Research and Scholarship Curricular Track—
Research and the Clinical Pharmacist in 2010
Activity No. 217-000-10-028-L01-P
This is an application-based activity.

Conducting Pharmacogenomics Research: A Primer

2:30 p.m.–4:30 p.m.
Convention Center: 213 D

Moderator: J. Herbert Patterson, Pharm.D., FCCP
Professor of Pharmacy and Research Professor of Medicine, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina

2:30 p.m.	Using the PBRN as a Research Tool for Pharmacogenomics Research *Grace M. Kuo, Pharm.D., MPH* Director of ACCP PBRN, American College of Clinical Pharmacy Research Institute, Lenexa, Kansas;Associate Professor, University of California, San Diego, California; Skaggs School of Pharmacy and Pharmaceutical Sciences; Associate Adjunct Professor of Family and Preventive Medicine, UCSD School of Medicine; Director of San Diego Pharmacist Resource & Research Network, La Jolla, California
3:00 p.m.	Sorting the Wheat from the Chaff: Statistical Issues with Pharmacogenomics *Alison A. Motsinger-Reif, Ph.D.* Assistant Professor, North Carolina State University, Raleigh, North Carolina
3:30 p.m.	Pro-Con Debate on Prospective Study Designs: Convenience Cohorts vs. Randomized Samples *Michael A. Pacanowski, Pharm.D.* Clinical Pharmacologist, U.S. Food and Drug Administration, Silver Spring, Maryland *Craig R. Lee, Pharm.D., Ph.D.* Assistant Professor of Pharmacy, University of North Carolina at Chapel Hill, Eshelman School of Pharmacy, Chapel Hill, North Carolina

Faculty Conflict of Interest Disclosures

Grace M. Kuo: consultant/member of advisory board for ACCP's Practice Based Research Network (PBRN); clinical investigator for PharmGenEd™ Education Program; received grant funding/research

support from Centers for Disease Control and ACCP Research Institute (RI); received assistance to attend this meeting from ACCP's RI.
Craig R. Lee: no conflicts to disclose.
Alison A. Motsinger-Reif: no conflicts to disclose.
Michael A. Pacanowski: no conflicts to disclose.

Learning Objectives

1. Provide examples of pharmacogenomics research that can be conducted within a practice-based environment such as a PBRN.
2. Identify challenges to conducting pharmacogenomics research within a practice-based environment.
3. Discuss benefits to conducting pharmacogenomics research within a practice-based environment.
4. Provide examples of appropriate statistical techniques for use with pharmacogenomics studies.
5. Discuss statistical challenges commonly encountered when conducting pharmacogenomics research.
6. Critically appraise statistical techniques used in published pharmacogenomics papers.
7. Identify factors to consider in choice of study design for a pharmacogenomics study.
8. Articulate the positive reasons for using a convenience cohort when conducting a pharmacogenomics study.
9. Discuss the logic against using a randomized sample in conducting a pharmacogenomics study.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/sf

Using the PBRN as a Research Tool for Pharmacogenomics Research

April 24, 2010

Presenter:
Grace M. Kuo, PharmD, MPH (UCSD)

Objectives

- Provide examples of pharmacogenomics research that can be conducted within a practice-based environment such as a PBRN.
- Identify challenges to conducting pharmacogenomics research within a practice-based environment.
- Discuss benefits to conducting pharmacogenomics research within a practice-based environment.

ACCP PBRN

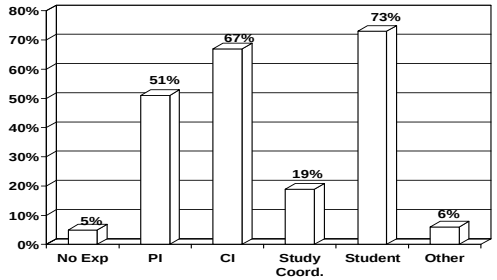
- **Mission Statement**
  - The mission of the ACCP PBRN is to facilitate collaborative research that promotes the safe, efficacious, and cost-effective use and delivery of medications and clinical pharmacy services.

