



11th Annual
FDA Science Forum

Personalized Medicine:

What Is It ?

How Will It Affect Health Care ?

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April 26, 2005
Washington, DC



The background of the slide is a soft-focus image of several colorful pills in shades of blue, green, and yellow, scattered across the frame. The text is overlaid on this background.

Medicine Is Personal:

We are all different.

Some of our differences translate to how we react to drugs – as individuals.

This is why individualized, or personalized medicine is important for you (and me).

For Example:

Why does someone need twice the standard dose to be effective ?

Why does this drug work for you but not me ?

Why do I have side-effects and you don't ?

Why do some people get cancer and others don't ?

A stack of several round, light-colored pills is shown on a reflective surface. The pills are stacked in a slightly offset manner, creating a sense of depth. The background is a soft, out-of-focus gradient of light blue and green. The text "1892:" is overlaid on the image in a large, bold, black font.

1892:

“If it were not for the great variability among individuals, medicine might as well be a science, not an art.”

Sir William Osler, Physician

Personalized Medicine

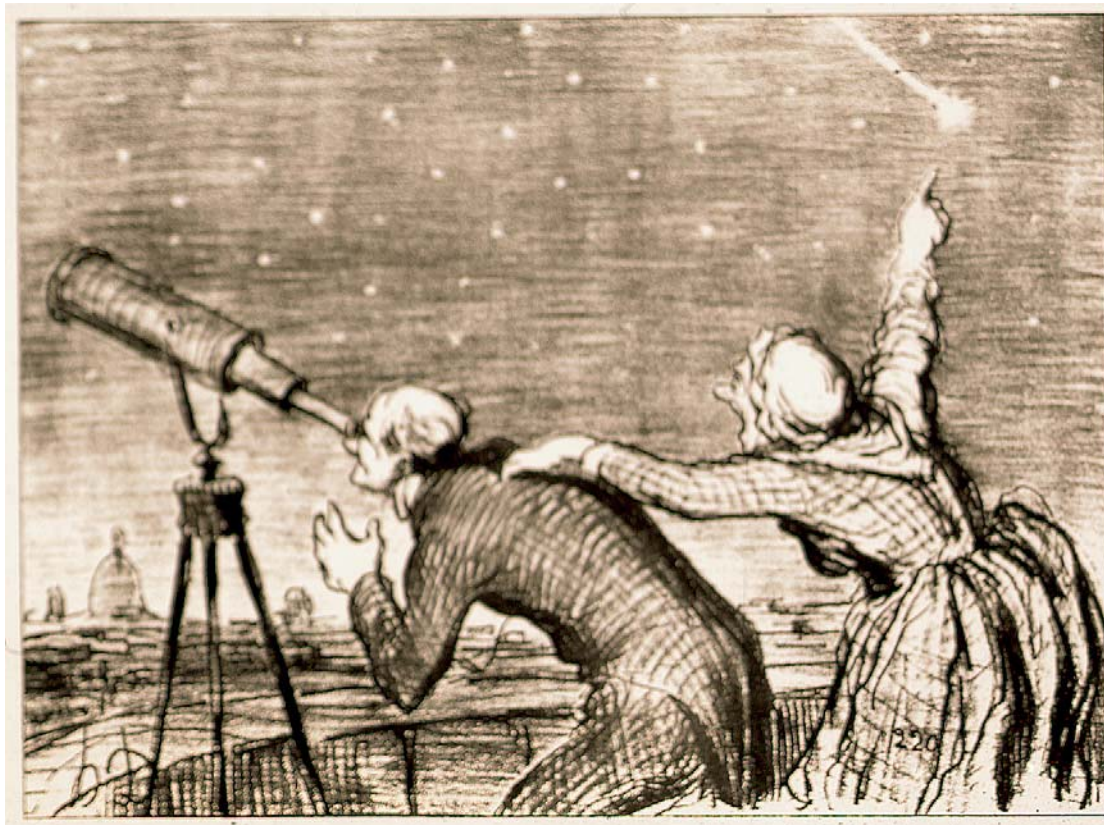
The **Right Dose** of
The **Right Drug** for
The **Right Indication** for
The **Right Patient** at
The **Right Time**.

Yesterday's Medicine:



**One Size
(Dose)
Fits All**

Drug Therapy: Let's Think Again...

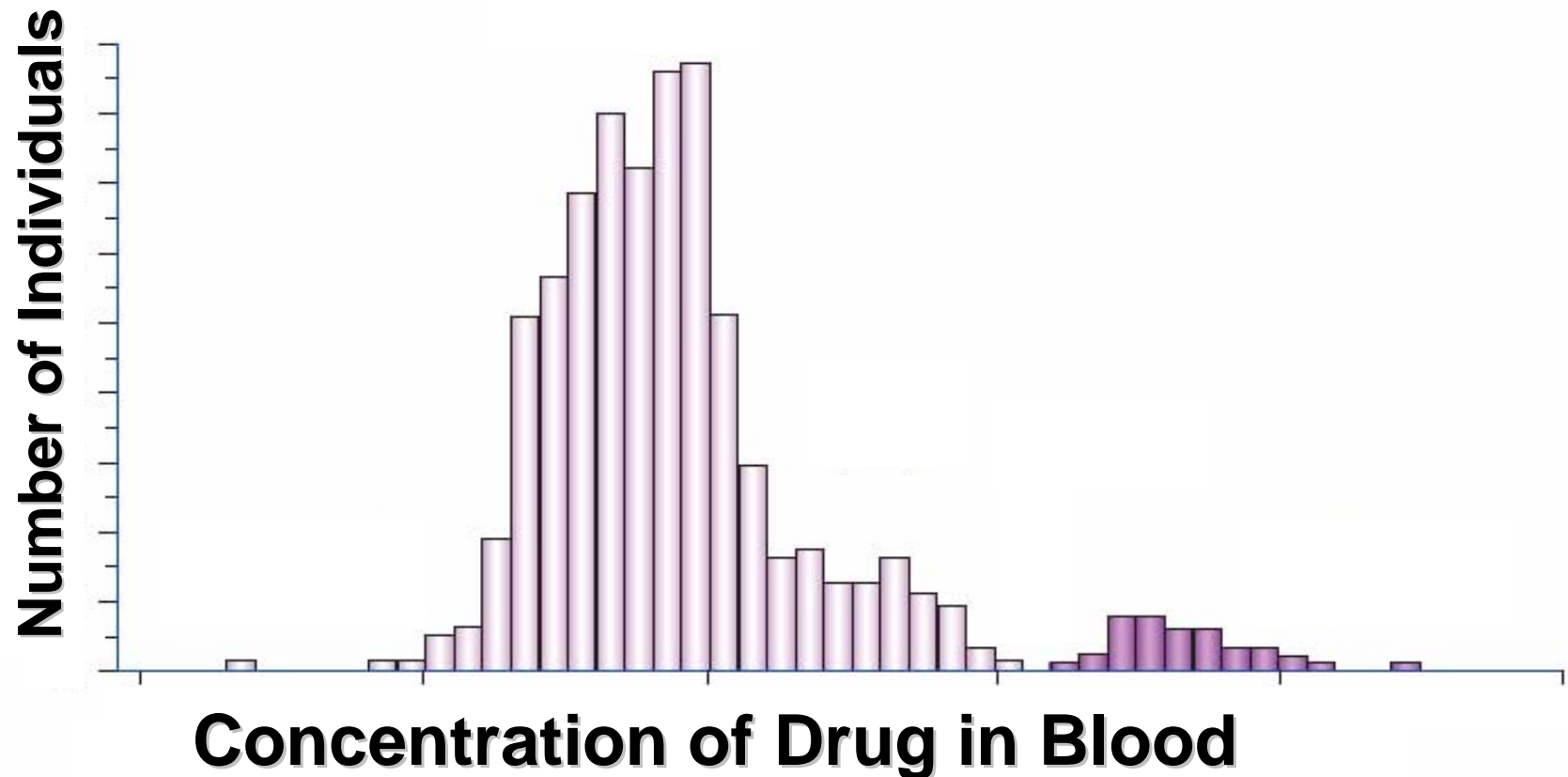


Example:

