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

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Overview

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

- Discovery
  - Exploratory
  - Whole genome SNP discovery

- Design
  - Determine
  - Dx signature
  - Design
  - Test prototype

- Pre-clinical & Clinical Trials
  - Confirmation testing
  - Retrospective studies
  - Prospective studies
  - Collect regulatory data

- Diagnostics

- Product launch
  - Regulatory approval
  - Product release

Biologically relevant

Clinically relevant

PGe research has a direct connection to clinical relevance
Genotyping platforms for pharmacogenetics diagnostic tests

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

Often a combination of methods is used
The AmpliChip™ CYP450 combines PCR and microarray technology

Sample Prep
- PCR sample preparation
  - e.g. QIAGEN

Amplification
- ABI 9700

Fragmentation/Labeling
- PCR sample preparation
  - 8 hrs

Workflow
1. Sample Prep
2. Amplification
3. Fragmentation/Labeling

Scanning & Analysis
- Array-based Detection

Hybridization & Staining
- Report

AFFYMETRIX
The Way Ahead™
PGe is in its infancy: There are many opportunities and challenges

- Microarrays
- Gels
- Mass Spectroscopy
- Beads

Metrics
- Terminology
- Standard controls
- Best Practices
- Data interpretation
- Biomarker validation
- Data standards
- Data sharing
Establish standard controls and guidelines

- External RNA Controls Consortium
  www.affymetrix.com/scientific community/Standards Program, and www.NIST.gov
- EuroGentest  www.eurogentest.org
- International Meeting of Clinical and Laboratory Genomic Standards www.imclgs.org
- Clinical and laboratory standards institute www.clsi.org
- IBM partnerships
Overview

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Challenge: Managing expectations

Genetics
THE FUTURE IS NOW
New breakthroughs can cure diseases and save but how much should nature be engineered

DRUGS GET SMART
How new medicines will more effectively target what ails you—and help prevent another Vioxx

DRUGS OF THE FUTURE
Amazing new medicines will be based on DNA
Find out how they will change YOUR LIFE

1994
2001
2005
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
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
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

Genomics
- DNA
  - Transcriptional control

RNA
  - Translational control

Proteomics
- Proteins
  - Post-translational control
- Networks & Function
  - Assembly
Integrating clinically relevant information for test and treatment decision making

Genetic factors
- gender
- disease status
- age
- body weight

Environmental factors
- diet
- drug interactions
- occupation
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
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
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
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