ACCP PBRN Members

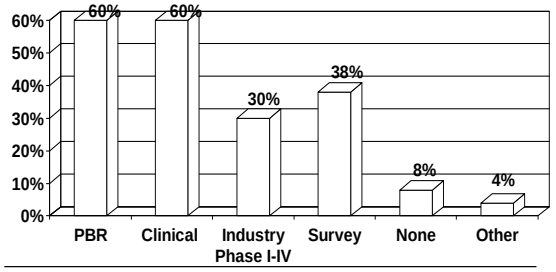
- Total n=695
  - 416 individual members +
  - 257 members (from existing PBRNs and integrated health systems +
  - 22 members opted out of this research arm.
- Currently involved in clinical research as an investigator, sub-investigator or study coordinator.
  - 248 (60%) are currently involved
- Average of 9 years since terminal degree/training.

ACCP PBRN Members (n=416) *one dot denotes one zip code

Clinical Research Experience Among PBRN Members (n = 416)



Types of Human Subjects Research Conducted by PBRN Members (n = 416)



ACCP PBRN Registry: PRN Counts*

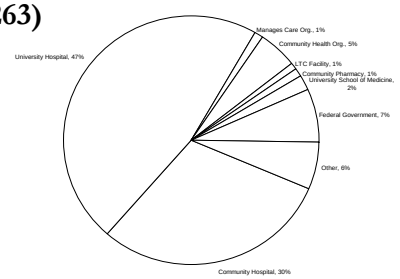
COUNT	PRN Code	PRN Name	COUNT	PRN Code	PRN Name
57	AMED	Adult Medicine	15	GILN	GI/Liver/Nutrition PRN
92	AMBU	Ambulatory Care	8	OCEC	Health Outcomes
68	CARD	Cardiology	38	HMON	Hematology/Oncology
13	CNSY	Central Nervous System	22	IMTR	Immunology/Transplantation
19	CADM	Clinical Administration	71	INFD	Infectious Diseases
85	CRIT	Critical Care	17	NEPH	Nephrology
8	DINF	Drug Information	17	PAIN	Pain and Palliative Care
45	EDTR	Education and Training	34	PEDI	Pediatrics
10	EMED	Emergency Medicine	3	INDU	Pharmaceutical Industry
22	ENDO	Endocrine and Metabolism	10	PKPD	Pharmacokinetics/Pharmacodynamics
15	GERI	Geriatrics	14	WOMN	Women's Health

**Note: An individual may belong to more than 1 PRN*

ACCP PBRN Registry: Unique Clinical Sites (n=263)

- 45 States Represented
- 263 Sites Registered + 105 sites from existing PBRNs and integrated health systems
- 95% of sites in urban areas vs. 5% rural areas
- Ethnicity distribution of patients seen at sites
  - Hispanic or Latino: 20%
  - Not-Hispanic and Latino: 77%
  - Unknown: 3%
- Racial distribution of patients seen at sites
  - White, Caucasian: 58%
  - Black, African American: 28%
  - Asian: 8%
  - Native Hawaiian/Other Pacific Islander: 2%
  - American Indian/Alaska Native: 2%
  - Unknown: 2%

ACCP PBRN Registry: Unique Clinical Practice Sites (n=263)



ACCP PBRN Registry: Unique Clinical Practice Sites (n=263)

	Inpatient (n)	Outpatient (n)
Community Hospital or Health System	81% (63)	38% (30)
University Hospital or Academic Center	74% (89)	51% (62)

ACCP PBRN Registry: Unique Clinical Sites (n=263)

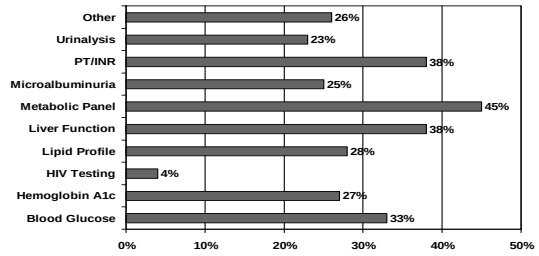
- 172(65%) site have EMR
- Patient chart characteristics:
  - 7% use paper charts
  - 23% are totally paperless
  - 70% use a hybrid system
- 37 (31%) of sites have a central IRB

