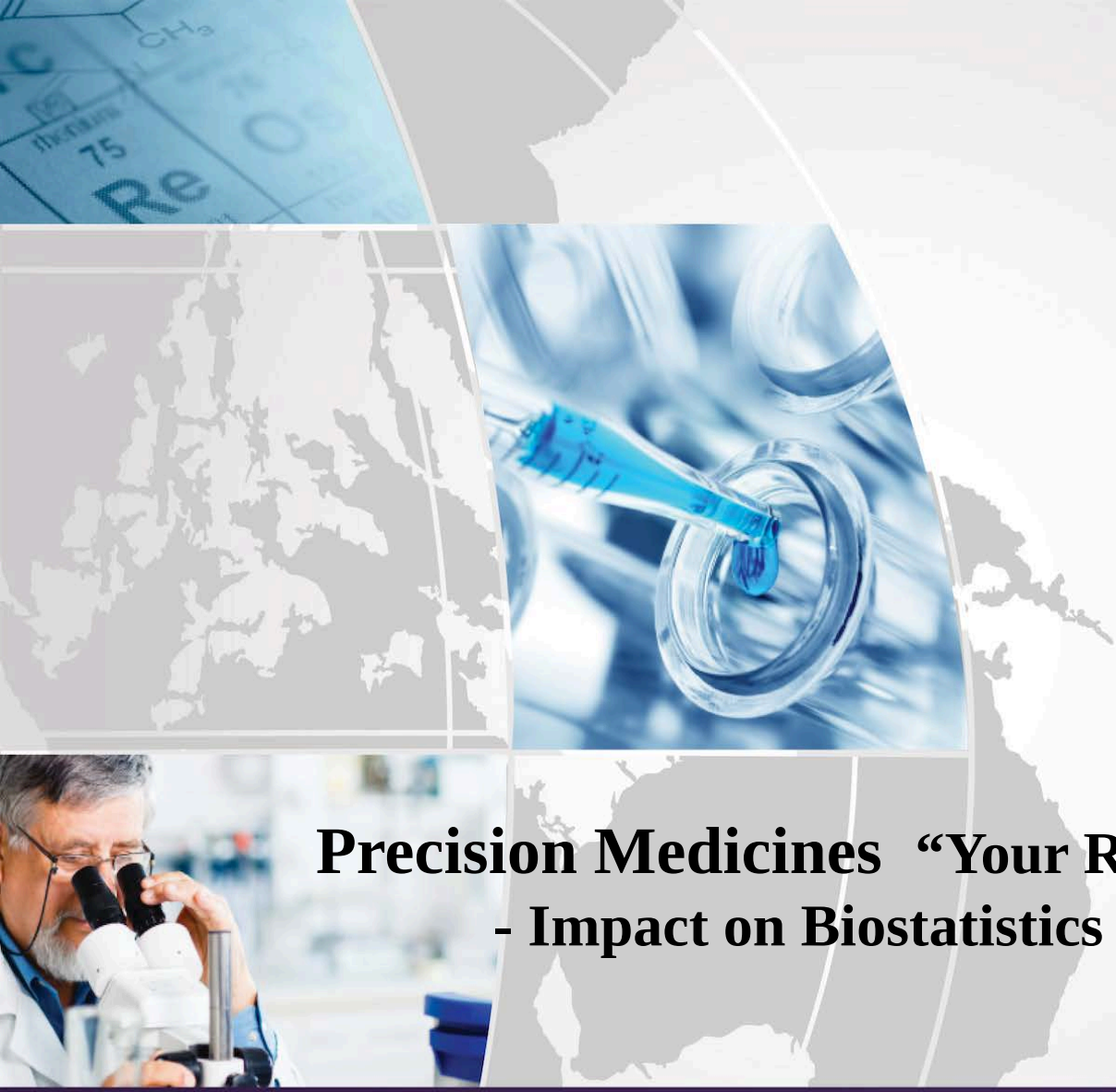


# Precision Medicines "Your Right to Right Medicines" - Impact on Biostatistics and Programming

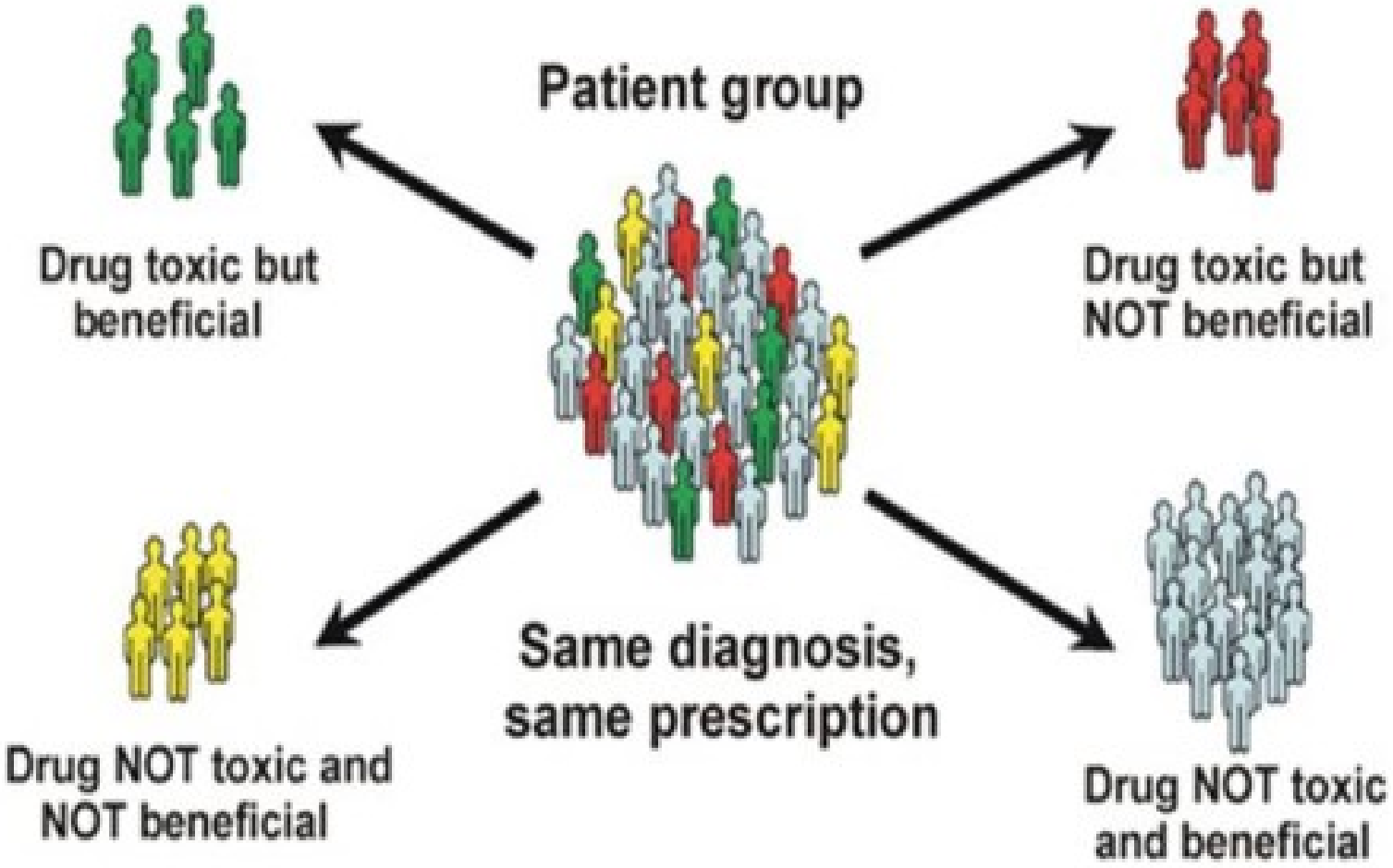
- Godfrey Machado

# Food for thought

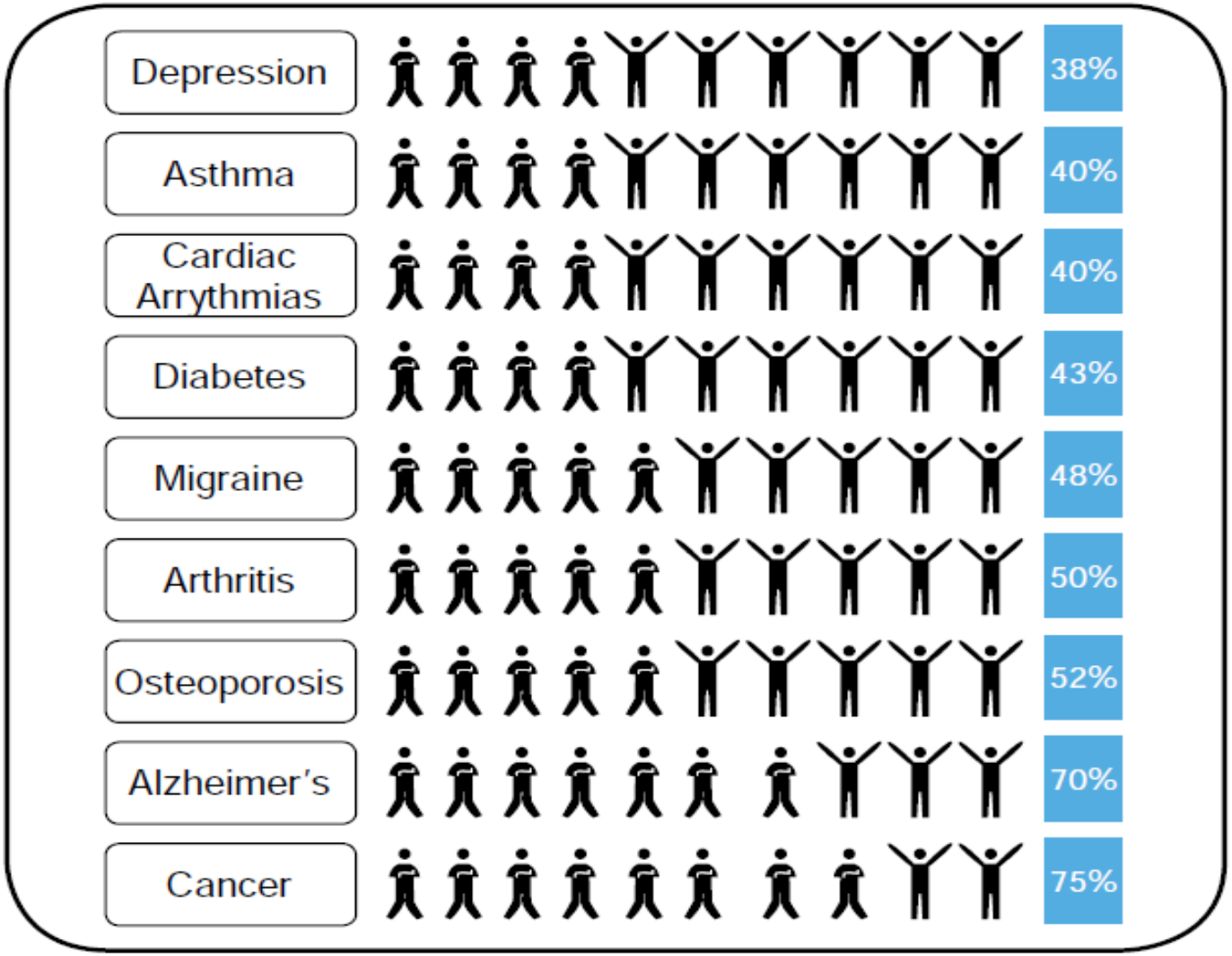
- *"It's far more important to know what person the disease has than what disease the person has".*

- "Clinicians have long observed that patients with similar symptoms may have different illnesses, with different causes; and similarly, that medical interventions may work well in some patients with a disease but not in others with apparently the same disease".

