

Joint Session: Biological Sciences,
Chemistry, and Pharmaceutics Sections:
General Overview

**Pharmacogenomics: Implementation and
Integration into the Curriculum**

William T. Beck

University of Illinois at Chicago

**ACCP Symposium
Boston, July 21, 2009**



Lecture Outline

- Why teach PGx?
 - PGx and individualized medicine
 - PGx tests required by FDA
 - How do we use PGx information in the clinic?
- Background – starting in 2002 (AJPE report)
- PGx in pharmacy curriculum
- Challenges and concerns
- Next steps
- Recommendations and Conclusions
- Specifics in next lectures

Why do we need to teach pharmacogenomics in colleges/schools of pharmacy?

The era of personalized medicine is fast approaching

- We are entering an era of Genomic Medicine
- We have the opportunity to think about individualized medicines with increased efficacy and decreased toxicity
- Pharmacogenomics (PGx) will impact on genomic medicine
- **Is this true?**





Pharmacogenomics

- One of the promises of the **human genome project**
- Will be a major thrust in post-genomic molecular medicine
- Has potential to revolutionize medicine by individualization of therapy
 - More effective medicines
 - Fewer side effects

* this drug knows everything about Mr. Holliday.

It's tailor-made for his DNA. IBM and IBM Business Partners are working to support research that is making personalized medicine a reality. From data-mining algorithms and vast supercomputing power to secure genomic information warehouses, we're helping pharma and biotech companies shorten drug development cycles, streamline clinical trials, and bring new targeted treatments to market. Want innovation for growth? Talk to the innovator's innovator. Call on IBM. To learn more, visit ibm.com/healthcare/personalized

what makes you special?

IBM



IBM, the IBM logo and What Makes You Special? are registered trademarks or trademarks of International Business Machines Corporation in the United States and/or other countries. Other company, product and service names may be trademarks or service marks of others. ©2008 IBM Corporation. All rights reserved.

Genetic tests are required, recommended, or mentioned by the FDA for the following drugs:

[Abacavir](#)
[Atorvastatin](#)
[Azathioprine](#)
[Carbamazepine](#)
[Clopidogrel](#)
[Dasatinib](#)
[Imatinib](#)
[Irinotecan](#)
[Rasburicase](#)
[Trastuzumab](#)
[Valproic acid](#)
[Warfarin](#)

Drugs with mounting pharmacogenomic evidence:

[HMG CoA Reductase Inhibitors](#)
[Phenytoin](#)

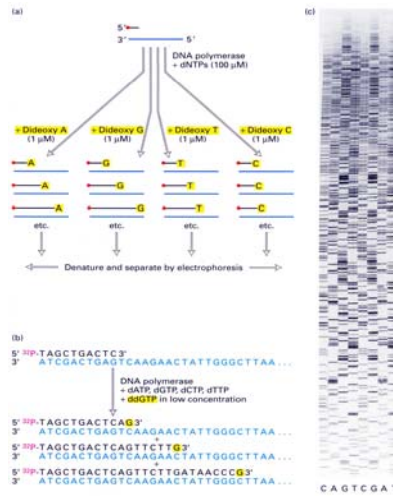
<http://www.pharmgkb.org/clinical/index.jsp>

Pharmacogenomics – How does it work? Markers of genetic variation

- **Single nucleotide polymorphisms (SNPs)**
 - **AGG** → **AGC**
 - **Arg** → **Ser**
- May encode novel or different amino acids, altering protein structure or expression
- Likely the basis of individual differences in responses to drugs.

How are SNPs measured?

- Collect patient tissue or blood and prepare DNA
 - **Issues of privacy**
- Markers of genetic variation are single nucleotide polymorphisms (SNPs).
- These are generally measured by sequencing DNA →
- In general, SNP analysis requires expensive sequencing machines and access to human tissues
- Correlate genetic variation (gene and protein expression) with clinical response
 - (genotype → phenotype)



Roche Applied Science
The LightType System
Genotyping as Easy as Phenotyping
 Simplify SNP Genotyping in Disease-Association Studies

- **Streamlined Workflow**
 Minimize post-PCR handling steps by genotyping with melting curve analysis; create a homogeneous assay by combining optimized LightType PCR Kits with either one SimpleProbe or a pair of Hydrolysis fluorescent probes.
- **Rapid Adoption**
 Amplify 10- or 20- μ l reactions in your current 96- or 384-well block-based thermal cycler. Use the provided Primer and Probe Design Software to simplify assay design.
- **Fast Results**
 Analyze each PCR plate in only 10 minutes immediately after PCR—determine up to 12,000 genotypes in 8 hours.
- **Automated Calling**
 Use the intuitive LightType Software to automatically call sample genotypes.

