Gaining Consensus On Emerging Science:The ADME Panel As An Exemplar

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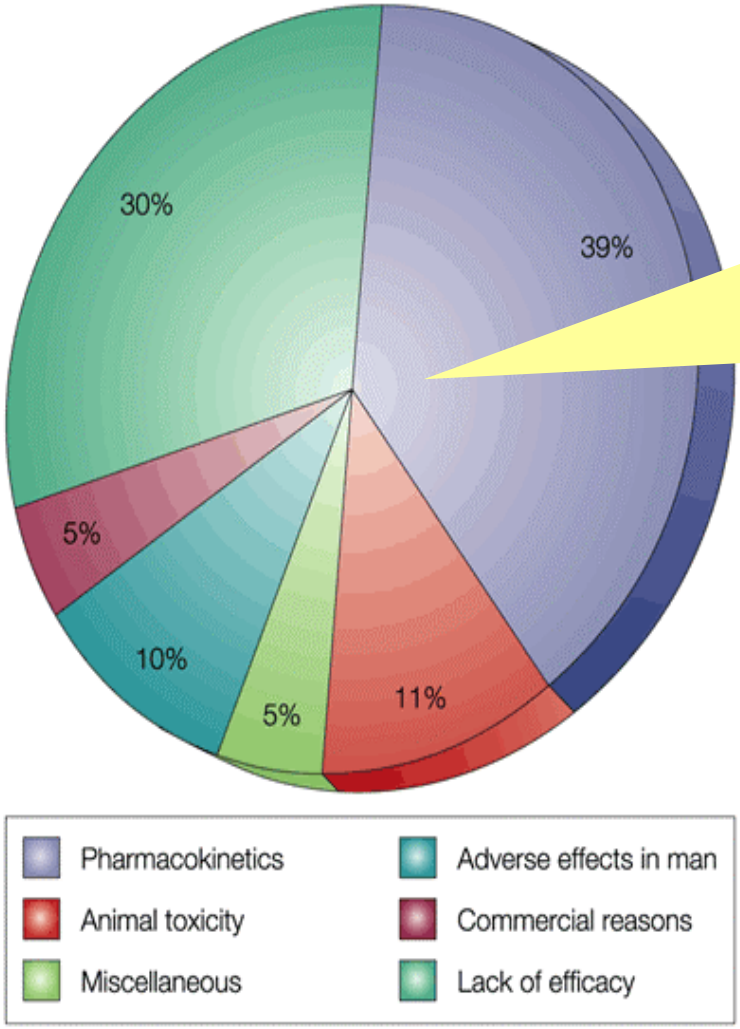
Outline

- Introduction
  - Need for an ADME panel in drug development
- Challenges in developing a panel
  - Organizational
  - Scientific
- Innovation is Powered by Collaboration
- ADME Panel Development
  - Development of a Consensus List of ADME Genes and Genetic Markers
  - Characterization & Compilation of an ADME List
  - Criteria & Selection of Genetic Variants
- Summary

Need for ADME Panel in Drug Development



40% of the Failure in Drug Development is Attributed to PK Issues

Nature Reviews, Drug Discovery, March 2003

Regulatory Impetus

FDA's Critical Path Initiative

EMEA Road Map to 2010

"There are currently significant needs, but also significant opportunities for developing tools that can more reliably and more efficiently determine the safety of a new medical product"

FDA White Paper, 16 March 2004

Challenges in Developing a Consensus ADME Panel

- **Organizational Challenge**
  - A number of pharma working together

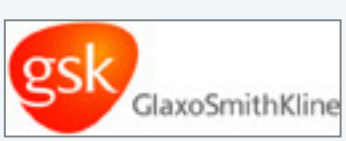
- **Scientific Challenges**
  - Determine which genes have enough evidence to justify testing on a routine basis, and which variations should be measured in these genes

Development of a Pharma Consensus ADME Panel

ADME Panel Working Group

Innovation is powered by collaboration!

