

# **Pharmacogenomics**

the good, the bad and acceptance



PGx course 4/24/08  
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# **update!**

## **FDA Guidance for Industry**

April 2008

E15 Definitions – contains nonbinding recommendations

### **Pharmacogenomics (PGx)**

The study of variations of DNA and RNA characteristics as related to drug response.

### **Pharmacogenetics (PGt)**

Subset of PGx

The study of variations in DNA sequence as related to drug response.

- Drug response includes the processes of PK, and drug effects (PD, drug efficacy and adverse effects).
- The definitions do not include other disciplines such as proteomics and metabolomics.

## **Benefits of PGx**

Select for patients more likely to benefit from a medicine.

- increase efficacy, better dosage

Identify patients more likely to suffer an adverse effect.

Generate better safety profiles for drugs already on market.

License medicines with a genetic test that would have been too dangerous to license without a test.

Conduct clinical trials more quickly and with smaller cohorts.

- reduce development cost

Increase in cost of medicines and diagnostics, result in larger savings in hospitalization and procedure costs.

## Issues with PGx

Use caution in expecting major savings in health care costs.

Increase complexity of health-care delivery

Exacerbate existing inequalities in health-care delivery due to wide variation in access to genetic tests

Concerns about patient confidentiality and privacy

- issue already addressed in non-genetic based testing

May limit or abolish access to particular medicines based on genetic PROBABILITY of toxicity or efficacy.

- Would insurance companies or health service providers refuse access even though there is a small chance of benefit?

## More issues with PGx

Discourage pharmaceutical companies from developing drugs that they deem to only benefit a small sector of the population.

- Current big pharma model – “blockbusters”.

End up stratifying society, especially when pharmaceutically significant polymorphisms correlate to varying degrees race or ethnicity.

- BiDil - Medicine for self identified African-Americans?
- Do this at varying degrees now.
  - transplantations and transfusions

# Day to day issues

Access to PGx test results.

- Direct to patient?
- Role of pharmacist?

Need to consider the costs, risks and benefits of any new drug/test.

- How to use a PGx-based drug when it is 10% more effective, 10% fewer side effects and costs twice as much?
- This is probabilistic data – used as only part of the decision making process.

When to do the PGx test?

- Do specific, regulated tests only when a patient needs to take a medicine.
- Long-term storing and using genotypes and samples throughout a person's life is more likely lead to privacy concerns and could be an expensive waste of health resources.

# Safety and efficacy in a complicated world

Limitations of clinical trials and monitoring after release to the market.

- Off label prescribing
- More “over the counter” sales
- Use of multiple medications
- Plans to expand the drug market to more “healthy” people, including the genetically susceptible ones.

Once a drug is hits the open market, less control to prevent adverse reactions from happening.

- Too much reliance on genetic tests might also mean that the warning signs of adverse reactions are ignored.
- Those with wrong or misinterpreted results.
- Those with “wrong genes” but have no other treatment options.
- Those who refuse to take the PGx test, do not have access to the test or belong to different populations for which the test might not be valid.

# **Confidentiality**

## storage and use of genetic information

Concerns about genetic privacy, confidentiality and discrimination.

Historically, many of the ethics/policies stem from the time lag between identifying the genetic predisposition to disease and the ability to prevent or treat the condition.

- PGx, the time lag is much shorter, thus privacy and discrimination is less of an issue.

Some PGx tests might reveal information that is relevant to the risk of future illnesses.

- Need access to genetic services and genetic counseling.

# Genetic Information Nondiscrimination Act (GINA)

**Title I: Genetic Nondiscrimination in Health Insurance** - prohibit a group health plan from adjusting premium or contribution amounts for a group on the basis of genetic information.

**Title II: Prohibiting Employment Discrimination on the Basis of Genetic Information** - Prohibits, as an unlawful employment practice, an employer, employment agency, labor organization, or joint labor-management committee from discriminating against an employee, individual, or member because of genetic information.