For information on the LightType System, visit www.lighttype.com or contact your local sales representative.

Roche Diagnostics
 Roche Diagnostics GmbH
 Roche Applied Science
 68298 Mannheim
 Germany

Genetic tests are required, recommended, or mentioned by the FDA for the following drugs:

- [Abacavir](#)
- [Atorvastatin](#)
- [Azathioprine](#) 6-MP: TPMT
- [Carbamazepine](#)
- [Clopidogrel](#)
- [Dasatinib](#)
- [Imatinib](#)
- [Irinotecan](#) UGT 1A1
- [Rasburicase](#)
- [Trastuzumab](#)
- [Valproic acid](#)
- [Warfarin](#)

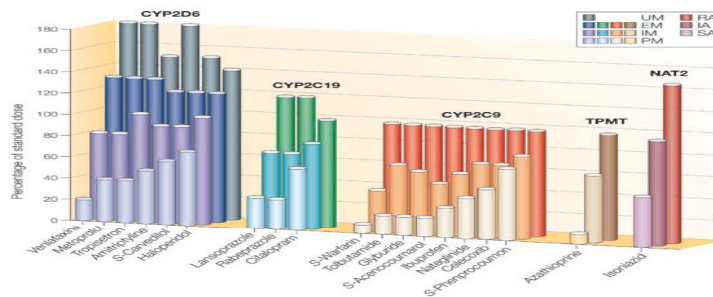
Drugs with mounting pharmacogenomic evidence:

- [HMG CoA Reductase Inhibitors](#)
- [Phenytoin](#)

<http://www.pharmgkb.org/clinical/index.jsp>

How do we use PGx in the clinic today?

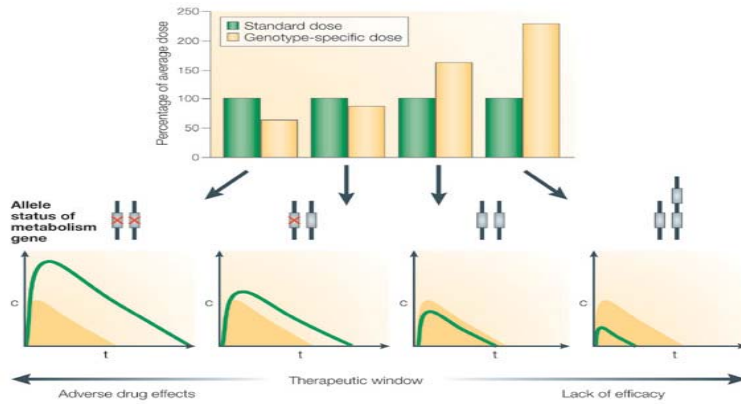
→ DOSE ADJUSTMENT ←



Copyright © 2005 Nature Publishing Group
Nature Reviews | Drug Discovery

Examples of dose adjustments based on PGDx.
Kirchheiner, Fuhr and Brockmoller. NRDD 4:639-647, 2005

How we use PGx information now: Dose Adjustment to reduce toxicity

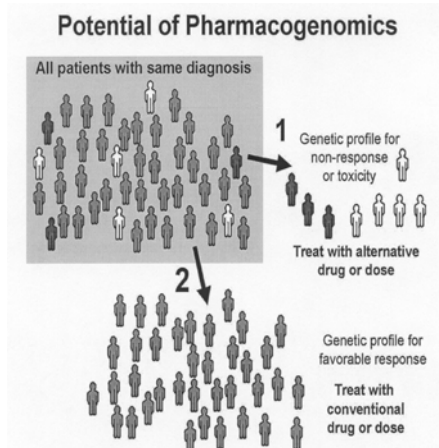


Copyright © 2005 Nature Publishing Group
Nature Reviews | Drug Discovery

Schematic showing the potential benefit of adjusting dose to genotype.
Kirchheiner, Fuhr and Brockmoller. NRDD 4:639-647, 2005

