Pharmacogenomics and Clinical Practice:
Ready for Prime Time?

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Disclosures

- Dr. Beier is the Chief Scientific Officer for Natural Molecular Testing Corp.

The Human Genome Project

The original goals of the Human Genome Project are complete:

- The complete draft sequence of the human genome was finished in April of 2003
- The vast majority of the 20,000 - 25,000 human genes have been identified
- This information is publicly available

But the story is far from over...

- Functions are still unknown for nearly half of known human genes
- Research is still ongoing at many genome research centers across the world

National Human Genome Research Institute

Genomic research for the future

- Personalized medicine
- Identifying genetic susceptibility to disease
- Fixing disease at the DNA level

National Human Genome Research Institute

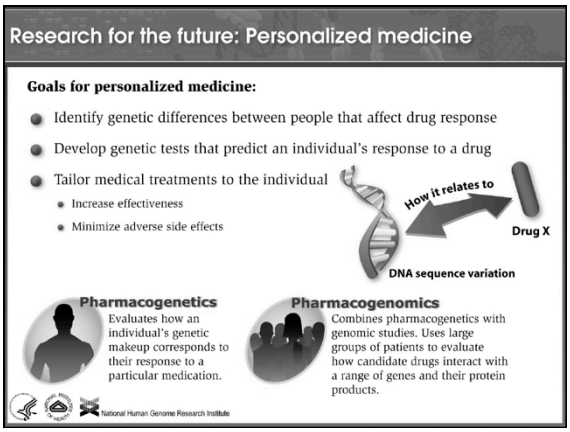
Single Nucleotide Polymorphisms (SNPs)

- Occur when a single nucleotide (A,T,C, or G) in the genome sequence is altered
  - Variable gene expressions that are found in >1% of population
- Most common type of genetic variation among people
  - ATCGCCGGA**T**ACCTAGAGAC…
  - ATCGCCGGA**G**ACCTAGAGAC…
- In an entire human genome there are approximately 10 to 30 million potential SNPs
- Found in both coding (i.e., gene) and non-coding regions of the human genome

The Need for Improved Therapeutics

The effectiveness of prescribed medications ranges from 20-95%

80% - analgesics
25% - cancer chemotherapy
30% - Alzheimer's disease
60% - depression
40% - incontinence
50% - rheumatoid arthritis
60% - schizophrenia
50% - migraine (prophylaxis)
60% - asthma
60% - cardiac arrhythmias



Drug Metabolizing Enzymes

- SNPs occur in transporters and receptors, causing inter-individual variability in drug response
- Numerous metabolizing enzymes are polymorphic
  - CYP2C9, CYP2C19, and CYP2D6 polymorphisms can be clinically significant and are well defined
  - CYP 3A4/5: has polymorphisms but not completely clinically defined

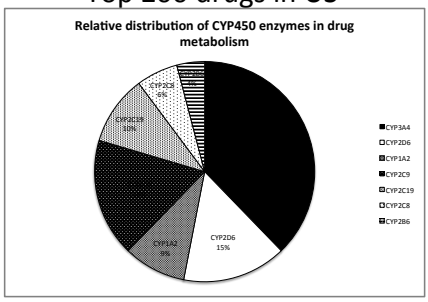
Polymorphism of human cytochrome P450 2D6 and its clinical significance: part I and II.
Zhou SF. *Clin Pharmacokinet* 2009; 48(12):761-804.

Pharmacokinetic Interactions

- Metabolism
  - Cytochrome P450 (CYP): have important SNPs
    - CYP1A2
    - CYP2C9
    - CYP2C19
    - CYP2D6
    - CYP2B6
    - CYP3A4/5 (literature evolving)
      - Most interaction tables combine the meds
      - Polymorphisms recognized but interpretation not clear cut
      - More important is inducer, inhibitor status of medication

Polymorphism of human cytochrome P450 2D6 and its clinical significance: part I and II. Zhou SF. *Clin Pharmacokinet* 2009; 48(12):761-804.