“Genetic-Discrimination Ban Move Ahead in Congress”

NYTimes 4/23/08

- First proposed in 1995. Multiple versions but never passed both houses in same session.

Still some concerns –

- Does not address life insurance, long-term care insurance.
- Insurance companies worry about ability to request genetic tests in order to determine best treatment.

# Regulation of drugs and tests

## Drugs

- Clinical research and regulatory submissions based on models of small number of genetically matched subjects.
  - How do regulators evaluate such trials?
- Need improved monitoring of approved drugs.
  - adverse drug reactions, off-label use
- Rescued drugs – previously failed drugs, clinically revived with genetic tests, what is length of the patent period?
  - Make it commercially viable to bring rescued drugs to market.

## Genetic tests

- Labels need to incorporate PGx tests as they already do for non-genetic tests such as liver and kidney function.
- Need to establish an open, transparent, independent body with statutory powers to assess the clinical validity, utility of all genetic tests.
- Mandatory registry of genetic tests.

# Bioethics of PGx

autonomy, beneficence, non-maleficence and justice

## **Nuffield Council of Bioethics**

- funded jointly by the Foundation, the Medical Research Council and the Wellcome Trust.
- examines ethical issues raised by new developments in biology and medicine.

## **Pharmacogenetics: Ethical Issues** (report published in 2003)

- What are the economic implications for provision of healthcare?
- Will the development of unprofitable, but desirable, medicines be neglected?
- Could the development of medicines for specific groups of the population exclude others?
- Do pharmacogenetic tests raise different issues from those raised by genetic tests concerned with disease?
- Will a new use of genetic data pose challenges to existing approaches to consent, privacy and confidentiality?
- Do pharmacogenetic tests differ from non-genetic tests, such as tests for cholesterol, which already have a role in treatment?

# FDA - drug labels that mention PGx data

## **6-mercaptopurine - leukemia**

**Laboratory tests are available, both genotypic and phenotypic, to determine the TPMT status.**

## **Azathioprine – organ transplant, immunosuppressive, prodrug**

**It is recommended that consideration be given to either genotype or phenotype patients for TPMT.** Phenotyping and genotyping methods are commercially available. The most common non-functional alleles associated with reduced levels of TPMT activity are TPMT\*2, TPMT\*3A and TPMT\*3C.

## **Atomoxetine - ADHD**

CYP2D6 metabolism — Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. **Laboratory tests are available to identify CYP2D6 PMs.** The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA.

## **Irinotecan – colon cancer**

Individuals who are homozygous for the UGT1A1\*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A1\*28 allele. Heterozygous patients (carriers of one variant allele and one wild-type allele which results in intermediate UGT1A1 activity) may be at increased risk for neutropenia; however, clinical results have been variable and such patients have been shown to tolerate normal starting doses.

# FDA - drug labels that mention PGx data

## **Carbamazepine – epilepsy, neuralgia**

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B\*1502 ALLELE SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXICEPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B\*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B\*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. **PATIENTS WITH ANCESTRY IN GENETICALLY AT RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B\*1502 PRIOR TO INITIATING TREATMENT WITH TEGRETOL.** PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK.

## **Warfarin – prevention of thrombosis and embolism**

PRECAUTIONS: Periodic determination of PT/INR is essential. (See DOSAGE AND ADMINISTRATION: Laboratory Control.) Numerous factors, alone or in combination including changes in diet, medications, botanicals, and genetic variations in the CYP2C9 and VKORC1 enzymes (see CLINICAL PHARMACOLOGY: Pharmacogenomics) may influence the response of the patient to warfarin.

# BiDil (NitroMed) for CHF

fixed dose hydralazine (antihypertensive) and isosorbide dinitrate (vasodilator)

African Americans with CHF respond less effectively to conventional treatments (esp. ACE inhibitors)

Taylor et al 2004 study

- BiDil reduced mortality by 43%, reduced hospitalizations by 39%, and quality of life markers in African Americans patients with CHF.
- Example of the importance of minority recruitment for clinical trials.