Pharmacogenomics and Individual Response

- **Goal** – to understand impact of genetics on therapeutic response outcome
- **Relationships** – phenotype-genotype
 - **Phenotype:** disease state, PK variability, response to (drug) therapy
 - **Genotype:** a specific variation in a DNA sequence from a “consensus” sequence
- **Ideally** – predict patient response to therapy based on genetic variation



Evans and Johnson, *Annu Rev Genomics Hum Genet* 2:9-39, 2001

TPMT polymorphisms and 6-MP toxicity: Dose Adjustments Based on PGx Markers

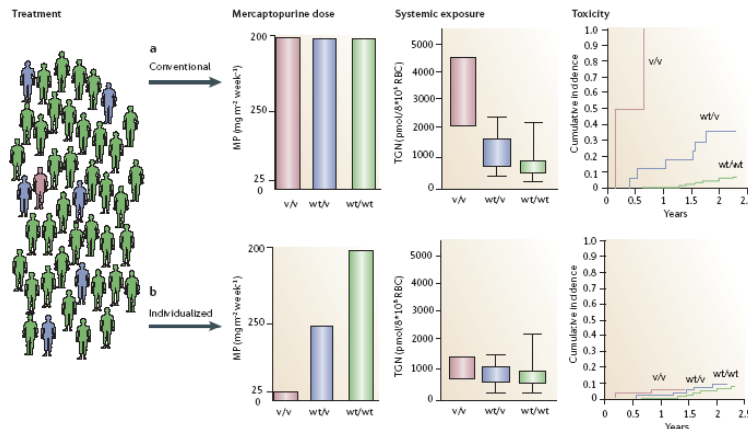


Figure 3 | Effects of thiopurine methyltransferase polymorphisms on the pharmacogenetics of mercaptopurine toxicity. When mercaptopurine (MP) treatment is given to a cohort of patients, dosing can be uniform (a) (that is,

Cheok and Evans, Nat Rev Cancer 6:117, 2006

Why do we need to teach
pharmacogenomics
in colleges/schools of pharmacy?

Because PGx is becoming increasingly important in pharmacotherapy management, especially to minimize drug toxicity, to help individualize treatment

Background – AJPE Report

- The new era of PGx in Pharmacy Education was ushered in by the Johnson report in AJPE in 2002
 - Johnson JA, Bootman JL, Evans WE, Hudson RA, Knoell D, Simmons L, Straubinger RM, Meyer SM. Pharmacogenomics: A scientific revolution in pharmaceutical sciences and pharmacy practice. Report of the 2001-2002 Academic Affairs Committee. *Am J Pharmaceutical Edu* 66 (Winter Supplement):S12-S15, 2002

The AJPE Report ...

- Stated that “the ultimate goal of PGx is to define the contributions of inherited differences in drug disposition and/or targets to drug response, and thereby improve the safety and efficacy of medications through the use of genetically guided, individualized treatment.”
- In other words, to provide for individualized medicine by a genetic/scientific approach
- And Pharmacists were to become leaders in this new era
- Are we getting there?

The AJPE Report asked several questions ...

- How will PGx change the practice of pharmacy?
- Over what timeframe will we see the impact of PGx on the practice of pharmacy?
- How might pharmaceutical education respond in light of this evolving knowledge base and meet the needs of the profession, health care system, and society?

The AJPE Report asked ...

- How will PGx change the practice of pharmacy?
 - Potential to yield a powerful set of molecular diagnostics – patient-specific genotype data – to aid pharmacists and physicians in selecting proper medicines and doses for each individual patient
 - A single blood sample will yield data on >50,000 SNPs by microarray
 - Envisioned a report from a secure database integrating SNP data with patient's diagnosis and an algorithm for treatment options
 - These data will complement standard clinical data and the traditional roles of pharmacists in adherence to treatment, drug interactions, etc
 - **PGx was envisioned to make the practice of pharmacy and medicine less of an art and more of a science by improving efficacy and reducing toxicity of pharmacotherapy**

The AJPE Report asked ...

