Pharmacogenomics

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CANCER GENOMICS CONSORTIUM

Pharmacogenomics (PGx)

- The study of how a person's genes affect his or her response to medications
- Goal is to help doctors select the correct drugs and prescribe the correct doses for each person
- Part of the field of precision medicine, which aims to treat each patient individually

Pharmacogenomics (nih.gov)

Drug-dependent phenotype

Phenotype is often not recognized in the patient until:

1. Patient **does not respond to a drug**
2. Patient has an **adverse drug reaction**

Goal is to **optimize drug dose** and **minimize adverse drug reaction**

History of PGx

- Observational evidence that some adverse drug reactions were more frequent in certain ethnic groups
- The term “pharmacogenetics” was coined in 1959 for the concept that drug reactions are under genetic control
- Late 1970’s-80’s: drug response patterns identified in families and candidate genes begin to be identified

Important Pharmacogenes

S. No.	Involve in	Biological function group	VIP Gene
1	PK (kinetics)	Metabolizer (33)	*ADH1A, ADH1B, ADH1C, ALDH1A1, ALOX5, COMT, CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP4F2, DPYD, G6PD, GSTP1, GSTT1, HMGCR, MTHFR, NAT2, NQO1, PTGIS, PTGS2, SULT1A1, TPMT, TYMS, UGT1A1, VKORC1*
		Transporter (06)	*ABCB1, CFTR, SLC19A1, SLC22A1, SLCO1B1, ABCG2*
2	PD (dynamics)	Receptor (13)	*ADRB1, ADRB2, AHR, ALK, DRD2, EGFR, ERBB2, NR1I2, P2RY1, P2RY12, RYR1, HLA-B, VDR*
		Signalling (07)	*ABL1, BRCA1, KIT, KRAS, NRAS, BRAF, BCR*
		Ion channel (04)	*KCNH2, KCNJ11, SCN5A, CACNA1S*
		Coagulation (01)	*F5*
		Ribosomal RNA (01)	*MT-RNR1*
		Regulator (01)	*ACE*

Red boxes = genes commonly tested by PGx assays

Pharmacokinetics:
absorption, distribution, metabolism, excretion

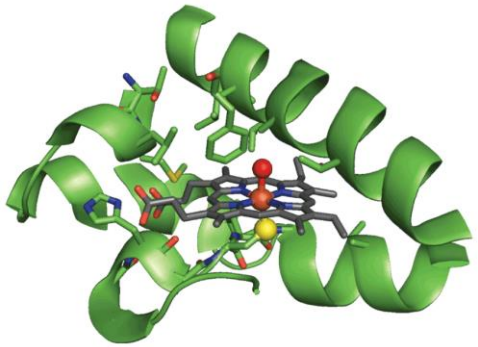
Pharmacodynamics:
perturbs proteins involved in a drug's mechanism, or immune regulation

Katara et al 2019. PMID: 31425740

Cytochrome P450 (CYP)

- Hemeprotein that plays a key role in the metabolism of drugs and other xenobiotics
- 57 functional CYP genes (58 pseudogenes)

