Emerging Genetic Technologies and their Medical and Public Health Applications

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Emerging Genetic Technologies and their Medical and Public Health Applications

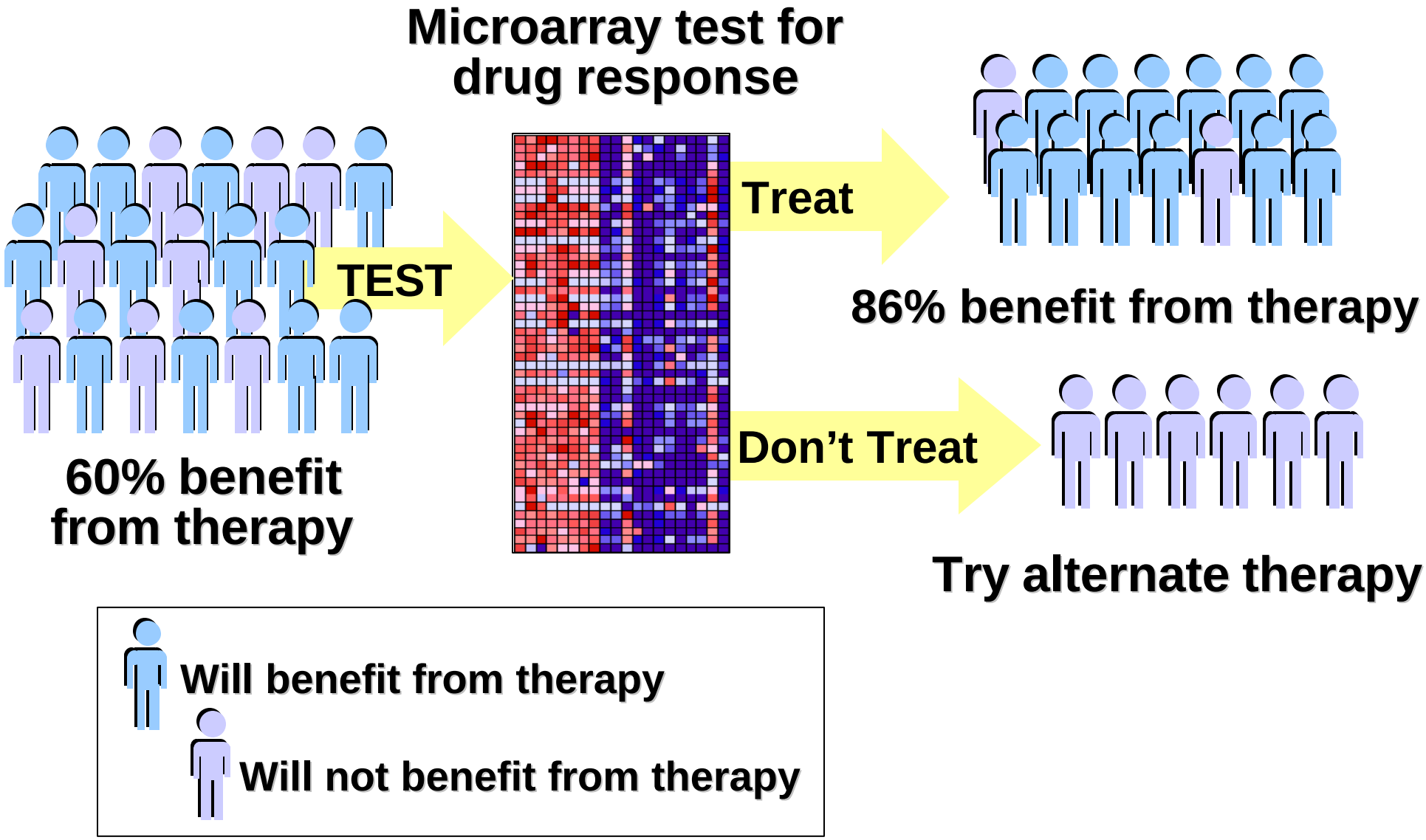
- What genetic technologies for health care and public health are on the horizon?
- What impact will these technologies have on the quality of health care and their accessibility and affordability?
- What new issues will be raised by the further development and integration of these emerging genetic technologies?
- What public policies need to be in place to allow for the evaluation, development, and integration of emerging genetic technologies?

What is Pharmacogenomics?

