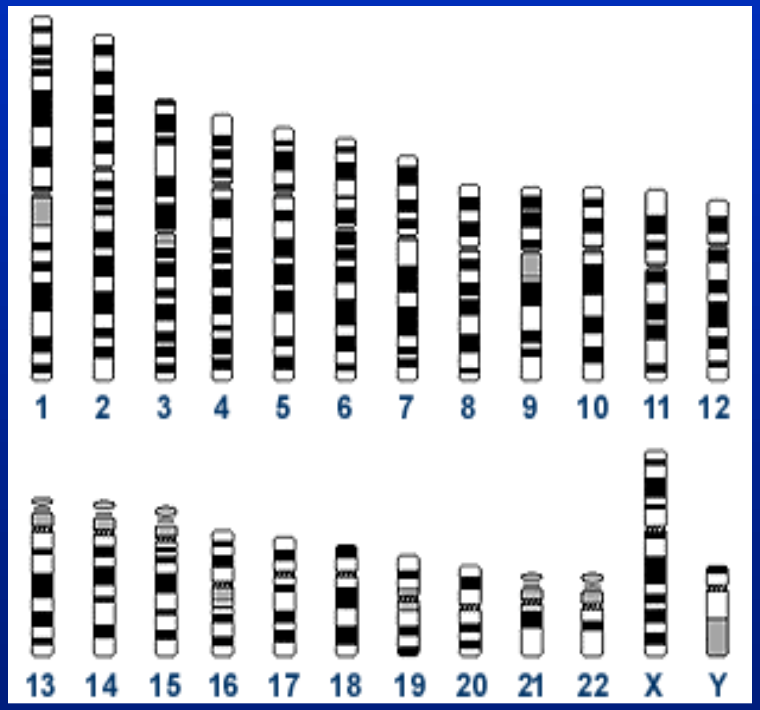
Ref

Het



Confirm by sequencing

Genome-wide SNP discovery

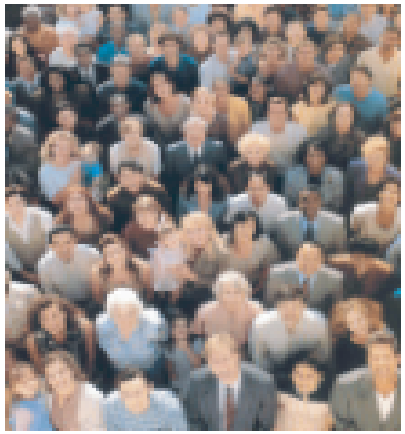


- The SNP Consortium
  - 10 corporate partners
  - 5 academic centers
- Goal:
  - 300,000 SNPs in two years
  - 23,000 to date at WI alone
- All placed in public domain

The Case for the Magnitude of Disease Causing SNPS

Human 1 Human 2

0.1% different
3 million SNPs



30,000 SNPs in coding regions

13,000 coding SNPs do not change amino acid (silent)

12,000 SNPs do not change character of amino acid significantly

5,000 SNPs change character of amino acid significantly but do not lead to protein functional change

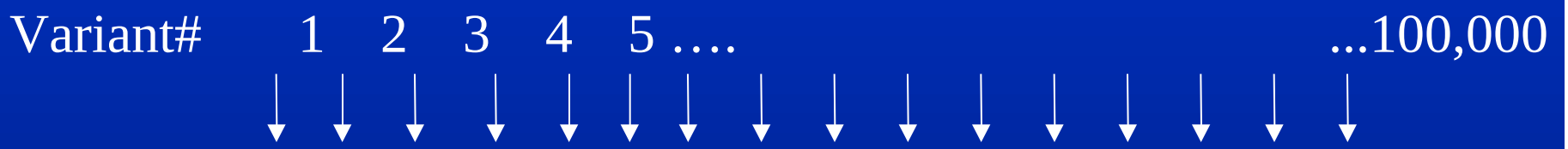
500 SNPs change amino acid significantly and lead to protein functional change that leads to disease

The most frequent genetic alterations are single nucleotide changes

There are many single nucleotide changes (polymorphisms (SNPs) few are expected to be involved in disease!

