CORIELL INSTITUTE
FOR MEDICAL RESEARCH

Coriell Personalized Medicine Collaborative:
Identifying Variants for Study Inclusion

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CORIELL
PERSONALIZED MEDICINE
COLLABORATIVE

Study Aims:

- to understand usefulness of receiving personal genome information

- to identify new genetic sites associated with common medical conditions and drug response

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Launched 2007
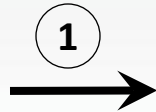
Goals of the CPMC Research Study

- 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

www.cpmc.coriell.org

Reporting Process Overview

SELECTION OF HEALTH CONDITIONS AND VARIANTS OR PGX DRUG-GENE PAIRS

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PREPARATION OF ICOB OR PAG SUBMISSION REPORT

↓

IF PGX - EVALUATION AND APPROVAL BY PAG

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ASSESSMENT AND APPROVAL BY ICOB

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REPORT DEVELOPMENT

↓

DEPLOYMENT OF REPORT TO PARTICIPANTS

← CPMC Technical Guidelines
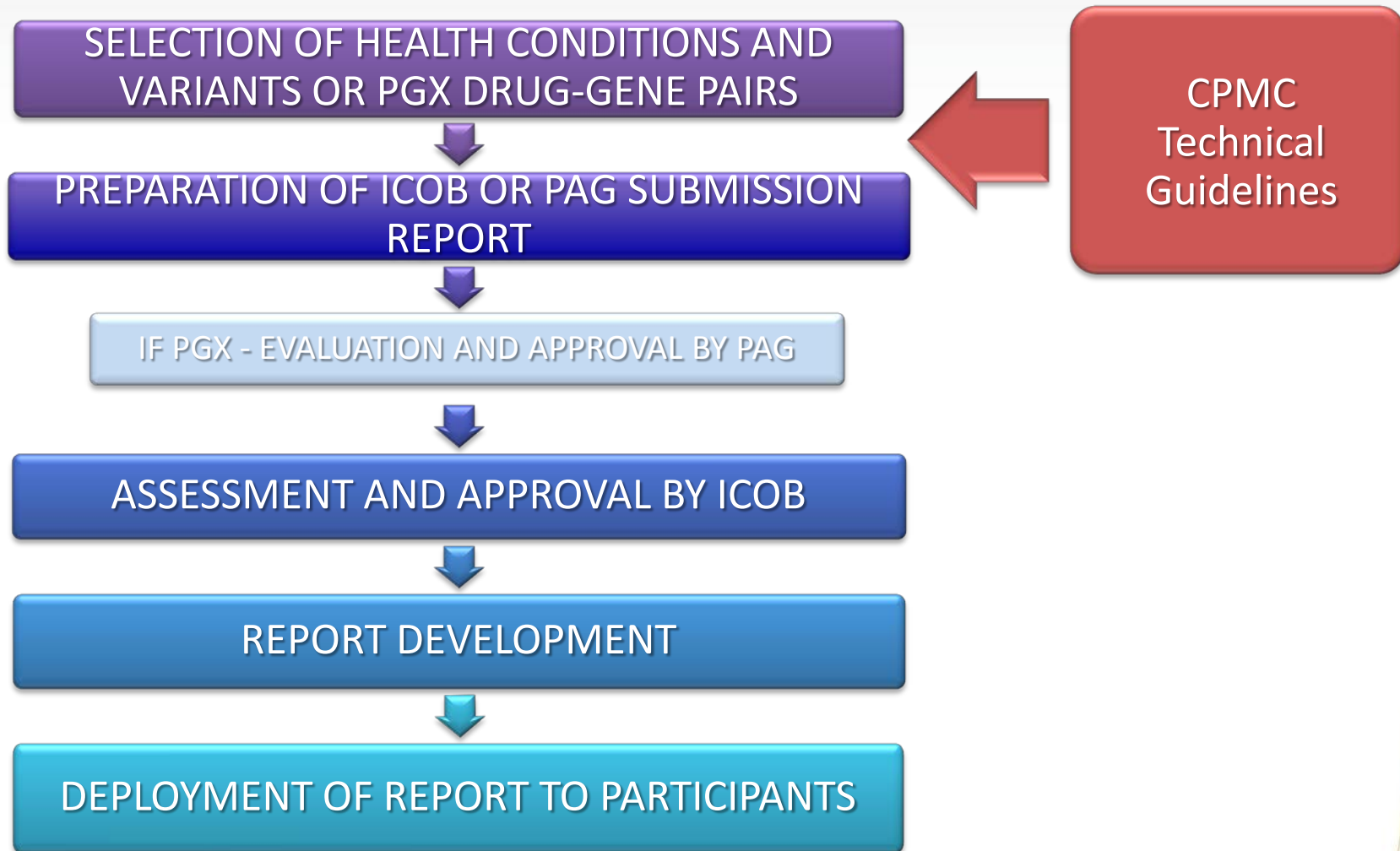
CPMC Technical Guidelines for Health Conditions