CYP Pathways: Top 200 drugs in US



Anal Bioanal Chem. 2008 Nov;392(6):1093-108

3A4 Family: Key Ones to Remember

- Substrates:
  - Macrolide antibiotics (also inhibitors): erythromycin
  - Benzodiazepines (alprazolam and "Z" drugs)
  - HIV antivirals (also inhibitors)
  - Calcium channel blockers (also inhibitors)
  - Some statins
  - CNS drugs: aripiprazole, buspirone, trazodone
- Inhibitors:
  - Antifungals (itraconazole, ketoconazole), fluvoxamine and as noted above
- Inducers:
  - Carbamazepine, phenobarb, phenytoin, rifampin, St. John's Wort

CYP2D6: Inhibitors Key Ones to Remember

- The enzyme is inhibited by several common drugs
  - Strong inhibitors
    - Fluoxetine, paroxetine, quinidine, bupropion, haloperidol
  - Moderate inhibitors: duloxetine
  - Weak inhibitors: amiodarone, cimetidine, citalopram, escitalopram, fluvoxamine, risperidone
  - Dose dependent?: sertraline

CYP Metabolic Activity: Four Bin Phenotypic Model

- Extensive metabolizer: an individual typically with the wild type or "normal" phenotype
  - Will likely metabolize a drug as anticipated in the package insert
- Intermediate metabolizer: an individual who possesses one partially functional or non-functional allele coding for a metabolizing enzyme
  - Will metabolize a drug, but at a reduced rate
- Ultrarapid metabolizer: an individual with increased expression of a metabolizing enzyme
  - Will metabolize a drug at a more rapid rate than "normal"
  - Will buildup active metabolites with prodrugs
- Poor metabolizer: an individual with decreased or no expression of a metabolizing enzyme
  - Will metabolize a drug very slowly or not at all
  - Will not produce active metabolite with **prodrugs**

Poor Metabolizers

- Can result in toxicity/extreme side effects
- *Will not produce active metabolite with prodrugs*
- To a lesser degree, intermediate metabolizers will experience similar effects

Ultrarapid Metabolizers

- Unlikely to experience therapeutic effect at normal therapeutic doses
- *Prodrugs will accumulate metabolites/active drugs quickly*

Medication Issues in Psychiatry

- Variation in individual clinical response
- Few experience complete symptom remission
  - Efficacy takes 6-8 weeks, longer in older adults
  - Long lag time before alternative med considered
- Majority continue to experience significant psychiatric symptoms
- Most have medication-induced side effects
- Watch out for drug-drug interactions!
- High risk of morbidity and mortality

Antidepressants and Response

- Many medications in different therapeutic classes
- Remission rate 35% - 45%!
- Variation in medication response dependent on a number of factors:
  - age, gender, renal and hepatic functioning, medical co-morbidity, nutrition, substance use, smoking (induces CYP1A2), prior response to therapy (if any), adherence, **genetics**

CYP2D6 Substrates: Expanded Version

Analgesics
Codeine
Dihydrocodeine
Hydrocodone
Oxycodone
Tramadol
Methadone

Cardiovascular drugs

Captopril	Alprenolol
Flecainide	Bufuraolol
Labetalol	Carvediol
Metoprolol	Mexiletine
Papaverine	Timolol
Penbutolol	Propafenone

Antidepressants

Clomipramine	Desipramine
Imipramine	Maprotiline
Nortriptyline	Paroxetine
Citalopram	Duloxetine
Venlafaxine	Doxepin