Studying genome variation with association

Discover and catalogue SNPs in human genes



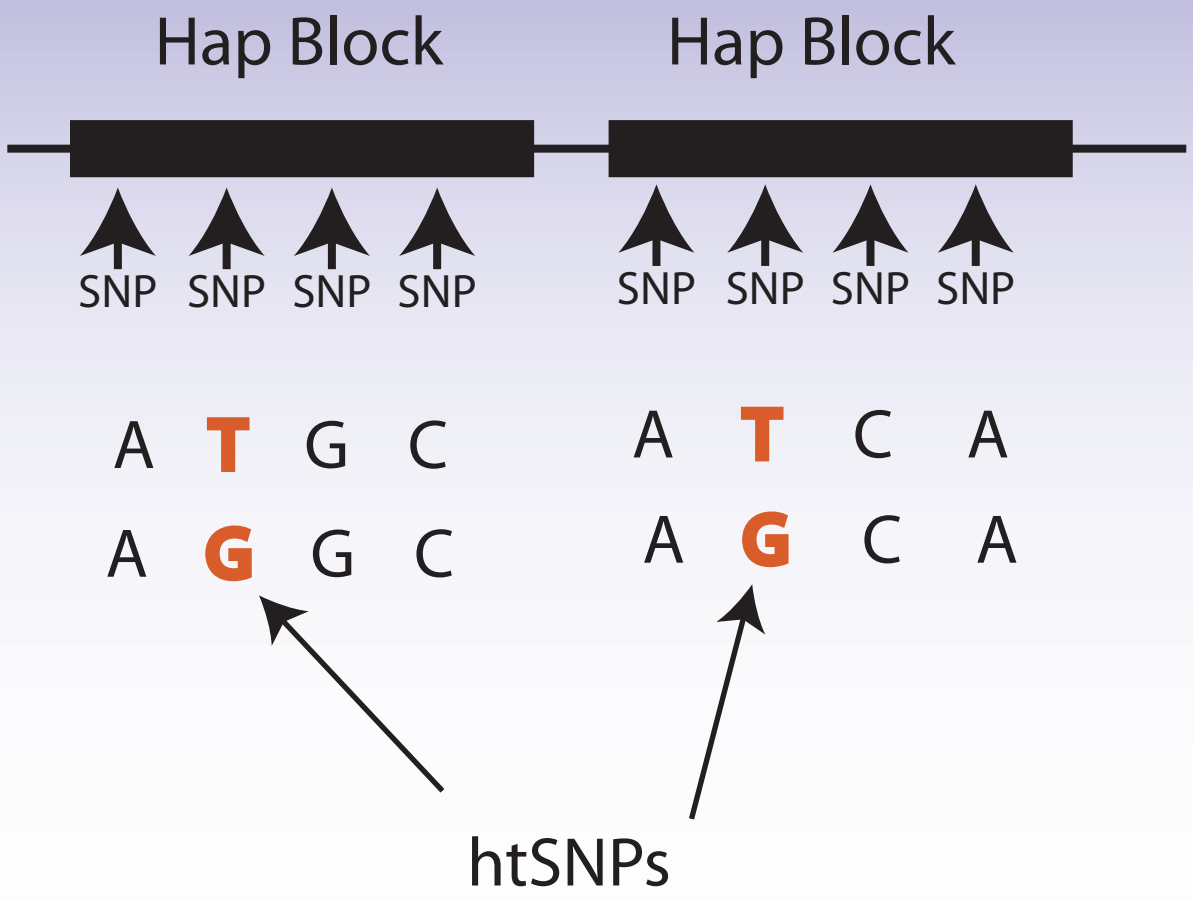
Test these variants for association with human diseases

diabetes

asthma

heart disease

The Human Haplotype Mapping Project



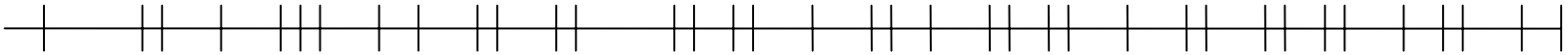
There are 3 M SNPs in the Human genome
As few as 50,000 ht SNPs can characterize a genome

