Study Aims:

- to understand usefulness of receiving personal genome information
- to identify new genetic sites associated with common medical conditions and drug response
Launched 2007

Goals of the CPMC Research Study

• Study the use of genome-informed medicine in a real-world clinical setting
• To identify new genetic sites associated with common medical conditions and drug response

More than 6,000 participants enrolled
How the CPMC Study works

1. Gathering data through questionnaires.
2. Processing the collected data using genomic microarrays.
3. Analyzing the data to identify genetic variations.
4. Mapping the genetic findings to online resources.
5. Sharing the research results with participants.

www.cpmc.coriell.org
Reporting Process Overview

1. Selection of Health Conditions and Variants or PGX Drug-Gene Pairs
2. Preparation of ICOB or PAG Submission Report
3. If PGX - Evaluation and Approval by PAG
4. Assessment and Approval by ICOB
5. Report Development
6. Deployment of Report to Participants

CPMC Technical Guidelines
CPMC Technical Guidelines for Health Conditions

Genetic Variant/Health Condition Selection:
- Literature search for published GWAS
- Replicated association in moderately-sized studies
- Association with complex disease (not trait)

Identification of disease associated variants

Selection of Single Genetic Variant per Health Condition

Variant Selection Hierarchy
1. Meta-analysis of multiple studies
2. Replication in multiple independent studies
3. Replication in multiple cohorts in single study

Informed Cohort Oversight Board Assessment
conditions with valid genetic variant associations

Summary of Genetic and Clinical data

Stack et al 2011
Identify and select Drug / Key gene(s)

Define Key alleles/Haplotypes by identifying minimum set of defining variants

Select Haplotypes for Inclusion based on Evidence Scoring

CPMC Technical Guidelines for PGx

Review of published and public data:
- FDA Table Drugs/Biomarkers
- PubMed
- PharmGKB
- CYP450 Drug Interaction Table
- National Prescription data
- CPMC cohort Med Use

Review of published and public data:
- Drug metabolism pathway (PK/PD)
- PubMed
- PharmGKB
- CYP allele nomenclature database
Strength of Evidence Scoring

Scientific and clinical studies can be broadly categorized into study types A (greatest PGx evidence) to D (lowest PGx evidence):

A. Clinical Outcomes studies
B. Pharmacokinetic (PK) and Pharmacodynamic (PD) studies
C. Molecular and cellular functional studies
D. Genetic variation screening studies
## Strength of Evidence Scoring

<table>
<thead>
<tr>
<th>Evidence code</th>
<th>Evidence Code Definition</th>
<th>Category type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Category A study looking directly at effect of genetic variant on drug of interest.</td>
<td>include</td>
</tr>
<tr>
<td>2</td>
<td>Category B study looking directly at effect of genetic variant on drug of interest.</td>
<td>include</td>
</tr>
<tr>
<td>3</td>
<td>Category C study looking directly at effect of genetic variant on drug of interest.</td>
<td>include</td>
</tr>
<tr>
<td>4n or 4scd or 4se or 4ae or 4ad or 4dp</td>
<td>Category C study looking at effect of genetic variant on <em>probe</em> drug (industry standard substrate used for evaluating enzyme function) <em>and</em> includes analysis of mutation type based on 6 categories defines in table footnote.</td>
<td>include</td>
</tr>
<tr>
<td>5n or 5scd or 5se or 5ae or 5ad or 5dp</td>
<td>Category A study looking at effect of genetic variant on another drug and includes analysis of the mutation type based on 6 categories defines in table footnote.</td>
<td>include</td>
</tr>
<tr>
<td>6n or 6scd or 6se or 6ae or 6ad or 6dp</td>
<td>Category B study looking at effect of genetic variant on another drug and includes analysis of the mutation type based on 6 categories defines in table footnote.</td>
<td>include</td>
</tr>
<tr>
<td>7n or 7scd or 7se or 7ae or 7ad or 7dp</td>
<td>Category C study looking at effect of genetic variant on another drug and includes analysis of the mutation type based on 6 categories defines in table footnote.</td>
<td>exclude</td>
</tr>
<tr>
<td>8</td>
<td>Category C study looking at effect of genetic variant on a probe drug only.</td>
<td>exclude</td>
</tr>
<tr>
<td>9</td>
<td>Category A study looking at effect of genetic variant on <em>another</em> drug only.</td>
<td>exclude</td>
</tr>
<tr>
<td>10</td>
<td>Category B study looking at effect of genetic variant on another drug only.</td>
<td>exclude</td>
</tr>
<tr>
<td>11</td>
<td>Category C study looking at effect of genetic variant another drug only.</td>
<td>exclude</td>
</tr>
<tr>
<td>12</td>
<td>Category A-C study that demonstrates no effect of the genetic variant on drug behavior or response.</td>
<td>exclude</td>
</tr>
<tr>
<td>13</td>
<td>Category D study (i.e. identified through sequencing but no additional functional or drug phenotype data available).</td>
<td>exclude</td>
</tr>
<tr>
<td>RV (add evidence code if available, e.g. RV2)</td>
<td>This category is specific to the CPMC study in that it is used to distinguish rare variants that are not on the DMET-plus (or Affymetrix 6.0) genepchip, that are assigned evidence code ≥7 and have maximum variant frequency of &lt;1% in any ethnic/racial group.</td>
<td>exclude</td>
</tr>
</tbody>
</table>