Antipsycotics
Chloromazine
Haloperidol
Thioridazine
Perphenazine
Risperidone

Miscellaneous: Diphenhydramine Detromethorphan Tamoxifen

Pharmacogenomic Info in FDA Labels for 2D6

FDA approved drugs with pharmacogenomic information in their labels for 2D6

- **Aripiprazole** Psychiatry
- **Atomoxetine** Psychiatry
- **Carvedilol** * Cardiovascular
- **Cevimeline** Dermatology and Dental
- **Chlordiazepoxide and Amitriptyline** Psychiatry
- **Citalopram** Psychiatry
- **Clomipramin e** Psychiatry
- **Clozapine** Psychiatry
- **Codeine** Analgesics
- **Desipramine** Psychiatry
- **Desloratadine and Pseudoephedrine** Allergy
- **Dextromethorphan and Quinidine** Neurology
- **Doxepin** Psychiatry
- **Fluoxetine** Psychiatry
- **Fluoxetine and Olanzapine** Psychiatry
- **Fluvoxamine** Psychiatry
- **Galantamine** Neurology
- **Gefitinib** Oncology
- **Iloperidone** Psychiatry
- **Imipramine** Psychiatry
- **Metoprolol** * Cardiovascular
- **Modafinil** Psychiatry
- **Nefazodone** Psychiatry
- **Nortriptyline** Psychiatry
- **Paroxetine** Psychiatry
- **Perphenazine** Psychiatry
- **Pimozide** Psychiatry
- **Propafenone** * Cardiovascular
- **Propranolol** * Cardiovascular
- **Protriptyline** Psychiatry
- **Quinidine** Antiarrhythmics
- **Risperidone** Psychiatry
- **Terbinafine** Antifungals
- **Tetrabenazine** Neurology
- **Thioridazine** Psychiatry
- **Tolterodine** Reproductive and Urologic
- **Tramadol and Acetaminophen** Analgesics
- **Trimipramine** Psychiatry
- **Venlafaxine** Psychiatry

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

How is Psychiatric Pharmacogenetics Useful?

- Pharmacogenetics seeks to better delineate medication choice by selecting:
  - medication that makes sense from a pharmacokinetic perspective (CYP 450 pathways)
  - medication that makes sense from a pharmacodynamic perspective (drug-receptor response)
    - More research needed
  - medication classes that appear to predict efficacy or side effect burden (CYP 450 pathways)

Specific Case Scenarios

JJ is a 66 year old Veteran

- presented to his clinician with depression
- otherwise physically healthy with a history of hypertension
  - Medications :
    - Amitriptyline 50 mg po hs for sleep
    - Metoprolol 50mg ER po daily
- doctor prescribed fluoxetine 40 mg daily for depression

CYP2D6: Inhibitors Key Ones to Remember

- The enzyme is inhibited by several common drugs
  - Strong inhibitors
    - Fluoxetine, paroxetine, quinidine, bupropion, haloperidol
  - Moderate inhibitors: duloxetine
  - Weak inhibitors: amiodarone, cimetidine, citalopram, escitalopram, fluvoxamine, risperidone
  - Dose dependent: sertraline

Case Scenario

- The patient (JJ) responded quickly to fluoxetine
- Several weeks later, the patient was found unconscious at home
- What happened??
  - Fluoxetine is a powerful inhibitor of 2D6
    - The other two are both metabolized by CYP2D6
    - Drop in BP and HR and increased sedation from the antidepressant

Analgesics and Pain: Role of Genotyping

Medication Issues in Pain

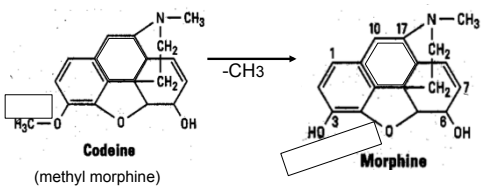
- Variation in individual clinical response
- Med-induced side effects
- Drug-drug interactions
- Drug-herb interactions (St. John's Wort)
- Pain does not exist in isolation
  - Coexists with anxiety, depression and mood disorders
  - Chronic pain often requires antidepressants and other mood altering meds
- Neuropathic pain management
  - Challenging and requires use of psychoactive meds

Mr. Jones, Age 79

Pneumonia

- Patient w/ pneumonia treated w/ antibiotics and w/ codeine for cough
- On treatment day 2 patient was found unresponsive
- Transfer into ICU, life support: intubation, respirator
- Supportive care was successful – patient recovered fully
- What happened?

Codeine is a Substrate of CYP2D6



Consider the variation in codeine's metabolism among PM, IM, EM, UM individuals

2D6 conversion accounts for it's analgesic activity

CYP2D6 and Phenotypes and Codeine

- Consequence of variants for prodrugs that need to be converted to active drugs:
  - PM: no active drug
  - IM: less active drug – approximately 20% lower concentrations of morphine than in EM
  - UM: more active drug – up to 800% higher concentrations of morphine than in EM
- Dose Adjustment (change from standard dose):
  - PM: select a different drug
  - UM: dramatic decrease in dose or use a different drug

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype.
Crews KR, et al. *Clin Pharmacol Ther* 2011: doi: 10.1038/clpt.2011.287.