Common Disease, Common Genomic Variability

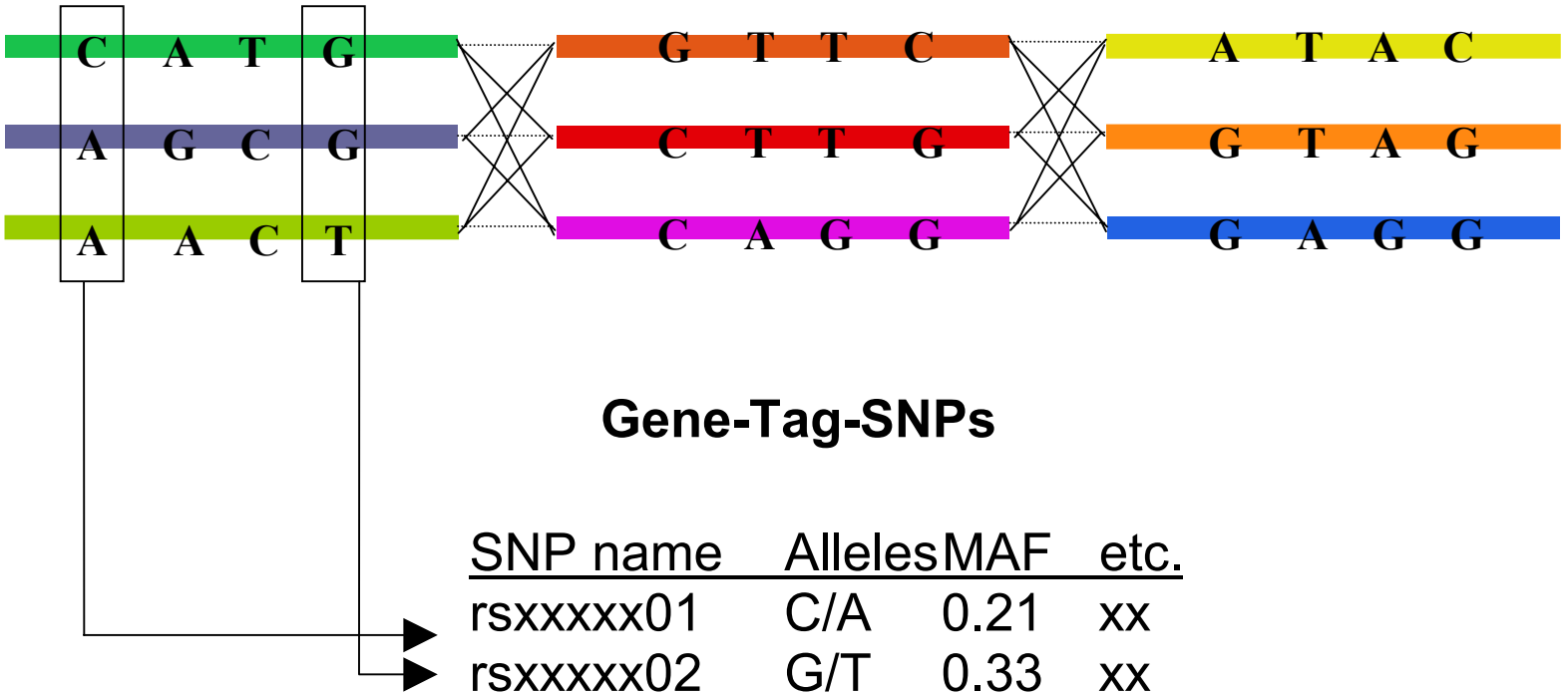
Haplotyping SNPs

Gene structure

SNP map



HapMap