Drug Metabolism

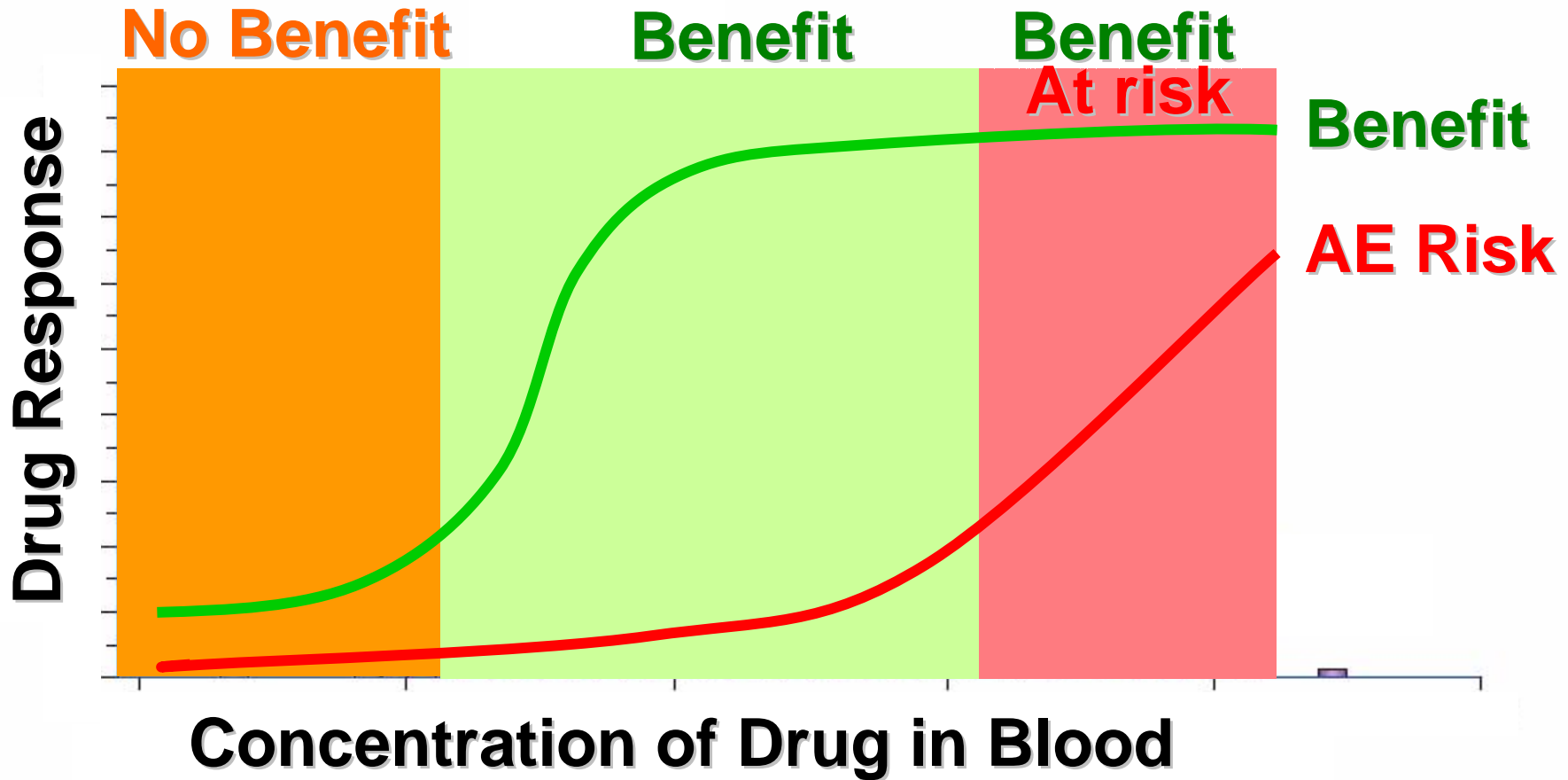
- After drug intake, the drug is processed (much like food) in the human body.
- A group of enzymes called “drug-metabolizing enzymes” (DMEs) is responsible for the breakdown of drugs in the body.
- Many of these enzymes are present in **different forms/amounts** in different individuals.
- This causes different people to process the same drug differently:

Drug Exposure as Function of Metabolism at a Fixed Dose



This variability is normal.

One Size (Dose) DOES NOT Fit All



This may or may not be important for a given drug

If Your Dose is Wrong, What Does It Mean For You?

Different forms of DMEs have an effect on Drug-

- Safety: **Some individuals** require up to e.g. 10-fold less medication than “standard” dose
 - They are at **risk to be overdosed** and exposed to potential adverse events.
- Efficacy: **Some individuals** require up to e.g. 5-fold more medication than “standard” dose
 - They are experiencing **no benefit** from drug therapy.
- **Where it matters**: cancer treatment vs. common cold

A row of several colorful, translucent pills or capsules is shown on a reflective surface. The pills are in various colors, including yellow, orange, and blue, and are arranged in a slightly curved line. The background is a soft, out-of-focus gradient of light blue and green.

**How Can We Explain
This Variability ?**

Versuche

1865: Mendel

Experiments in Plant Hybridization - Inheritance

Pflanzen

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

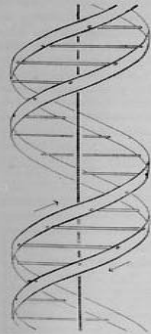
WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey¹. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory.

(1) We believe that the material of X-ray diagrams is the salt, not the acid. The acidic hydrogen atoms it is not possible to hold the structure together. The negatively charged phosphates repel each other. (2) Some of the distances appear to be too small.

Another three-chain structure suggested by Fraser (in the press), in which the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds, is rather better. This structure is rather better than the one proposed by Pauling and Corey.

We wish to suggest a structure for the salt of deoxyribose nucleic acid. This helical chain has the same axis as the one proposed by Pauling and Corey. The chain consists of phosphate-ester groups linked to ribofuranose rings. The phosphate-ester groups are not their base pairs. Both chains are right-handed helices. The dyad axis is perpendicular to the fibre axis. The atoms in the dyad are in opposite positions. The chain is loose. The bases are not in the helix and are perpendicular to the fibre axis. The structure is purely diagrammatic. The two ribbons symbolize the two phosphate-sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis.