Demonstrates ability to resuscitate a “dead” drug through PGx.

Currently ~3% of patients that could benefit from BiDil are taking it.

- High pricing and exclusion from formularies including Medicare.
  - BiDil is priced high at \$1.80 per pill with an average prescription of 3.4 pills per day and the average yearly cost ranges from \$1400 to \$2800 a year.
  - Generics for the 2 components exist
- Self-limited market, race controversy also contributed to its demise.

Current efforts by NitroMed

- Still available but the sales force was slashed in January 2008.
- Studies to determine genetic basis for the response to BiDil.
- Extended release formulation of BiDil (1x day)





# Warfarin



FDA economists estimated that the genotyping of 2C9 and VKORC1 could save annually the US healthcare system ~\$1.1 billion and avoid 85K serious bleeding events and 17K strokes.

- Based on assumptions, not evidence and could be overly optimistic.
- No direct evidence linking genotyping and avoidance of bleeding or stroke events. Only retrospective studies and used stable maintenance dose as an outcome.
- Need a prospective cohort study with lifetime horizon of analysis.

Most likely genotyping's impact greatest for the short term.

In the medium term (1-3 months), any differences observed between genotyped and non-genotyped patients will likely diminish, as INR monitoring will continue for all patients regardless of genotyping status.

**Warning – do not set expectations unrealistically high.** Great majority of novel healthcare technologies provide improved patient outcomes with an overall increase in healthcare costs but this does not mean that they are not good value for money.

# DTC Personal Genome Analysis

## **Knome**

Pricing starts at \$350,000 and includes both sequencing and a comprehensive analysis from a team of leading geneticists, clinicians and bioinformaticians.

## **23andme**

- Illumina ~600k SNPs for \$999.
- Gene journal and 23andme odds calculator.



## **deCODEme**

Illumina 1 million SNP chip for \$985.

Will calculate genetic risk for 26 diseases or traits: Age-related macular degeneration, Alcohol Flush Reaction, Alzheimer's disease, Asthma, Atrial fibrillation, Bitter Taste, Breast Cancer, Coeliac Disease, Colorectal Cancer, Crohn's disease, Exfoliation Glaucoma, Heart Attack, Hemochromatosis, Lactose Intolerance, Lung cancer, Male Pattern Baldness, Multiple sclerosis, Nicotine Dependence, Obesity, Peripheral Arterial Disease, Prostate cancer, Psoriasis, Restless legs, Rheumatoid arthritis, Type 1 Diabetes, Type 2 Diabetes.

## **SeqWright Personal Genomics**

- Affymetrix 1 million SNP chip for \$998.

# DTC Personal Genome Analysis



## Navigenics

Affymetrix 1 million SNP chip + genetic counselor for \$2500

- Alzheimer's disease, Breast cancer, Celiac disease, Colon cancer, Crohn's disease, Diabetes, type 2, Glaucoma, Graves' disease, Heart attack, Lupus, Macular degeneration, Multiple sclerosis, Obesity, Osteoarthritis, Prostate cancer, Psoriasis, Restless legs syndrome, Rheumatoid arthritis

Prevention and early intervention strategies are presented on their Web site and may include:

- Behavior modification, Exposure reduction, Medications, Proactive screening, Recognition of early symptoms, Early treatment

Classify prevention measures into three categories:

- "Clinically proven" strategies - shown, in repeated clinical trials, to prevent, delay or lessen the severity of the illness.
- "Promising" strategies - shown to have significant positive effects in several clinical trials.
- "Preliminary" strategies - some support from population, animal or laboratory studies.

# Sources of Patient to Patient Variability



Intrinsic Factors	Extrinsic Factors
Age	Medical practice
Sex	Diet
Concomitant disease	Concomitant drugs
Organ function	Adherence
Genetic variations	Smoking