





# **Why do clinical trialists want to collect samples: industry perspective**

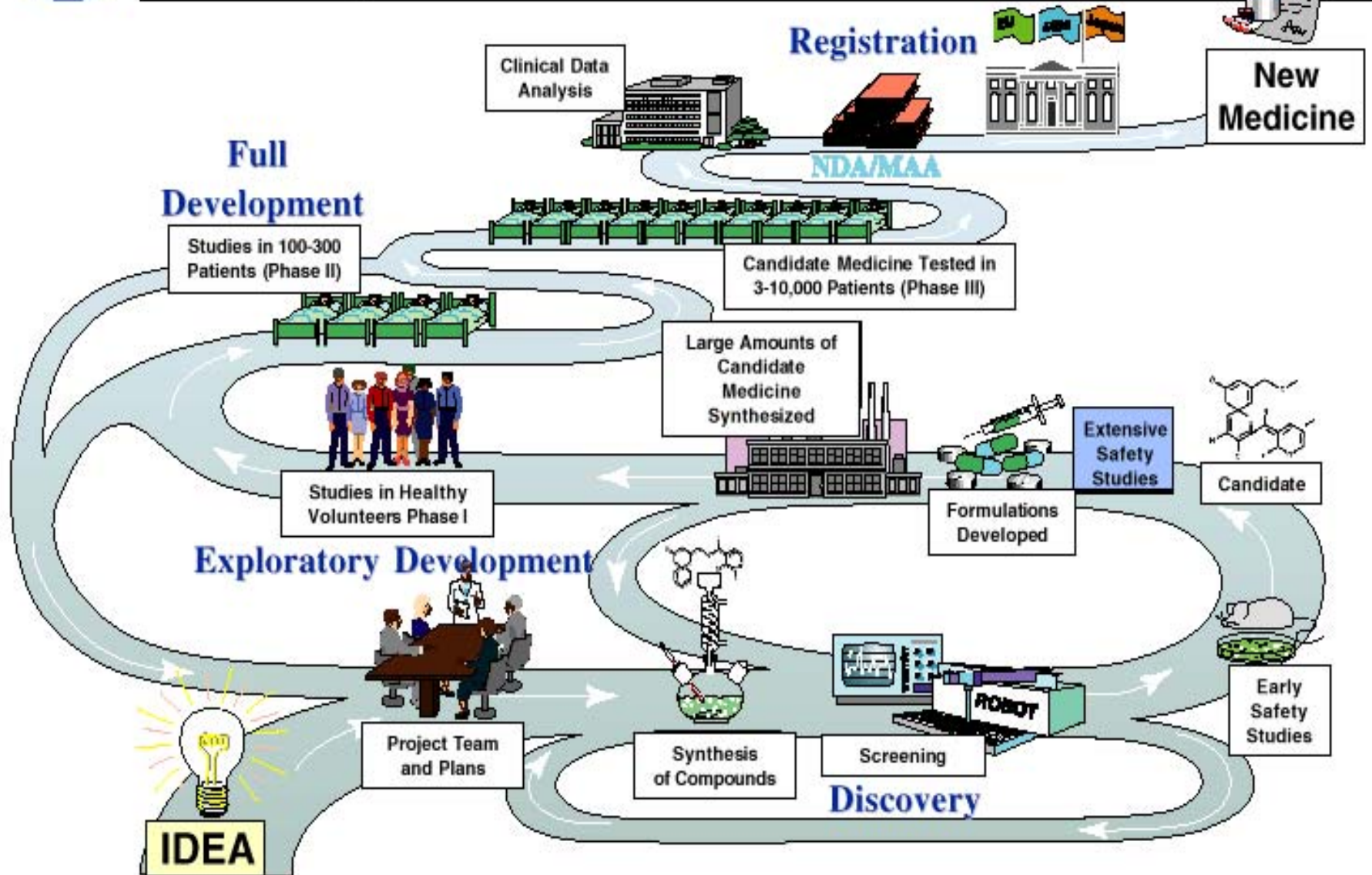
**Anne Heatherington, PhD  
Pfizer Ltd**

# Outline

- Background from an industry perspective
- Types of sample collection
- Examples of application in drug development
  - Genomics
  - Safety biomarkers
- Pfizer's biobank



# The Long Road to a New Medicine



# Key Areas of Understanding Needed

## Safety

Will signal in animals be seen in healthy volunteers?

Will it be worse in patients?

Is there a mechanistic rationale?