- Over what timeframe will we see the impact of PGx on the practice of pharmacy?
 - As of 2002, it was envisioned take a decade or more to be fully developed
 - Applications 7 years ago were mostly for anticancer drugs, but the expectation was that PGx relationships for drugs for other indications would be developed
 - The report was prescient in that it foreshadowed
 - the increased activity of pharma, genomic and biotech companies, academic centers;
 - progressively lower cost of individual complete genomic sequence; and
 - the challenge of determining the combinations of genes that are important in determining drug effects in patients

The AJPE Report asked ...

- How might pharmaceutical education respond in light of this evolving knowledge base and meet the needs of the profession, health care system, and society?
 - Building on the 1990 AACP white paper on the impact of biotechnology upon pharmacy education, the AJPE report noted that teaching genomics and similar subjects remained elementary, but ...

- “Pharmacy colleges and schools and practitioner organizations must play a central role in educating health professionals on how best to use the applications of advancing pharmacogenetic and pharmacogenomic research, and
- in articulating the role of pharmacists and pharmaceutical scientists in the development and use of gene-based therapies, as well as in making treatment choices as a result of available patient-specific genetic information.”
- Are we there yet? Are we doing this?

AJPE Report Conclusions ...

- Curricular outcomes and instructional strategies
 - *Recommendation* - revise course offerings
- Faculty development needs
 - *Recommendation* – AACP should compile and maintain online inventory of activities of member institutions re PGs, PGx, bioinformatics for patient care, education, etc
 - *Recommendation* – focus on impact of PGx and bioinformatics in the AACP academic sections for the 2003 mtg
 - *Recommendation* – list of competencies in PGx for pharmacists
- **These recommendations have been around for some time!**
- Have we met our curricular needs? PGx competencies?
- Do we have online inventories of PGx and bioinformatics offerings in all of our colleges/schools of pharmacy?

So where are we now?

- Several studies have assessed the extent to which PGx is taught in colleges/schools of pharmacy
- For example ...

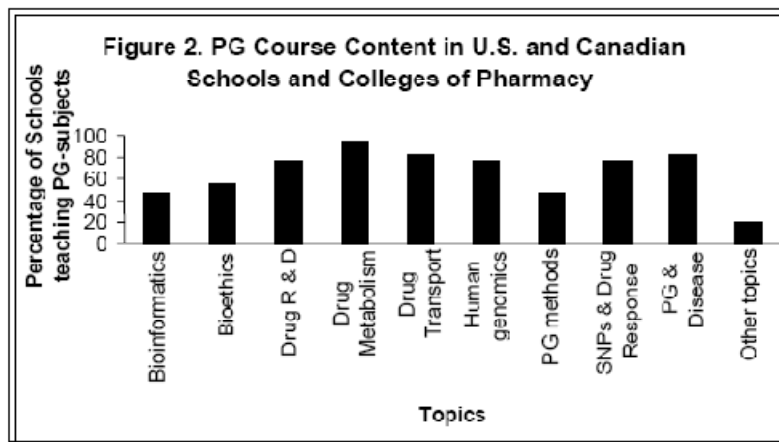
There have been some efforts to quantify PGx offerings in colleges/schools of pharmacy

- Latif and McKay. *Pharmacogenetics and pharmacogenomics instruction in colleges and schools of pharmacy in the United States*. AJPE 69(2) Article 23:152-156, 2005
- Zdanowicz, Huston, and Weston. *Pharmacogenomics in the professional pharmacy curriculum: content, presentation and importance*. Int J Pharmacy Ed, Issue 2:1-12, Fall 2006

