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# **Diagnostic platforms and approaches for pharmacogenetics testing: Meeting the predicted demands and integrating bioinformatics to facilitate test interpretation**

*Janet A. Warrington, Ph.D.  
Vice President  
Emerging Markets and Molecular Diagnostics  
Research and Development  
Affymetrix Inc.*



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# Overview

- Diagnostic platforms and approaches for pharmacogenetics testing
- Predicted demands for pharmacogenetics testing
- Integration of bioinformatics to facilitate test interpretation



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# Definitions

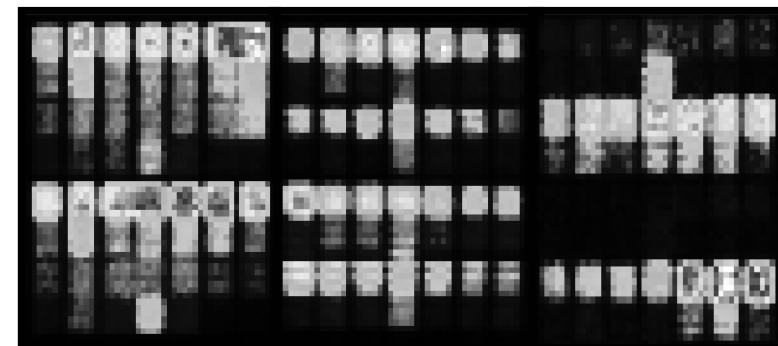
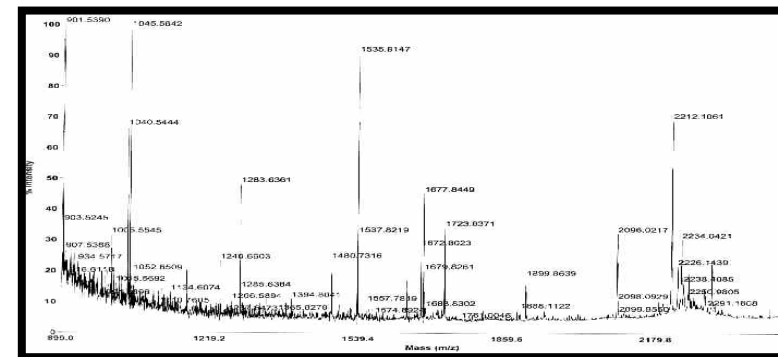
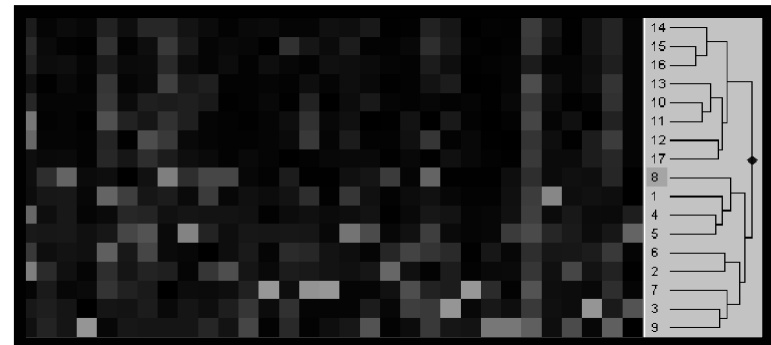
- Pharmacogenetics Research: Discovering why different people respond to drugs differently.
- Pharmacogenetics Testing (Dx): Measuring likelihood of having an adverse drug response or therapeutic failure.



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# There are two major categories of pharmacogenetics knowledge

- **Phenotyping**
  - Pharmacokinetics
  - Pharmacodynamics
  - Gene expression
  - Protein function
  - Clinical outcome
- **Genotyping**
  - Polymorphism
  - Gene copy number