ACCP PBRN Registry: Clinical Practice

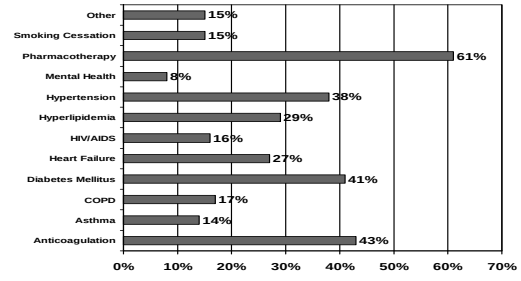
Mean (+/- SD)

- 344 practices registered
- 83% Provide clinical pharmacy services
  - Half-days/week: Mean 5.4(4)
  - Number of patients seen/week: Mean 42(42)
- Patient distribution:
  - Adults: 76%
  - Pediatric: 9%
  - (unspecified:15%)
- 35% have collaborative practice agreements
- 33% have scope of practice agreements

Tests Pharmacists Perform/ Order (n=344)



Conditions Routinely Managed By Pharmacists (n=344)

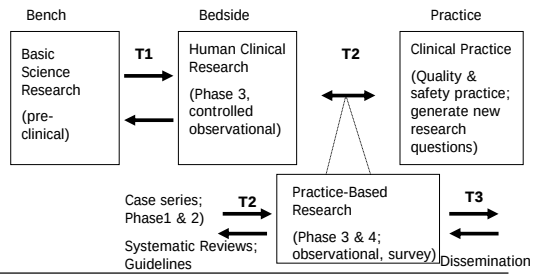


Summary of ACCP PBRN

- ACCP PBRN includes over 600 pharmacists representing almost every state in the US.
- Most members have research experience.
- Majority of clinical practice sites are located in the urban areas serving patients with multiethnic backgrounds.
- Clinical services provided by network pharmacists include pharmacotherapy and chronic disease management (anticoagulation, diabetes, hypertension, hyperlipidemia, heart failure, etc.).

Practice-Based Research—"Blue Highways" on the NIH Roadmap

Adapted from: Westfall, JM, Mold J, Fagnan L. Practice-Based Research—"Blue Highways" on the NIH Roadmap. JAMA 2007;297(4): 403-06



Examples

- Clinical trials
  - Case-series
  - Observational, population studies
  - Case-control or Cohort studies
  - Randomized Controlled trials
- Clinical practice
  - Practice patterns
  - What/how pharmacogenomics is integrated into clinical practice
- Bridging the gap
  - Health-system interventions and implementation
  - Training programs
  - Assessment and evaluation of clinical practice based on guidelines and evidence-based recommendations

Challenges

- Multiple IRB approval processes and requirements
- Lack of resources to support multi-site studies
- Consistency in multiple investigator training and subject recruitment
- Lack of integration of informatics tools from multiple sites
- Need for central coordinating center and statistical cores

Benefits

- Large sample sizes and study power
- Wide geographical distribution of sites
- Collaborative efforts among investigators and participants
- Community engagement
- Enhanced academic and community partnerships
- Increased generalizability

Questions or Comments?

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Sorting the Wheat from the Chaff: *Statistical Issues with Pharmacogenomics*

Alison Motsinger-Reif, Ph.D.
Bioinformatics Research Center
Department of Statistics
North Carolina State University
motsinger@stat.ncsu.edu

Learning Objectives

- Provide examples of appropriate statistical techniques for use with pharmacogenomics studies.
- Discuss statistical challenges commonly encountered when conducting pharmacogenomics research.
- Critically appraise statistical techniques used in published pharmacogenomics papers.

Steps in "Gene Mapping"

- Defining a phenotype for association mapping
- Determining the genetic component of a trait
- Study designs and analytical tools
- Genotyping strategies
- Replication, validation, and interpretation of results

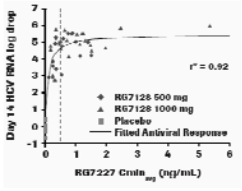
Steps in "Gene Mapping"

- Defining a phenotype for association mapping
- Determining the genetic component of a trait
- Study designs and analytical tools
- Genotyping strategies
- Replication, validation, and interpretation of results
- Statistics plays a crucial role in EVERY stage

of gene mapping!