### Study Type Category:
- **A** = *In vivo* Clinical Outcome
- **B** = *In vivo/ ex vivo* PK/PD
- **C** = *in vitro* enzyme activity
- **D** = no *in vivo* or *in vitro* data

- **n** = null mutation (abolishes function)
- **scd** = mutation located in known important substrate-binding or catalytic domain or in a highly evolutionarily conserved residue
- **se** = mutation leading to splicing error/protein truncation (this can reduce or abolish function)
- **ae** = mutation leading to altered gene expression (this can reduce or increase protein function)
- **ad** = mutation leading to accelerated degradation of protein or mRNA (this can reduce or abolish function)
- **dp** = gene duplication (this may increase protein function)
SELECTION OF HEALTH CONDITIONS AND VARIANTS OR PGX DRUG-GENE PAIRS

PREPARATION OF ICOB OR PAG SUBMISSION REPORT

IF PGX - EVALUATION AND APPROVAL BY PAG

ASSESSMENT AND APPROVAL BY ICOB

REPORT DEVELOPMENT

DEPLOYMENT OF REPORT TO PARTICIPANTS

CPMC Technical Guidelines
Who decides what genetic information is reported?

• Informed Cohort Oversight Board (ICOB)
  – External advisory board
  – Composed of scientists, medical professionals, ethicist, community members

• Pharmacogenomics Advisory Group
  – A second external advisory board, expert in pharmacogenomics
  – Provides recommendations to the ICOB
  – Composed of pharmacists, pharmacologists, ethicist, clinicians
Informed Cohort Oversight Board (ICOB)

Robert C. Green, MD, MPH
Harvard University

Steven A.R. Murphy, MD
Personalized Medicine Group, CT

Erin O’Shea, PhD
Harvard University

Reverend Floyd White
Woodland Community Development, NJ

Jennifer Hoheisel, MS
Camden County College, NJ

Ellis J. Neufeld, MD, PhD
Children’s Hospital Boston

David Pellman, MD
Harvard Medical School

Marc Lenburg, PhD
Boston University School of Medicine

Charles Rotimi, PhD
National Human Genome Research Institute

Kenneth Offit, MD, MPH
Cornell University
ICOB Charge

To determine:

• Whether each health condition or gene involved in drug metabolism is at minimum potentially actionable

• Whether genetic associations are statistically valid
Who decides what genetic information is reported?

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  - Provides recommendations to the ICOB
  - Composed of pharmacists, pharmacologists, ethicist, clinicians
Pharmacogenomics Advisory Group (PAG)

Calvin H. Knowlton, PhD
RevolutionCare, Inc., NJ

Howard L. McLeod, PharmD
University of North Carolina

Michael F. Murray, MD
Brigham and Women’s Hospital

Steven A.R. Murphy, MD
Personalized Medicine Group, CT

Michael Phillips, PhD
Pharmacogenomics Centre, Quebec

Wolfgang Sadée, PhD
Ohio State University College of Medicine

Issam Zineh, PharmD, MPH
US Food and Drug Administration

Marialice Bennett, BS, RPh
Ohio State University

Art Caplan, PhD
University of Pennsylvania

Michael D. Ezekowitz, MBChB, DPhil, FRCP, FACC
Thomas Jefferson University

David A. Flockhart MD, PhD
Indiana University School of Medicine

Andrew Godwin, PhD
University of Kansas Cancer Center

Amalia M. Issa, PhD, MPH
College of Pharmacy, University of Houston Methodist Hospital Research Inst.

Teri Klein, PhD
Stanford University
PAG Charge

To determine:

• Whether there is sufficient evidence to support the role of each gene in the metabolism of the proposed drug

• Whether the impact of one or more haplotypes is clinically relevant with respect to the proposed drug

• Whether the drug-gene pair is potentially actionable
ICOB and PAG Work Flow

CPMC submits to PAG
Drug Gene Pairs

PAG Reviews for Actionability and Validity of Association

Recommends

May re-submit in future with additional data

ICOB Reviews for Potential Actionability and Validity of Association

Inclusion in CPMC

Approves

Rejects

CPMC submits to ICOB
Health Conditions, Associated Genetic Variants, and Drug Gene Pairs

Rejects

Approves
Currently Approved for Inclusion

Complex Disease

Age-related macular degeneration; Asthma; Breast cancer; Bladder cancer; Chronic obstructive pulmonary disease; Chronic Periodontal Disease; Colon cancer; Coronary artery disease; Inflammatory bowel disease; Hemochromatosis; Lupus; Melanoma; Obesity; Osteoarthritis; Prostate cancer; Rheumatoid arthritis; Stroke; Testicular cancer; Type 1 diabetes, and Type 2 diabetes

Drug Metabolism

CYP2C19/Plavix and PPIs; CYP2C9/Warfarin; CYP4F2/Warfarin; VKORC1/Warfarin; CYP2D6/Tamoxifen and Codeine; TPMP/Thiopurines
Acknowledgements:

Michael Christman  ICOB Members
Norman Gerry  PAG Members
Courtney Kronenthal  Participants
Catharine Stack
Neda Gharani
Tara Schmidlen
Rachel Kasper
Lisa Wawak
Joe Mintzer
Margaret Keller