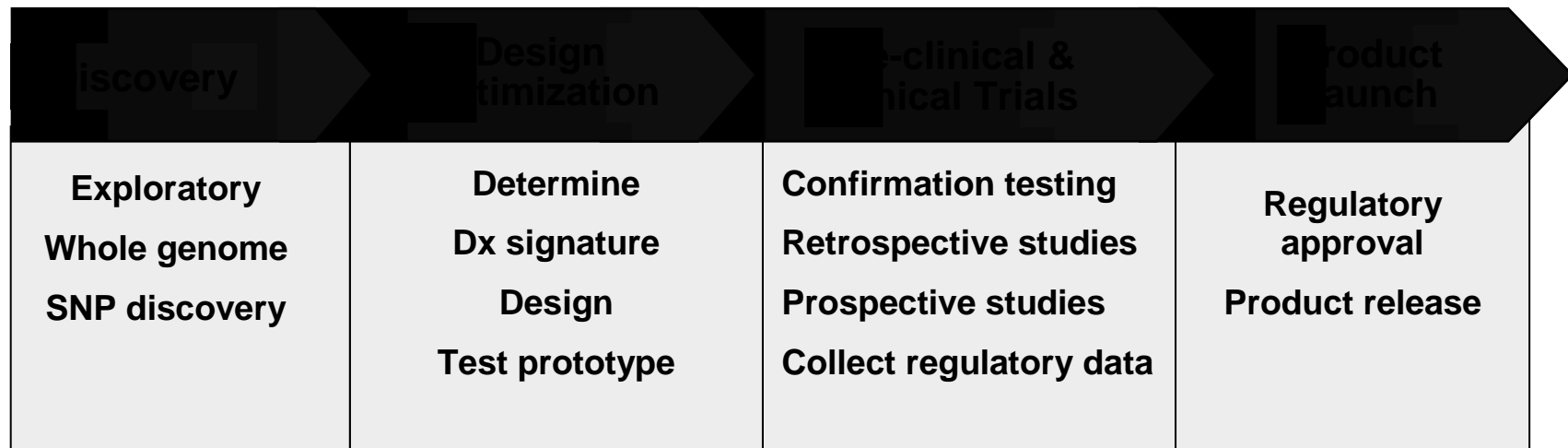


# Research and development path for diagnostic tests

**Research**



**Diagnostics**



**Biologically relevant**



**Clinically relevant**

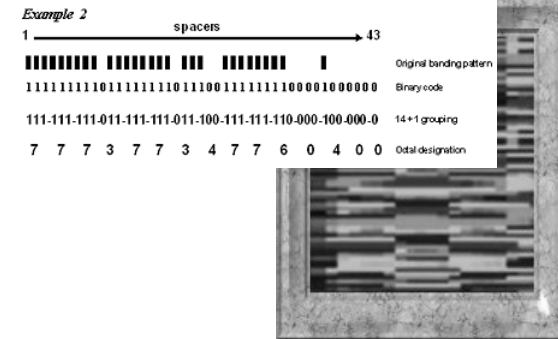
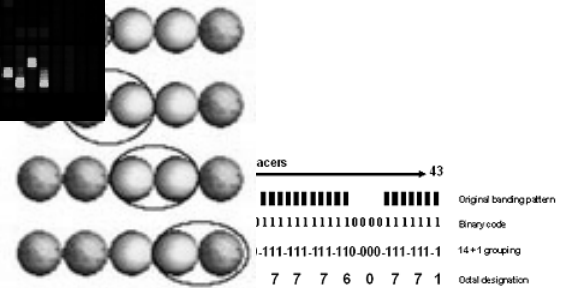
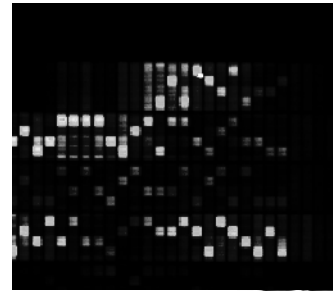
**PGe research has a direct connection to clinical relevance**



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# Genotyping platforms for pharmacogenetics diagnostic tests

