



Stanford - South Africa

Biomedical Informatics Program



Introduction to Pharmacogenomics

Russ B. Altman, MD, PhD
Professor of Genetics, Bioengineering &
Medicine
Stanford University



Instructors

- Russ B. Altman, MD, PhD
- Caroline Thorn, PhD



Define Pharmacogenetics

“The role of genetics in drug responses.”

F. Vogel, 1959



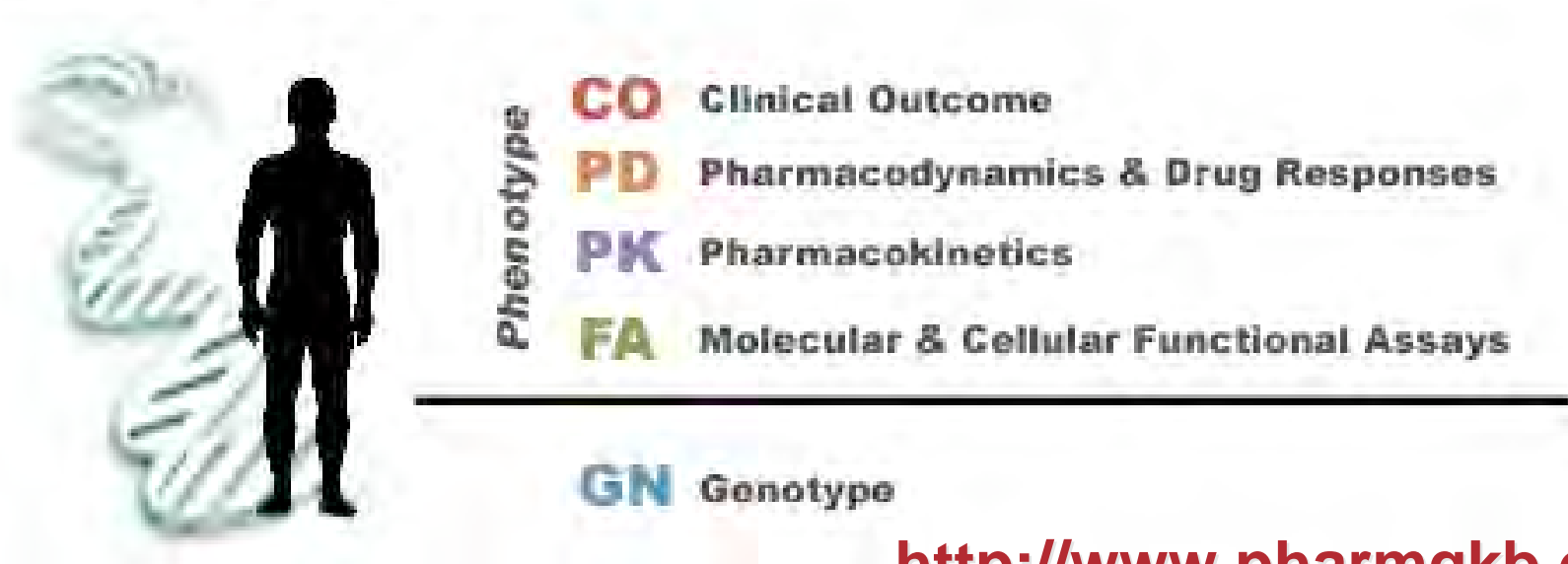


Objectives of Pharmacogenetics

1. Identify variation in response
2. Elucidate molecular mechanisms
3. Evaluate clinical significance
4. Develop screening tests
5. Individualize drug therapy



Genomic data, molecular and cellular phenotype data, and clinical phenotype data are accepted from the scientific community at large. These data are then organized and the relationships between genes and drugs are then categorized into the following categories:



<http://www.pharmgkb.org>

Goals of course

- Understand informatics challenges in pharmacogenetics & pharmacogenomics
- Understand the basic sciences behind pharmacogenomics: pharmacology & genomics
- Understand how bioinformatics intersects with clinical informatics



Learning Objectives I

1. Understand basic pharmacology concepts: drug discovery, pharmacokinetics, pharmacodynamics, adverse events
2. Understand role of genetics in response to drugs
3. Define pharmacogenomics vs. pharmacogenetics