Latif and McKay (2005) Conclusions

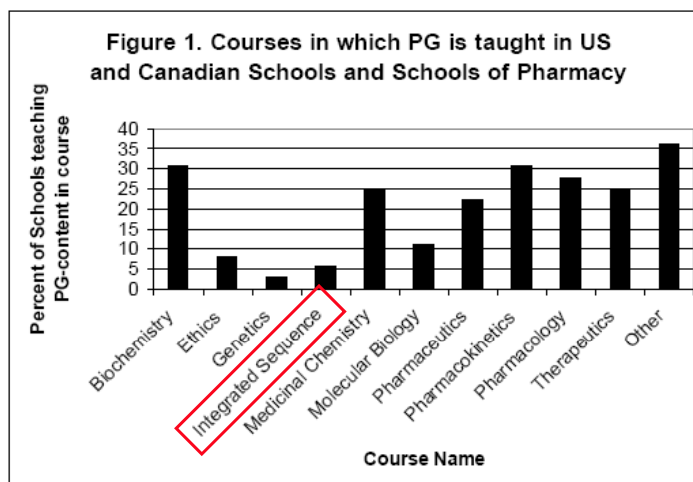
- In a small sample (n=41) of respondents, most reported that they provide some instruction in PGx and plan to increase it in the coming years.
- However, many presently do not provide the depth recommended by the AACP's Academic Cabinet
- That said, you will learn here and in the next lectures that PGx is becoming embedded in some aspects of the curriculum

PGx in the professional pharmacy curriculum



Zdanowicz, Huston and Weston, Int J Pharm Ed, 2:1-12, Fall 2006

PGx in the professional pharmacy curriculum



Zdanowicz, Huston and Weston, Int J Pharm Ed, 2:1-12, Fall 2006

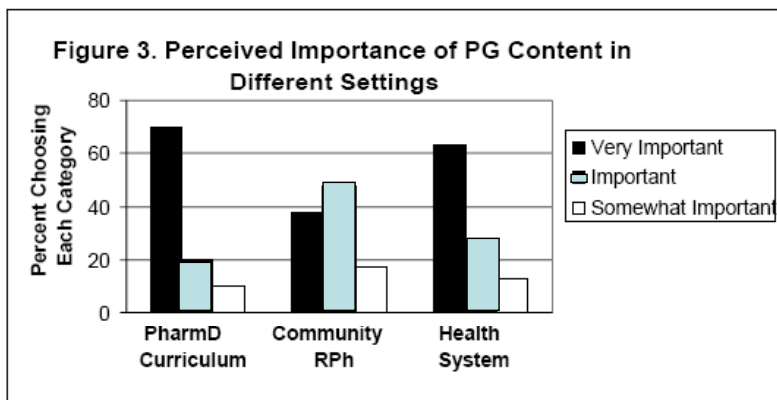
Faculty opinions as to the adequacy of PGx content in their current programs

Table 3. Faculty opinions as to the adequacy of PG content in their current programs.

Question	Those Including PG Content (N=39)	Those not including PG Content (N=7)
The current level of PG content is:		
Less than adequate	60%	NA
Adequate	37.5%	NA
More than adequate	0	NA
I believe that in the future the amount of PG content in the curriculum will:		
Decrease	0	0
Remain the Same	32.5%	16.7%
Increase	67.5%	83.3%

Zdanowicz, Huston and Weston, Int J Pharm Ed, 2:1-12, Fall 2006

PGx in the professional pharmacy curriculum



It appears that the importance of PGx in the curriculum has not yet filtered out of academia into the community

Zdanowicz, Huston and Weston, Int J Pharm Ed, 2:1-12, Fall 2006

Introducing pharmacy students to PGx tests

- P2s extracted salivary DNA
- Performed SNP analyses of NAT2
- Calculated frequency of polymorphic alleles of NAT2
- Stratified class into different acetylators (hi, med, low)
- Attitudinal survey to evaluate whether goals had been achieved
- **Conclusion:** introduction of modern, fast-throughput genotyping technologies to curriculum facilitated comprehension of the potential and relevance of PGx for pharmacy practice

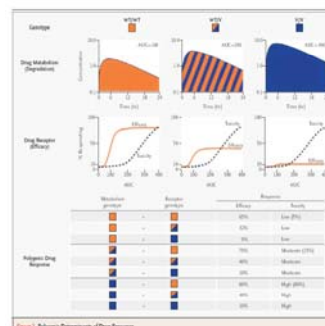
Krynetskiy and Calligaro, AJPE 73(4): Article 71 (2009)

PGx is now taught in many colleges and schools of pharmacy

- Major emphases at UCSD, UCSF, Buffalo, others
- Many others have PGx integrated into many aspects of their curricula (UIC, U Conn, OSU, U Wash, U Minn)
- Even an undergraduate major at GWU, in conjunction with the Dunn School of Pharmacy (even a Dept of Pharmacogenomics) at Shenandoah Univ
- Institute of Pharmacogenomics and Individualized Therapy (IPIT) at UNC (McLeod)
- Center for Pharmacogenomics at UCSF (Giacomini)
- Apologies to those not listed

What are the challenges and concerns in the pharmacogenomics field?