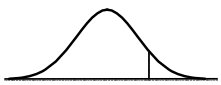
Defining a Phenotype

- Defining a phenotype is both a biological and statistical choice
- Especially true in PGX
  - Outcomes are often generated through modeling
  - ADME modeling, PK/PD modeling, etc.



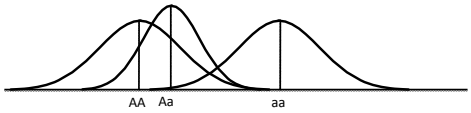
Broad Classes of Phenotypes

- Qualitative traits
  - Presence or absence
    - Toxicities: Affected or unaffected
    - PGX: responders vs. nonresponder
    - "unaffected" does not equal absence of trait
  - Threshold-based diagnosis
    - Toxicities, response, etc
    - May lose information



Broad Classes of Phenotypes

- Quantitative traits
  - Continuous measurements
    - Stable dose, blood pressure, etc
  - Advantages of quantitative traits
    - Many complex traits have quantitative characteristics that are directly related to trait risk
    - Can provide more effective descriptions of complex diseases
    - Analyses on quantitative traits can be powerful alternatives to analyses directly on disease status



Summary Points on Phenotyping

- Well defined phenotypes are crucial for association mapping!
  - Becomes increasingly important as association studies grow in scale
- Any type of phenotype can be evaluated in any study design.
  - Just need to match up
- When planning or reviewing a study, need to think about the consequences of the phenotype definition choices.

Determining the Genetic Component of a Trait

- First step in a gene mapping study is determining whether a trait has a genetic component.
  - Characterizing the sharing
- Characterizing the genetic basis of a trait is important before starting a mapping study.
  - This can be a particular challenge in PGX outcomes!!!

Methods for Assessing the Genetic Component of a Trait

- Familial aggregation
- Twin Studies
- Segregation analysis
- Increased risk to relatives
- Animal models

Heritability of a Quantitative Trait

- h^2: Proportion of observed variance in phenotype explained by genetic factors
  - $h^2 > 0$ indicates the presence of genetic contributions to the trait
  - Magnitude indicates "how genetic" the trait is
- Decomposition of total variance:
- $\sigma_T^2 = \sigma_G^2 + \sigma_E^2$
  (total = genetic + environmental)
- $\sigma_G^2 = \sigma_a^2 + \sigma_d^2 + \sigma_I^2$
  (genetic = additive + dominance + interaction among genes)
- $\sigma_E^2 = \sigma_f^2 + \sigma_e^2$
  (environmental = familial/household + random/individual)
- Broad sense heritability $h_B^2 = \sigma_G^2/\sigma_T^2$
- Narrow sense heritability $h_N^2 = \sigma_a^2/\sigma_T^2$ (more commonly used)

Estimation of Heritability

- Twin studies: $h^2 = 2(r_{MZ} - r_{DZ})$
- Pedigree data: Estimate σ_G^2 (or σ_a^2) using information on relationship, ascertainment criteria, and covariates (age, gender, etc) using variance components methods
  - MERLIN
    http://www.sph.umich.edu/csg/abecasis/merlin/
    - Abecasis GR, Cherny SS, Cookson WO and Cardon LR. (2002) Merlin-rapid analysis of dense genetic maps using sparse gene flow. Nat Genet 30:97-101
  - SOLAR http://solar.sfbrgenetics.org/
    - Almasy L, Blangero J (1998) Multipoint quantitative trait linkage analysis in general pedigrees. Am J Hum Genet 62:1198-1211.