1953: Watson & Crick 1953

Structure of DNA

2001:
Public and
Private efforts
Sequence of the
Human Genome

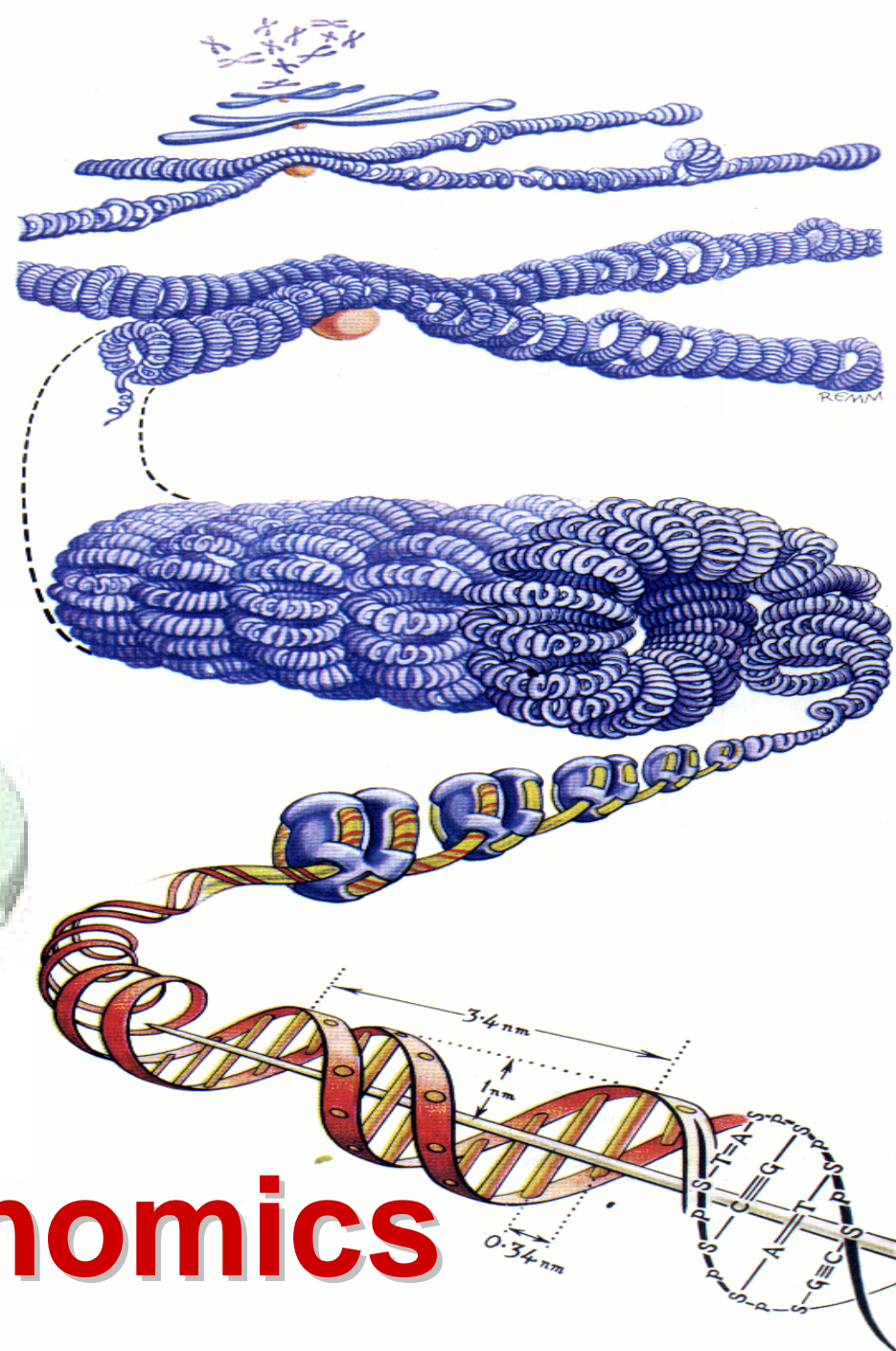


The Human Genome

Every genome is different:

- ~ 3 billion basepairs (100%)
 - ~ 100 new variations per individual
 - ~ 3 million genetic variations (0.1%)
- Genetic variations can be used to explain inter-individual differences in drug response.

Drugs and Genes



Pharmacogenomics



Pharmacogenomics

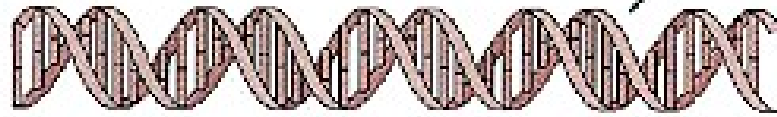
The science that allows us predict a response to drugs based on an individual's genetic makeup.

The Genome and Drugs

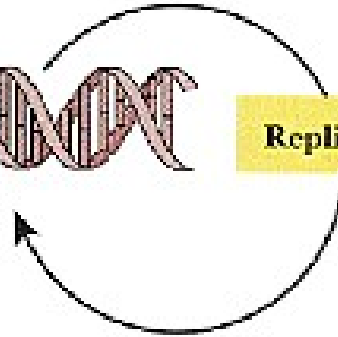
- Genes “encode” proteins or enzymes.
- Differences in the sequence of a gene can cause differences in enzymes.
- This is why enzymes appear in different forms in individuals.
- This is also why different people process one and the same drug differently.

"Dogma"

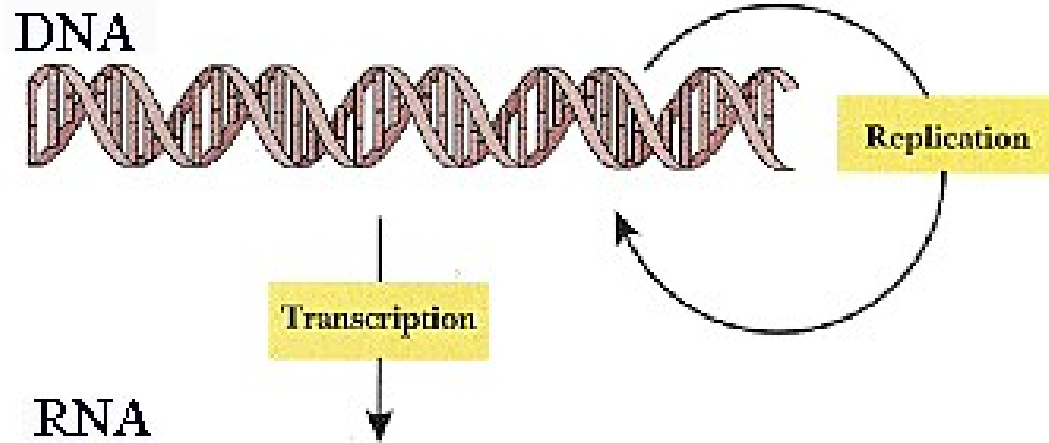
DNA



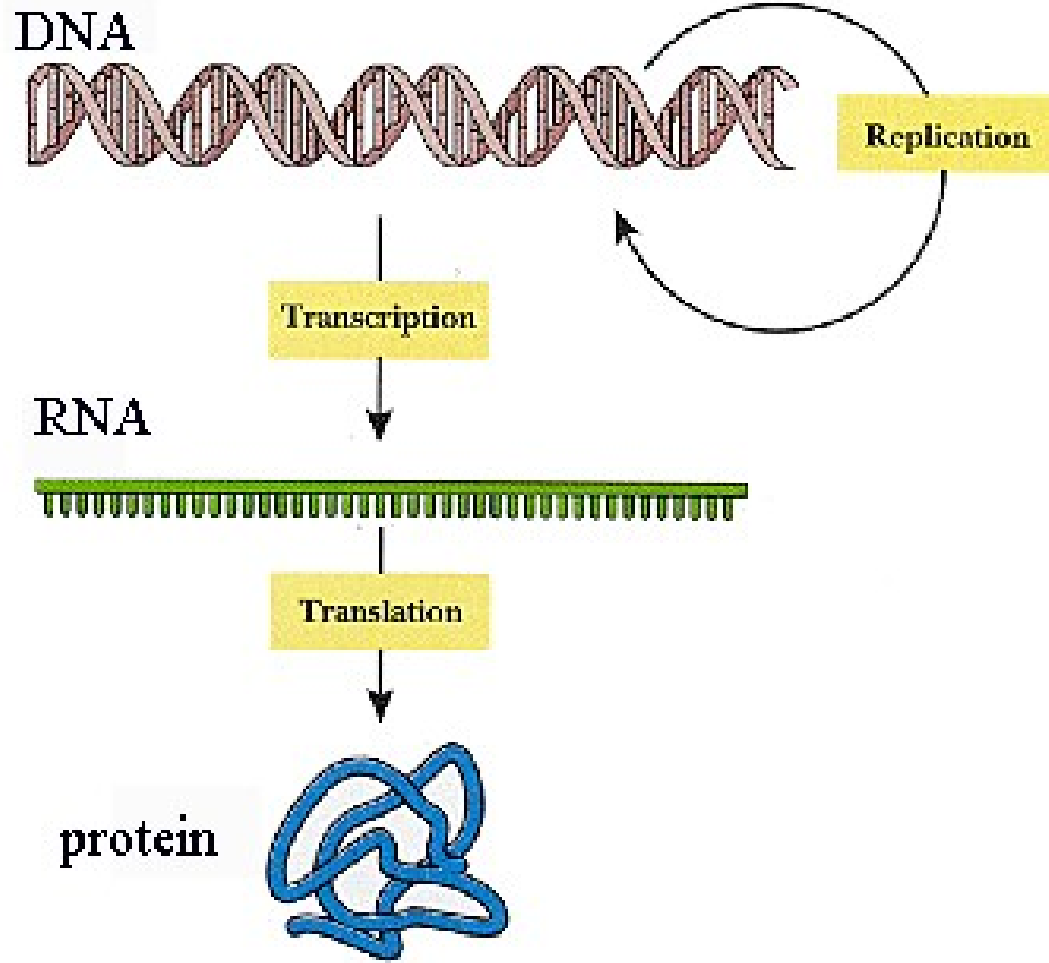
Replication



“Dogma”

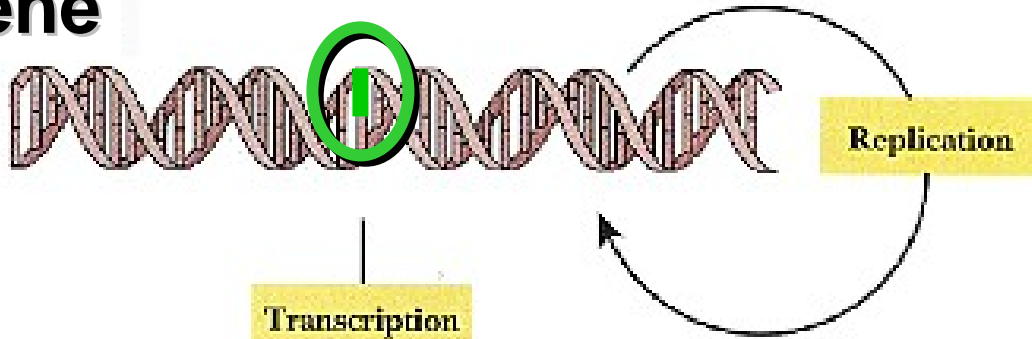


"Dogma"