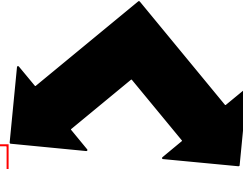
## Efficacy

Why do some people develop the disease?

What drives disease severity?

What distinguishes responders from non-responders?

# Variation

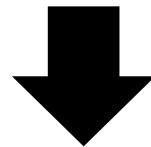


## Safety

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## Efficacy

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**Target selection and patient selection**

# Variation



Humans are 99.9% identical to each other

- it is the 0.1% that creates individual differences

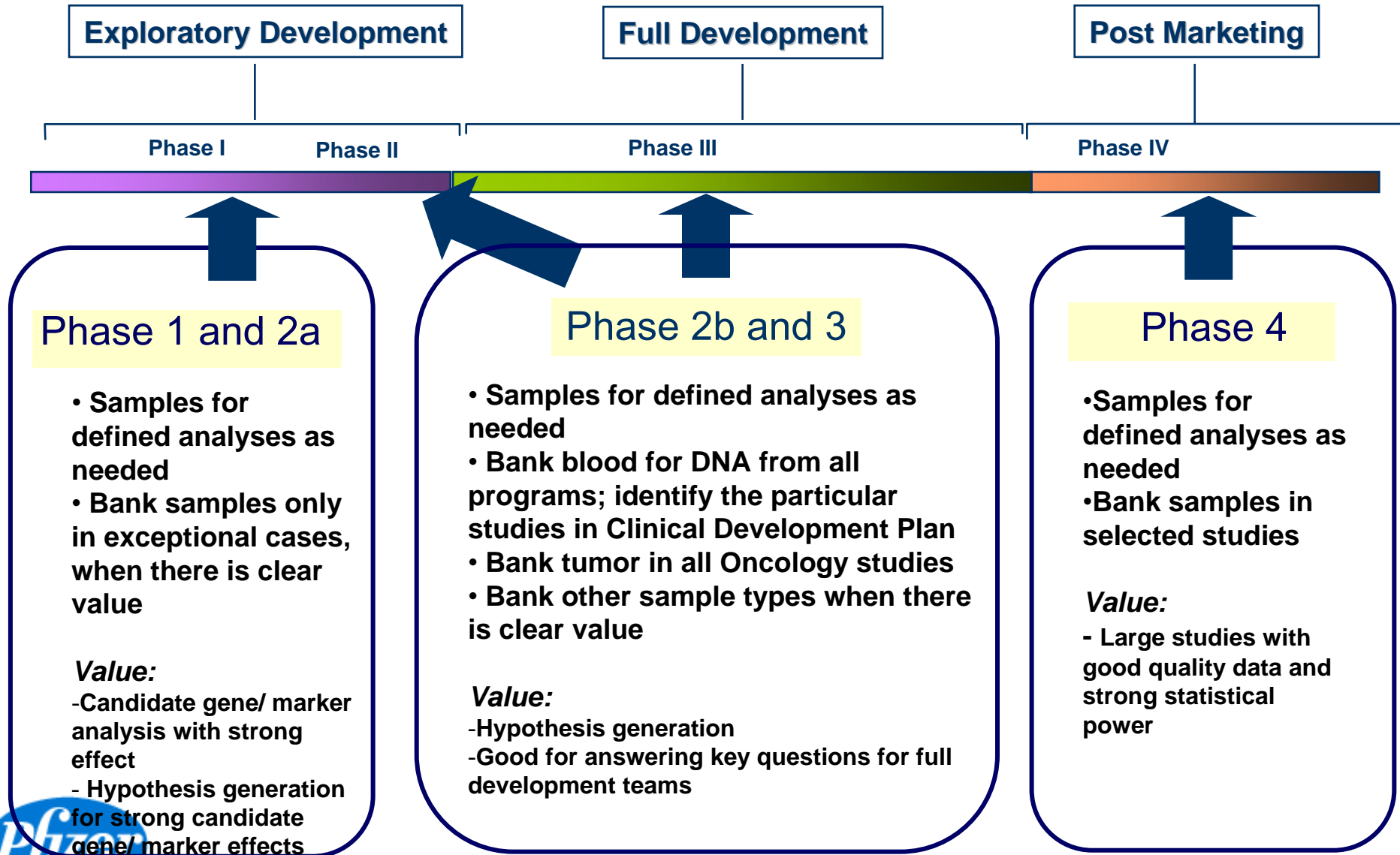
- estimated to be about 10 million common single nucleotide polymorphisms