- **Pharmaceutical Companies**



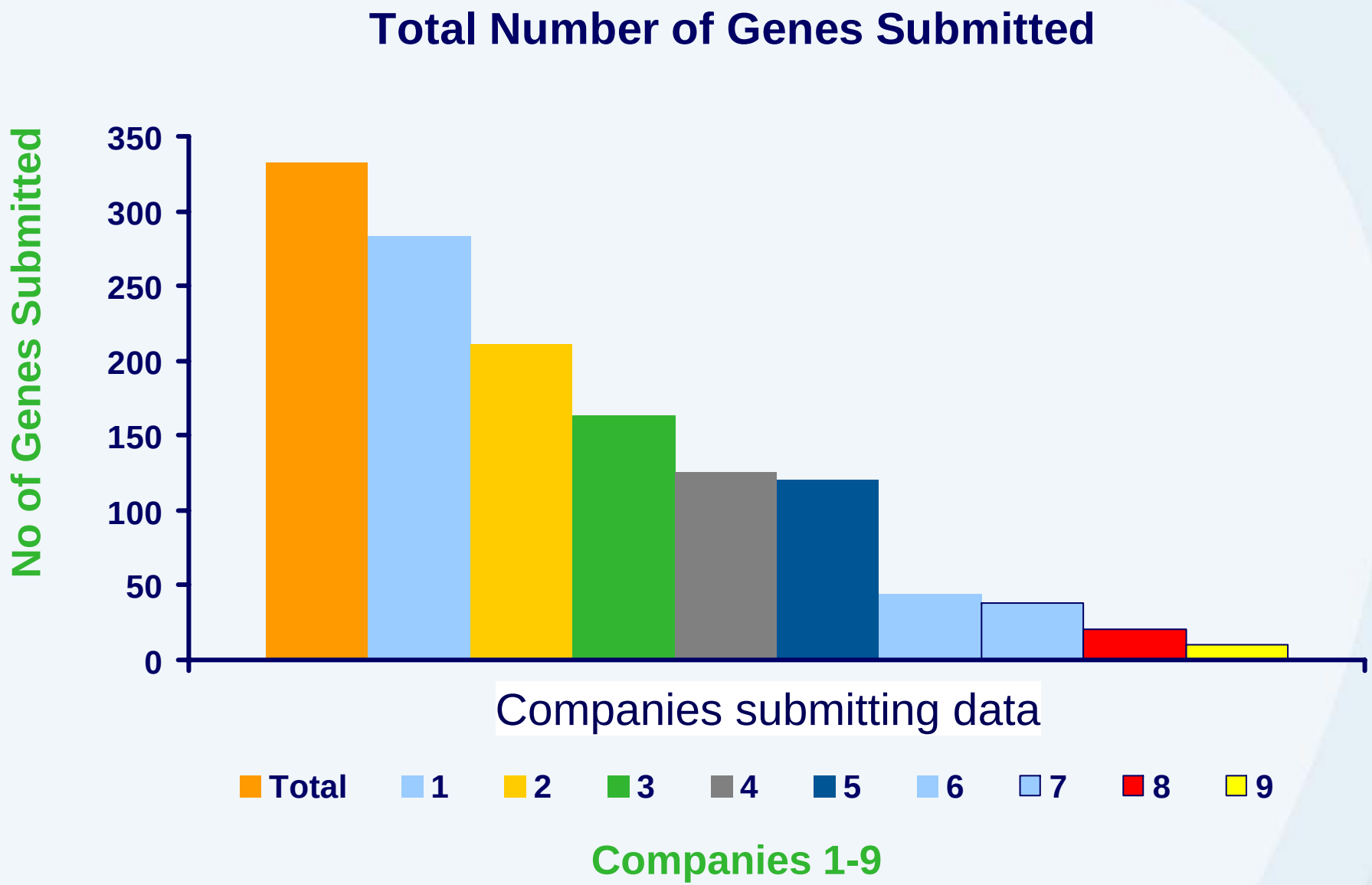
- **Academic Center**
  - Genome Quebec & Montreal Heart Institute Pharmacogenomics Centre
- **Genotyping Biotech Companies**

Gene Selection of ADME Panel

- Collation of gene lists submitted by participants ~332 genes Submitted
  - Drug metabolism
    - phase I
    - phase II
    - transporters
  - Drug Targets
  - Channels
  - ADME modulators
    - Nuclear Receptors (PXR)

Class	No of Genes	%
Phase 1	126	43
Phase 2	68	23
Transporters	77	26
Modifiers	24	8

Genes Submitted By Pharma Companies



Defining the ADME "Core List"