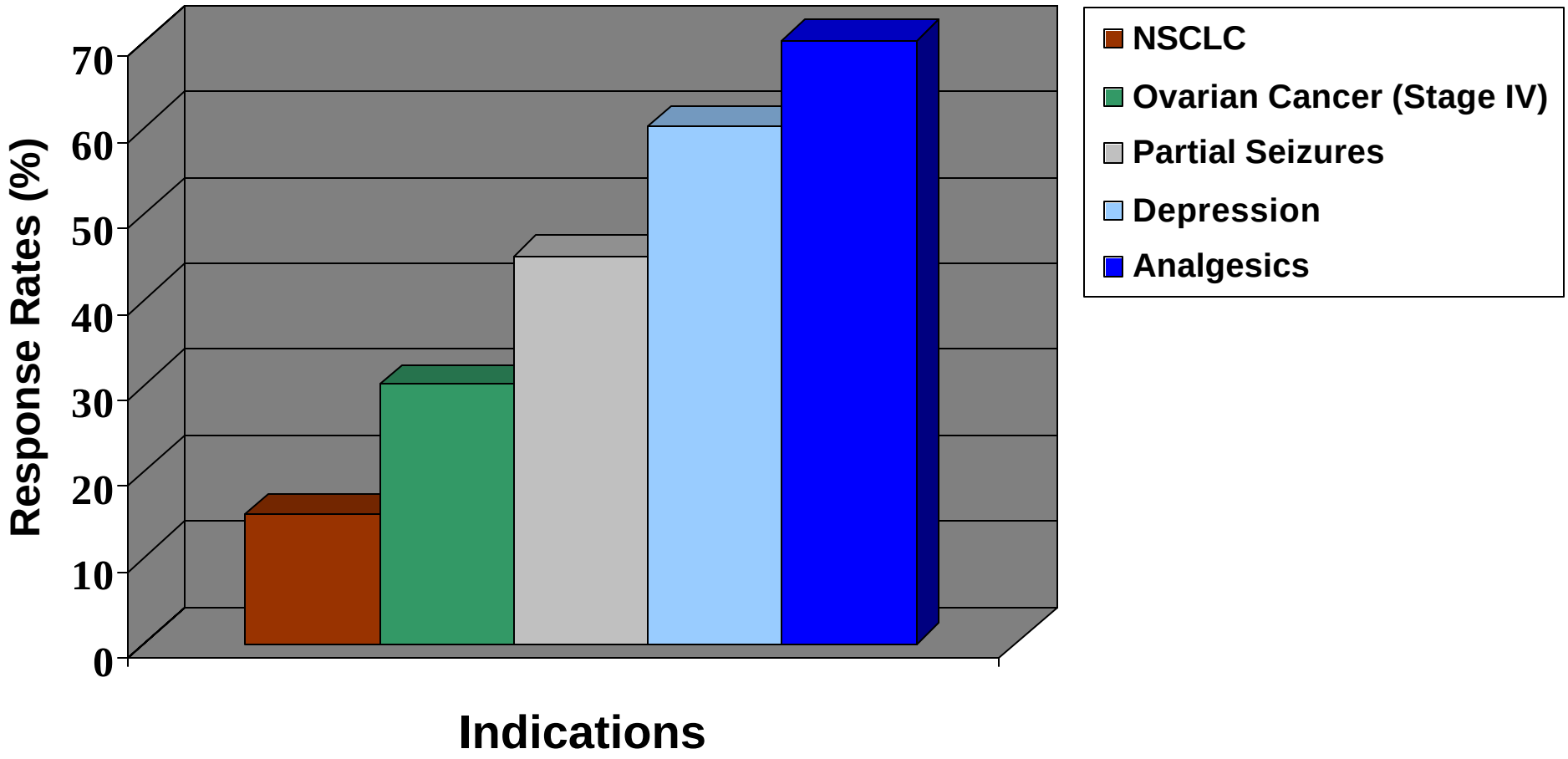
The use of markers of biological variation (DNA, RNA or protein) to predict:

- Patient response to pharmaceuticals
  - Prediction of adverse events
  - Prediction of drug efficacy
- Define subclasses of disease with different response to pharmaceuticals

Pharmacogenomics: Leading the Way to Personalized Medicines



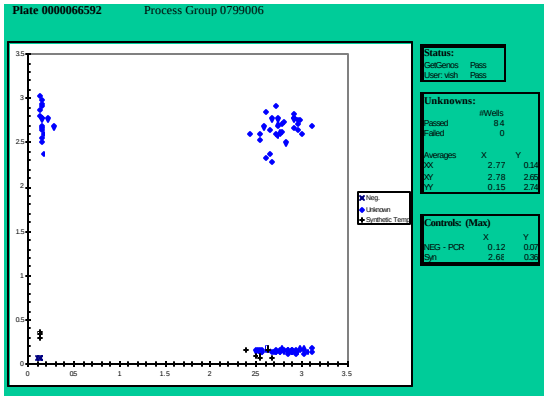
Why Do You Need Pharmacogenomics in Drug Development?