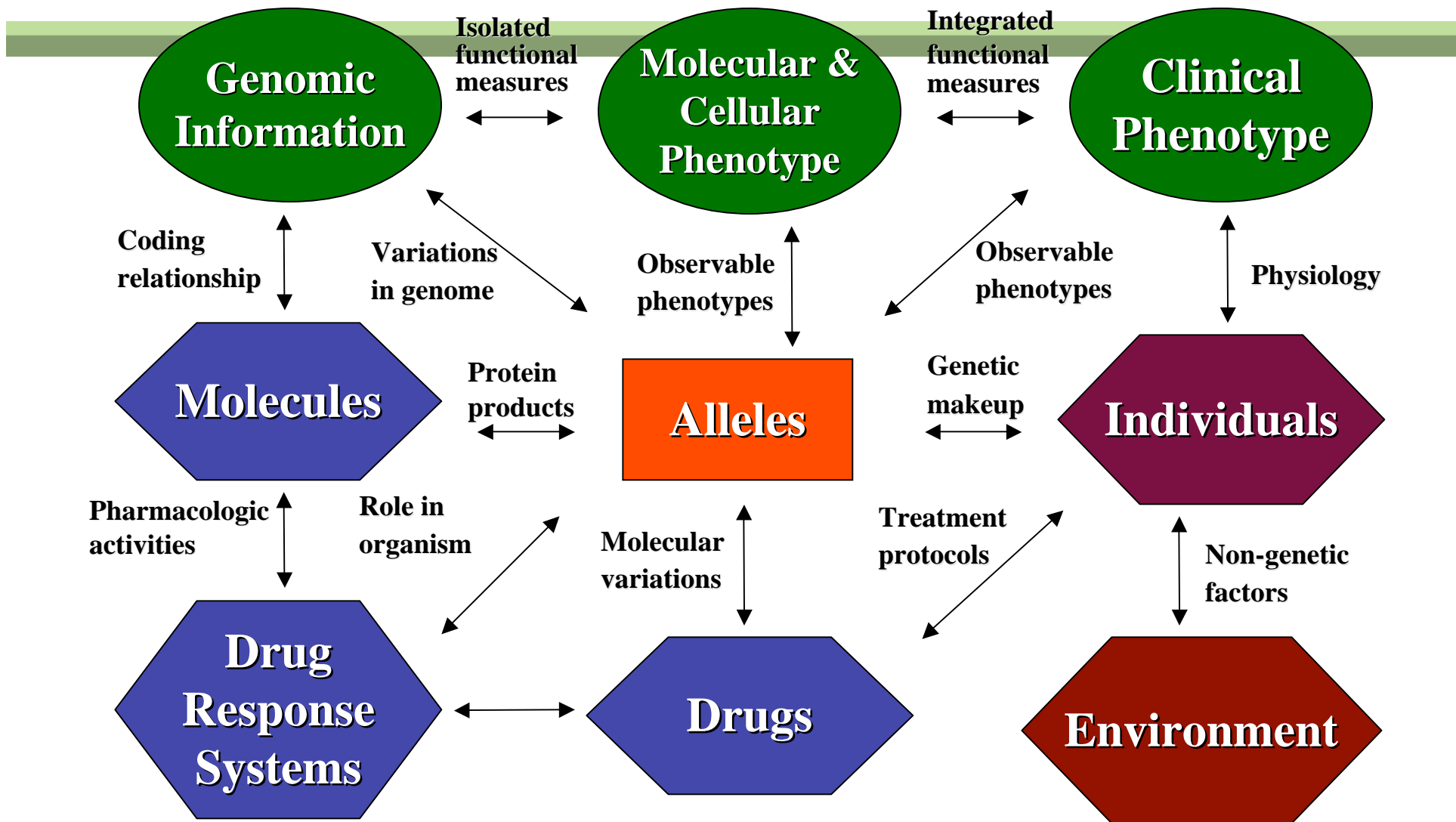


Learning Objectives II

4. Understand categories of phenotypic information
5. Learn classical examples of pharmacogenetics
6. Learn current applications of PGx
7. Understand social, ethical, legal issues associated with PGx
8. Learn how to use PharmGKB (<http://www.pharmgkb.org/>)



Complexity of Relationships in Pharmacogenetics



"Omics"

X-omics = study the entire collection of X

Genomics = study all genes

Proteomics = study all proteins

Pharmacogenomics = study all
pharmacogenes

What is a pharmacogene?!



Pharmacogene

Any gene involved in the response to a drug

Thus,

Pharmacogenomics = study of all genes involved in the response to a drug.