# Traditional clinical trial approach



# Percentage of patients for whom drugs are ineffective.



# Statistics on Adverse Drug Events:

- 82% of American adults take at least one medication and 29% take five or more. (CDC).
- Adverse Drug Events (ADE) cause over 700,000 emergency department visits each year. (CDC).
- Nearly 120,000 patients each year need to be hospitalized for further treatment (CDC).
- Over 100,000 people die each year due to adverse drug events (FDA).
- 4th leading cause of death, Ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents and automobile deaths (FDA).
- ADEs cause injuries or death in 1 of 5 hospital patients. (New England Journal of Medicine).

# Statistics on Adverse Drug Events:

- $3.5 billion is spent on extra medical costs dues to ADEs annually (CDC).
- 75% of the US population doesn't metabolize medications "normally" (FDA)
- Approximately 2.2 million adverse drug events occur annually in the U.S. (CDC)
- The FDA lists more than 100 drugs that have a Black box warning suggesting a PGX be performed prior to taking (FDA)
- 1/3 of all clinically significant drug interactions are caused by drug/gene interactions, not drug/drug interactions (CDC)
- ADVERSE DRUG EVENTS ARE PREVENTABLE

# Precision Medicines/ Personal Medicines/ Tailored Medicine..

*"The use of new methods of molecular analysis to better manage a patient's disease or predisposition to disease"*