Codeine & CYP2D6:
FDA Guidance 2007 and new 2012

- Limited evidence suggests that individuals who are ultra-rapid metabolizers (those with a specific CYP2D6 genotype) may convert codeine to its active metabolite, morphine, more rapidly and completely than other people.
- In nursing mothers, this metabolism can result in higher than expected serum and breast milk morphine levels.
- In a nursing mother known to be or suspected to be an ultra-rapid metabolizer of codeine, consider other options for relieving pain or persistent cough.
- Implications for geriatric/pediatric patients prescribed opioids containing codeine for pain relief??

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124889.htm
Koren et al. Lancet 2006; 368:704 and N Engl J Med 2004;351:2827-31.
CYP2D6 in the metabolism of opioids for mild to moderate pain. Lepper W. Pharmacology 2011;87:274-285

Clinical Pearl

- An individual with an extensive (normal) or intermediate metabolic phenotype (for 2D6) can be converted to a poor metabolizer when treated with an SSRI such as fluoxetine

What Other 2D6 Mediated Opioids?

- Tramadol: converted to more active drug
  - Paroxetine (2D6 inhibitor) decreased efficacy in one trial
- Hydrocodone: converted to hydromorphone, which is 10-33 times more potent than hydrocodone
  - inhibition by 2D6 affects some efficacy
  - 3A4 also forms norhydrocodone (not active)
- Oxycodone : metabolized by 2D6 and 3A4
  - To Oxymorphone (only 11%, but more potent)
  - To Noroxycodone by 3A4 is major pathway (less active than oxycodone)
  - So, 2D6 inhibitors AND 3 A4 inhibitors are relevant

CYP3A4 Substrates Important in Pain and Psychiatry

- Anticonvulsants: carbamazepine
- Narcotic analgesics: fentanyl, methadone, meperidine
- Antipsychotics: quetiapine, ziprasidone
- Antidepressants: nefazodone, sertraline, trazodone, desipramine
- Hypnotics: alprazolam, midazolam, zolpidem, triazolam

Top Drug-drug Interactions in Pain/Psychiatry

- Combinations involving 2D6 inhibitors and 2D6 substrates
- Combinations involving opioids (codeine, methadone, oxycodone, tramadol) AND
  - 2D6 and/or
  - 3A4 inhibitors (antifungals, fluvoxamine)
- Carbamazepine and phenytoin and St. John's Wort as 3A4/5 inducers when combined with 3A4 substrates

The Case of Warfarin

Warfarin Monitoring Woes

- Therapeutic range: INR 2-3 (2.5-3.5 for prosthetic heart valves)
- INR <2: risk of thromboembolic event
- INR >3: risk of bleeding complications
- Huge Monitoring Hassle Factor!

Lesko LJ. The critical path of warfarin dosing: finding an optimal dosing strategy using pharmacogenetics. *Clin Pharmacol Ther* 2008; 84(3):301-3.

Source of Variability in Warfarin Dose Requirements

- Many clinical and environmental factors can influence warfarin response
  - Age, gender, race, height, weight, concomitant medications, foods (vitamin K), herbal ingestion etc.
  - Wide inter-individual variability in therapeutic efficacy
  - Remember the "3Ds"
- Despite knowledge of these factors, a large proportion of variability in warfarin dose requirements remains uncertain

Arch Intern Med 2005; 165:1095-1106.
Beier MT. *J Am Med Dir Assoc* 2008; 9(3):199-200.

Warfarin Dosing

FDA Label Revisions

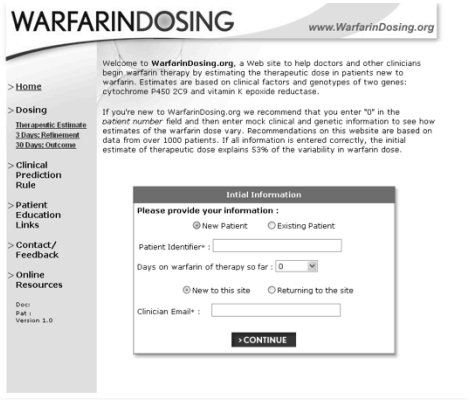
- 2 million patients start warfarin every year!
- Changed package insert for warfarin August 2007
  - Further revised Feb 2010 (includes genetic testing info)
- Label now provides information regarding altered metabolism in CYP2C9 and VKORC1 genetic variants (may account up to 40% in variability)

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf

Warfarin Pharmacogenetics

- CYP2C9
  - Metabolizes >90% of active (S-Warfarin)
  - Variant alleles associated with increased sensitivity to warfarin (CYP2C9*2, *3)
- Vitamin K epoxide reductase (VKORC1)
  - Inhibited by warfarin (PD effect)
  - Important for replenishment of vitamin K
  - Variant alleles of *VKORC1* gene associated with altered response to warfarin: G/G, G/A, A/A

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf.