25,000 genes

??? Unknown number of pharmacogenes

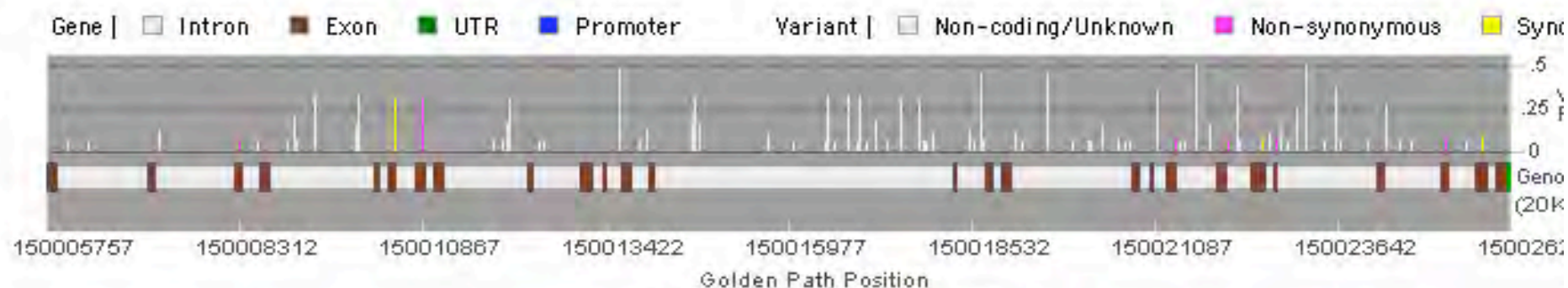


Human Genome

- Sequence completed in 2001
- 3,000,000,000 bases of DNA
- Divided into 23 chromosomes
- In females, all diploid (two copies)
- In males, X and Y are haploid (one copy each)
- 25,000 genes
- 99.8% of genome identical in humans



Variant Positions on NOS3



Click To: Move Magnify

Current Position:

Move:

Magnify:

Legend

- deletion

* feature derived from NCBI RefSeq

Number of variant positions: 121

Golden Path Position	Variant	Strand	Feature	AA Translation	Frequency (%)	Sample Size
chr7:150004282	T/A	plus			52.13/47.87	94
chr7:150004311	A/T	plus			98.94/1.06	94
chr7:150004375	G/T	plus			97.87/2.13	94
chr7:150004621	C/T	plus			98.94/1.06	94

What was promise of genome?

- New prognostic tools (predicting things that may happen)
- New diagnostic tools (identifying things that are happening)
- New therapeutic tools (creating things to affect what is happening)

Pharmacogenomics relates to therapeutics, sometimes called “personalized medicine.”