  ↳ **a dozen CYP genes together metabolize ~70-80% of drugs**

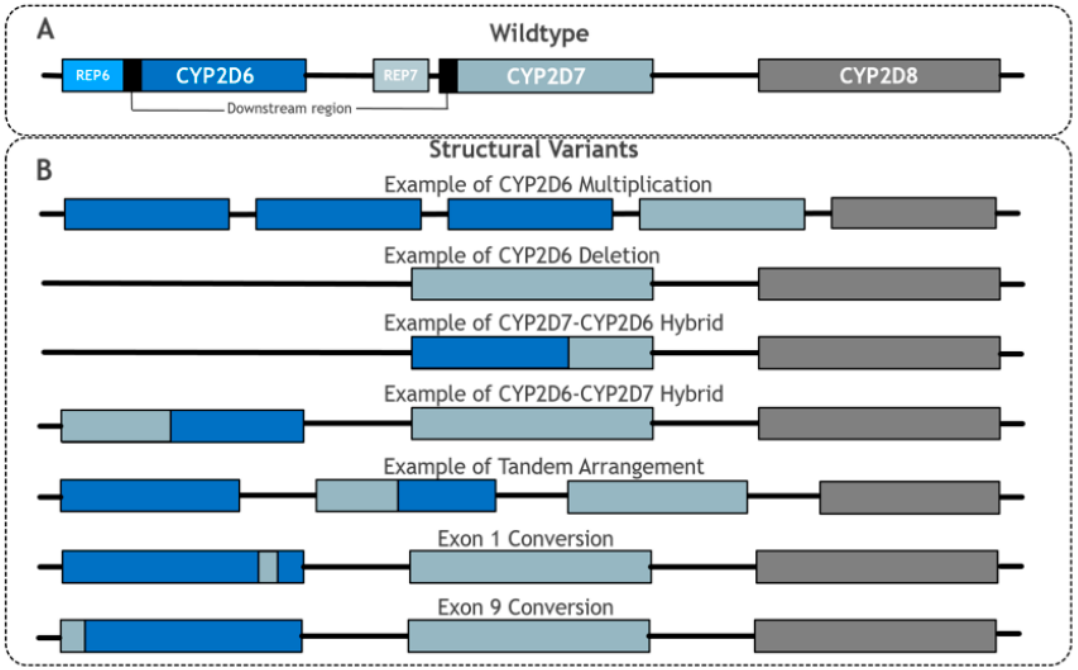


Typical active site of cytochrome P450 with heme group shown in the middle

https://f1000research.com/articles/4-178

- ➢ family number (CYP2)
- ➢ subfamily letter (CYP2D)
- ➢ individual enzyme (CYP2D6) ➡ **CYP2D6 metabolizes ~20% of commonly used drugs**