# Clinical Trials Sampling Strategy

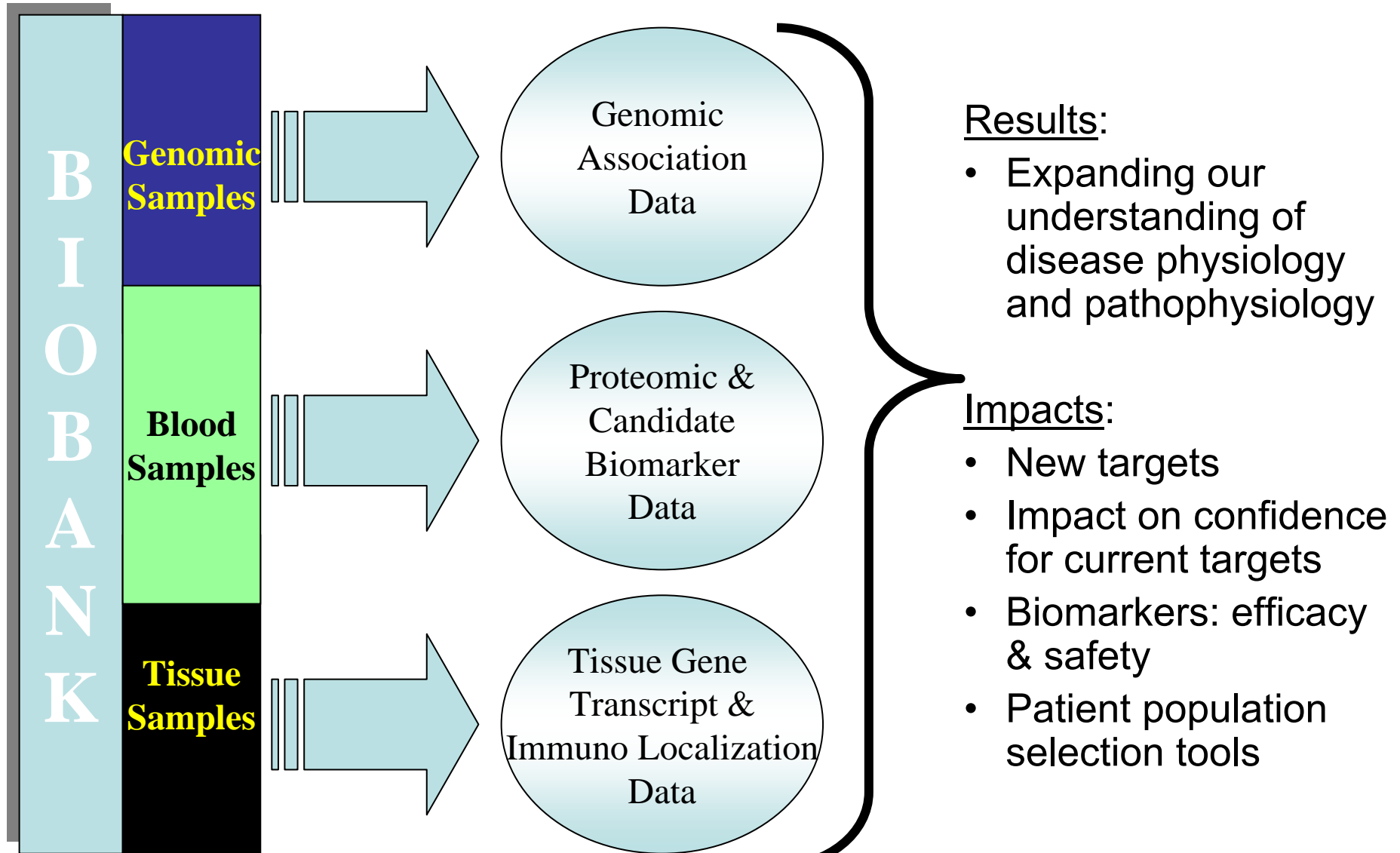
Within a protocol, two independent sample collections

- ***Defined Measures:*** Allows for performance of pre-specified assays (validated or not) which are part of the clinical protocol , eg changes in a pharmacodynamic marker
- ***Exploratory Research:*** Allows for the investigation of known and novel biomarkers for future research and is not part of the specified research described in the clinical protocol (anonymized)