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

Informed Cohort Oversight Board Assessment

Identification of disease associated variants

conditions with valid genetic variant associations

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

Summary of Genetic and Clinical data

Stack et al 2011

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CPMC Technical Guidelines for PGx

Identify and select Drug / Key gene(s)
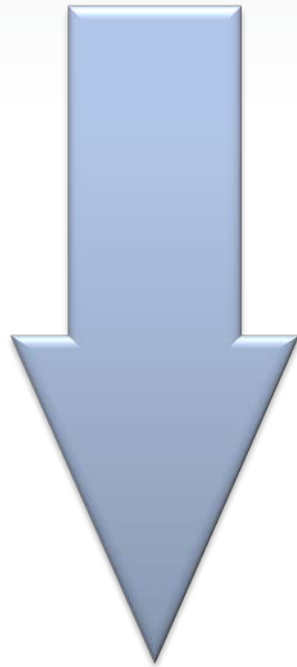
Review of published and public data:
- FDA Table Drugs/Biomarkers
- PubMed
- PharmGKB
- CYP450 Drug Interaction Table
- National Prescription data
- CPMC cohort Med Use

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

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

Select Haplotypes for Inclusion based on Evidence Scoring

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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

Evidence code	Evidence Code Definition	Category type
1	Category A study looking directly at effect of genetic variant on drug of interest.	include
2	Category B study looking directly at effect of genetic variant on drug of interest.	include
3	Category C study looking directly at effect of genetic variant on drug of interest.	include
4n or 4scd or 4se or 4ae or 4ad or 4dp	Category C study looking at effect of genetic variant on *probe* drug (industry standard substrate used for evaluating enzyme function) *and* includes analysis of mutation type based on 6 categories defines in table footnote.	include
5n or 5scd or 5se or 5ae or 5ad or 5dp	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.	include
6n or 6scd or 6se or 6ae or 6ad or 6dp	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.	include
7n or 7scd or 7se or 7ae or 7ad or 7dp	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.	include
8	Category C study looking at effect of genetic variant on a probe drug only.	exclude
9	Category A study looking at effect of genetic variant on *another* drug only.	exclude
10	Category B study looking at effect of genetic variant on another drug only.	exclude
11	Category C study looking at effect of genetic variant another drug only	exclude
12	Category A-C study that demonstrates no effect of the genetic variant on drug behavior or response.	exclude
13	Category D study (i.e. identified through sequencing but no additional functional or drug phenotype data available).	exclude
RV (add evidence code if available, e.g. RV_2)	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) genechip, that are assigned evidence code ≤ 7 and have maximum variant frequency of <1% in any ethnic/racial group.	exclude