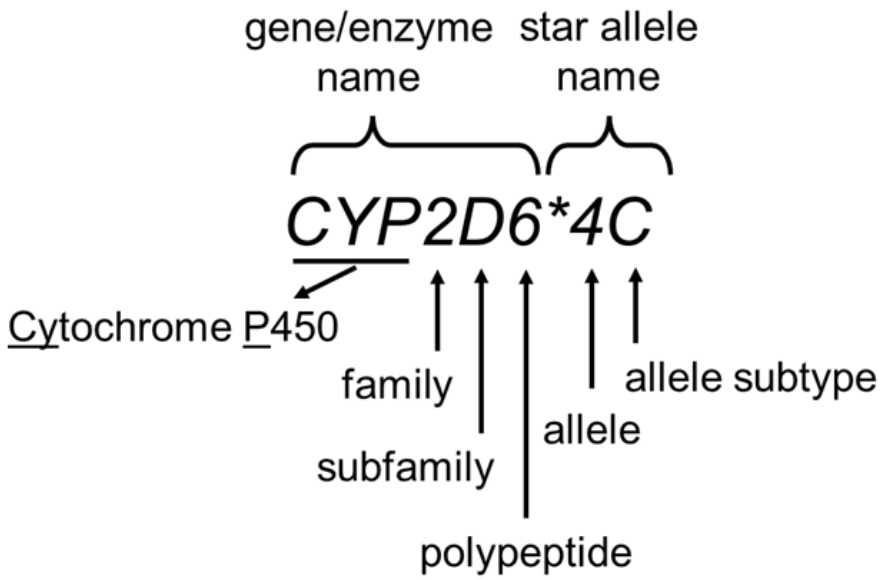
CYP2D6:
a complex genomic region



Taylor et al 2020. PMID: 33143137

PharmVar: Structural Variation CYP2D6

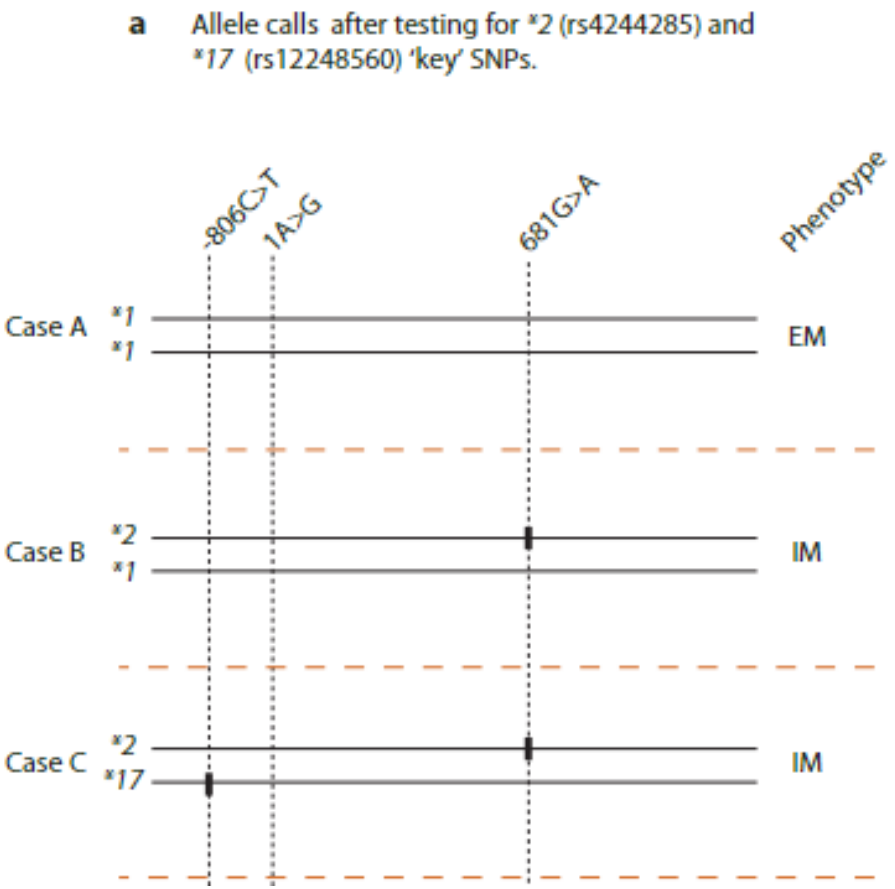
Star (*) allele nomenclature



- *1 alleles are normal/wild type/fully functional alleles
- star alleles are numbered in the order in which they were identified, not by their sequential order in the gene