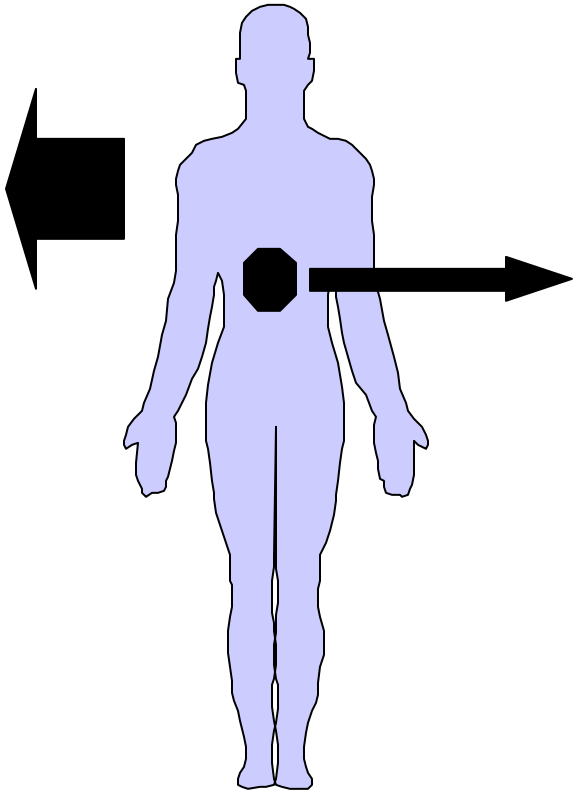


Source: Decision Resources

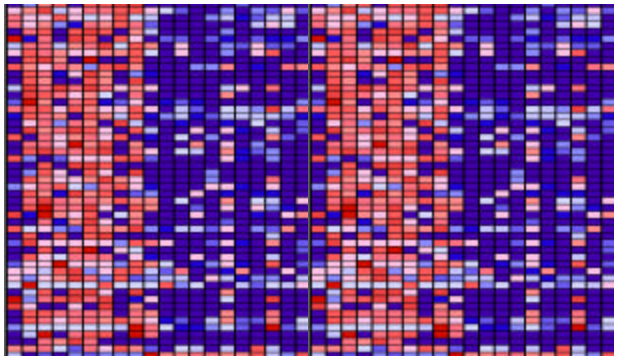
Cancer Pharmacogenomics

Host:
Germline variants including drug transport and drug metabolism genes (eg. TPMT).





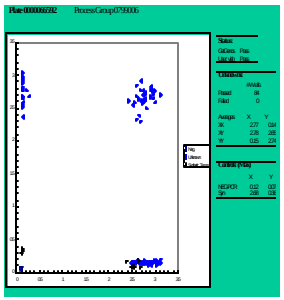
Tumor:
Somatic changes that affect important regulatory pathways or the drug target (p53, Ras, Tubulin, HER2 etc.).



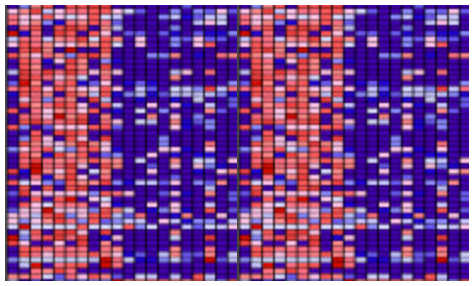
Pharmacogenomic Profiling Technologies

- ***Proteomics***
- >100,000 proteins
- Maximum resolution of ~2,500 proteins/ experiment
- Hypothesis driven:
  - need to select pathways/ proteins

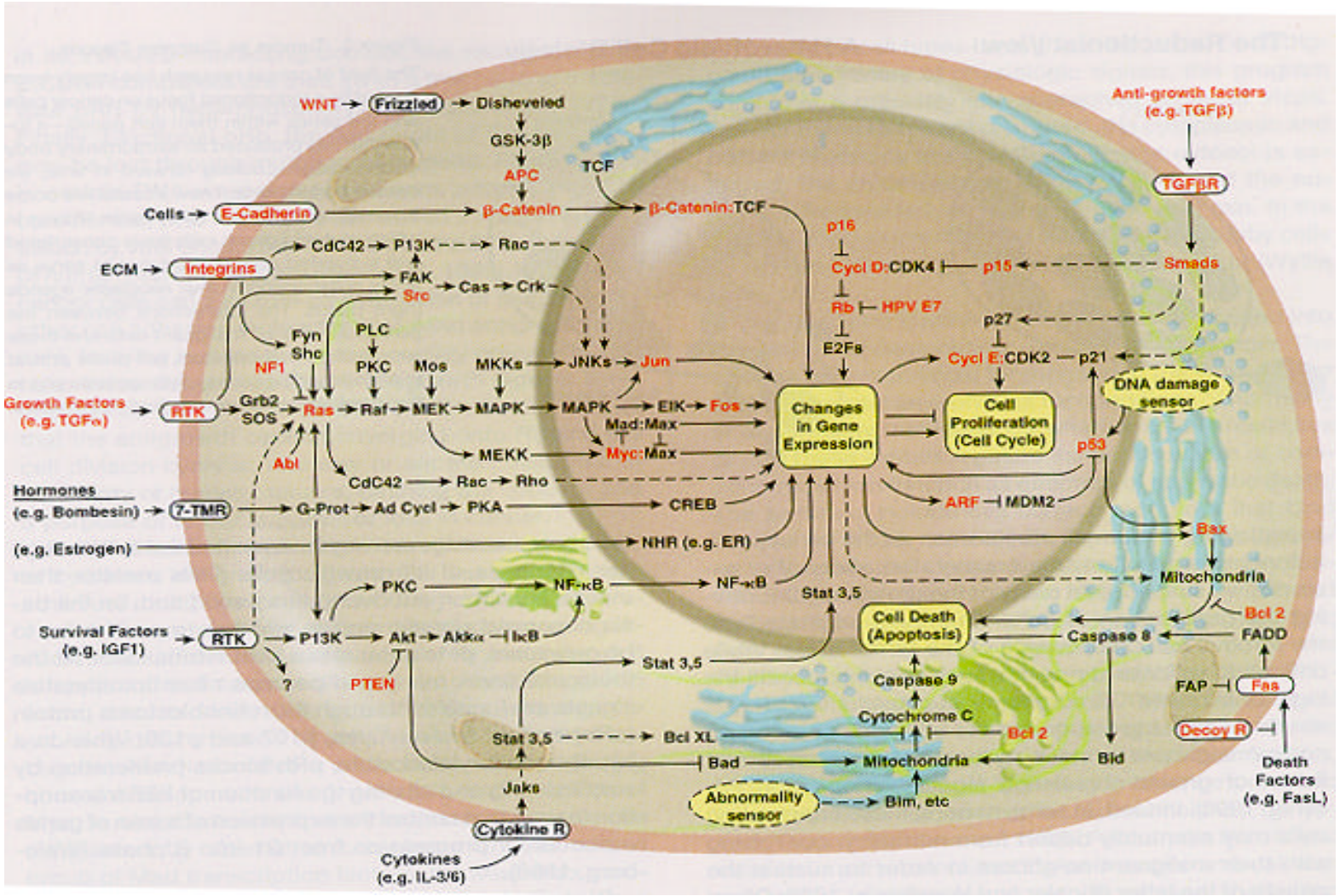
- ***SNP Genotyping***
- >1.5 million SNPs
- Limited by cost and technology
- Hypothesis driven:
  - need to select candidate genes