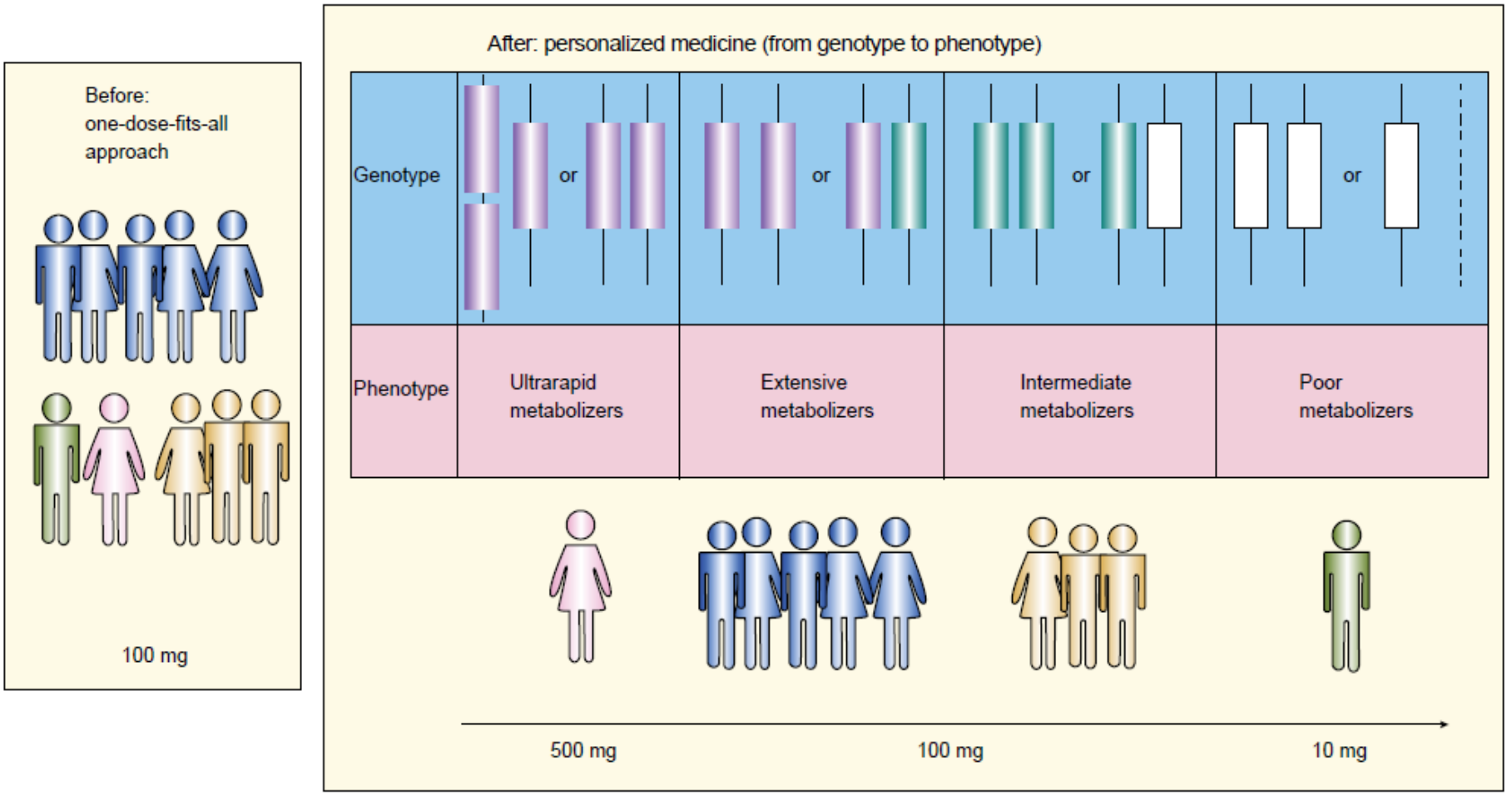
*"Providing the right treatment to the right patient, at the right dose at the right time." – European Union"*

*"The tailoring of medical treatment to the individual characteristics of each patient." – President's Council of Advisors on Science and Technology"*

*"Health care that is informed by each person's unique clinical, genetic, and environmental information." – American Medical Association*

*"A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease." – National Cancer Institute, NIH*

# Representation of the trial-and-error or one-dose-fits-all approach versus personalized medicine.



# Several “targeted therapies” approved in the past two years

- Kalydeco (G551D mutation) cystic fibrosis only 4% of cases in the United States (approximately 1200 people)
- Kalydeco is one of several “targeted therapies” approved in the past two years. Several cancer drugs – crizotinib, vemurafinib, dabrafenib, and tremetinib – have each been approved

Recent approval:

- Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah(TM) (CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice

# Pharmacogenomics

- “Pharmacogenomics” (PGx) – the study of variations of DNA and RNA characteristics as related to drug response

- Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.