Star alleles are determined by SNPs

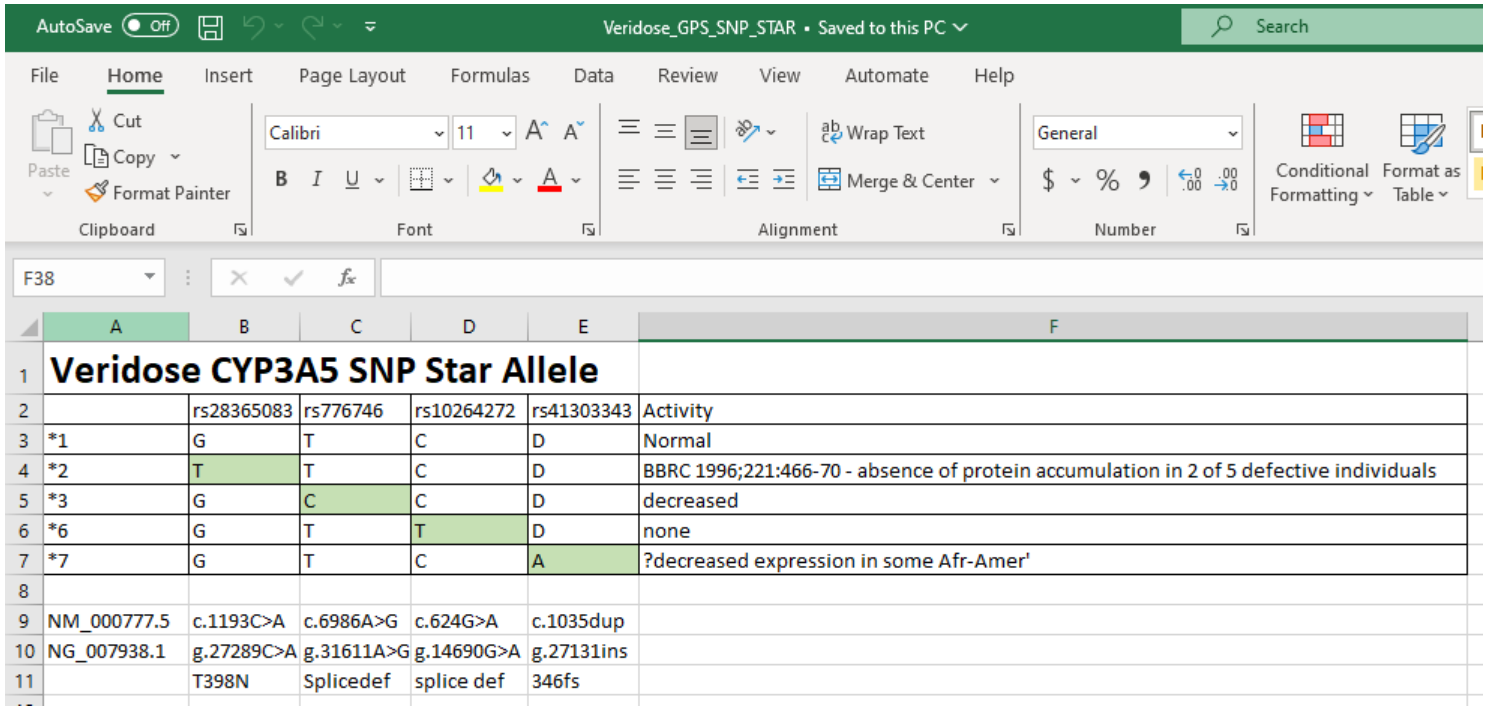
CYP2C19



EM = extensive metabolizer
IM = intermediate metabolizer

Kalman et al 2016. PMID: 26479518

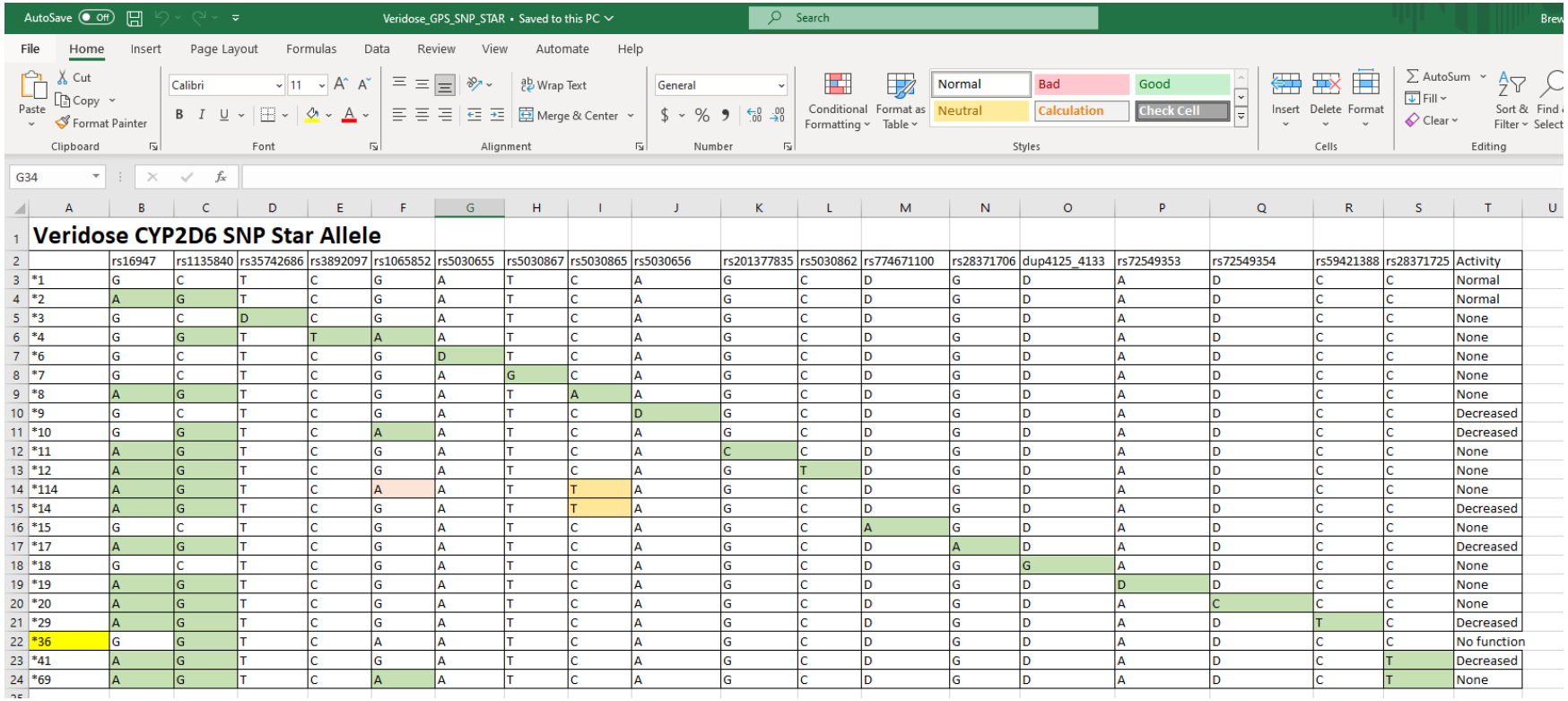
Example of how SNPs determine star alleles in CYP3A5