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)
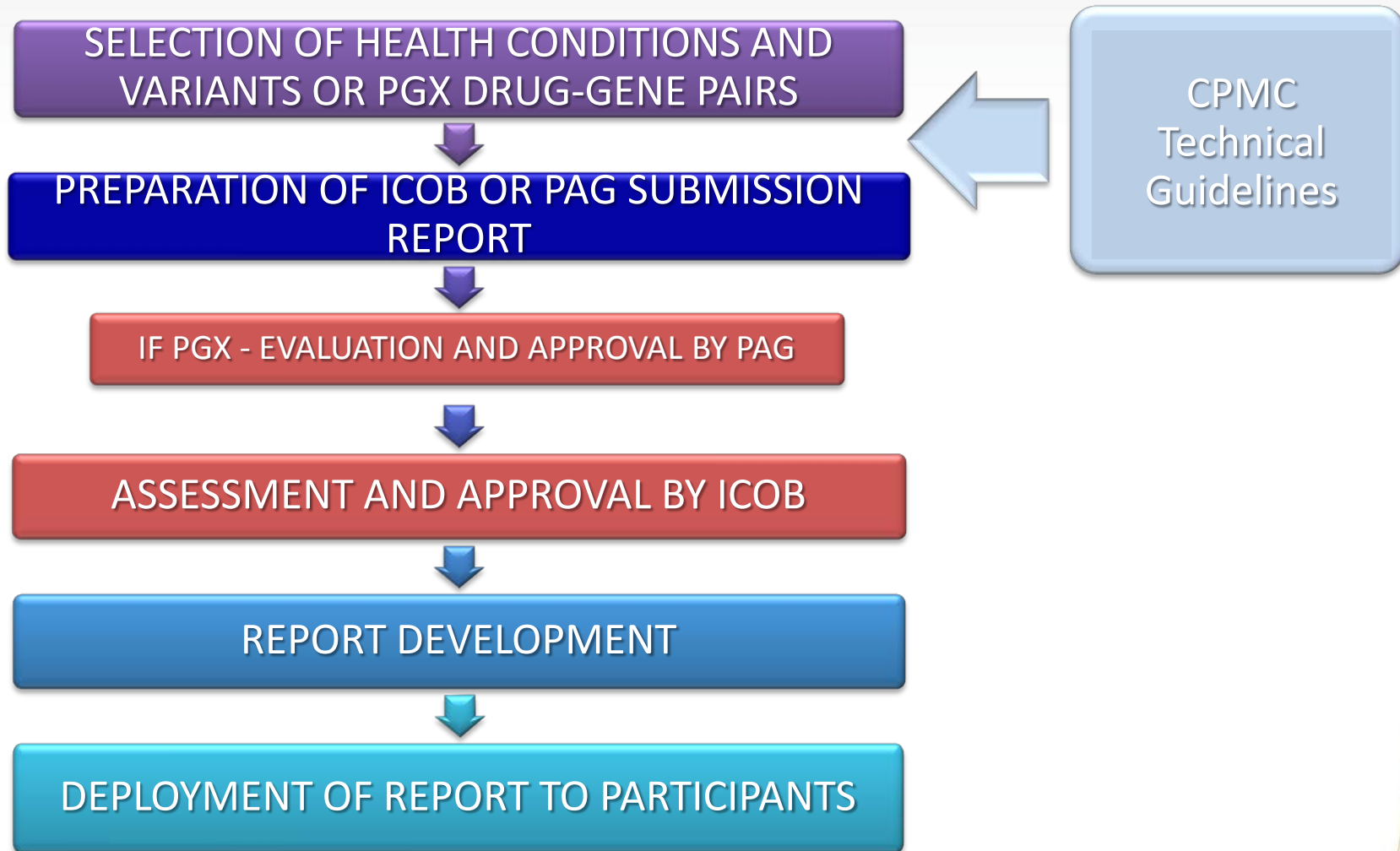
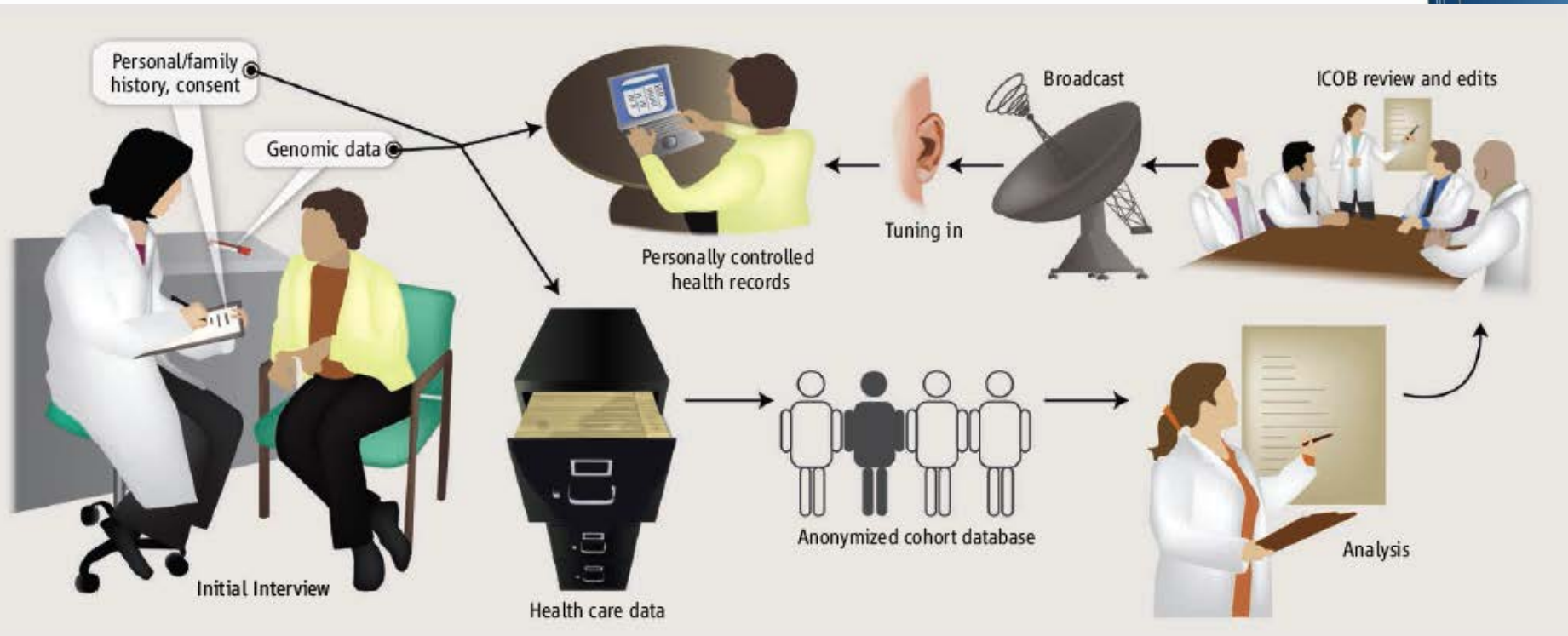CORIELL.ORG