- Microarrays
- Beads
- RFLP
- Gel based sequencing
- Mass spectroscopy

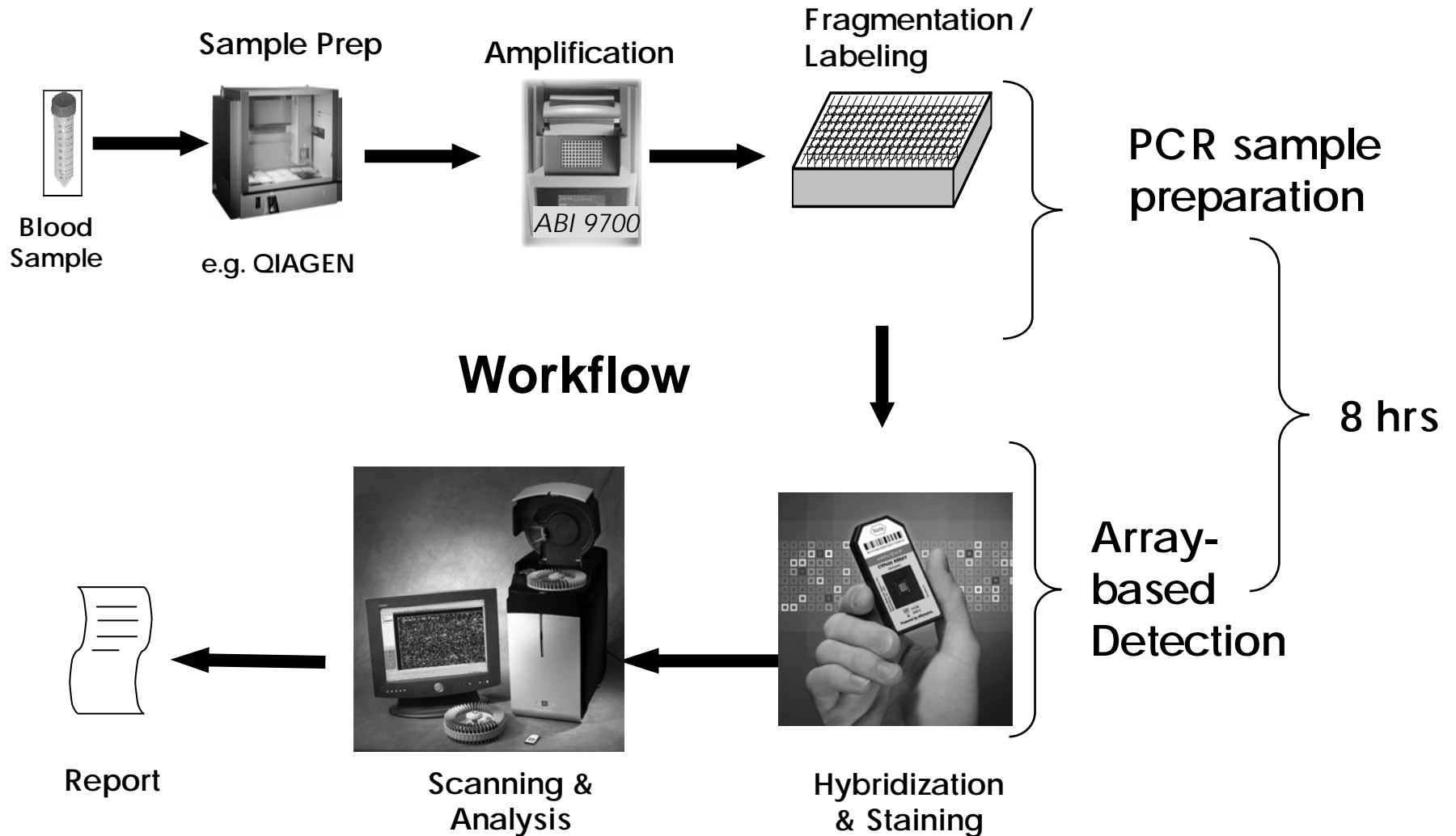


Often a combination of methods is used



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# The AmpliChip™ CYP450 combines PCR and microarray technology





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# PGe is in it's infancy: There are many opportunities and challenges



**Microarrays**

**Gels**

Metrics  
Terminology  
Standard controls  
Best Practices  
Data interpretation  
Biomarker validation  
Data standards  
Data sharing

**Mass Spectroscopy**

**Beads**



# Incremental and doable: International efforts are underway

- Establish standard controls and guidelines
  - External RNA Controls Consortium  
[www.affymetrix.com/scientific community/Standards Program](http://www.affymetrix.com/scientific_community/StandardsProgram), and [www.NIST.gov](http://www.NIST.gov)
  - EuroGentest [www.eurogentest.org](http://www.eurogentest.org)
  - International Meeting of Clinical and Laboratory Genomic Standards [www.imclgs.org](http://www.imclgs.org)
  - Clinical and laboratory standards institute [www.clsi.org](http://www.clsi.org)
  - IBM partnerships