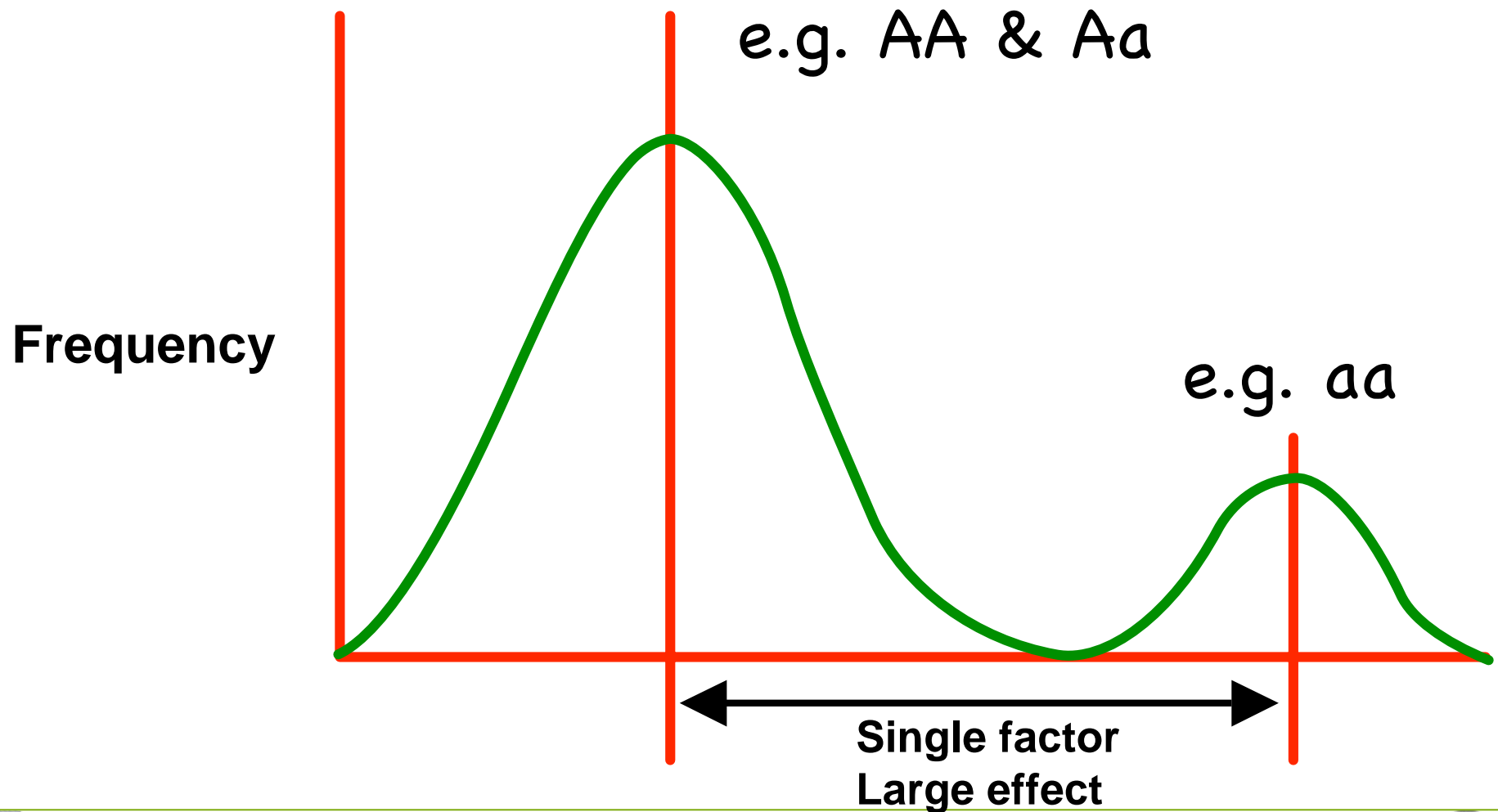


Genetics

- Simple Mendelian Genetics
 - Categorical traits (e.g. presence/absence of a disease) associated with a single gene
 - Two alleles A , a (allele = version of gene), one from mom, one from dad
 - AA , aa = homozygous diploid
 - Aa = heterozygous diploid
- IF Dominant Allele A : $AA = Aa$ (same phenotype)
- IF Recessive Allele a : $aa =$ (alternate phenotype)