- ***Transcription Profiling***
- >30,000 genes
- Comparatively lower cost per gene
- Not hypothesis driven
  - Can screen all known genes

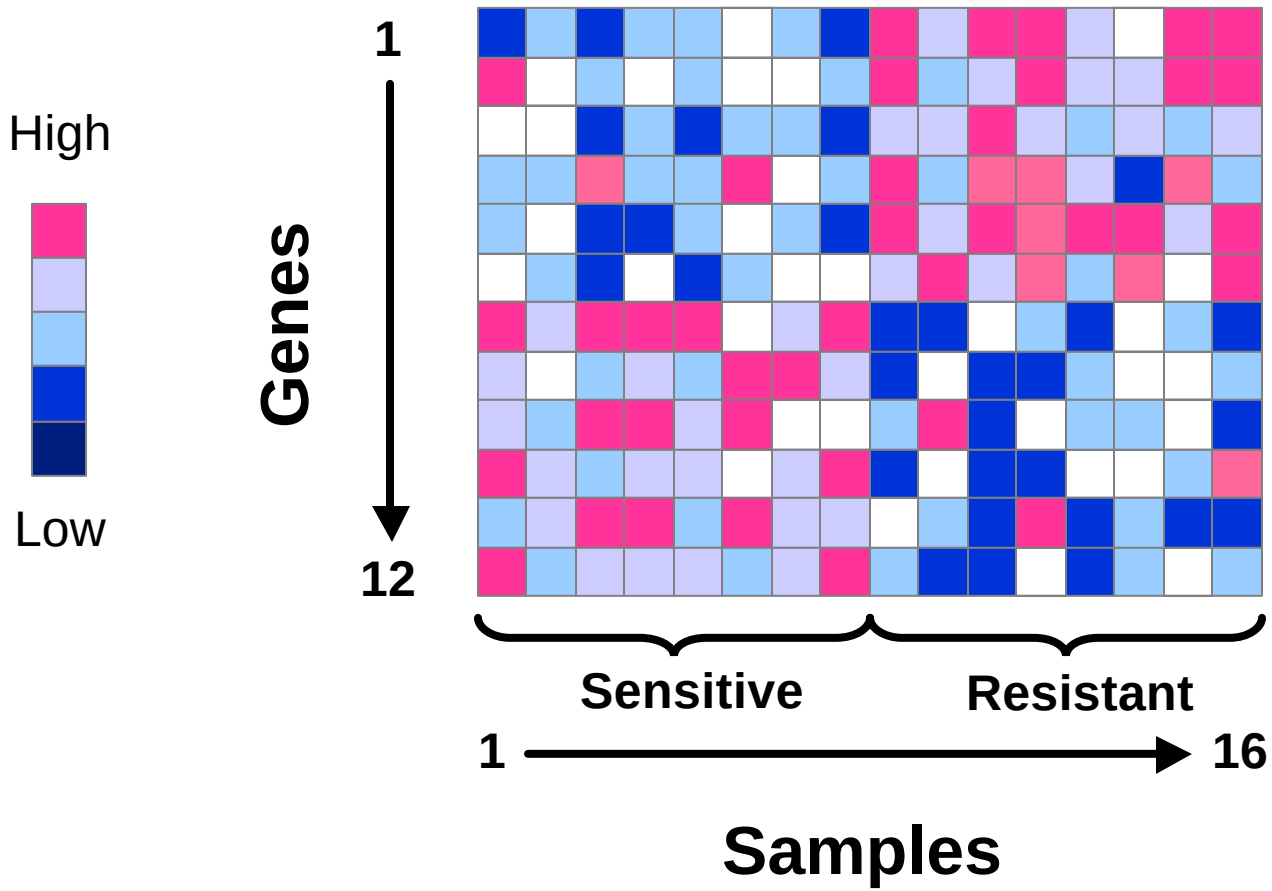