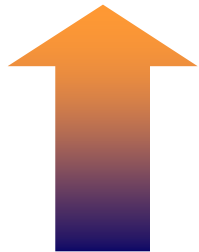
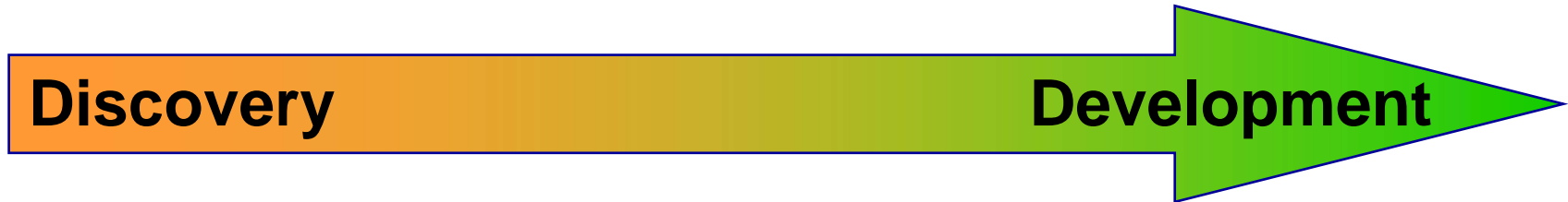
# The Value of Sampling in Clinical Trials



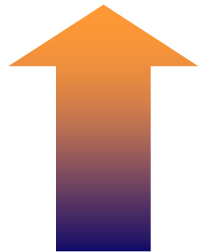
# Use of Samples to Facilitate Drug Discovery



# The Application of Pharmacogenomics



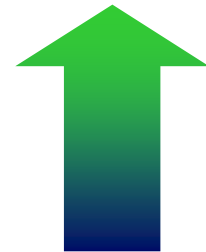
Increase C.I.R. and target selection by using human genetics to understand disease etiology



Evaluate how common variants in the target will influence the efficacy of the compound

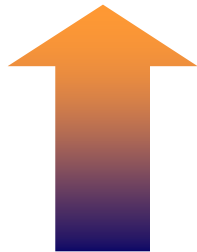
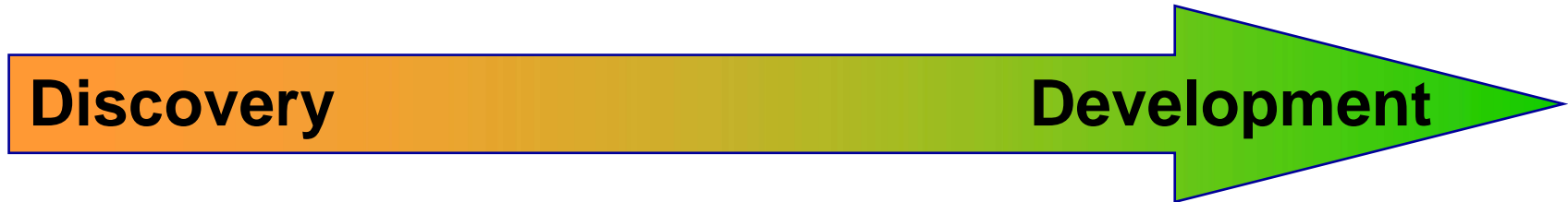


Select subjects or stratify populations in early efficacy studies to improve quality of decision making