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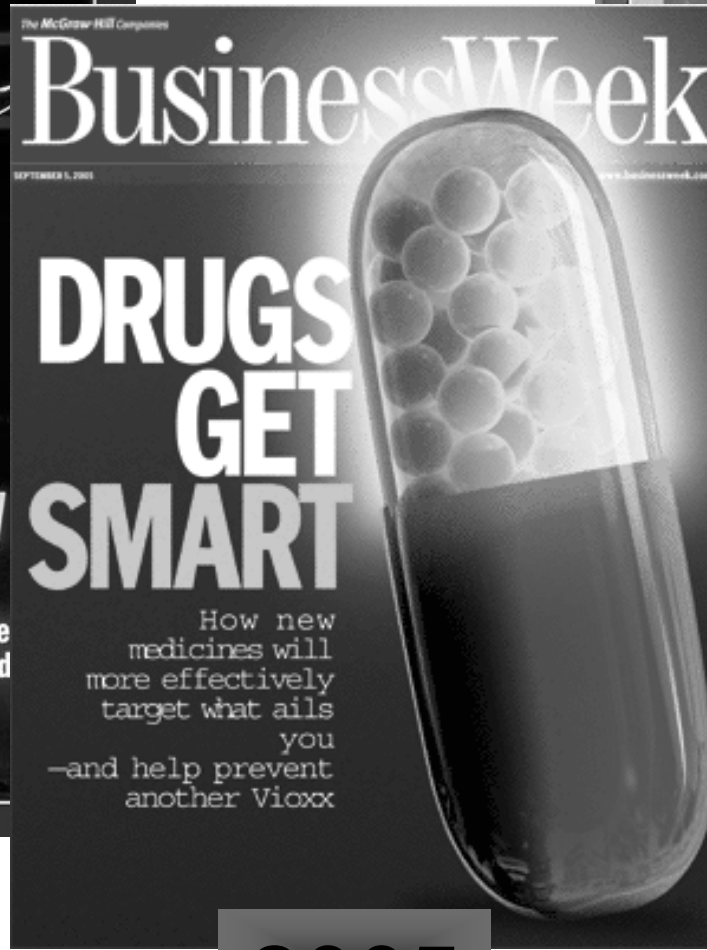


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# Challenge: Managing expectations



1994



2005



2001



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## Why the hope and hype?

- Rx expenditure: 400.6 B\$ worldwide, 2002
- Incidence of serious ADR: 6.7% of hospitalized patients
- Incidence of fatal ADR: 0.32% of hospitalized patients
- Costs associated with drug related problems  
177.4 B\$, US, 2000

<http://www.imshealth.com>, Guzey and Spigset 2004



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# Increased awareness drives demand for access to information

- **Predictive adverse drug response and/or therapeutic failure screening**
  - P450 drug metabolism genes, 2D6,2C19 etc. (22% top 50 Rx)
  - Thiopurine methyltransferase, TPMT (6-mercaptopurine)
  - UDP glucuronosyltransferase, UGT1A1 (irinotecan)
  - Vitamin K epoxide reductase (warfarin)
- **Companion diagnostics**
  - Gleevec inhibition of tyrosine kinase encoded by bcr-abl fusion
  - Herceptin inhibition of Her 2/neu receptor in breast cancer
  - Aminoglycoside antibiotics to treat Pseudomonas
  - EGFR activating mutations, gefitinib
  - Thymidylate synthase promoter, fluorouracil
  - P53/MDM2 allelic variants, cancer
- **Clinical trials**
  - Screening cohorts



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# Roche AmpliChip™ CYP450 Array