“Circuit Diagram” for Cancer



Hanahan & Weinberg, 2000

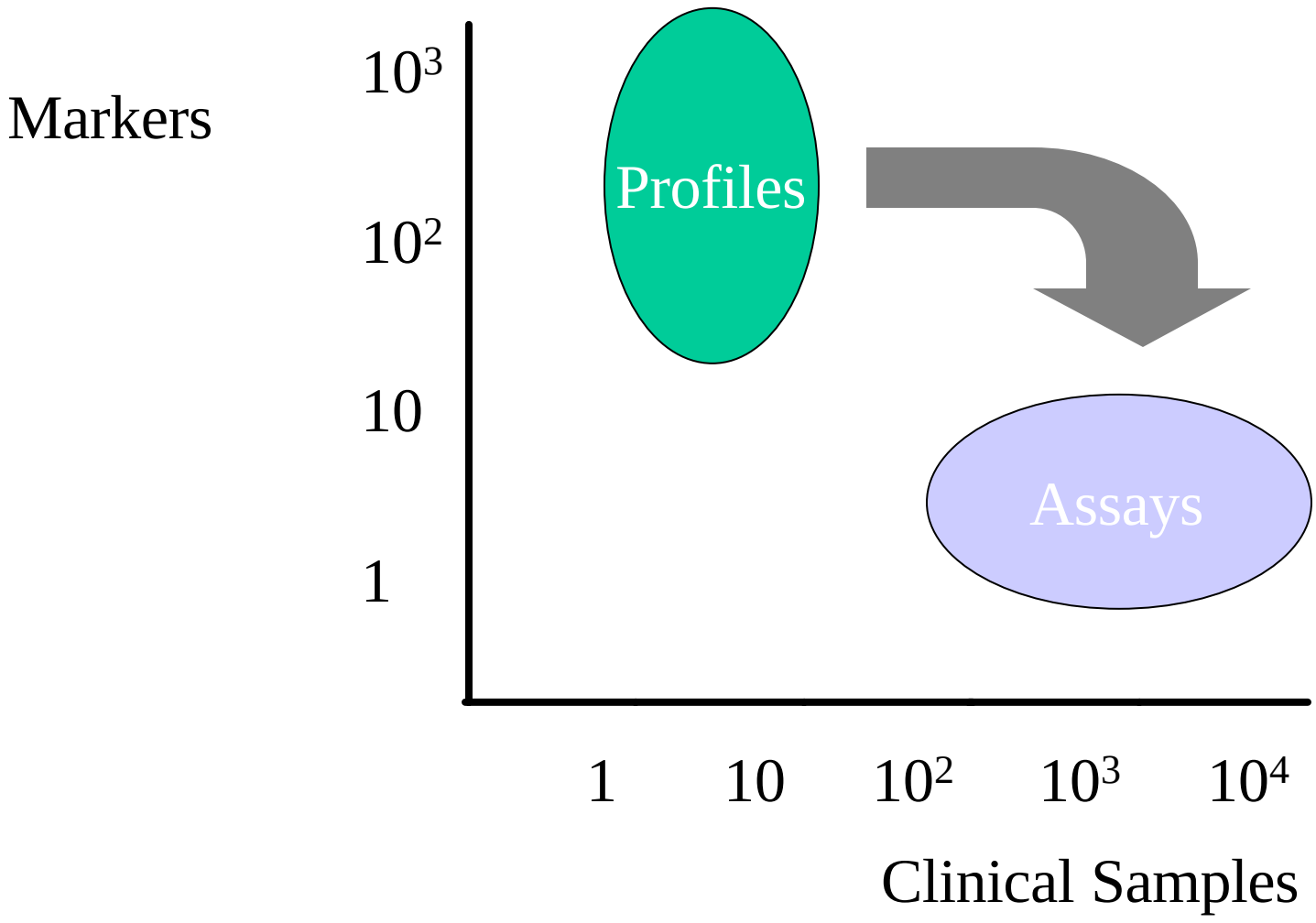
Molecular Profiling Analyses



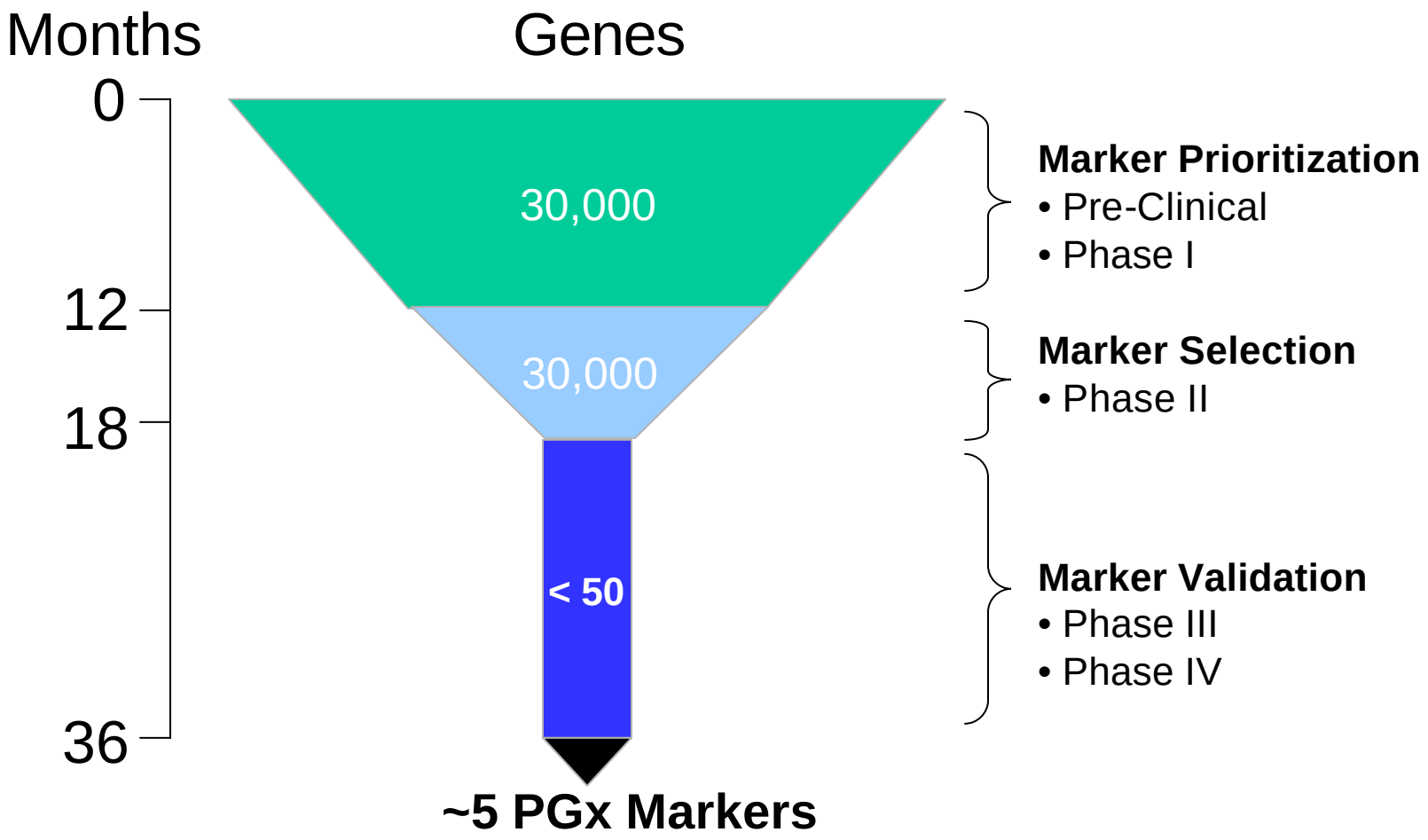
Non-Random Pattern:

PGx Markers

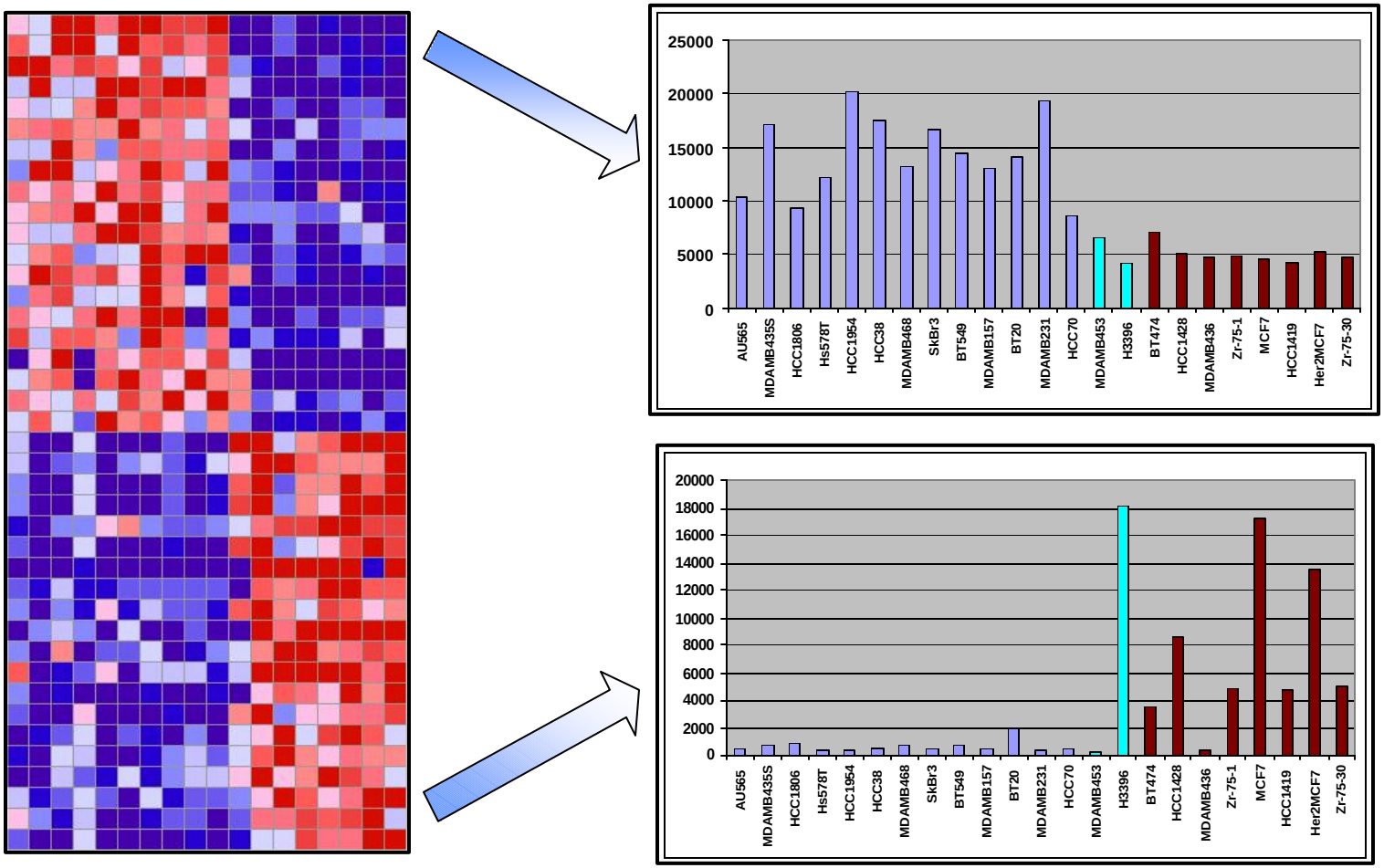
Profiles to Assays



Marker Selection & Validation

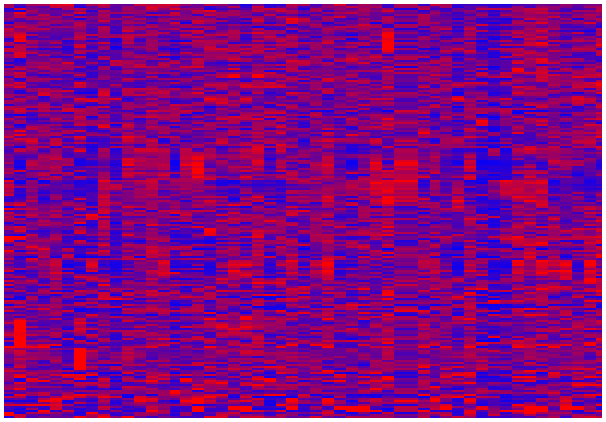


Gene Expression Profiling to Predict Drug Response

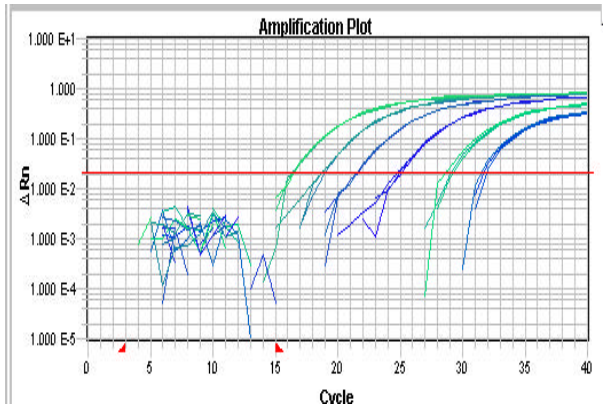


Transcript Profile

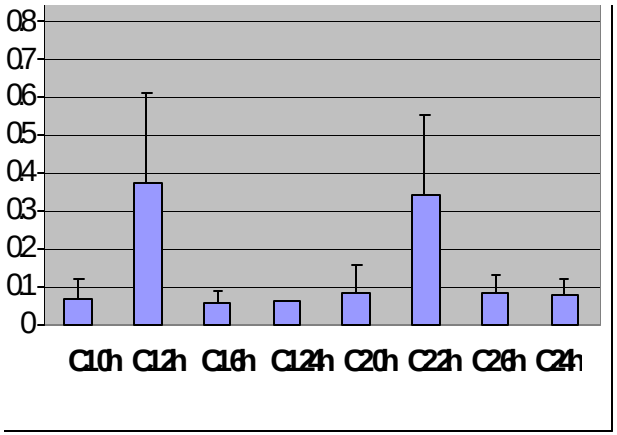
Gene Expression Profiling to Predict Drug Dose



Transcription profiling of drug treated target and surrogate tissues