Prediction of efficacy and adverse events based on a subject's genotype

# The Application of Pharmacogenomics



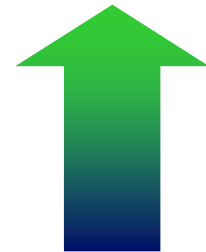
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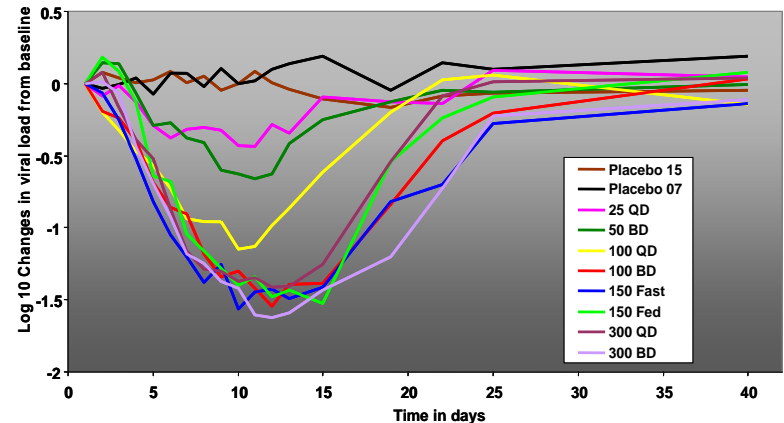
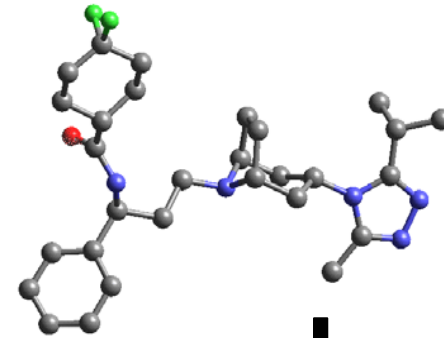
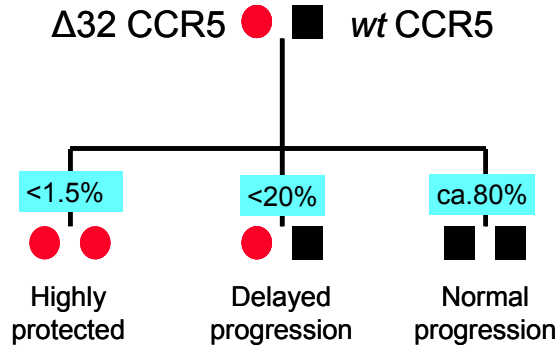
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# Genomics & Target Selection: Maraviroc

Impact of genotype on HIV disease progression provides rationale for target



**approved treatment for CCR5-tropic HIV-1 infection**



# Genomics and Drug Response: statins

- Sample collection is critical in Ph2/3/4 for retrospective analysis of adverse events and drug response, as well as exploratory biomarker work. Data can be used for patient stratification and Personalized Medicine.
- Example: Statin response
  - Statin therapy substantially reduces the risk for cardiovascular disease in multiple patient subgroups
    - wide inter-individual variation: plasma lipoprotein response and clinical outcome.
  - Incidence of AEs per 100,000 patient years is 5150 for minor muscle pain, 97 for myopathy, and 4.4 for rhabdomyolysis.
  - Genome-wide association studies may yield a set of markers for predicting statin efficacy and muscle toxicity.
    - Combining data from several large studies can and has been used to increase power, especially when effect size is small

**RESULT:** The identification of a novel locus for statin response by combining samples from 3 statin trials (PLoS, in press)

# Using Clinical Trial Samples to Identify Safety Biomarkers

## PGRD Safety Councils

Provide access to Pfizer's internal experts

Leverage portfolio experience to enable consistent risk management strategies

Support activities to influence the external environment

Develop integrated preclinical & clinical research strategies

→ Safety Biomarkers



## IMI SAFE-T consortium



## Qualification of Translational Safety Biomarkers

- 36 M € research budget over 5 yrs
- Kick-off meeting June 2009

## Goals

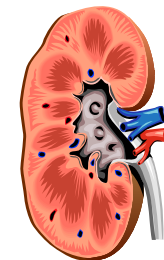
- Evaluate safety biomarkers to monitor organ safety in humans
- Develop assays & devices for clinical applic<sup>n</sup>
- Compile enough evidence to qualify safety biomarkers for regulatory decision making
- Gain evidence for how safety markers may be used in disease diagnosis & clinical practice

# Organs Susceptible to Drug-induced Injury

Focus on organs with less than ideal clinical monitoring

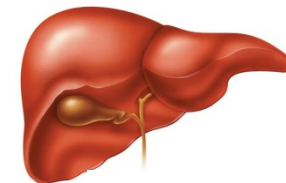
**Kidney:** Current standards (Serum Creatinine, BUN) are only increased when 50-60% of the kidney function is lost

Better kidney safety markers → monitoring for early signs of damage  
→ permit more experimental drugs to be taken into the clinic



**Liver:** Current standards such as transaminases are not specific and do not predict who will recover and who will develop fulminant hepatitis or cirrhosis

Better liver safety markers → early signals of liver damage  
→ adapt to drugs  
→ idiosyncratic DILI