Gene Selection Process

Inclusion Criteria

- Genes deemed to be directly involved in drug metabolism and/or have the ability to influence a drug's pharmacokinetic profile
- Identified by FDA as a validated biomarker
- Supported by published literature of more than one group that the variation alters gene function
- Support by KOLs (Pharma DMET groups) in drug metabolism field as having altered protein function

Defining the ADME "Core List"

Gene Selection Process

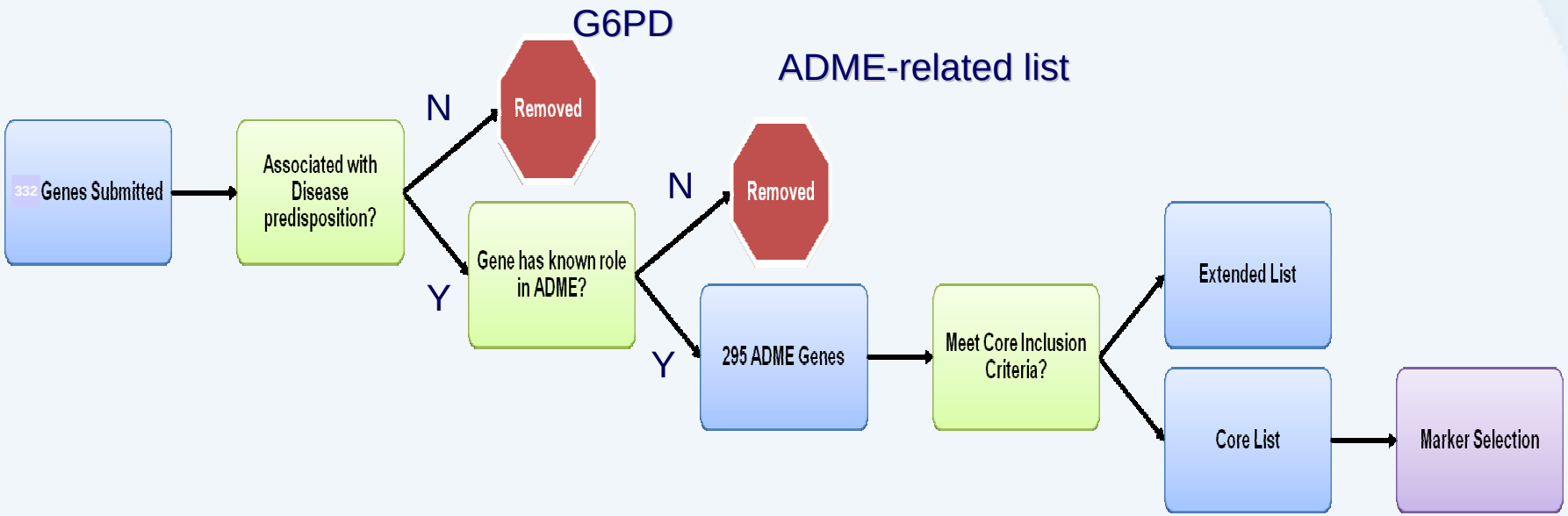
Exclusion Criteria

- Genes involved in disease predisposition and prognosis were ineligible due to the ethical and legal considerations

For example,

- glucose-6-phosphate dehydrogenase (G6PD)
- influence a patient's response to 6-mercaptopurine