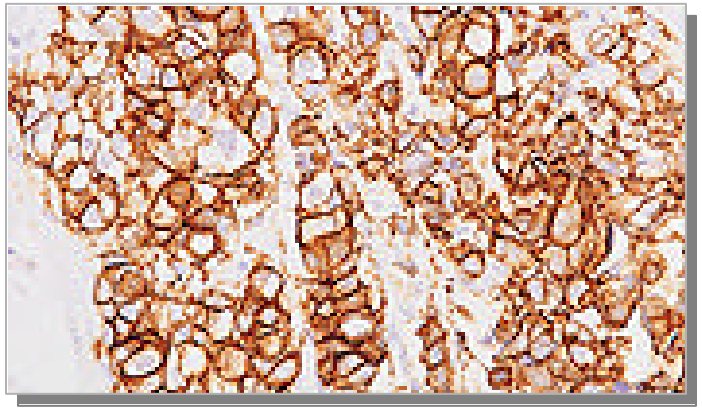


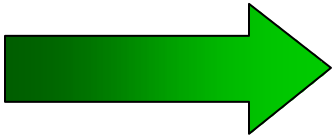
Replication of positively associated markers by quantitative PCR

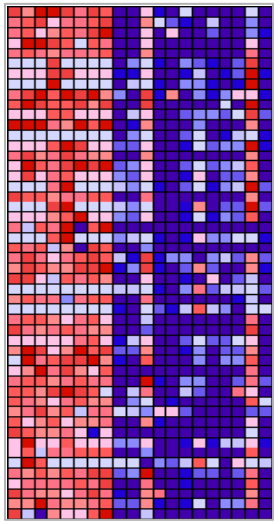


Validated Clinical Assay

Oncology PGx: Today & Tomorrow







Dako Herceptin™ Test

- Single analyte test
- Dx test = Drug target
- Single indication
- Standard technology