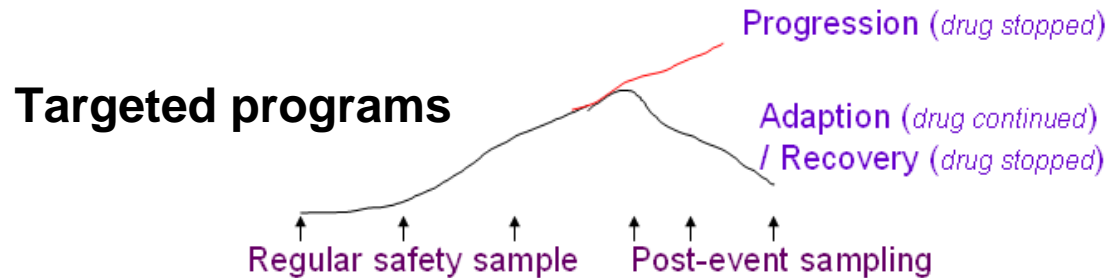
**Vascular System:** preclinical vascular injury → lack of understanding of translatability to humans → lack of specific & sensitive biomarkers to monitor risks to humans → compounds deprioritized for uncertain and/or unmanageable risk

Better vascular safety markers → permit more experimental drugs to be taken into the clinic

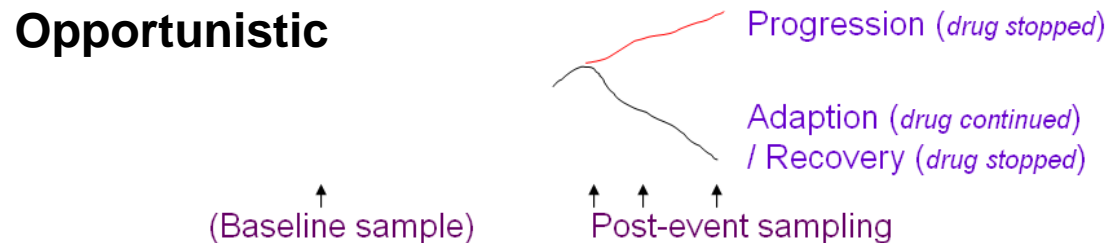


# Sample Collection Proposal (March 2010)

1. Collect a baseline blood sample from **all patient studies** to assess population variability associated with disease/gender/age/ethnicity/concomitant medication
2. Collect an additional blood sample when regular safety monitoring is included in a study due to a previously observed signal or an anticipated signal