Bimodal Distribution in drug response

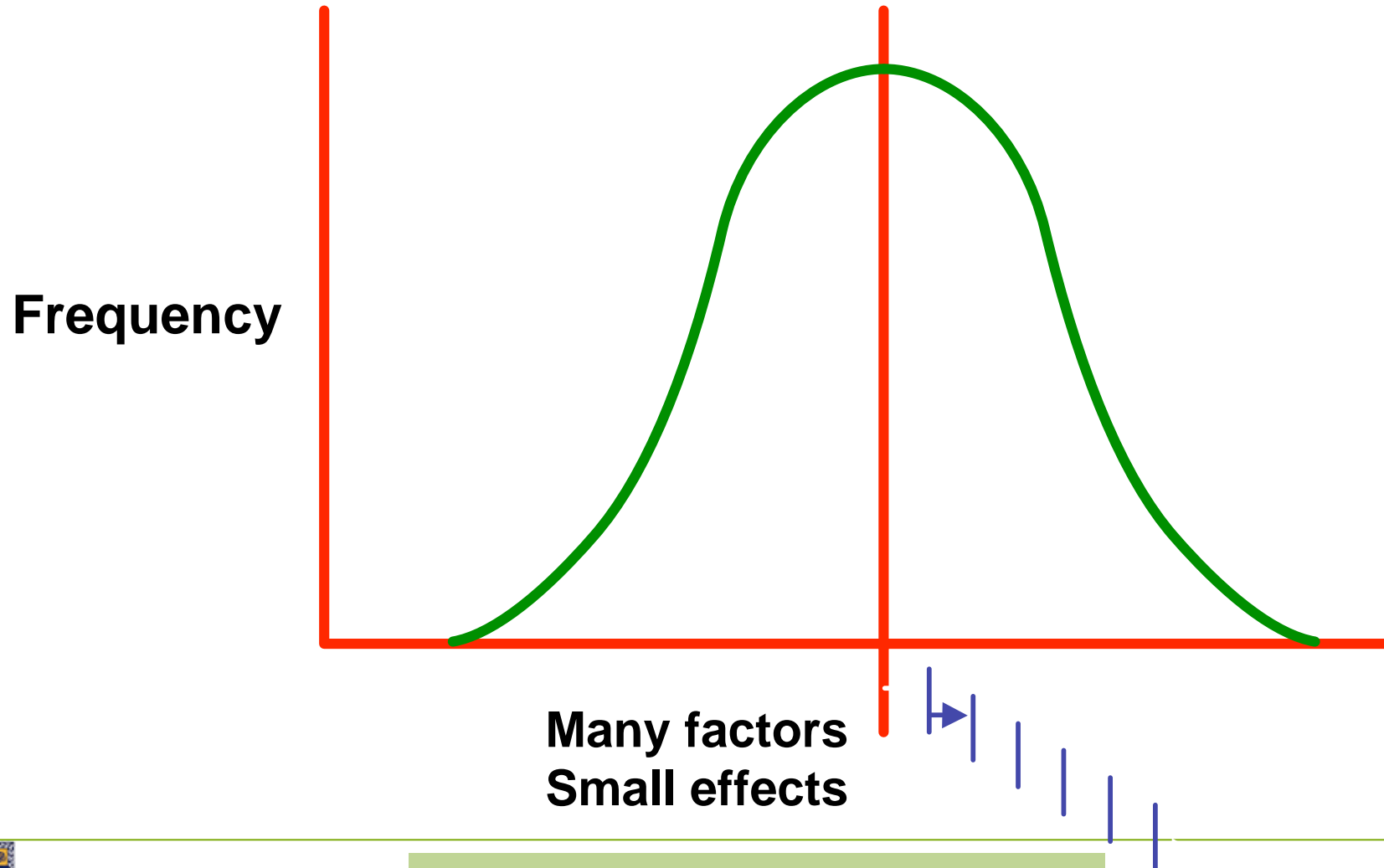


More genetics

- Quantitative trait = not categorical, but a continuous variable (e.g. height)
- Complex trait = depends on more than one gene (quantitative traits usually complex)
- **Example:** 4 genes with two alleles each: Aa, Bb, Cc, Dd
- Many possibilities: **ABCD, aBCD, abCD, abcD, abcD, Abcd, ABcd, ABCd, etc...**
- Each possibility may be associated with a different quantitative trait value



Unimodal Distribution in drug response



Brief History of PGx

- Genetics rises in late 1800's early 1900's with interest in agriculture/husbandry
- Initial analysis of medical applications in the 1950's
 - Mendelian simple trait analysis of families
 - Definition of dominant/recessive/x-linked patterns of inheritance in human disease
 - Recessive genes causing disease = rare disease.



History of PGx

- 1970s: analysis of clinical phenotypes related to known genes
 - E.g. hemoglobinopathies leading to sickle cell anemia, thalassaemia, clotting disorders

Leads to an interest in finding genetic causes of other diseases that show familial heredity patterns.



1950's/60's classic PGx examples

- Glucose-6-phosphate-dehydrogenase
 - Severe anemia in some African-Americans upon taking primaquine, later found in 400 million Africans.
- Isoniazid (INH) for tuberculosis
 - Slow and rapid metabolizers, related to N-acetyltransferase variants (more than 100)
- Unusually long anesthesia with succinylcholine
 - Prolonged effects due to atypical cholinesterase



1960's - 1970's: CYP2D6

- Discovery that response to debrisoquine (blood pressure medicine) and opioids (pain medications) was related to the level of cytochrome p450 activity
- Cytochrome 450 found in all animal kingdom, involved in metabolism of foreign substances
- Later found to be CYP2D6, with many (> 80) polymorphisms in human population