Gene Type ("Variation") A

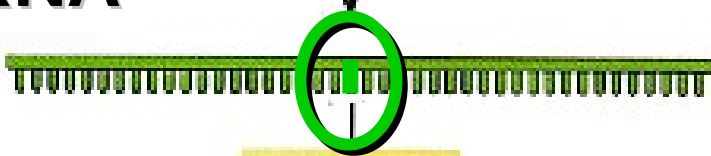
Gene



Type A

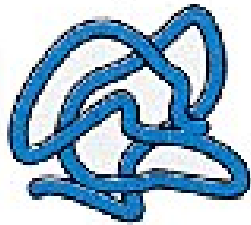
mRNA

Transcription



Translation

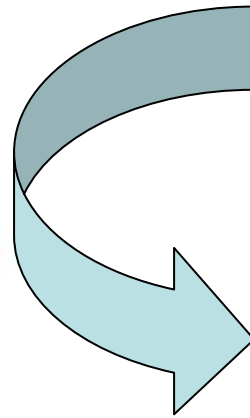
Enzyme



Drug X

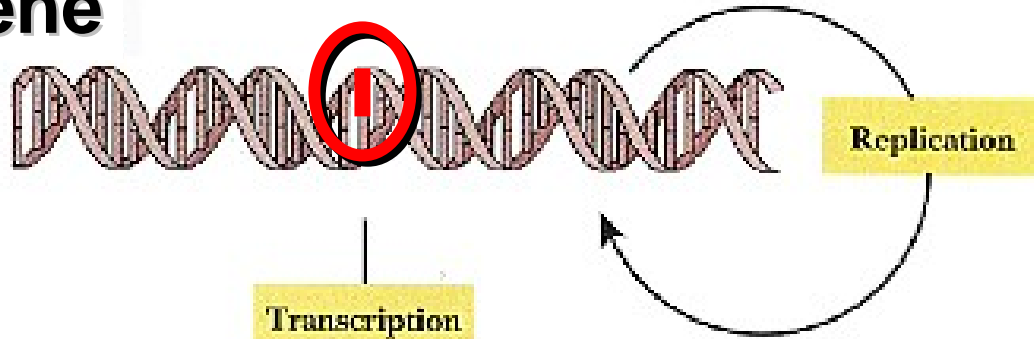
Form
(Amount) A

Metabolite of Drug X



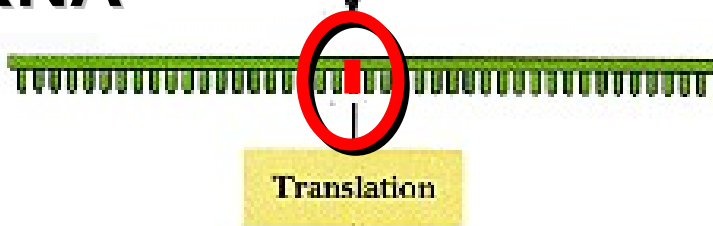
Gene Type ("Variation") B

Gene

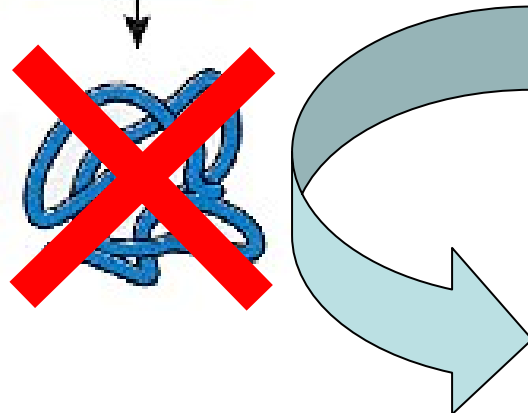


Type B

mRNA

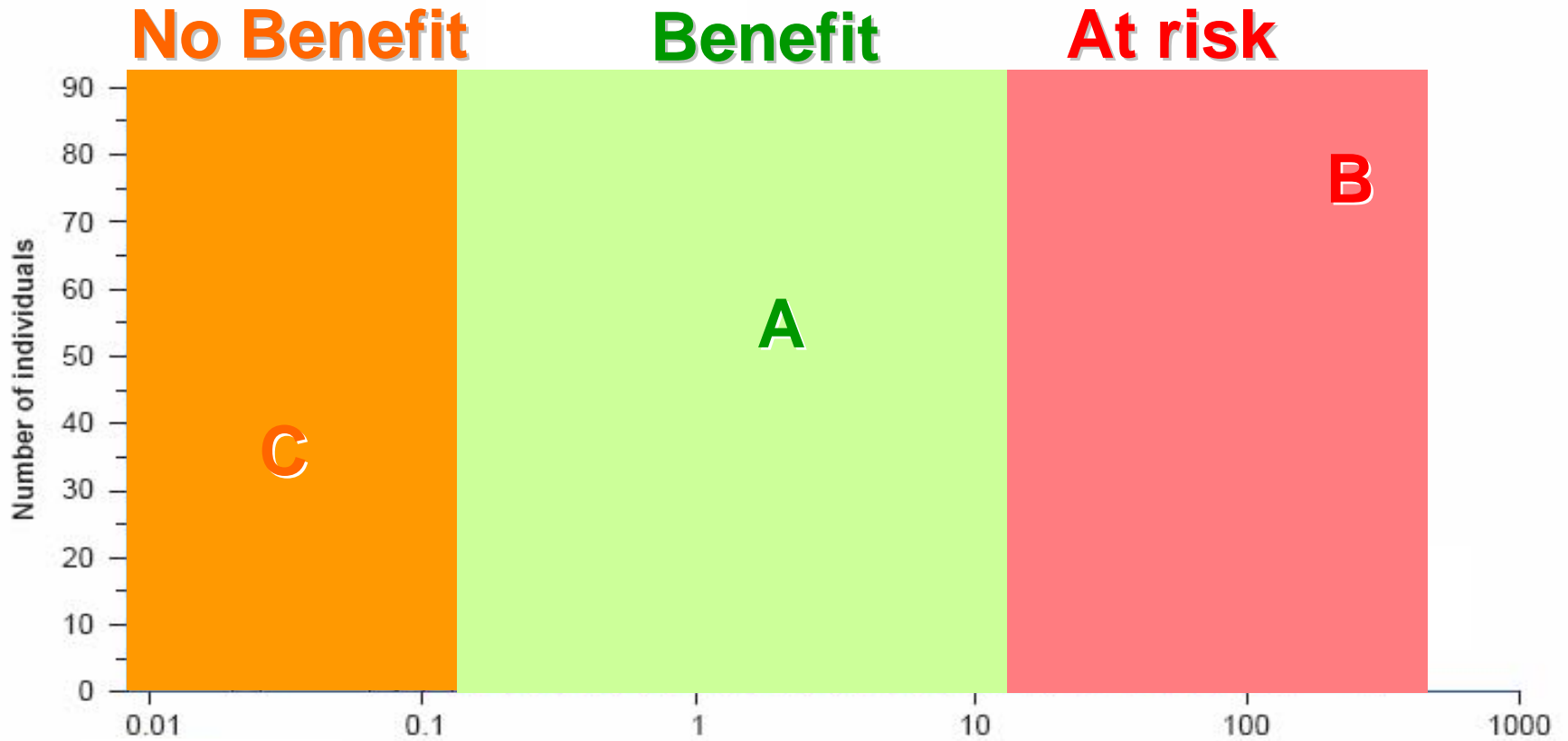


Enzyme

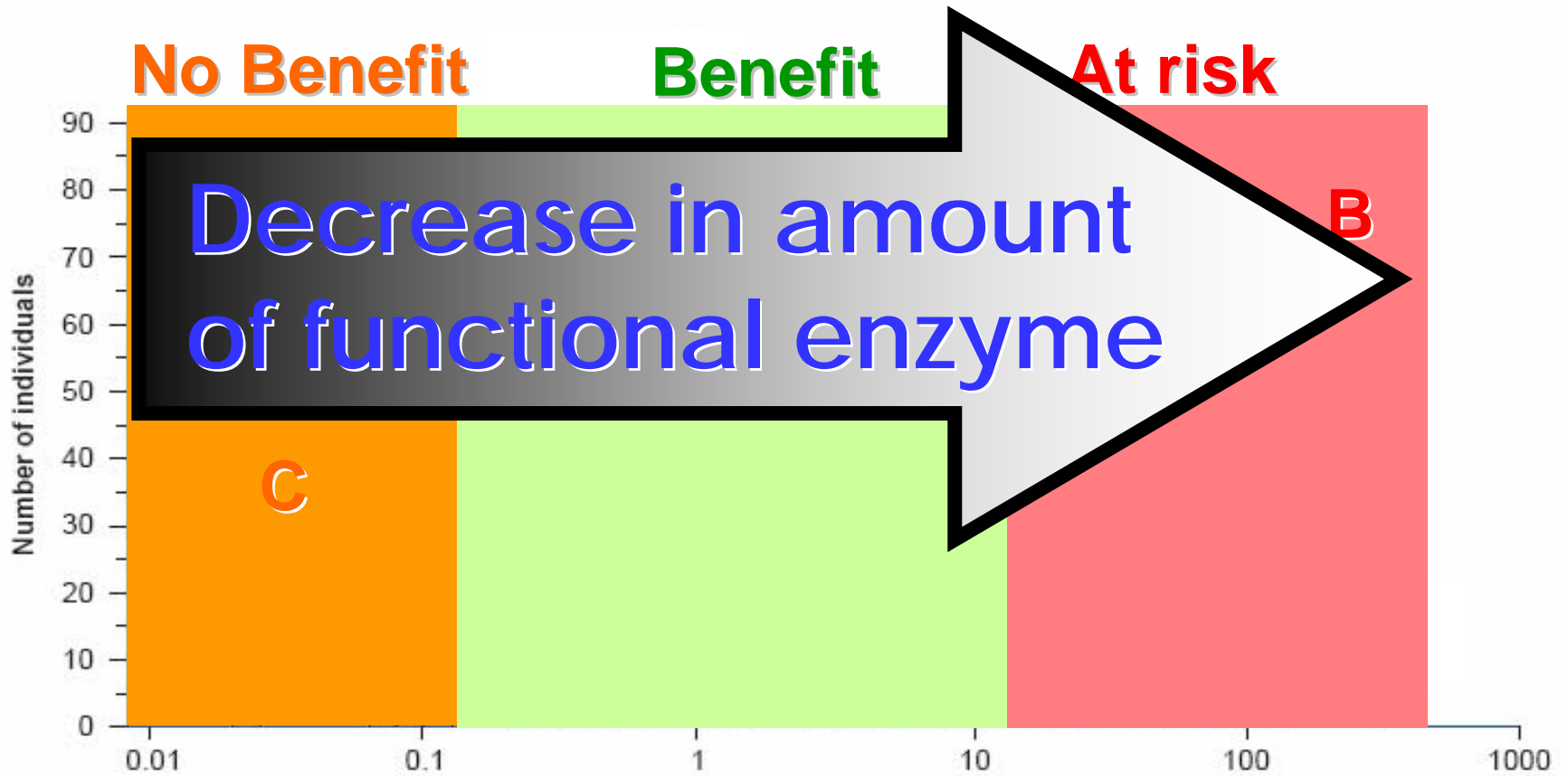


Form
(Amount) B

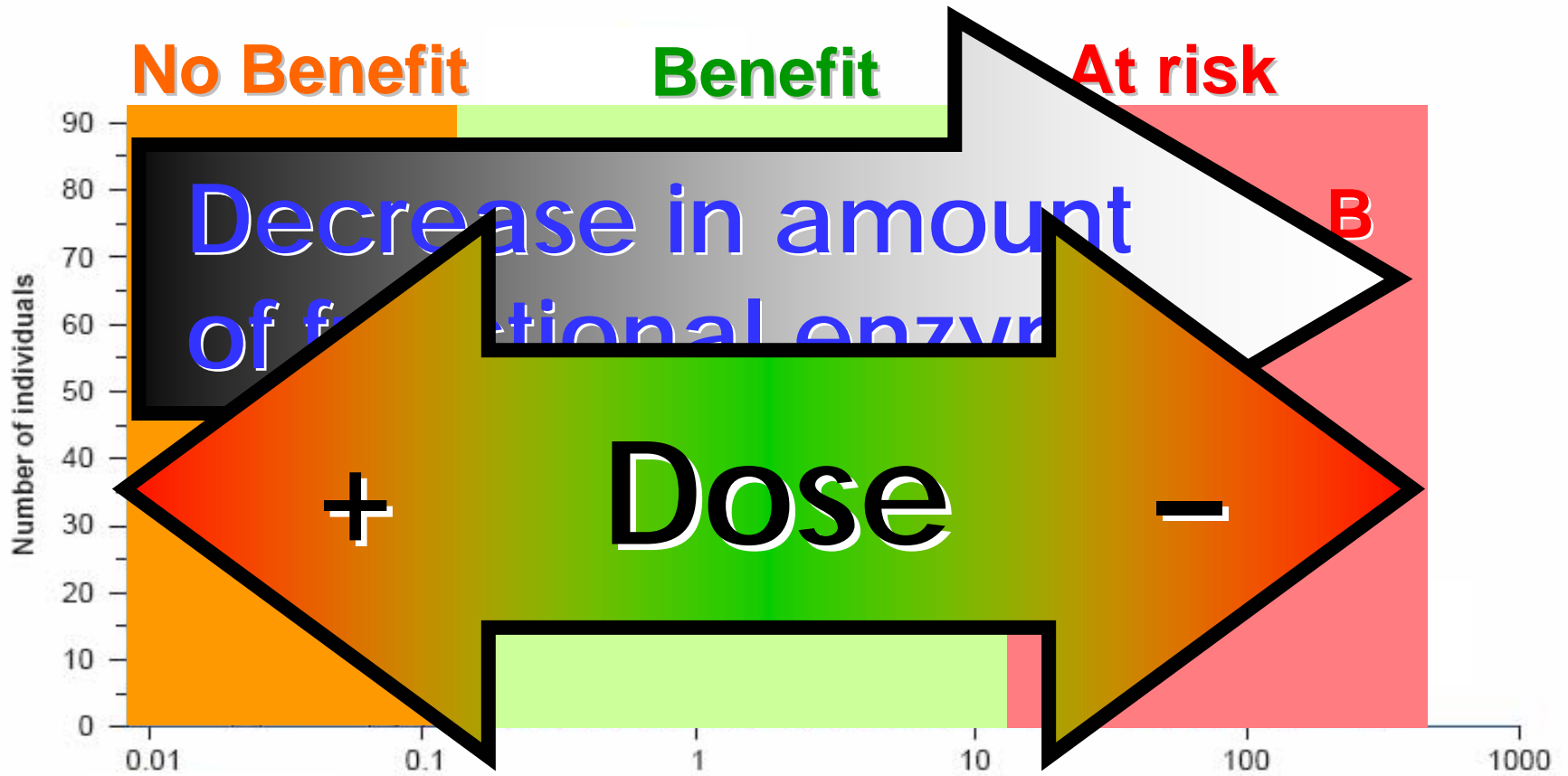
"Personalized" Therapy



"Personalized" Therapy



"Personalized" Therapy



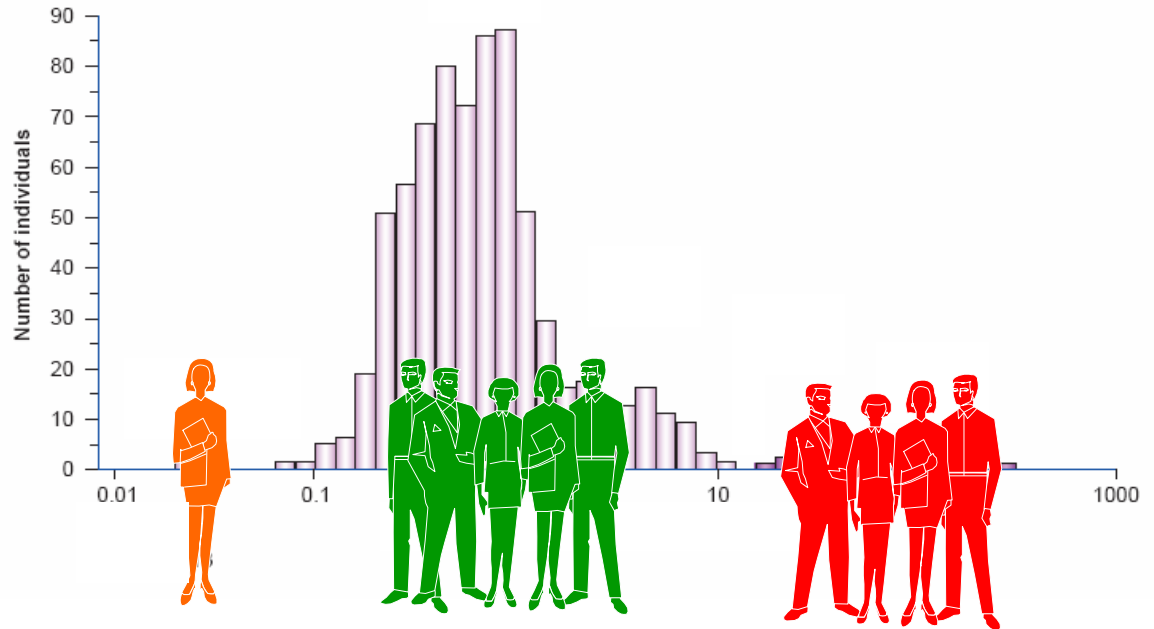
Which Dose Is Right For You?

Before:
Trial and Error



100mg

After: Pharmacogenomics-Driven



500mg

100mg

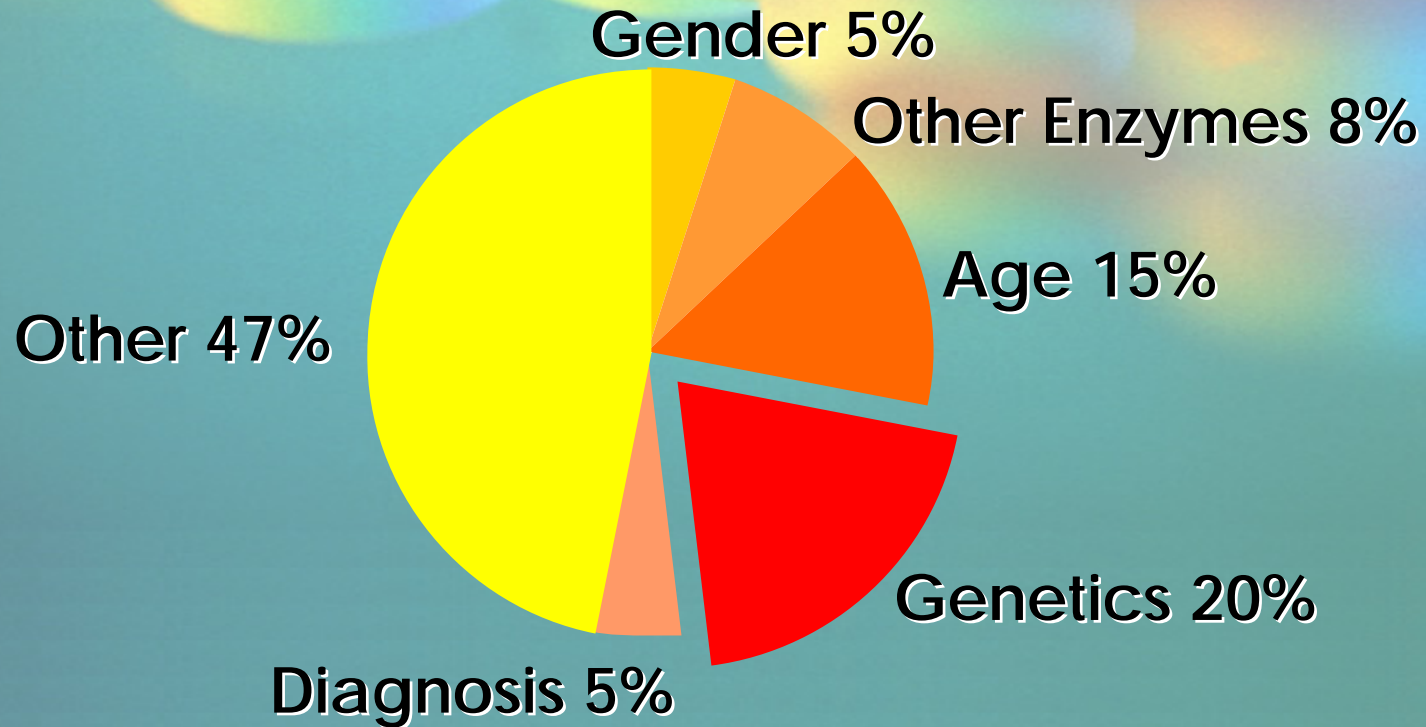
(10mg)

Daily dose has been “personalized”

What Does It Mean ?