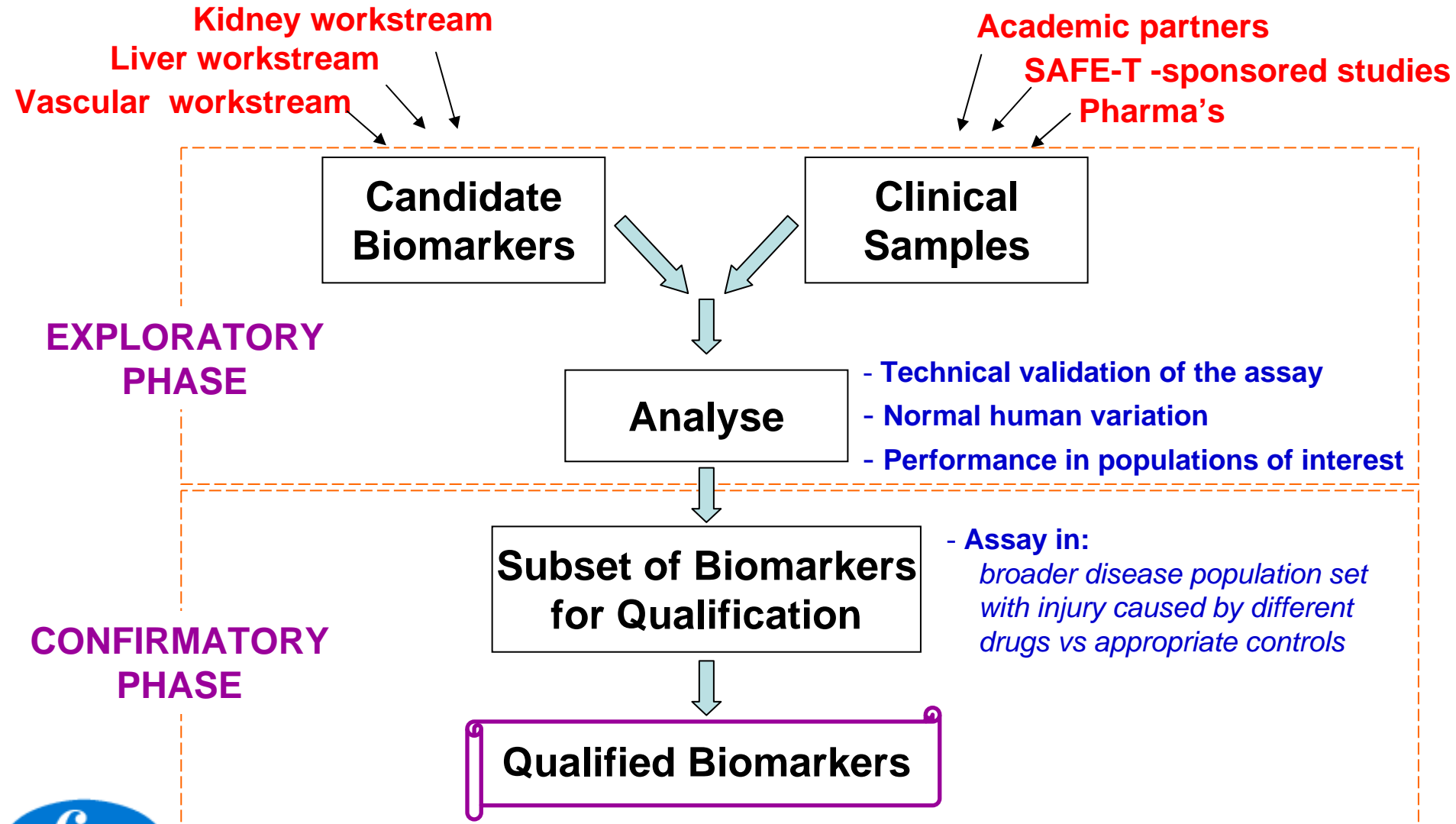


3. Collect an additional blood sample when safety monitoring is initiated after patients exceed specific trigger levels – *expect few in number, but valuable*



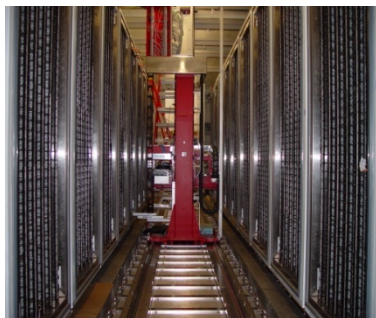
# How samples will be used?

## Clinical Safety Biomarker Qualification Process

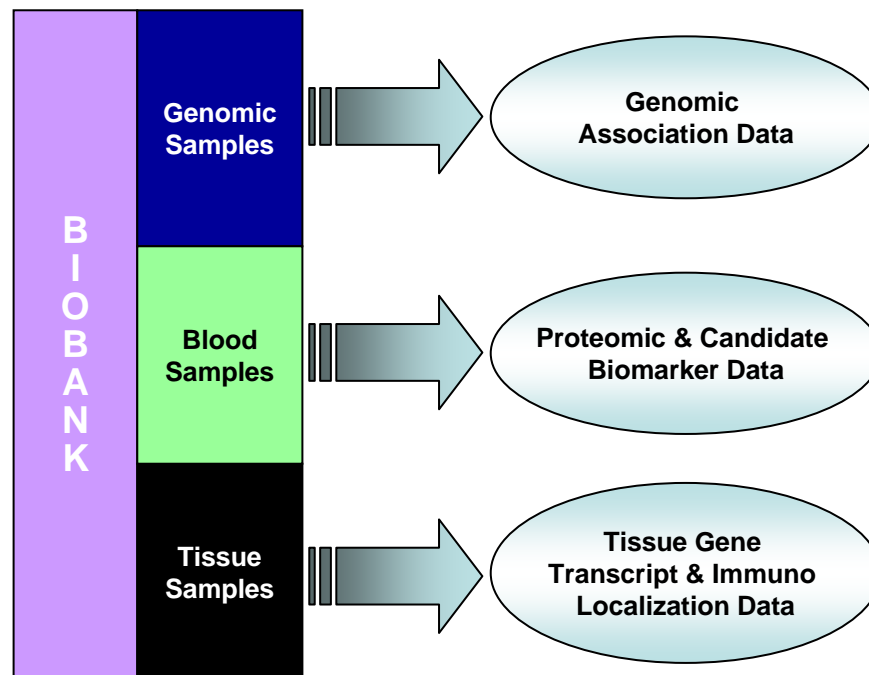


# Combining Scale And Innovation

In July 2006, Pfizer opened its state-of-the-art BioBank. This repository stores human biospecimens collected from Pfizer clinical trials and provides scientists with access to human samples for research into disease and drug response as well as for discovering and validating new biomarkers.