**FDA cleared December 2004**



*Roche AmpliChip™ CYP450 Array*



*Roche AmpliChip™ CYP450 Test (IVD)*



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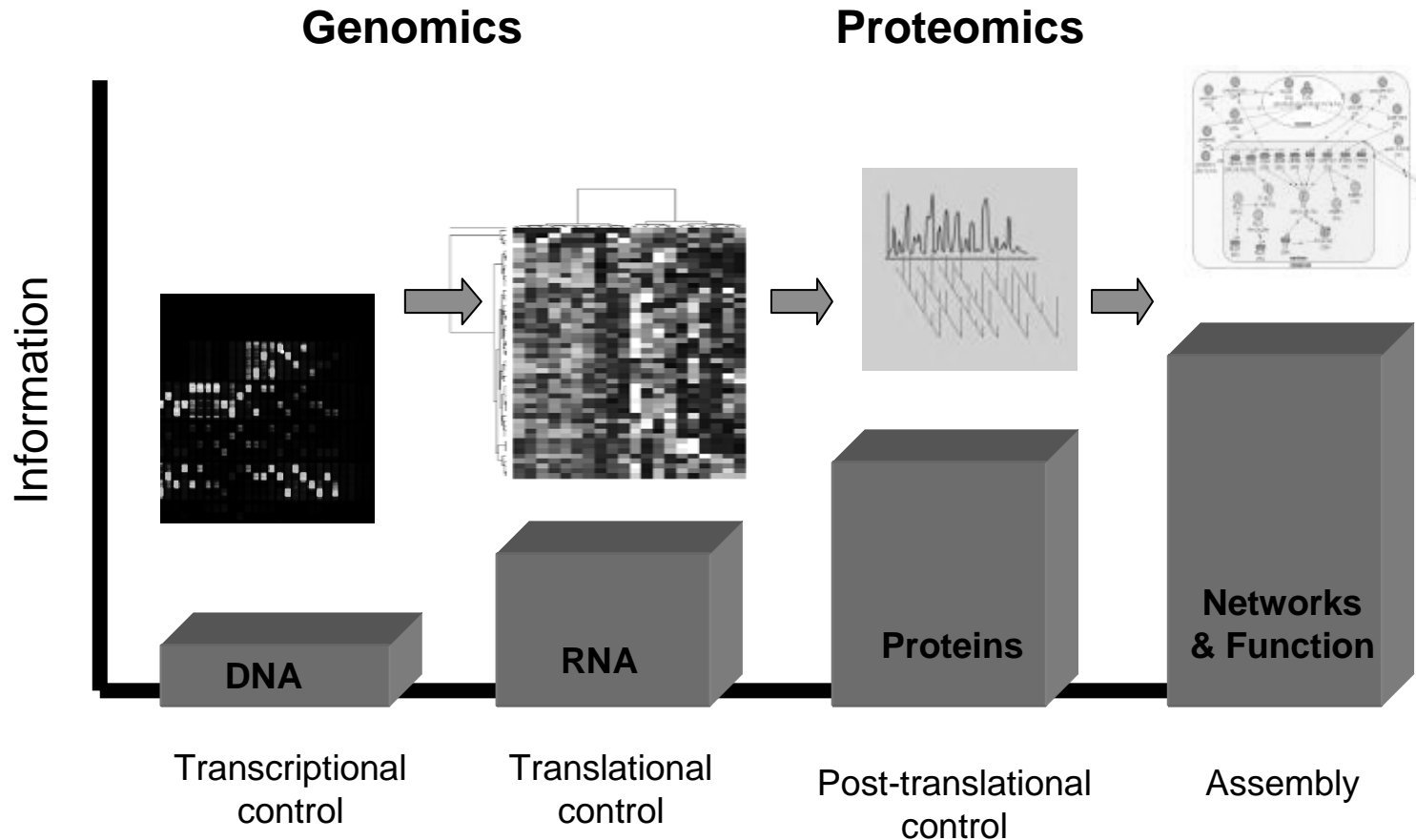
# Why is integration needed?

## Key drivers

- Improved care
  - 1 in 4 MDs surveyed felt scope of care they are expected to provide is beyond their knowledge base
  - Unable to maintain expert knowledge at rate new clinical information is produced
- Error reduction
  - Institute of Medicine report: 98,000 deaths (US) attributed to medical error annually
- Cost reduction
  - Laboratory services = 3-5% hospital budget
  - Impacts 60-70% of costs in admissions, discharges timing, medications