- Knowing about genetic variability can:
- Identify **People at Risk (Safety)**
 - Can be excluded from treatment or treated at a lower dose, preventing risk of adverse events
- Identify **People with no benefit (Efficacy)**
 - If safe, can be prescribed a higher dose to reach therapeutic drug plasma levels

Genes Aren't Everything:



Is it better with Pharmacogenomics (or not) ?

21th Century Medicine:



Is This Drug For You ?

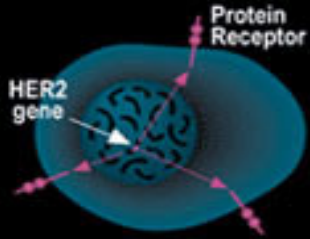
The background of the slide is a soft-focus image of several pills in various colors (yellow, blue, green) scattered across a light blue surface. The pills are out of focus, creating a bokeh effect.

“Targeted” Therapy:

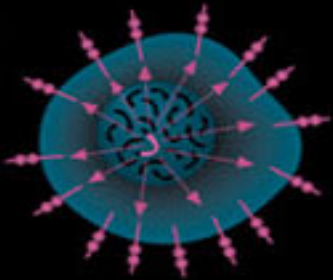
Personalized Medicine as a Means
to Identify Responders and Non-
Responders to Specific Therapies

Interaction of drugs with targets
they are “designed” for

Trastuzumab (Herceptin®)