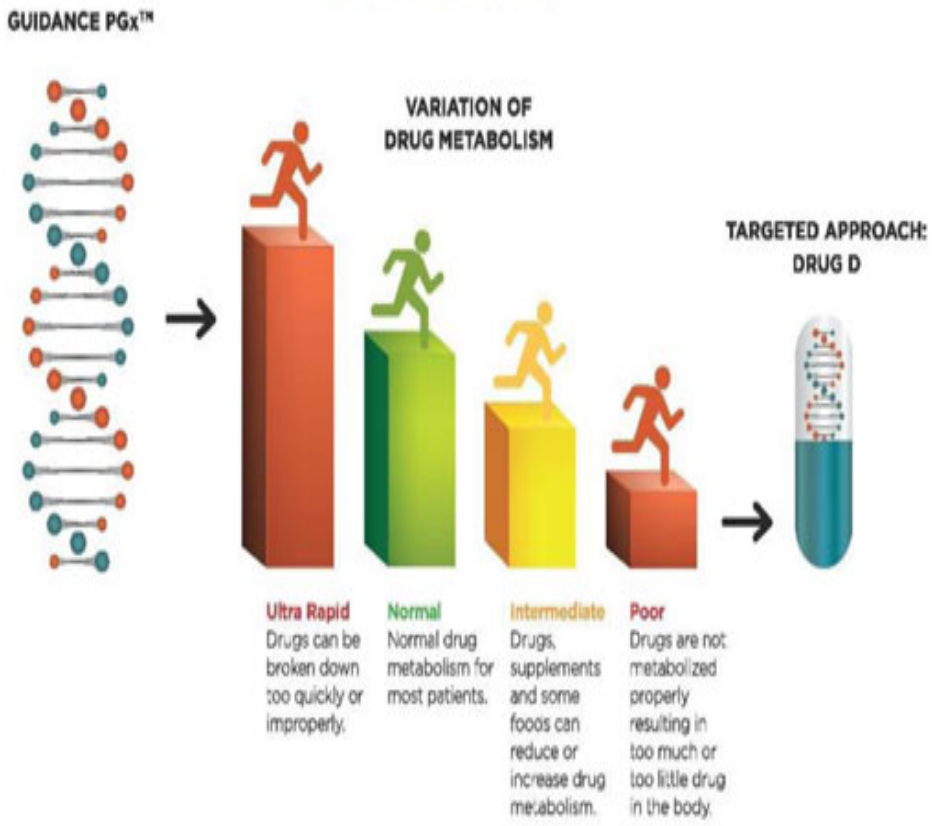
## What are the goals of Pharmacogenetic Testing?

- Avoiding serious Adverse Drug Reactions (ADRs) and drug-drug interactions
- Replacing traditional drug choice and dosage trial-and-error treatment plans
- Optimizing a clinician's drug choice based on a patient's unique genetic information
- Helping decrease overall healthcare costs

## What are the benefits of Pharmacogenetic Testing?

- Increased Patient Safety
- Improved Patient Outcomes
- Decreased Adverse Drug Reactions
- Patient Relief, Life Improvement, Life Saving
- Lower Patient Medication Expenses
- Lower Healthcare Costs
- Selection of appropriate medication therapy
- Maximize drug efficacy
- Protection from non-productive toxic medication treatment

