Personalized Medicine: What Is It? How Will It Affect Health Care?

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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?
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’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
How Can We Explain This Variability?
1865: Mendel
Experiments in Plant Hybridization - Inheritance

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 to 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”
“Dogma”
“Dogma”

1. DNA → Transcription → RNA
2. RNA → Translation → Protein
3. Replication
Gene Type ("Variation") A

Gene

mRNA

Enzyme

Drug X

Metabolite of Drug X

Form (Amount) A
Gene Type ("Variation") B

Gene

mRNA

Enzyme

Drug X

Metabolite of Drug X

Form (Amount) B
“Personalized” Therapy

No Benefit | Benefit | At risk

Number of individuals

0.01 | 0.1 | 1 | 10 | 100 | 1000

C | A | B
“Personalized” Therapy

No Benefit

Benefit

At risk

Decrease in amount of functional enzyme
"Personalized" Therapy

- No Benefit
- Benefit
- At risk

Decrease in amount of functional enzyme

Dose

Number of individuals

0.01 0.1 1 10 100 1000

0 10 20 30 40 50 60 70 80 90
Which Dose Is Right For You?

Before:
Trial and Error
100mg

After: Pharmacogenomics-Driven
Daily dose has been “personalized”

500mg 100mg (10mg)
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:

- Gender 5%
- Other Enzymes 8%
- Age 15%
- Diagnosis 5%
- Genetics 20%
- Other 47%

Is it better with Pharmacogenomics (or not) ?

21st Century Medicine:

Is This Drug For You?
“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
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 a dramatic effect on 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?
How to find genetic variations

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
Menu:
Hamburger  Fish  Taco  
Cheeseburger  Fries  Bouillabaise  
Dine In  Take Out  Dr Pepper  

Nutritional Data:

Burger Boy

Order Here

Thank You For Not Gagging

Drive Thru
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
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.

www.fda.gov/cder/genomics