1970's/80's: Rise in use of genetic linkage analysis

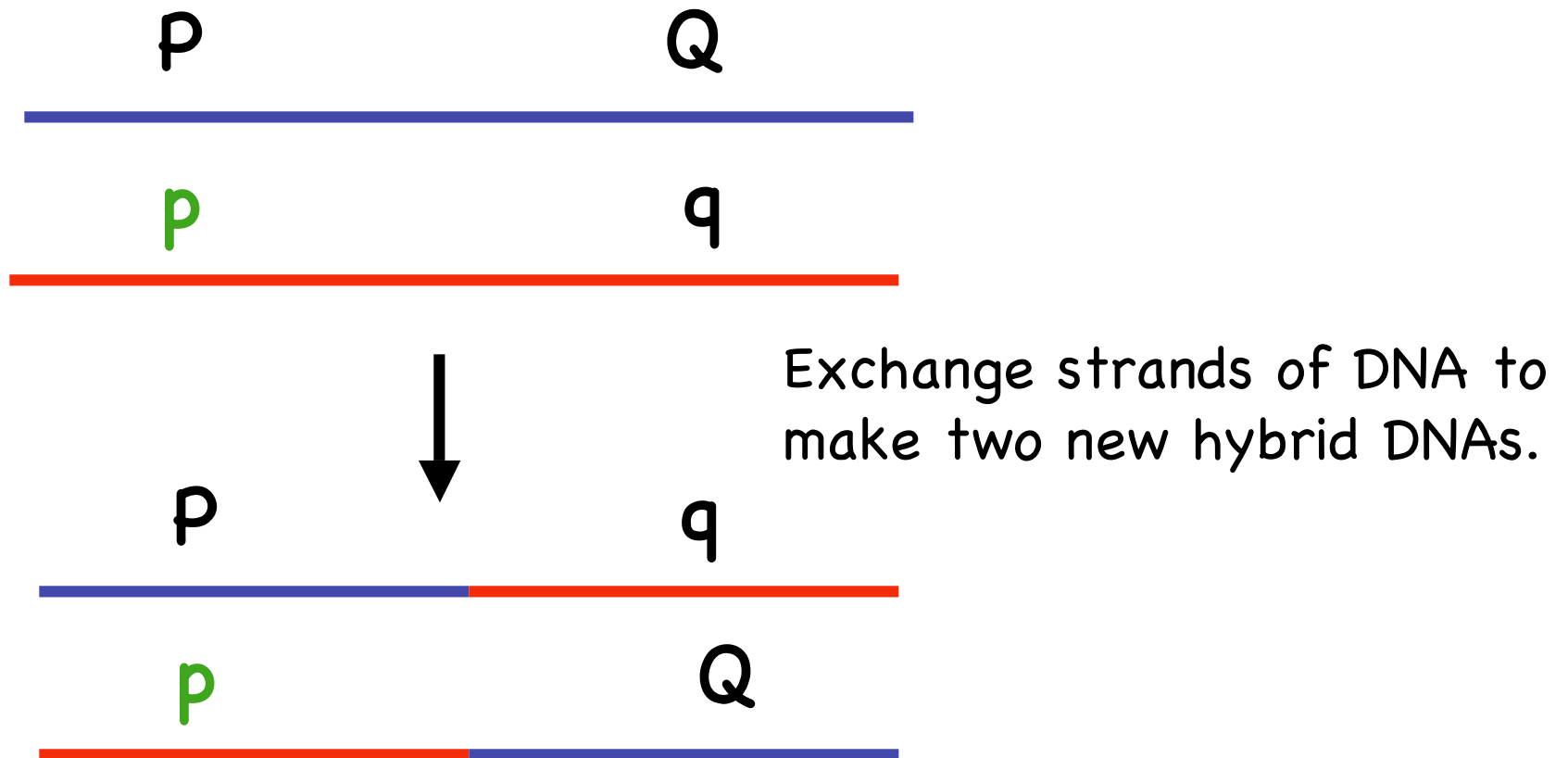
If two genes (or genetic features) are (1) close to one another on a chromosome, and (2) each have at least two different alleles, then

It is likely that a disease allele for one gene would be inherited