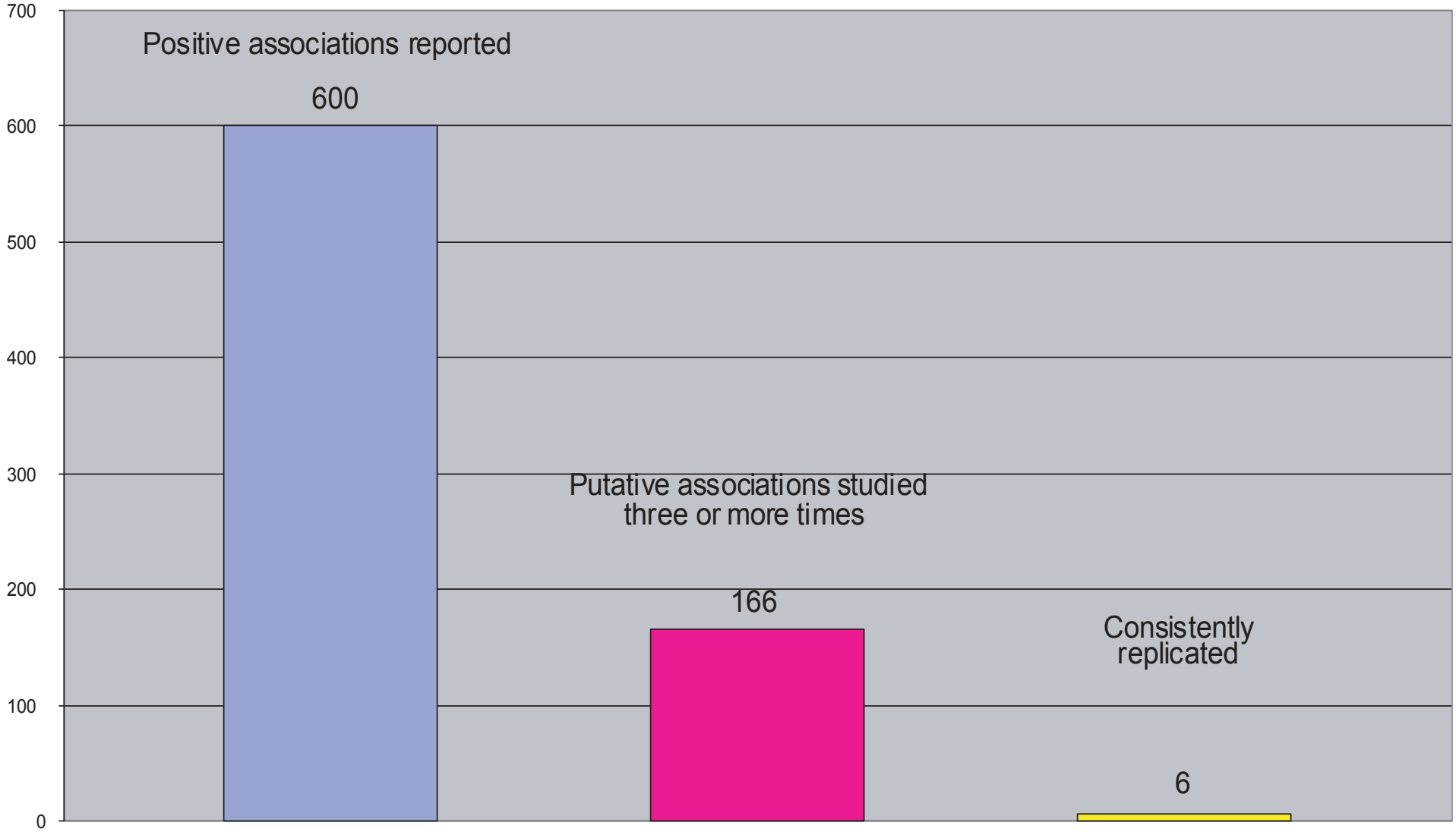


Gene-Tag-SNPs

SNP name	Alleles	MAF	etc.
rsxxxxx01	C/A	0.21	xx
rsxxxxx02	G/T	0.33	xx
rsxxxxx03	A/C	0.35	xx