# Genotype Based Treatment

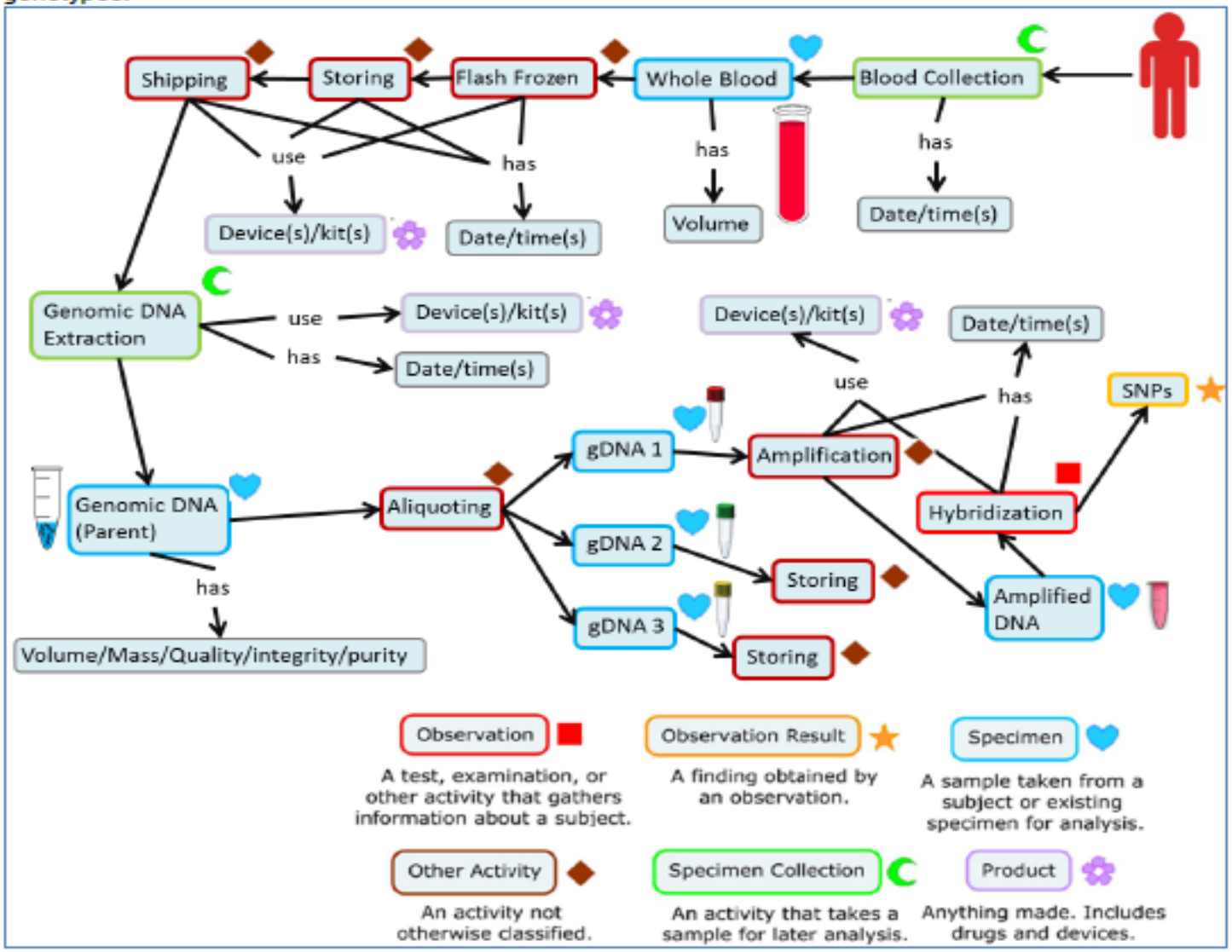



# PHARMACOGENOMICS

Data collection

Standards

Figure 1. Sample handling and preparation process from collection of whole blood to identification of genotypes.



# PGx domains

Table 1. Data category and domain class for PGx datasets.

| Class / Category | General Observation Class | | Special-Purpose |
|---|---|---|---|
| | Event | Finding | |
| **Data about biospecimens** | BE | BS | RELSPEC |
| **Data about genetic observations** | | PF, PG | |
| **Data that define a genetic biomarker or assign it to a subject** | | | PB, SB |

**PGXIG1.0 IS DESIGNED TO ACCOMMODATE THE FEATURES OF PGX STUDY**

# PGx domains

**Data about Bio specimens**

BE – The Bio specimen Events

BS – The findings related to specimen handling

RELSPEC – the Related Specimens domain documents the hierarchy of specimen relationships.

# PGx domains

**Data about Genetic Observations**

PF – Data about genetic observations is included in Pharmacogenomics/Genetics Findings domain.

PG – Pharmacogenomics/Genetics Methods and Supporting Information domain holds the methods, algorithms and parameters used in the analysis.

# PGx domains

**Data that define a genetic biomarker or assign it to a subject**

PB – The Pharmacogenomics/Genetics Biomarker domain

SB – the Subject Biomarker domain connect biomarkers observed in PF domain with the medical conclusions documented in the PB domain for each subject.