Estimation of Heritability

- Caveats:
  - Estimates are dependent on model assumptions
  - Estimates may be difference across populations even if the genetic contribution is the same
  - Over-estimation may result from failure to adjust for important covariates, failure to include important variance components, failure to correct for ascertainment
  - Under-estimation may result from the inclusion of too many covariates in the model

Genetic Component of Qualitative Traits

- λ_x: relative risk ratio; risk to relative (x) of an affected individual compared to the risk in general population (K = prevalence)
  - $\lambda_x > 1$ indicates the presence of genetic contributions to the trait
  - Generally the magnitude indicates "how genetic" the trait is
  - Could also reflect shared environment

$$\lambda_x = \frac{K_x}{K}$$

Genetic Component of Qualitative Traits

$$\lambda_x = \frac{K_x}{K}$$

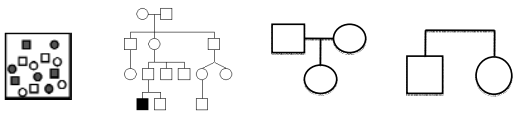
- Encompasses all genetic and shared environmental effects, not just those due to a single locus
- K for the general population is often estimated from previous studies
- Note: the magnitude of the estimate is very dependent on the frequency in the population

Summary Points on Establishing Genetic Components

- When planning or reviewing a study, evaluate "how genetic" a trait is.
- How much of the variation is explained by known genetic components?
  - Gap between heritability and known effects motivates follow up studies

Designs for Association Studies

- Population-based and family-based designs
  - Can evaluate any type of phenotype within any study design
  - Practical and theoretical advantages and disadvantages of each design, particularly for PGX outcomes
- Wide range of association tools available
  - Specifics depend on study design and types of independent and dependent variables
- Main goal is the same: correlate phenotypic and genotypic variability!



Study Design	Description
Cross-Sectional	Genotype and Phenotype collected across a random sample of the population; quantitative or qualitative traits
Cohort	Genotype subsection of population and follow disease incidence for a specific time period
Case-Control	Genotype collection of individuals with trait/phenotype, matched with samples without the trait
Extreme Values	Genotype collection of individuals at the upper and lower extremes of quantitative trait distribution
Trios; Sibling Pairs	Genotype affected individuals plus their parents or
Case-parent-grandparent septets	Genotype affected individuals plus their parents and grandparents
General Pedigrees	Genotype and phenotype random sample or trait selected sample of families from the general population
Case-only	Genotype only affected individuals

Study Design	Advantages	Disadvantages
Cross-Sectional	Inexpensive; provides estimates of disease prevalence	Few affected individuals if the disease is rare
Cohort	Provides estimate of disease prevalence	Expensive to follow-up; drop-out can cause issues
Case-Control	No need to follow-up; provides estimates of exposure effects	Requires careful selection of controls; potential for confounding (population stratification, etc)
Extreme Values	Genotype only the most informative individuals so save on genotyping costs	No estimate of true genetic effect sizes
Trios; Sibling Pairs	Robust to population stratification; can estimate maternal and imprinting effects	Less powerful than case-control design
Case-parent-grandparent septets	Robust to population stratification; can estimate maternity and imprinting effects	Grandparents rarely available
General Pedigrees	Higher power with large families; samples may already exist from linkage studies	Expensive to genotype; many missing individuals
Case-only	Very powerful design for detection of interactive effects	Very sensitive to population stratification

Study Design	Statistical Analysis Method
Cross-Sectional	Logistic regression, Chi-Square tests of association; linear regression; nonparametric
Cohort	Survival analysis methods
Case-Control	Logistic regression; Chi-Square tests of association; nonparametric
Extreme Values	Linear regression, non-parametric, or permutation approaches
Trios; Sibling Pairs	Transmission/disequilibrium test; conditional logistic regression, log-linear models
Case-parent-grandparent septets	Linear models
General Pedigrees	Pedigree Disequilibrium Test (PDT); Family-based Association tests (FBAT); Quantitative Transmission/disequilibrium test (QTDT)
Case-only	Logistic regression; Chi-Square tests of association; nonparametric

Specific Concerns In PGX

- Family based samples are rarely available
- Rare adverse events can limit sample size
- Nesting within clinical trials can limit study design and sample size
  - Consent
  - Treatment arms

Study Design Conclusions

- Lots of options for study design
  - Sample collection and genotyping
- Choices depend on resources
  - Sample availability, budget
- Analytical methods depend on details of study design

Statistical Methods for Data Analysis

- The study design, type of phenotype, and distributional assumptions make a decision tree for the choice of statistical test
  - Parametric vs. nonparametric tests
- Genotypes enter the statistical model as categorical variables
  - Encoding makes genetic assumptions
  - Dominance, additivity, etc.