Reporting Process Overview

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 Concept

Kohane et al., Science 2007

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

David Pellman, MD
Harvard Medical School

Charles Rotimi, PhD
National Human Genome Research Institute

Reverend Floyd White
Woodland Community Development, NJ

Jennifer Hoheisel, MS
Camden County College, NJ

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

Marc Lenburg, PhD
Boston University School of Medicine

Kenneth Offit, MD, MPH
Cornell University

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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

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Pharmacogenomics Advisory Group (PAG)
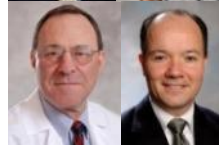
Marialice Bennett, BS, RPh
Ohio State University

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

Art Caplan, PhD
University of Pennsylvania

Howard L. McLeod, PharmD
University of North Carolina

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

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

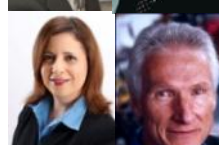**David A. Flockhart MD, PhD**
Indiana University School of Medicine

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

Andrew Godwin, PhD
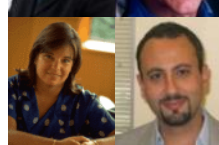*University of Kansas Cancer Center*

Michael Phillips, PhD
Pharmacogenomics Centre, Quebec

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

Wolfgang Sadée, PhD
Ohio State University College of Medicine

Teri Klein, PhD
Stanford University

Issam Zineh, PharmD, MPH
*US Food and Drug Administration*

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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
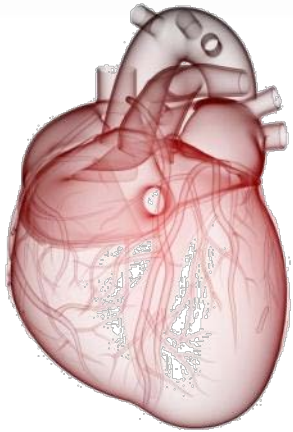
- Whether the drug-gene pair is potentially actionable