together with a particular allele of the other gene.

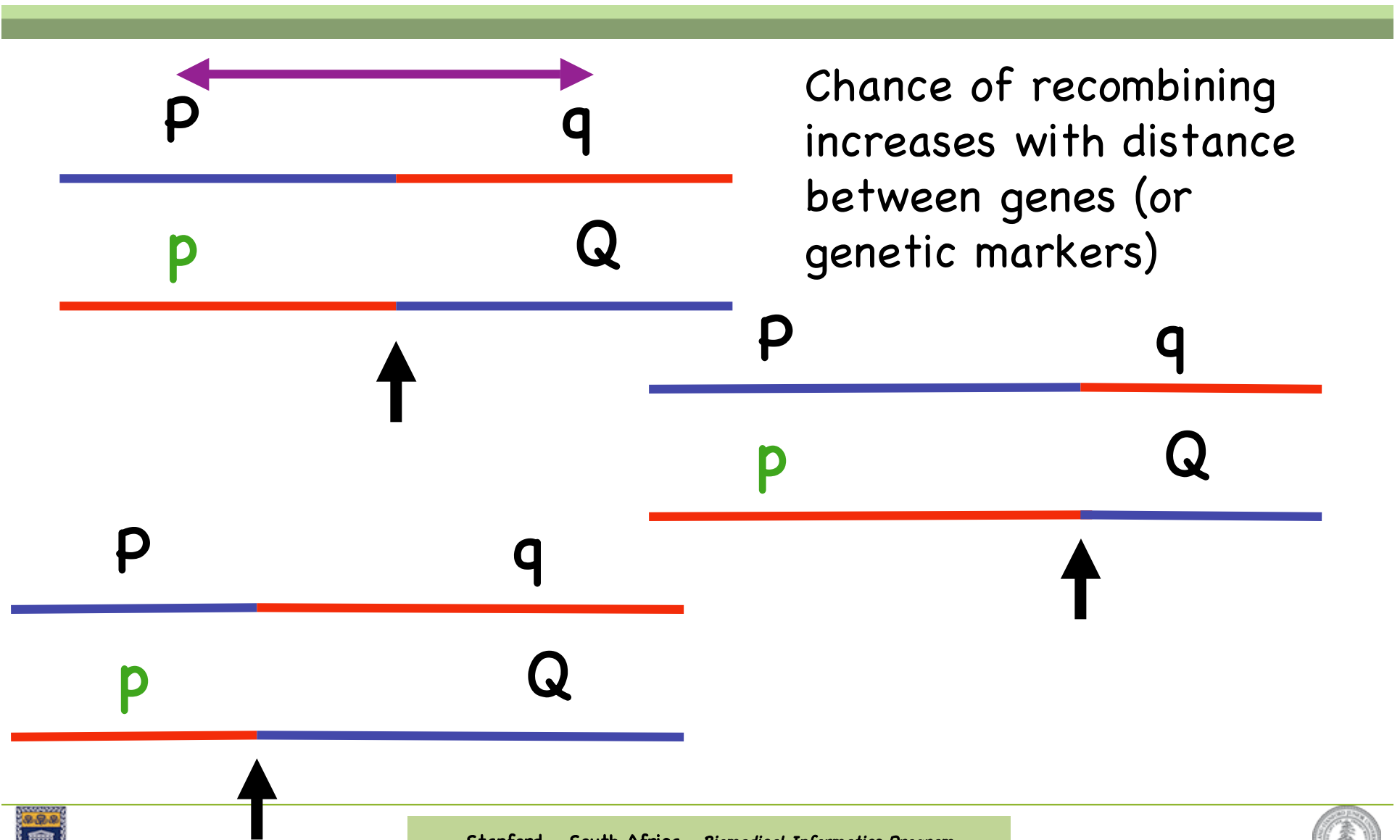
If the "other gene" has an easy to measure phenotype, then the presence of the disease allele could be inferred from the presence/absence of this phenotype [usually checked in parents/children].