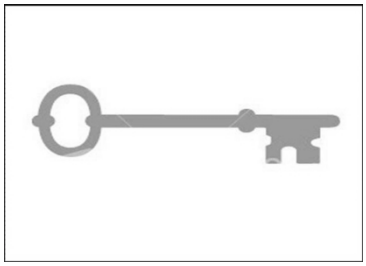


Prospective Warfarin Trials

- Clarification of Optimal Anticoagulation Through Genetics (COAG)
  - http://www.clinicaltrials.gov/ct2/show/NCT00839657
  - compare two approaches to warfarin dosing
  - Estimated Study Completion Date: July 2013
- Genetics Informatics Trial (GIFT) of Warfarin to Prevent DVT
  - http://www.clinicaltrials.gov/ct2/show/NCT01006733?term=GIFT&rank=2
  - Estimated Study Completion Date: August 2015

http://clinicaltrials.gov/ct2/show/NCT00839657.
http://clinicaltrials.gov/ct2/show/NCT01006733?term=GIFT&rank=2.

The Case of Clopidogrel



Clopidogrel and Pharmacogenetics:

The Conundrum

- FDA Drug Safety Communication 3/12/10: Reduced effectiveness of clopidogrel in patients who are poor metabolizers of the drug
  - http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm

FDA: Black Box Warning Revised 2010 (from Label)

DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

Clopidogrel and Pharmacogenetics
So, What's the Problem?

- Clopidogrel is a prodrug: it has to be metabolized by CYP2C19 before it can be biologically active
- Clopidogrel metabolism shows genetic polymorphisms
- Possible drug interactions with proton pump inhibitors (PPIs)?
  - Omeprazole is a 2C19 inhibitor, other PPIs too
  - Conflicting data so far in clinical studies
  - For those who require a PPI, pantoprazole is probably the best choice

Clopidogrel and Pharmacogenetics: CYP2C19

- The CYP2C19*1 allele has fully functional metabolism
- The CYP2C19*2 and *3 alleles have no functional metabolism
- These two alleles account for most of the reduced function alleles in patients of Caucasian (85%) and Asian (99%) descent classified as poor metabolizers
- A patient with two loss-of-function alleles (as defined above) will have poor metabolizer status

Clinical Event Rates in Studies

Clinical Event Rate for PM and URM

- Meta-analysis of data from nine pharmacogenetic studies of clopidogrel involving 9685 patients :
- the hazard ratio for stent thrombosis was 2.67 (95% confidence interval 1.69–4.22) and 3.97 (95% confidence interval 1.75–9.02) in IMs and PMs, respectively, compared with NMs
- The risk for bleeding was greatest among URM, with an odds ratio of 3.27 (95% confidence interval1.33–8.10) compared with NM

JAMA. 2010;304(26):1821–1830.
Circulation. 2010;121(4):512–518.

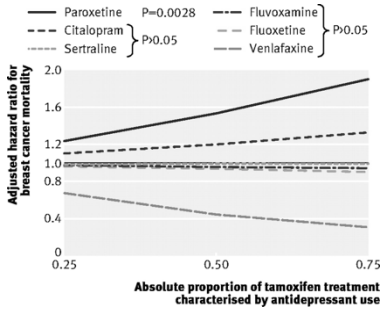
Tamoxifen

Tamoxifen and CYP2D6
What are the Facts?