# Statistical aspects

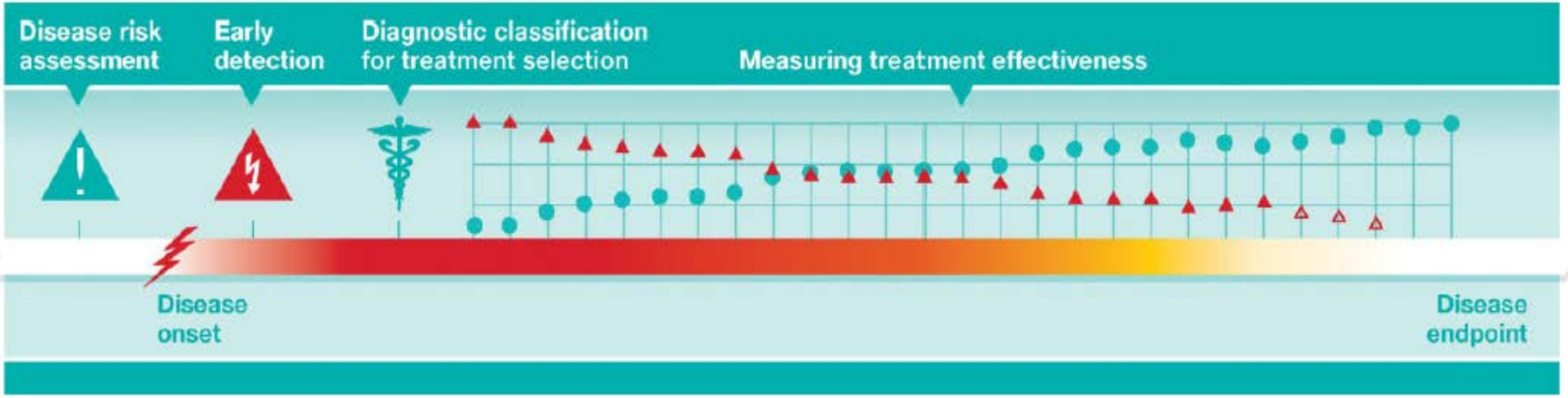
Development and Validation of the Biomarkers

Trial designs (BASKET, UMBRELLA, SUPER UMBRELLA/ CUSTOM)

Patient recruitment

# Development and Validation of the Biomarkers

Use of Statistical principals and methods to minimize the Bias and maximize the Precision




Early detection vs Disease risk assessment

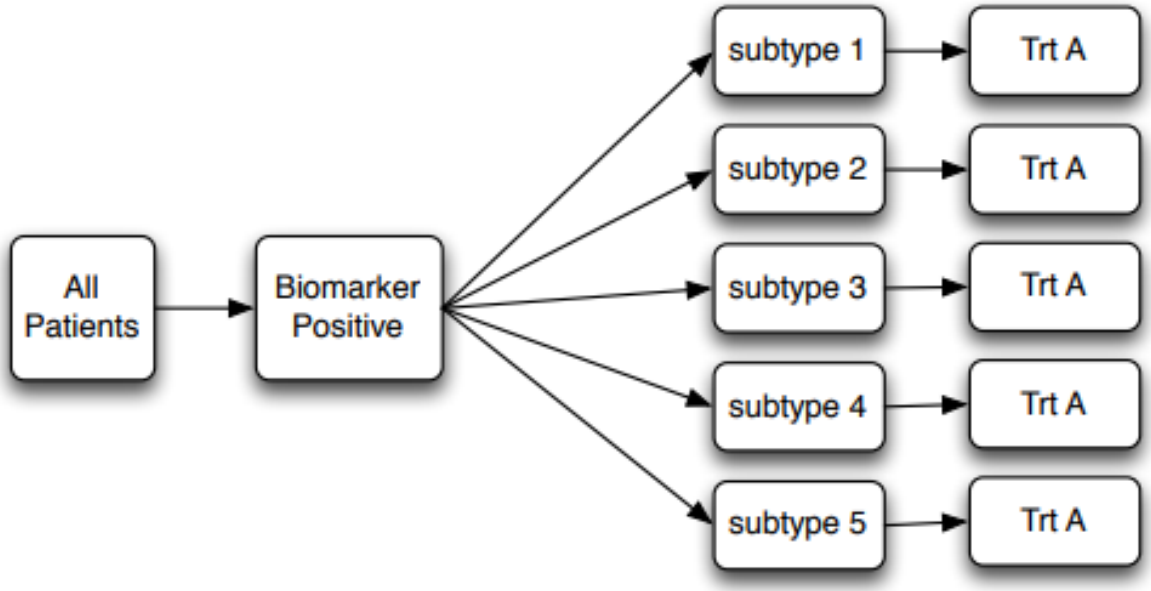
# Trial Designs: Umbrella and Basket Trials