Flow Chart of Core ADME Gene List Selection Process

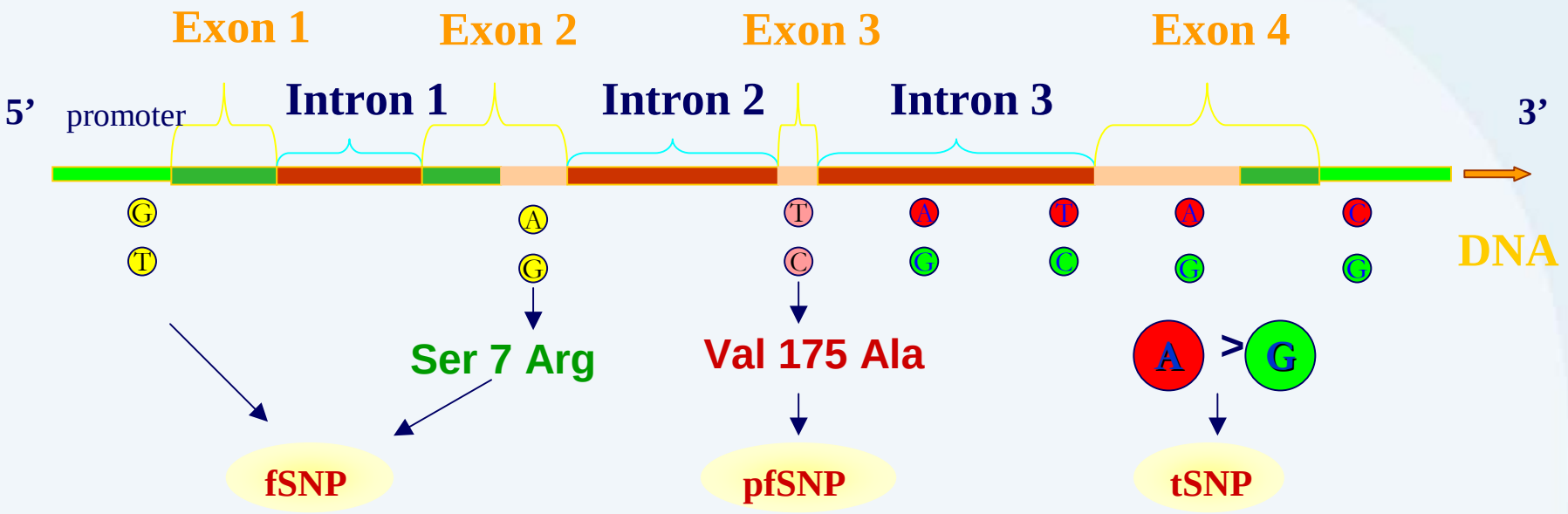


ADME Core Gene List

32 genes

Gene	Functional Class	Gene	Functional Class
CYP1A1	Phase I	NAT2	Phase II
CYP1A2	Phase I	SULT1A1	Phase II
CYP2A6	Phase I	TPMT	Phase II
CYP2B6	Phase I	UGT1A1	Phase II
CYP2C19	Phase I	UGT2B15	Phase II
CYP2C8	Phase I	UGT2B17	Phase II
CYP2C9	Phase I	UGT2B7	Phase II
CYP2D6	Phase I	ABCB1	Transporter
CYP2E1	Phase I	ABCC2	Transporter
CYP3A4	Phase I	ABCG2	Transporter
CYP3A5	Phase I	SLC15A2	Transporter
DPYD	Phase I	SLC22A1	Transporter
GSTM1	Phase II	SLC22A2	Transporter
GSTP1	Phase II	SLC22A6	Transporter
GSTT1	Phase II	SLCO1B1	Transporter
NAT1	Phase II	SLCO1B3	Transporter

Genetic Markers in ADME Panel



- **Functional Markers (fSNPs)**
  Reported to change the function of or modify the amount of the gene product generated and associated with a known ADME endpoint
- Putatively Functional Markers (pfSNPs)
  Changes amino acid sequence; likely to influence protein function, though not yet reported in the public domain
- Tagging SNPs (tSNPs)
  Additional SNPs that may be correlated with other genetic variants not included in the study (Caucasian)

Criteria For Selection of Genetic Variants

- FDA list of validated genetic variants
- Published literature from more than one group supports that the variation altered gene function
- Key opinion leaders in the drug metabolism field support that the genetic variants alters gene function
- Genetic variants cause an amino acid change in the protein encoded by the gene

Sampling of Genetic Variants in the ADME Core List

Gene	Core Genetic Markers
CYP1A1	*2A, *4, *3, *5, *8, *6, *7
CYP1A2	*1K, *1C, *1F, *7
CYP2A6	*2, *9 , *11, *17, *8, *6, *7, *5, *12, *1X2a, *1X2b, *20, *4
CYP2B6	*8, *16, *28, *6, *4, *2
CYP2C19	*4, *17, *8, *2, *3, *6, *7, *12, *5
CYP2C8	*3, *4, *3, *2, *5, *7, *8
CYP2C9	*3, *2, *9, *11, *5, *8, *10, *6, *12, *13, *15, *25, *4
CYP2D6	*10, *2a, *2, *15 , *17, *41, *4, *6, *12, *11, *7, *3, *14, *8, *9,
CYP2D6 (contd)	*18, *19, *20, *21, *38, *40, *42, *44, *5, *56
CYP2E1	*2
CYP3A4	*6, *2, *20
CYP3A5	*6, *10, *3, *5, *7
DPYD	*9A, *8, *9B, *10, *7
GSTM1	*B , *X2, Null
GSTP1	V114A, V105I
GSTT1	Null
NAT1	*14, *11 , *15 , *19 , *17 , *22, *5
NAT2	*12, *6, *7, *5, *13, *11, *14 , *19
SULT1A1	*3, *2, *4, Null, XN
TPMT	*3c, *3b, *2 , *4, *8, *3a
UGT1A1	*6, *7, *27, *60,, *28 _ *36 _*37, *29