In a normal breast tissue cell, the Her-2 gene is expressing cell surface receptor required for normal cell growth.



In certain types of breast cancers, the Her-2 gene is **over-expressing** this cell surface receptor, contributing to cancerous cell growth.

This is the case in ~30% of breast cancers.

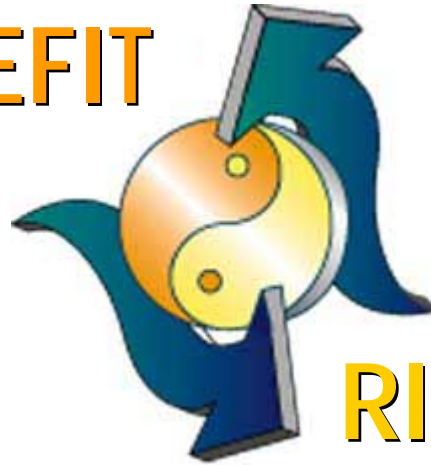


Herceptin (trastuzumab) is an antibody that blocks the cell surface receptor and thereby prevents further growth. As a result, disease progression is slowed down.

What Does It Mean ?

- Often, drugs are only effective in specific “sub-populations” (responders).
- Early identification of responders can have dramatic effect of treatment success.
- Treatment of non-responders puts these individuals at unnecessary risk of adverse events, while providing no benefit.
- Personalized Medicine allows the identification of responders and non-responders for targeted therapies. This is happening today!