Analysis Method	Description	Software	Links
Logistic Regression	Model log of odds of disease as a linear function of genotype	Standard statistical packages	www.r-project.org www.sas.com www.insightful.com/products/splus www.stata.com
Chi-Square Test of Association	Test for independence of disease status and genotype status	Standard statistical packages	Above
Linear Regression	Model quantitative trait as a linear function of genotype	Standard statistical packages	Above
Survival Analysis	Model survivor function or hazard as a function of genotype	Standard statistical packages	Above
Transmission/Disequilibrium Test	Test for departure of allele transmission from heterozygous parents to affected offspring from null hypothesis of 1/2	Various (ex: GeneHunter, GenAssoc, Unphased)	http://linkage.rockefeller.edu/soft/gh/ http://www-gene.cimr.cam.ac.uk/clayton/software/stata/genassoc/ www.mrc-bsu.cam.ac.uk/personal/frank/software/unphased/

Analysis Method	Description	Software	Links
Conditional Logistic Regression	Calculate conditional probability of affected offspring genotypes given parental genotypes	GenAssoc Unphased	http://www-gene.cimr.cam.ac.uk/clayton/software/stata/genassoc/ www.mrc-bsu.cam.ac.uk/personal/frank/software/unphased/
Log Linear Models	Model counts of genotype combinations for mother, father, and offspring	Standard statistical packages	See previous slide
Pedigree Disequilibrium Test	Test for departure of allele transmission to affected pedigree members from null	PDT	http://www.chg.duke.edu/software/pdt.html
Family-Based Association Tests	Test for linkage or association between traits and haplotypes using family based controls	FBAT	http://biosun1.harvard.edu/~fbat/fbat.htm
Quantitative TDT	LD analysis based on variance components	QTDT	http://www.sph.umich.edu/csg/abecasis/QTDT/

Considerations in Data Analysis

- Are the methods applied appropriate?
  - Match the study design, etc.
  - Distributional assumptions were checked
- What were the genetic assumptions in the model and were they appropriate?
- Was the study well powered? How does this influence conclusions?

Genotyping Strategies

- Genotyping technology is rapidly changing genotyping strategies in association studies
  - Association analyses are the same within each strategy
  - Scale is different
- Candidate Gene
- Genome-Wide Association Studies
- Next-generation Sequencing
  - Open methods questions…..

Statistical Issues in Genotyping

- Just as statistics plays an important role in phenotyping, it plays a crucial role in genotyping as well.
- Important steps in quality control (QC) for genotype data:
  - Tests for Hardy-Weinberg Equilibrium
    - Can detect genotyping error
    - Chi-square, trend, or exact tests used to test observation versus expectation of genotype frequencies
  - Genotyping efficiency
    - Statistical algorithms for genotype calling
  - Population Stratification
    - Principle Component Analysis (PCA) can be used to detect association

Candidate Gene Studies

- How are candidate genes chosen?
  - Biological/network knowledge, drug mechanism
  - Clinical knowledge
  - Previous studies
- How do you pick variants within genes?
  - Potential functional significance
  - Population frequencies
  - Linkage disequilibrium in the gene
- Higher power than GWAS when the candidates are correct
  - Fewer tests
- Limited in potential to identify “novel biology”

Genome Wide Association Studies

- Genotype 100K to 3M SNPs per individual
- Two Major Platforms:
  - Affymetrix
    http://www.affymetrix.com/
  - Illumina
    http://www.illumina.com/
  - Differences in design and coverage

Advantages of GWAS

- Compared to candidate gene studies
  - unbiased scan of the genome
  - potential to identify totally novel susceptibility factors
- Compared to linkage-based approaches
  - capitalize on all meiotic recombination events in a population
    - Localize small regions of the chromosome
    - enables rapid detection causal gene
  - Identifies genes with smaller relative risks

Concerns with GWAS

- Expense
- Power dependent on:
  - Allele frequency
  - Relative risk
  - Sample size
  - LD between genotyped marker and the risk allele
  - disease prevalence
  - …….
- Study Design
  - Replication
  - Choice of SNPs
- Analysis methods
  - IT support, data management
  - Variable selection
  - Multiple testing

Major Assumptions….