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ICOB and PAG Work Flow
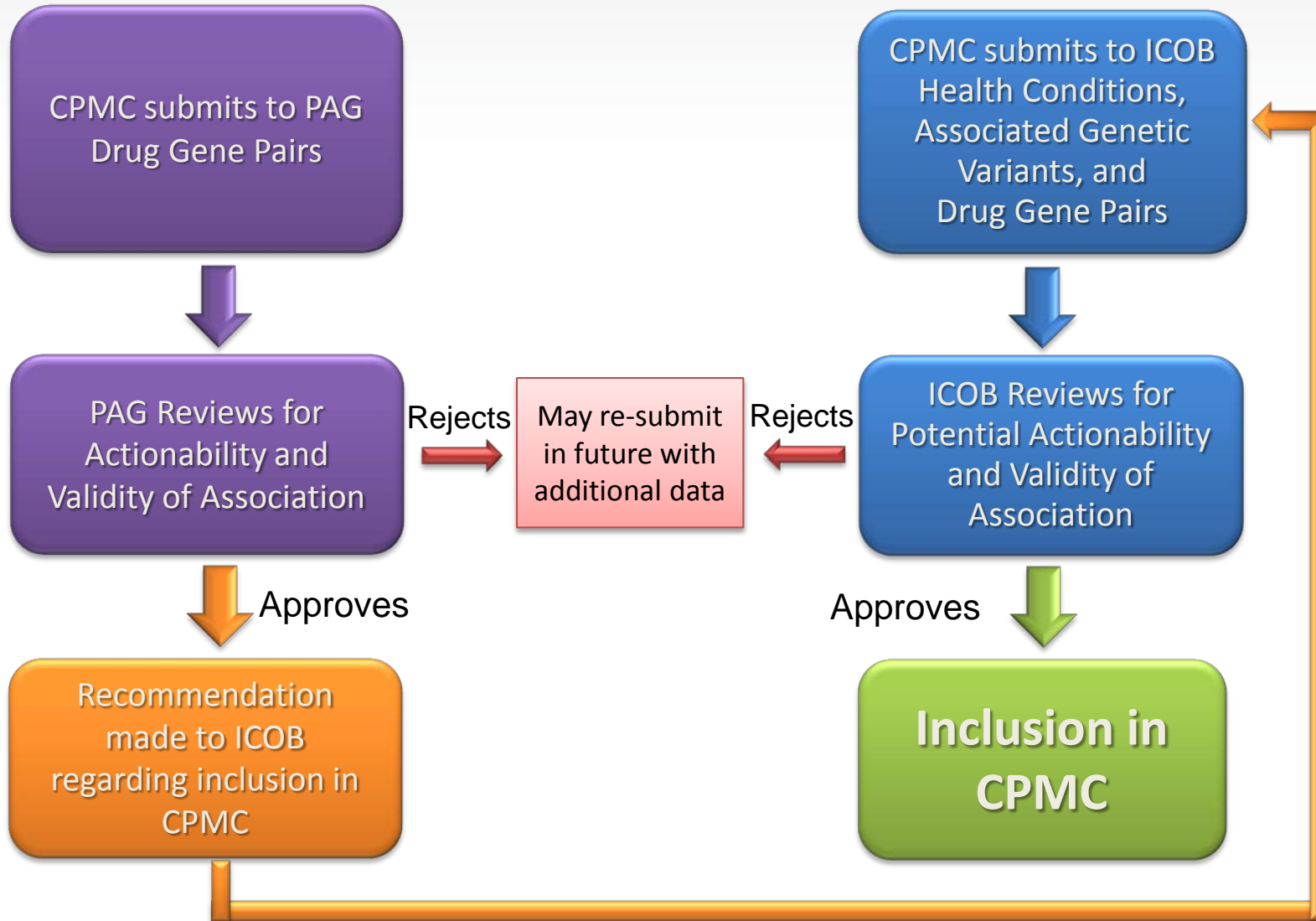
Currently Approved for Inclusion

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

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Norman Gerry

Courtney Kronenthal

Catharine Stack

Neda Gharani

Tara Schmidlen

Rachel Kasper

Lisa Wawak

Joe Mintzer

Margaret Keller

ICOB Members

PAG Members

Participants

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