- As a prodrug, tamoxifen is metabolized into its most active metabolite, endoxifen, by the CYP2D6
- Metabolism blocked in women who carry loss-of-function variant CYP2D6 alleles or who take drugs that inhibit CYP2D6 function
- Among the drugs that inhibit CYP2D6 are the SSRI antidepressants
  - Up to 25% of patients with breast cancer experience a major depressive disorder
  - Paroxetine and fluoxetine potently inhibit CYP2D6
  - Consider mirtazapine, venlafaxine, escitalopram

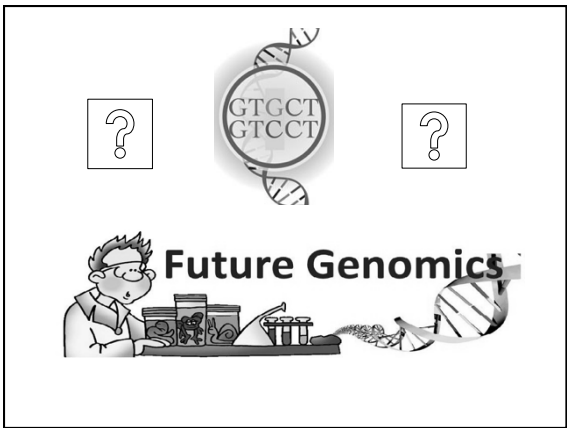
J Clin Psychiatry 2009; 70:1688-1697.
BMJ 2010; 340:c693. doi: 10.1136/bmj.c693.
http://medicine.iupui.edu/clinpharm/COBRA/Tamoxifen%20and%202D6v7.pdf

Fig 1: Risk of Breast Cancer Mortality Associated with Increasing Proportions of Antidepressant Use During Tamoxifen Treatment



BMJ

Kelly CM, et al. *BMJ* 2010; 340:bmj.c693



Enzymes/Receptors Some Sound Science

Pharmacokinetics: what body does to drug

- Catechol-*O*-methyltransferase (*COMT* Val158Met)
- Drug transporters such as ABCB1/MDR1
- Serotonin Transporter SLC6A4/5HTTLPR
- UDP-glucuronyltransferase (UGT) enzymes
  - two families, UGT1 and UGT2

Pharmacodynamics: what drug does to body

- Serotonin Receptor (5HT2C): weight gain from antipsychotics
- serotonin 2A receptor polymorphism (*HTR2A*, T102C)
- Brain-derived neurotrophic factor (BDNF)
- opioid receptor gene (*OPRM1, p.118 A/G)*

Preemptive Pharmacogenomic Testing

- Low cost sequencing
- Theoretically be available prior to any prescribing decision
- Considered for every patient just like allergy and age!!
- Storing the sequencing info for the future
  - In an iron-gated, encrypted cloud?
  - Accessible in the future when needed

Potential Usefulness of Pharmacogenetic Testing

- Prediction of dose (initial and ongoing)
- Prediction of toxic side effects
- Prediction of therapeutic effects
- Prediction of drug-drug interactions
- Positive effects on measurable outcomes?
  - ER visits, hospitalizations, ⇧ quality of life, ⇩ cost
  - Some published, some ongoing

General Items to Ponder

- Cost Issues: Who Will Pay?
  - Potential emotional and financial liability associated with genetic information
- Consumer Protection and Privacy
  - In May 2008, the Genetic Information Nondiscrimination Act or GINA, was enacted
- Direct to Consumer Genome wide Profiling?
  - Has the time come?
  - Oversight of labs and quality control
    - FDA does not regulate most laboratory- developed tests
    - Evaluation of Genomic Applications in Practice and Prevention (EGAPP) http://www.egappreviews.org/default.htm

Cinnamon S. Bloss, Ph.D., Nicholas J. Schork, Ph.D., and Eric J. Topol, M.D.January 12, 2011 (10.1056/NEJMoa1011893)

Select Useful Websites

- http://www.genome.gov The National Human Genome Research Institute (NHGRI)
  - http://www.youtube.com/user/GenomeTV
- http://www.stsiweb.org/index.php The Scripps Translational Science Institute (STSI)
- http://www.pharmgkb.org/page/cpic Clinical Pharmacogenetics Implementation Consortium
- http://www.cdc.gov/genomics/gtesting/EGAPP/index.htm
- http://www.pharmacogenomics.ucsd.edu PharmGenEd™
- http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

Online Resources for Evidence Based Guidelines

Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network (CPIC)	www.pharmgkb.org/page/cpicGeneDrugPairs
Evaluation of Genomic Applications in Practice and Prevention (EGAPP)	www.egappreviews.org/resources/links.htm#evidence
Agency for Healthcare Research and Quality (AHRQ)	www.guideline.gov/search/search.aspx?term=pharmacogenetics