Microarray test for drug response

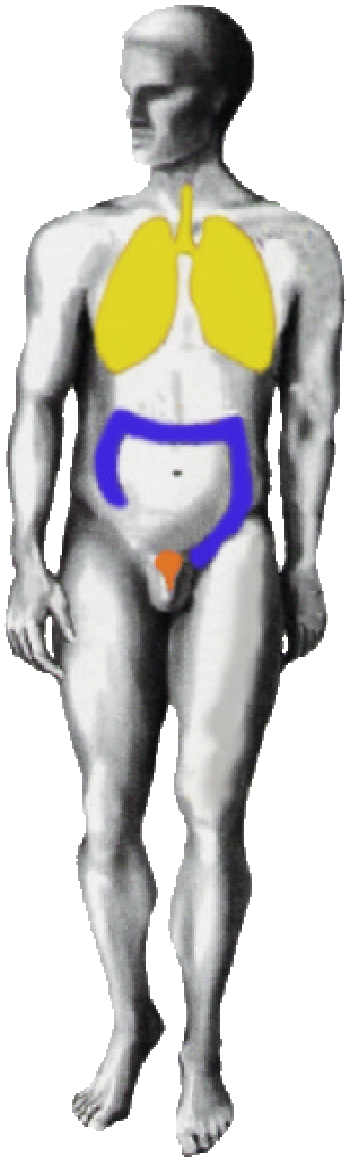
- Multi-Analyte test
- Dx test ? Drug target
- Multiple indications
- New Dx technology

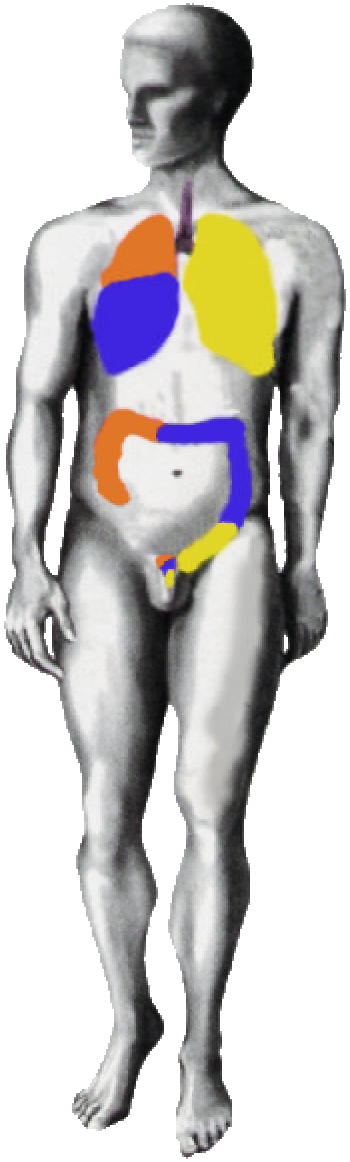
Pharmacogenomics Redefines Tumor Classification

Lung

Colon

Prostate





P53 / ras Genotype

RNA Profile I

RNA Profile II

What genetic technologies for health care and public health are on the horizon

- High capacity/low cost profiling:
  - DNA (>2,000,000 known SNPs)
  - RNA (~30,000 genes)
  - Protein (>100,000 proteins)
  - Metabolites (100 - 1,000 metabolites)
- RNAi for drug target validation
  - An evolving technology to study gene expression that will have enormous impact on target validation in drug development

What impact will these technologies have on the quality of health care and their accessibility and affordability?

- Better definition of disease causation will lead (eventually) to better therapeutic approaches
  - First pharmacogenomic products have reached the market
- Molecular definition of disease will have broad impact:
  - Market segmentation
  - Identify new indications
  - Increased efficacy and safety will lead to lower attrition rates
- Better diagnostics will result in more “orphan” diseases
  - Subsets of common diseases will be shown to be unresponsive to existing therapies and identify new unmet medical needs
- PGx testing costs will be built into pharmaceutical pricing

What new issues will be raised by the further development and integration of these emerging genetic technologies?

- Regulatory guidance for PGx development
  - New policies needed to support co-development of diagnostics and therapeutics
- New technology needed to deliver complex genetic and proteomic diagnostic tests in the marketplace
  - Evolution of discovery tools to clinical tools
  - Multi-analyte tests
- Resistance to genetic testing for diagnostic and medical purposes

What public policies need to be in place to allow for the evaluation, development, and integration of emerging genetic technologies?

- Protect privacy of genetic data (similar to other medical data)
- Develop clear guidelines and regulatory requirements for incorporation of pharmacogenomics in drug development
- Public funding for pharmacogenomics research
  - Databases
  - Tissue banks (anonymized with full informed consent)
- Public-Private consortium efforts
  - SNP Consortium
  - Mouse genome sequencing Consortium
- Support public education about genomic sciences to alleviate fear of modern genetic technologies

Summary

- Profiling technologies will move rapidly from research to diagnostic labs
- New market opportunities for drug development companies and third party diagnostic companies
- Pharmacogenomic testing is already on the market, and will increase rapidly over the next few years
  - Medical need will define major pharmacogenomic opportunities
  - Development of highly sensitive and specific tests will be rate limiting
- Pharmacogenomic testing will utilize multiple technologies for different drugs and diseases:
  - There is no single “killer application” on the horizon, but many targeted opportunities for a diverse list of new and existing drugs