Updating the Core and Other Gene Lists

- To address the evolution of our knowledge with respect to variation in drug metabolism pathways
  - Group agreement to meet on an annual or bi-annual basis to review, update and discuss the information as required

- The *www.PharmaADME.org* website set up
  - intended to be a public portal for this information

- Link to PharmGKB
  - intended to be a point of access where individual researchers can make suggestions for the inclusion of additional genes and variants to either list

Summary

- The pharma ADME Core list is an industry-academic consensus set of genes and a full set of functional genetic variants that may be used in drug development
- Provide consistency across studies leading to more useful comparisons across studies and across compounds
- This is today's list which might change in the future as science evolves
- Provides a framework for the various technology platform providers to create standardized products

Collaborators

Genome Quebec & MHI Pharmacogenomics Centre

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F. Hoffmann-La Roche

Klaus Lindpaintner

Sanofi-Aventis

William Brian

Merck and Co.

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Back-Up

Genes with FDA Validated SNPs

Phase I Phase II Transporters Modifier

The ADME "Extended List"

- Probable involvement in drug metabolism
- Lacking burden of proof of Core

267 Additional Genes Ranked by Pharma

Rank	Gene Symbol	Full Gene Name	Class
7	ABCB8	ATP-binding cassette, sub-family B (MDR/TAP), member 8	Transporter
7	ABCC12	ATP-binding cassette, sub-family C (CFTR/MRP), member 12	Transporter
7	ABCC3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	Transporter
7	ABCC4	ATP-binding cassette, sub-family C (CFTR/MRP), member 4	Transporter
7	AHR	aryl hydrocarbon receptor	Modifier
7	ALDH4A1	aldehyde dehydrogenase 4 family, member A1	Phase I
7	ALDH5A1	aldehyde dehydrogenase 5 family, member A1	Phase I
7	ALDH6A1	aldehyde dehydrogenase 6 family, member A1	Phase I
7	CES1	carboxylesterase 1 (monocyte/macrophage serine esterase 1)	Phase I
7	CES2	carboxylesterase 2 (intestine, liver)	Phase I
7	CYP7A1	cytochrome P450, family 7, subfamily A, polypeptide 1	Phase I
7	EPHX1	epoxide hydrolase 1, microsomal (xenobiotic)	Phase I
7	FMO3	flavin containing monooxygenase 3	Phase I
7	GSTA1	glutathione S-transferase A1	Phase II
7	GSTA2	glutathione S-transferase A2	Phase II
7	GSTA3	glutathione S-transferase A3	Phase II
7	GSTA4	glutathione S-transferase A4	Phase II
7	GSTA5	glutathione S-transferase A5	Phase II
7	GSTM2	glutathione S-transferase M2 (muscle),glutathione S-transferase M4	Phase II
7	GSTM3	glutathione S-transferase M3 (brain)	Phase II
7	GSTM4	glutathione S-transferase M4	Phase II
7	GSTO1	glutathione S-transferase omega 1,glutathione S-transferase omega 2	Phase II
7	GSTO2	glutathione S-transferase omega 2	Phase II
7	GSTT2	glutathione S-transferase theta 2	Phase II
7	SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	Transporter
7	SLC15A1	solute carrier family 15 (oligopeptide transporter), member 1	Transporter
7	SLC22A11	solute carrier family 22 (organic anion/cation transporter), member 11	Transporter

Alternate List of ADME Related Genes

- Genes involved in pharmacodynamic mechanisms
  - being drug targets (VKORC1, HMGCOR, MAO)
  - receptors
  - ion channels
  - genes involved in individual drug effect mechanisms
- Example; catechol-o-methyltransferase (COMT)
  - degradative pathways for catecholamine transmitters
  - did not fulfill the required criteria of a “drug metabolizing”

Public Website