- Common-Disease Common Variant (CDCV) Hypothesis
  - predicts that common disease-causing alleles, or variants, will be found in all human populations which manifest a given disease
  - each variant at each gene influencing a complex disease will have a small additive or multiplicative effect on the disease phenotype
  - Assumes traits are evolutionary neutral in part because so many genes influence the traits
  - Has held true for many diseases
    - APOE ε4 and Alzheimer's disease
- Likely not true for many diseases
  - Schizophrenia

Major Assumptions….

- Alternative…
- Common-Disease Rare Variant (CDRV) Hypothesis
  - proposes that a significant proportion of the inherited susceptibility to relatively common human chronic diseases may be due to the summation of the effects of a series of low frequency dominantly and independently acting variants of a variety of different genes
  - each conferring a moderate but readily detectable increase in relative risk
  - will mostly be population specific because of founder effects resulting from genetic drift
- GWAS chips will not detect rare variants

Sequencing

- New technologies provide the ability to process millions of sequence reads in parallel
- Major platforms:
  - Roche(454) www.454.com
  - Illumina(Solexa) www.illumina.com
  - SOLiD www.solid.appliedbiosystems.com
- Will be able to detect ALL variation in the genome
- Analysis to perform mutation detection, then association….

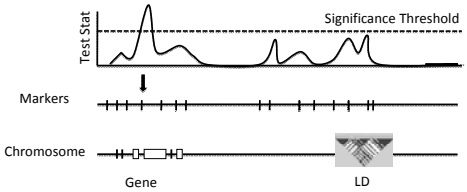
Sequencing

- Annotation of sequencing data is an important bioinformatics challenge
  - Statistics need to address the error in the data
- Rare variants present an important statistical challenge
  - How do you do association?
  - First approaches use collapsing approaches
  - Collapse by gene, by function, etc.

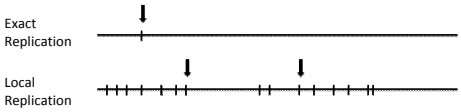
Replication and Validation

- After an association is identified…. Now what? How do you follow-up?
- Replication is gold standard
  - Detection of the same association in an independent sample
- Challenges
  - There are many negative replication studies even in the most replicated genetic associations
  - Additionally, when associations are replicated, it is often in different phenotypes, with different polymorphisms, or with different alleles

Initial Study Results



Replication Strategy



Replication Study Outcomes

Same Trait	Same Gene	Same Variant	Same Risk Model	Explanation
□	□	□	□	Exact Replication
□				Genetic Heterogeneity
□	□			Allelic heterogeneity
□	□	□		Population Differences
				Phenotypic heterogeneity

Additional Challenges

- How do you collect well-powered independent samples?
  - Expanding phenotype introduces heterogeneity
- Potential resources
  - Other data types?
  - Similar phenotypes?
  - Meta-analysis?
  - Functional studies?

New Approaches for Analysis

- Traditional statistical approaches typically cannot model the complexity of PGX traits
  - Heterogeneity
  - Interactions
  - Pathways/networks
  - New technologies create an immense variable selection problem
- Many new data-mining approaches are now being developed and applied
  - Motsinger AA, Ritchie MD, Reif DM. Novel methods for detecting epistasis in pharmacogenomics studies. Pharmacogenomics. 2007 Sep;8(9):1229-41.

Conclusions

- Statistics plays a crucial role in EVERY stage of gene mapping
- Careful consideration should be given to the appropriateness of the statistics used

Questions?