BENEFIT



RISK

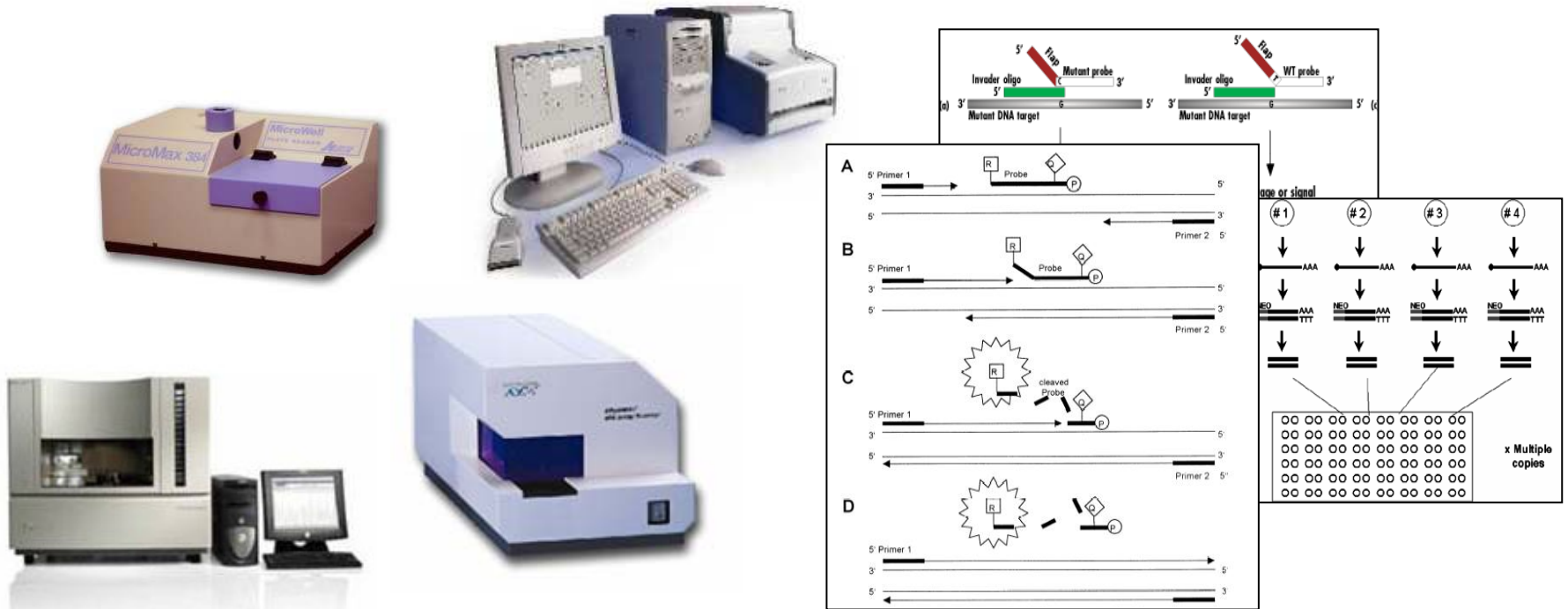
Adverse events
Alternative therapy
Cost

WHAT WOULD YOU DO ?

A hand in a white glove points at a glowing blue screen displaying a DNA microarray or gel electrophoresis image. The background is dark blue with a faint, glowing DNA double helix structure.

Reading the Genome: How to Avoid Trial and Error

Tools and Methods



Test/method must be:

- Analytically and clinically validated
- Clinically meaningful

New Tools for Personalized Medicine

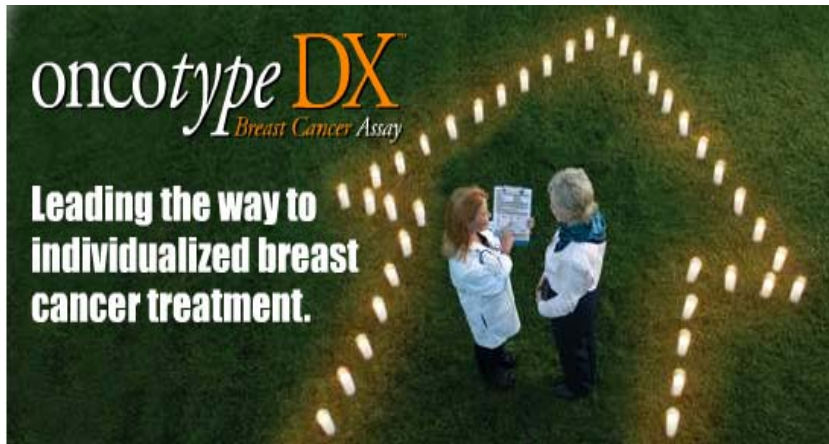


“FDA Clears Test for Patient DNA to Screen for Drug Effectiveness”

Wall Street Journal, January 11, 2005

- Chip measures alleles of CYP2C19 and CYP2D6
- Tool to reduce over- and under-dosing
- Estimated 20% reduction in adverse events

New Tools for Personalized Medicine

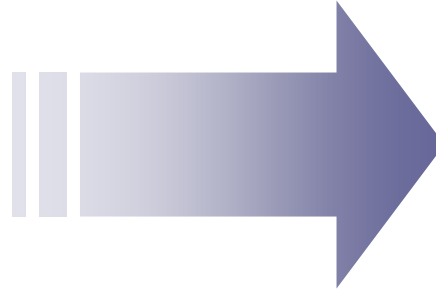
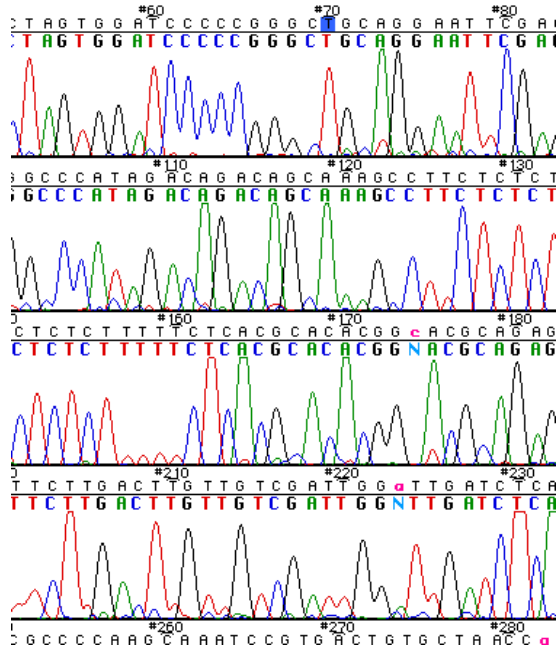


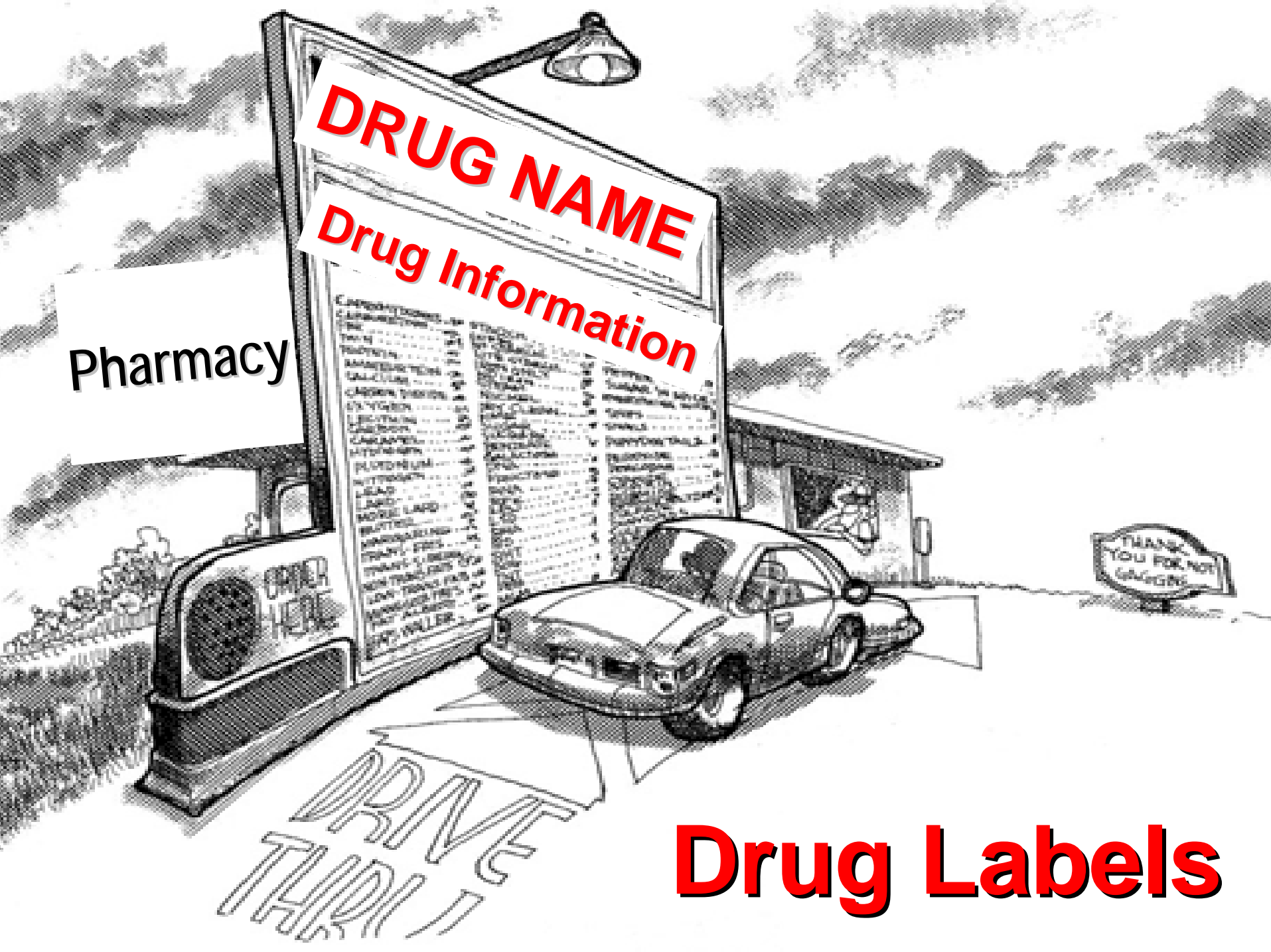
Gene expression profile of a panel of 16 cancer-related genes