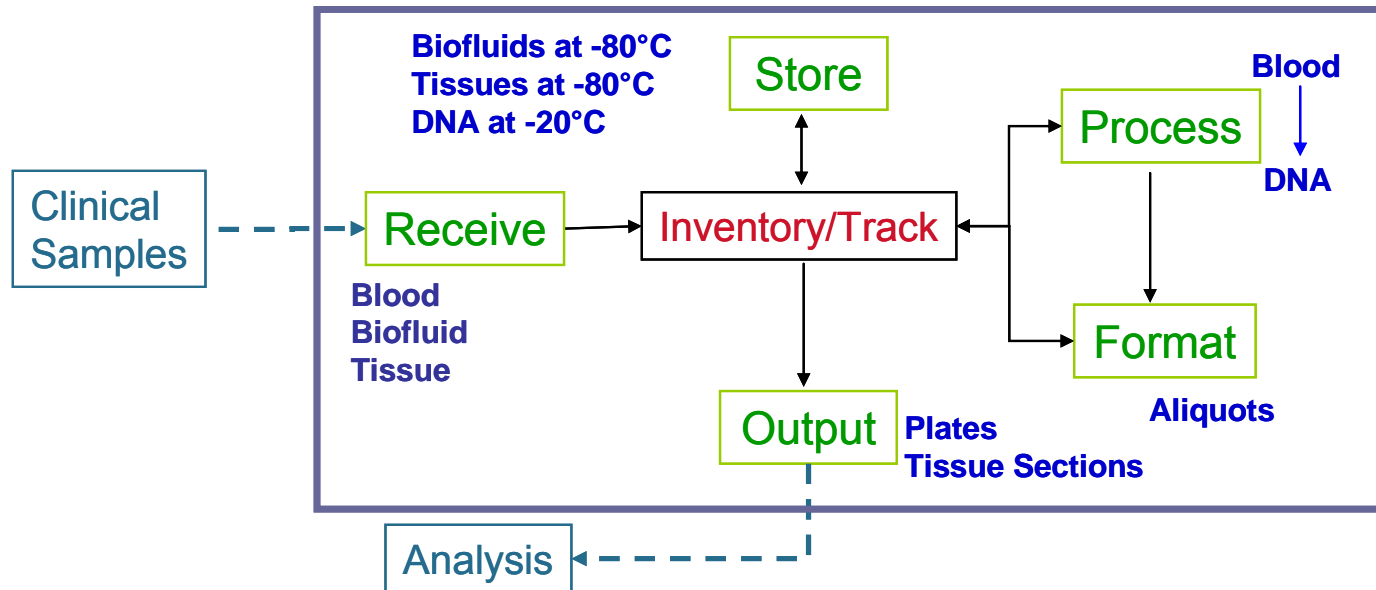
- Pfizer's BioFluids Bank is the world's first fully automated large scale storage and retrieval system at -80°C
- Automated extraction and storage of DNA
- Capacity:
  - 2.6 MM tubes at -20°C (DNA)
  - 5.4 MM tubes at -80°C (biofluids)



Our world class BioBank enables research to better understand diseases and drug response, and discover, develop and validate biomarkers

# BioBank

A state-of-the-art facility to process, store and distribute DNA, biofluids & tissues



**DNA & Biofluids Inventory:**  
~150,000 DNA samples across various disease areas  
~ 10,000 biofluids samples

linked via a single sample mgmt & ordering system

**Tissue Bank Inventory:**  
~12,000 frozen blocks and paraffin embedded tissues

# Pfizer BioBank Value

- Supports research on drug response, disease and biomarkers
- Enables applications of emerging technologies for 'wet' biomarkers
- Connects researchers to a large inventory of high quality samples from clinical trials, collaborations and vendors
- Frees scientists from practicalities of custodianship of samples, including ethical oversight
- Bulk storage of samples with long-term value to multiple users
  - not a storage facility for samples that cannot be housed elsewhere due to space limitations
- Potential role in external collaborations, consortia and regulatory filings
- Adds more value from clinical trials
- Cost-efficient and reliable global resource
- Vehicle to promote best practices



# Our hypothesis

## Logistics

- Biobank
- Protocol
- Informed consent

## Scientific methods

- Gene identification
- Protein assessment
- Bioanalytical capability

**Questions re**  
variation in  
efficacy and  
safety

**Improve target and patient selection**