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Pro-Con Debate on Prospective Study Designs:
Convenience Cohorts Versus Randomized Samples

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Limited Incorporation of PGx into Clinical Guidelines

- Pre-requisite for pushing PGx into practice
- The epitome of evidence-based medicine
- In cardiology:
  - 11% level A (multiple RCTs or meta-analyses)
  - 41% level B (a single RCT or nonrandomized studies)
  - 48% level C (expert opinion, case studies, or standards of care)

19% of class I recommendations, i.e., procedure/ treatment is useful or effective, are based on level A evidence

Califf, et al. 2009 [PMID 19244190]

Personalized Medicine
Is this really a new concept?

Definition

- Integrating evidence generated at the population level (e.g., registries, RCT's) into clinical decisions for individual patients.
  - Diagnostics, pharmacotherapy

Can we integrate "omics" into what we already do?

The "Omics" Definition

- Integrating "omics" technology into clinical decisions
  - Genomics, biomarkers (e.g., transcriptomics, proteomics, metabolomics)

Questions to Consider

- What evidence do you need to make effective clinical decisions?
- When is it necessary to prospectively evaluate pharmacogenetic markers?

Primary Objective

In order to validate the utility of pharmacogenetic markers in a manner which will facilitate implementation into clinical practice,

we will debate the pros/cons of using:

"convenience sample" studies

versus

prospective, randomized, controlled clinical trials

"Convenience Sample" Studies
Definition

Obtaining DNA (or other biological specimens) from subsets of participants enrolled in:

an observational / registry study

OR

a prospective, controlled trial

without regard to time of enrollment and without any specific hypotheses

Key Study Design Issues to Discuss

- Scientific Rigor
- Practicality
- Potential for translation

Scientific Rigor

"Convenience Sample" Studies

Pros:

- Large numbers of samples / events can be obtained
  - Conducive to evaluation of rare events
  - Ability to assess clinical outcomes
- Opportunities for unbiased identification of the "best" pharmacogenetic marker (e.g., GWAS)

Prospective RCT's

Cons:

- Must identify the "best" pharmacogenetic marker (and therapeutic strategy) *a priori*
- Difficult to utilize clinical outcomes as endpoint
  - Typically surrogate measures

Scientific Rigor

Prospective RCT's

Pros:

- Prospectively defined hypothesis and power
- A replicated RCT provides the highest level of evidence
- Study endpoints clearly defined *a priori*

"Convenience Sample" Studies

Cons:

- No prospectively defined hypothesis or endpoints
- Subject to confounding
- Limited by number of samples collected
  - Typically subsets that may not be reflective of the overall study population (voluntary nature, temporal issues)

Case Study

***KRAS* mutations and efficacy of anti-EGFR therapy**

Practicality

"Convenience Sample" Studies

Pros:

- Opportunity for rapid validation of pharmacogenetic associations across multiple, independent studies
- Opportunity to evaluate the impact of new markers as they are discovered

Prospective RCT's

Cons:

- Substantial cost and length
  - Fewer opportunities for replication

Practicality

Prospective RCT's

Pros:

- An adequate, well-controlled trial provides eliminates need for numerous, less-than-adequate studies
- Yields actionable information

"Convenience Sample" Studies

Cons:

- Limited to available data
- "Fishing expeditions"

Case Study

***CYP2C19* genotype and clopidogrel hyporesponsiveness**

Potential for Translation

"Convenience Sample" Studies

Pros:

- Generalizable findings
  - Broad sampling of patient populations
  - Data collection in a real-world clinical environment (registries)

Prospective RCT's

Cons:

- Less generalizable findings
  - Narrowly defined populations
  - "Control" conditions may not be representative of standard of care in the real-world clinical environment
  - Trial procedures (e.g., genetic testing, monitoring) may not be feasible in clinical environment

Potential for Translation

Prospective RCT's

Pros:

- Opportunity to build in assessment of comparative treatment effects and cost-effectiveness
- Opportunity to evaluate a clinical strategy
  - Value to payers and clinicians

"Convenience Sample" Studies

Cons:

- Comparative effectiveness studies difficult

Case Study

***VKORC1*/*CYP2C9* genotyping to guide warfarin dose selection**

Questions Revisited

- What evidence do you need to make effective clinical decisions?
- When is it necessary to prospectively evaluate pharmacogenetic markers?