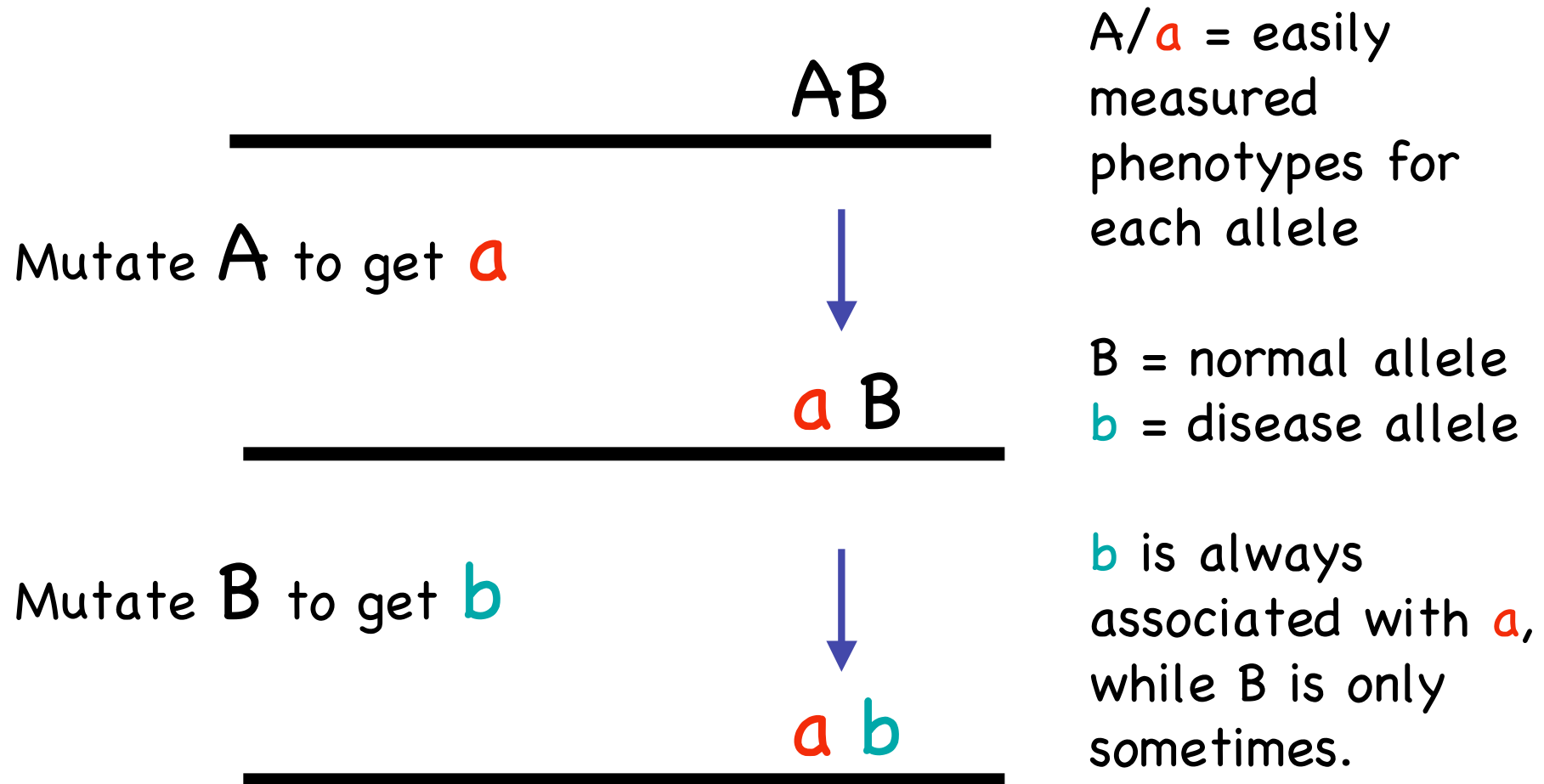
Recombination



Recombination



Linkage Example



But which genes/markers are easy to phenotype?

- Initially, easy to measure traits like: eye color, blood group
- 1970's: Restriction fragment length polymorphisms (RFLP) provided 100's of markers throughout genome.
- 2000s: Genome sequence provides millions of markers

These provided the easy to measure phenotypes that allowed genes to be associated with linked genetic regions (loci).



RFLP

Enzyme cuts
GGGAGG

ACATAGAGGGAGGAGACCAGA



ACATAGAGGG + AGGAGACCAGA

But does not
cut GGGGGG

ACATAGAGGGGGGGAGACCAGA



ACATAGAGGGGGGGAGACCAGA

Thus, easy phenotype = 2 fragments vs. 1 fragment.



Human Genome

- The sequencing of the full human genome provides millions of potential markers for these types of studies.

(We will review these later today)



Routine application of PGx?

Pharmacogenetics is NOT routinely used clinically. Why?

- G6PD tests available and cost effective, but not used
- Other considerations to be addressed later in course.



NEWS

Preventing Toxicity With a Gene Test

To test or not to test? That is the question clinicians are asking about screening for genes that affect how the body metabolizes drugs

For more than 30 years, doctors have been using a powerful cell-killing compound to cure leukemia in children. This wonder drug—6-mercaptopurine (6MP), synthesized by the late Gertrude Elion and George Hitchings—has saved thousands of lives. But it has a dark side. Researchers discovered more than 20 years ago that it is extremely toxic in patients with an inherited metabolic flaw. The drug can accumulate rapidly, wiping out essential bone marrow and leading to infections.

About 8 years ago, teams led by William Evans of St. Jude Children's Research Hospital in Memphis, Ten-

community remains skeptical. Like other promised benefits of genomic medicine, this one has run into complaints about its cost (\$100 to \$300 per test), technical issues about how to recalibrate drug doses, and doubts about physicians' ability to under-



U.S. Food and Drug Administration (FDA) seems unlikely to recommend one.

The resistance has surprised champions of genomic medicine. A leader in pharmacogenetic studies, Russ Altman of Stanford University, acknowledges that genotyping for drug risks has been a hard sell. In all, says FDA pharmacogenetic expert Larry Lesko, about 20 drug labels now mention reactions that may be influenced by genetic differences, but none recommends a gene test or related dose guidelines. Adds Altman: "Everyone thought *TPMT* would be the big one to do first. I must admit there is not a single case of a genetic variation where the standard of care is to test first. ... We have not yet broken through."

Still, the *TPMT* case suggests that genomic medicine is gaining momentum, albeit slowly. Geno-



PGx in Developing World

- G6PD
 - Some anemia is self-limited, other versions profound and life threatening
 - Enzyme based tests exist and evaluated
 - Still not clearly cost-effective overall



PGx in Developing World

- ABCB1 (transporter molecule with variations)
 - Higher variation in West Africa
 - May be due to different environmental exposures
 - Affects levels of HIV drugs



PGx in Developing World

- Malaria
 - Need cheaper and more effective tests
 - DNA tests are emerging that predict organism resistance to drugs
 - Testing of metabolism enzymes may be important for evaluating new drugs in proper populations.



Conclusions

- Pharmacogenomics still a relatively new field.
- Human genome provides full information to catalog human variation, gene locations, marker locations
- Initial pharmacogenetic examples are simple, with one gene-one drug.
- Future lies in complex drug responses involving many genes and quantitative response.