Replication of Studies is Critical

A review of genetic association studies



SNPs and Clinical Medicine

* Resistance to Rituximab is correlated with a SNP in the FcRIII molecule

* Epirubicin metabolism is related to a SNP in UDP-glucuronosyltransferase (UGT) 2B7

* Taxotere half life correlates with a SNP in cytochrome P450 3A4

Drug efficacy and toxicity may be predicted by pre-treatment determination of specific genotypes.

Examples of Clinically Useful and Cost-Effective Genetic Tests

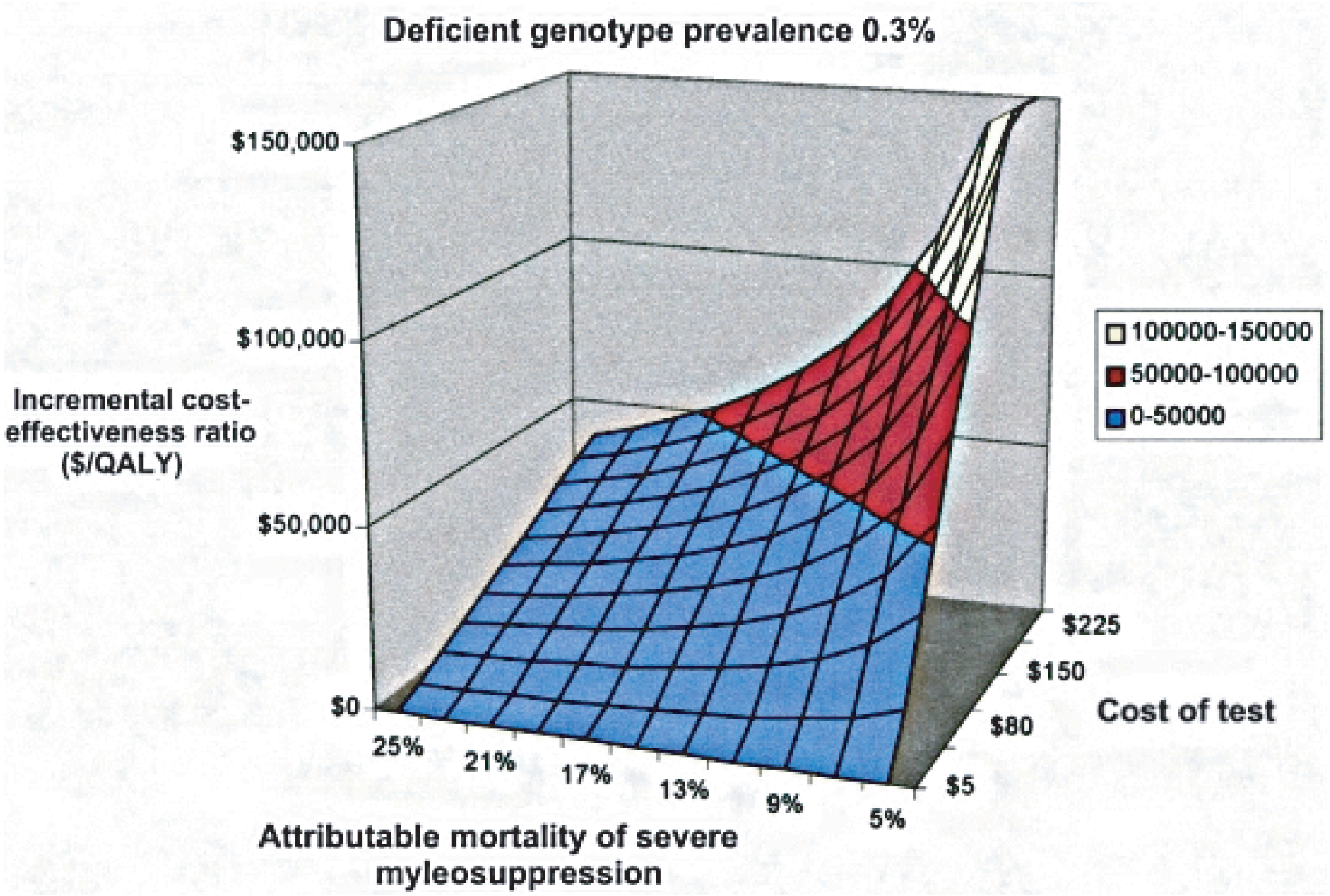
Oncology:

Childhood ALL is treated with 6-MP.
Is metabolized by thiopurine-S-methyl transferase
Variant allele is associated with severe liver toxicity.

Doing test costs $5000 per QALY.

Assumes: cost of treating myelosuppression is about $5000, patients with TPMT deficiency have a probability of myelosuppression of 90% without test and 10% with test, patients not dying have a QALY expectation of 10 yrs.

Incremental Cost-Effectiveness of TPMT testing in Children undergoing 6-MP therapy for ALL



The FDA is promoting pharmacogenomics

* Like it or not, pharmacogenomics is here to stay.

* Buffy coat DNA should be banked on all trial subjects and the consent should make genetic testing and commercialization possible.

* Pharmacogenetic "use guidelines" will increase early adoption and prescription of a higher costing drug.

Pharmacogenomics will be focused on individual drugs, not on the spectrum of genetic diversity.

Ontario Cancer Research Network
Tumor Bioprofiling Project

Brent Zanke MD PhD FRCPC
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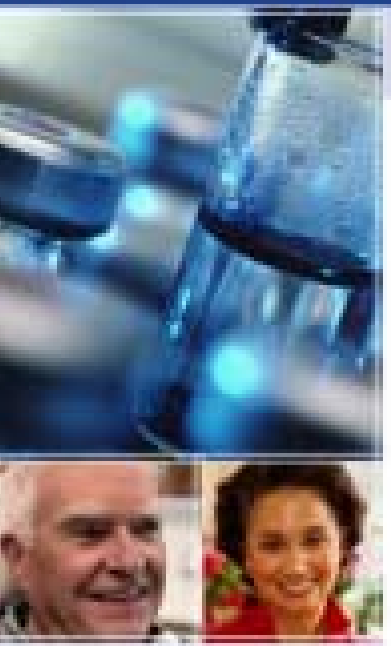

Vision and Mission

OCRN

Created in January 2002 with a budget of $100 million and a 4-year mandate

Vision

Ontario will be a recognized international leader in translational research in cancer.

Mission

To accelerate the development and testing of promising new cancer therapies in order to bring innovative treatments to patients sooner.

Programs of OCRN

- Cancer Research Fund - $71 million
  - $58 million for direct support of research
  - $13 million for infrastructure to support clinical studies
- Virtual Information Network - $12 million
- Tumour Bank Network - $10 million

Tumour Bank

- Collect at least 10,000 samples/year (20% of all cancer patients); samples in liquid nitrogen
- All samples linked to patient data with frequent updates of outcomes
- Proactively make biological and genetic measurements on a subset of tumour samples
- Distribute both specimens and data
- Will be self-supporting in 4 years

OCRN Measures of Success

- Patients will have access to a broader spectrum of new cancer therapies; physicians can offer more options for treatment
- Hospitals will see clinical studies as enhancing patient care
- Industry will find Ontario an ideal place to spend their research dollars
- Academics will be able to do research that is better than in any other jurisdiction
- Government will be recognized internationally as an innovator in supporting cancer research