NEJM (2004), 351:2817-26

- Predict risk of breast cancer recurrence (score: 1 – 100)
- Identify women who will benefit most from chemotherapy
- Avoid adverse events in those who will not benefit

Applying the Results in Clinical Practice





DRUG NAME

Drug Information

Pharmacy

DRIVE THRU

THANK YOU FOR NOT GAGGING

Drug Labels

DRUG NAME

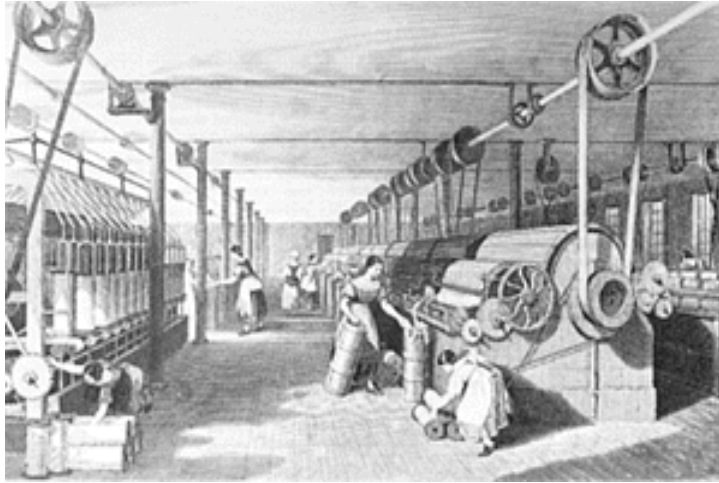
- (a) Description**
- (b) Clinical Pharmacology**
- (c) Indications and Usage**
- (d) Contraindications**
- (e) Warnings**
- (f) Precautions**
- (g) Adverse Reactions**
- (h) Drug Abuse and Dependence**
- (i) Overdosage**
- (j) Dosage and Administration**
- (k) How Supplied**
- (l) Animal Pharmacology and/or Animal Toxicology (if necessary)**
- (m) Clinical Studies/References**

DRUG NAME



**The best consumer is
an informed consumer.
Ask your doctor if it's
the right drug
at the right time
and the right dose
for YOU!**

A New Kind of Revolution



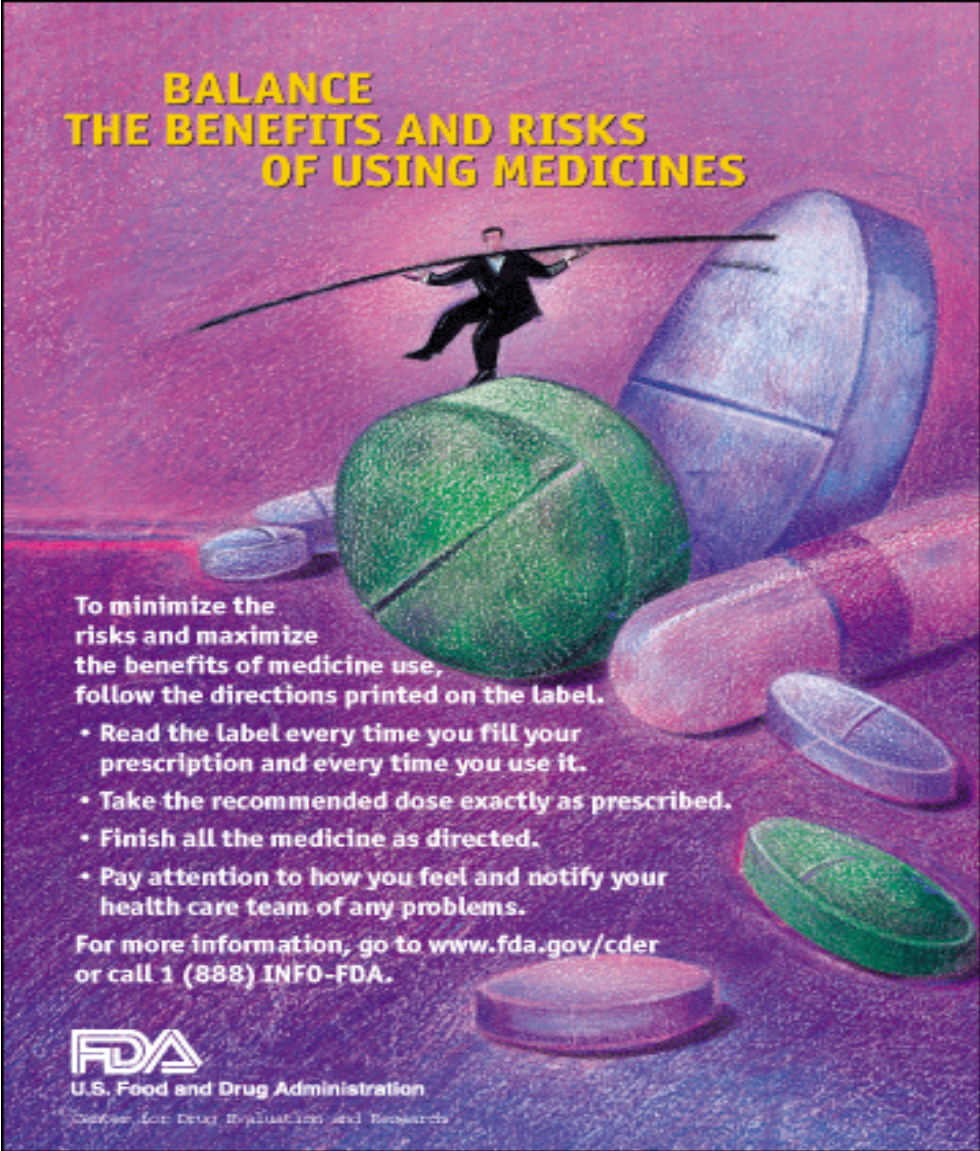
"Personalized Drugs"

- Herceptin (breast cancer, target: Her2/neu)
- Erbitux (colorectal cancer, target: EGFR)
- Tarceva (lung cancer, target: EGFR)
- Strattera (attention-deficit/hyperactivity disorder, Metabolism: P4502D6)
- 6-MP (leukemia, Metabolism: TPMT)
- Antivirals (i.e. resistance based on form of HIV)
- etc. and the list is growing rapidly ...

In Conclusion

- Genomics is changing modern medicine
- Not all drugs are for everyone:
the “one-size-fits-all” model is outdated
- The FDA is encouraging the use of
pharmacogenomics and is supporting its
translation into personalized medicine
- Drug Labels contain important information
- Educated consumers will benefit the most

BALANCE THE BENEFITS AND RISKS OF USING MEDICINES



To minimize the risks and maximize the benefits of medicine use, follow the directions printed on the label.

- Read the label every time you fill your prescription and every time you use it.
- Take the recommended dose exactly as prescribed.
- Finish all the medicine as directed.
- Pay attention to how you feel and notify your health care team of any problems.

For more information, go to www.fda.gov/cder or call 1 (888) INFO-FDA.



U.S. Food and Drug Administration

Center for Drug Evaluation and Research

www.fda.gov/cder/genomics