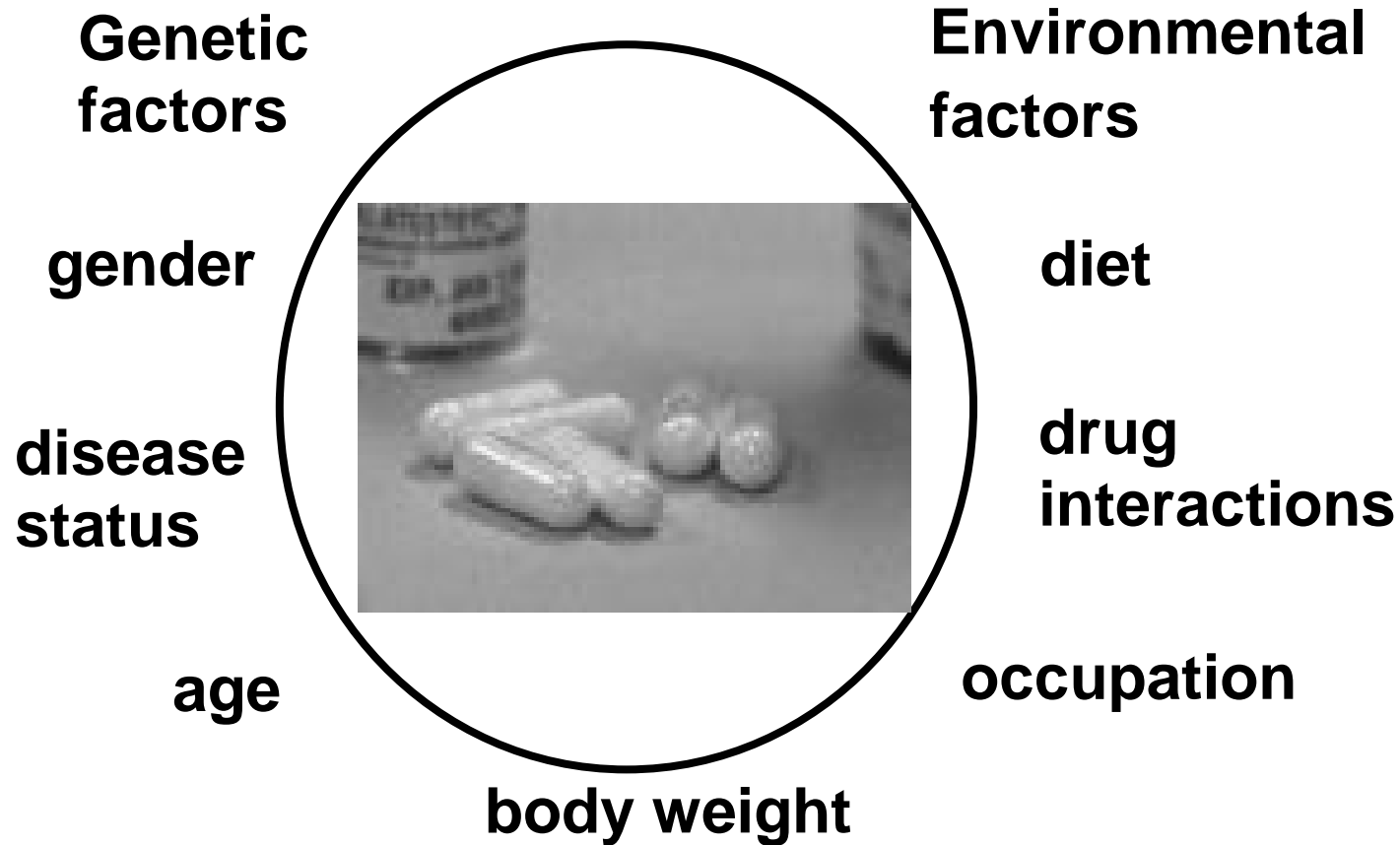
# Information flow and density: Optimizing test design and results reporting





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# Integrating clinically relevant information for test and treatment decision making.





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## Innovative information approaches are needed

- Identify end-user/s
- Data management
  - Two-way, three-way, four-way information flow
  - Clinician: clinical laboratory: pharmacy: patient
- Consensus on terminology, metrics, quality, content, portability, access
- Address security and privacy requirements
- User friendly: low activation energy
- Regulatory and reimbursement utility



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# Challenges to be addressed

- Data has utility in multiple settings
  - Can we develop databases versatile enough to address needs in laboratory, pharmacy, clinician's practice?
  - Can we incorporate information that can be used for assessing test and platform reliability?
- What information should be/can be provided to the clinician prior to decision-making?
- What is the role of instrument and diagnostic manufacturers, laboratories, pharmacists and others in providing information needed by clinicians?
- How to address the need? Shortage of expertise
  - Poor/no reimbursement for clinical interpretation (US)
  - "Clinical turf" perception could slow acceptance

Laposta M., 2005, Lubin I., personal communication



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## Current initiatives

- **CDC\***
  - Centers for Disease Control, USA
  - Model study: Cystic fibrosis
  - What information impacts decision making
  - Timing of information exchange
  - Laboratories, clinicians, payers
- **METI, ISO, FDA, NCI, IBM, AT&T...others?**
- **Harmonization? Desirable and possible.**

**\*Ira Lubin, Joe Boone**



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## Conclusions

- Technologies enabling access to complex information will continue to evolve
- International efforts to build consensus on platform independent controls and guidelines are key to adoption and implementation of new tests
- Timely commitment of resources to the development of model systems for integrating molecular and clinical information is needed
- Education is essential and timing sensitive