Basket Trials Single treatment and single biomarker, different histologies placed in baskets

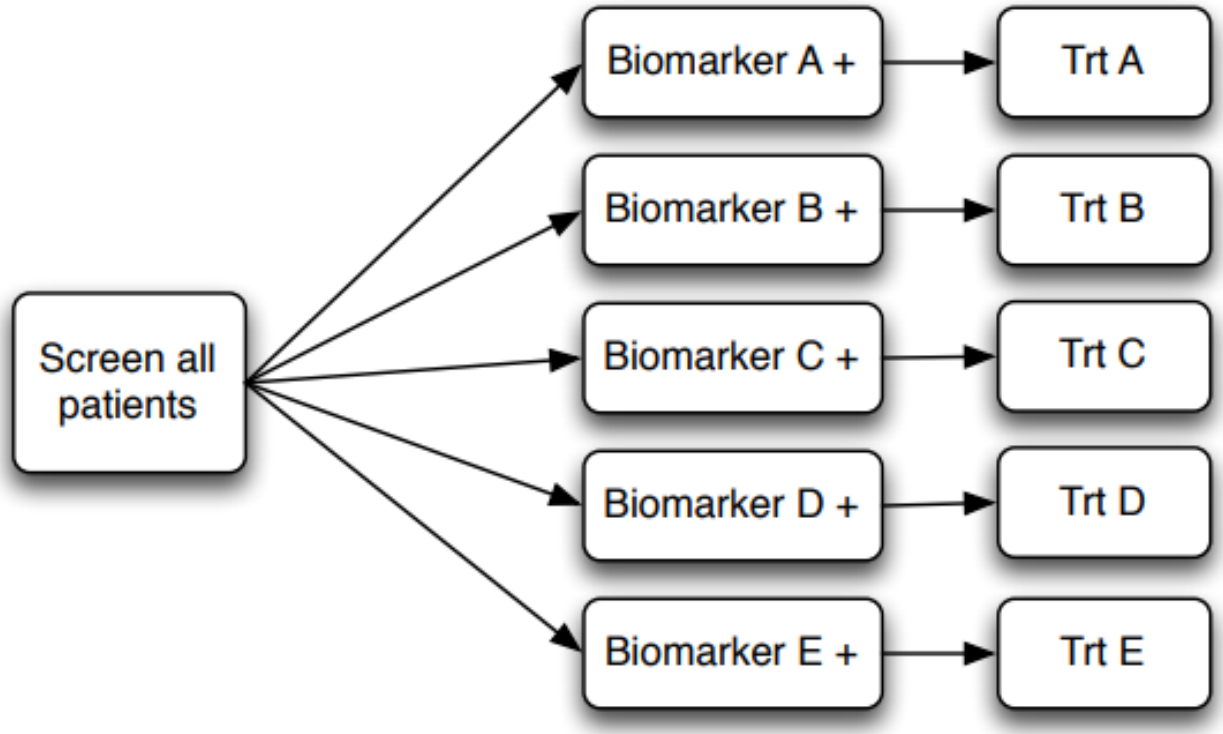
Umbrella Trials Single histology, multiple biomarkers each matched to treatments

# Basket Trials

If the interest is in the effect of a specific treatment within a biomarker positive subgroup, a basket (or bucket) trial is an option



# Umbrella Trials




In contrast to basket trials, the umbrella trial evaluates many treatments within a single histology. A multiplex assay is used for treatment arm eligibility. Each arm is a biomarker enrichment design.

# Super Umbrella Trials

The combination of the bucket trials and the umbrella trials creates the "Super Umbrella Trials"

The design is the same as the Umbrella trials, but open to multiple histologies. Examples are the NCI-MATCH study and the CUSTOM study

# Importance of subgroup analysis

Role of subgroup analysis is elevated from secondary/sensitivity analysis to Primary

We will have more subgroup analysis comparing the safety and efficacy results as per different

# Patient recruitment

Subjects grouped as per PGx.

Homogeneity in patient characteristics to reduce the Sample size for the trial

# Do we need region specific trials in future?

Migration of global population makes region impact secondary against genotype categorization

Can supportive or exploratory trials suffice the requirement?

# References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- Genomic biomarkers in predictive medicine An interim analysis- Richard Simon
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# Information for further communication

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Thank You


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