- PGx does not explain all variability in drug response
 - Due to other factors? Other genes?
- Complex (multigenic) diseases
 - Cardiovascular disease
 - Rheumatoid arthritis
 - Asthma
 - Drug addiction
 - Depression
 - Inflammatory bowel disease
 - Diabetes
 - Cancer



*Evans and McLeod,
NEJM 348:538-549, 2003*

Other PGx Challenges

Challenge	Potential Approaches
Establishing that drug responses are heritable	Twin studies; family studies Linkage between drug response and genomic loci in cell lines, or model organisms
Defining candidate genes	Pharmacokinetic Pharmacodynamic Drug targets Biological milieu in which drugs act Disease genes and pathways Whole genome approaches
Defining drug responses	Biomarkers Surrogates "Hard" end points
Data management, including uniform representation of phenotypic data	Improved informatics Centralized, Web-accessible public database relating genetic variants and drug responses: www.PharmGKB.org
Reproducibility	Replication sets Large study populations
Statistical analysis of associations	New statistical methods, including consideration of haplotypes
Interrogating very large sets of polymorphisms in large numbers of patients	New platforms (e.g., chip- or bead-based)
Moving to practice	Reproducible study results Cost-effectiveness Health care provider education

Roden et al. Ann Internal Med 145:749-757, 2006

Pharmacogenomics concerns

- Serious social and ethical issues
- Identification of groups
 - How representative are the sample sets?
 - How valid are the genomic databases?
- Defines ethnic populations
 - Do we need better methods of identifying ethnically defined populations?
- Collection of highly personal and sensitive genetic information
 - DNA collection must be anonymized
 - Considerable diversity within an ethnic group

So, what's next?

And what do we as pharmacy educators do about it?

Linking oncogenic pathways with therapeutic opportunities

- Understanding the precise genetic variations that define the spectrum of cancer genomes will be essential for improved patient treatment and potential cure (The Cancer Genome Atlas)
- Develop a comprehensive understanding of the consequences of these alterations – the changes in gene activity and regulation that ultimately define a cancer phenotype
 - (Bild et al, Nat Rev Cancer, 2006)
- I would argue that pharmacists need to be involved in these efforts in order to improve pharmacotherapy management

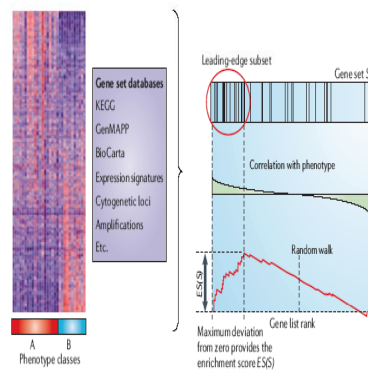


Figure 1 | Gene-set-enrichment analysis. Genes in an expression profile selected to distinguish two

*Bild et al. Nat Rev Cancer
6:735-741, 2006*

Conclusions

- We can do a better job in integrating PGx into the entire curriculum of pharmacy education
- We as a community need to address the AJPE conclusions:
 - Make the practice of pharmacy less of an art and more of a science
 - Play a central role in educating health professionals on how best to use the applications of advancing PGx research
- I support the conclusions of the AJPE report that the AACP should
 - compile and maintain an online inventory of PGx activities and courses of member institutions, and, importantly,
 - develop a list of competencies in PGx for pharmacists.

Lecture Summary

- Why teach PGx?
 - PGx and individualized medicine
 - PGx tests required by FDA
 - How do we use PGx information in the clinic?
- Background – starting in 2002 (AJPE report)
- PGx in pharmacy curriculum
- Challenges and concerns
- Next steps
- Recommendations and Conclusions
- Specifics in next lectures

Thank you for your attention

Questions?