	A	B	C	D	E	F
1	**Veridose CYP3A5 SNP Star Allele**					
2		rs28365083	rs776746	rs10264272	rs41303343	Activity
3	*1	G	T	C	D	Normal
4	*2	T	T	C	D	BBRC 1996;221:466-70 - absence of protein accumulation in 2 of 5 defective individuals
5	*3	G	C	C	D	decreased
6	*6	G	T	T	D	none
7	*7	G	T	C	A	?decreased expression in some Afr-Amer'
8						
9	NM_000777.5	c.1193C>A	c.6986A>G	c.624G>A	c.1035dup	
10	NG_007938.1	g.27289C>A	g.31611A>G	g.14690G>A	g.27131ins	
11		T398N	Splicedef	splice def	346fs	

*__Disclaimer__: the SNP combinations shown here are just examples of how star alleles are determined and should not be used for clinical test interpretation

CYP2D6 shows how complex star alleles can get



Veridose CYP2D6 SNP Star Allele																			
	rs16947	rs1135840	rs35742686	rs3892097	rs1065852	rs5030655	rs5030867	rs5030865	rs5030656	rs201377835	rs5030862	rs774671100	rs28371706	dup4125_4133	rs72549353	rs72549354	rs59421388	rs28371725	Activity
*1	G	C	T	C	G	A	T	C	A	G	C	D	G	D	A	D	C	C	Normal
*2	A	G	T	C	G	A	T	C	A	G	C	D	G	D	A	D	C	C	Normal
*3	G	C	D	C	G	A	T	C	A	G	C	D	G	D	A	D	C	C	None
*4	G	G	T	T	A	A	T	C	A	G	C	D	G	D	A	D	C	C	None
*6	G	C	T	C	G	D	T	C	A	G	C	D	G	D	A	D	C	C	None
*7	G	C	T	C	G	A	G	C	A	G	C	D	G	D	A	D	C	C	None
*8	A	G	T	C	G	A	T	A	A	G	C	D	G	D	A	D	C	C	None
*9	G	C	T	C	G	A	T	C	D	G	C	D	G	D	A	D	C	C	Decreased
*10	G	G	T	C	A	A	T	C	A	G	C	D	G	D	A	D	C	C	Decreased
*11	A	G	T	C	G	A	T	C	A	C	C	D	G	D	A	D	C	C	None
*12	A	G	T	C	G	A	T	C	A	G	T	D	G	D	A	D	C	C	None
*114	A	G	T	C	A	A	T	T	A	G	C	D	G	D	A	D	C	C	None
*14	A	G	T	C	G	A	T	T	A	G	C	D	G	D	A	D	C	C	Decreased
*15	G	C	T	C	G	A	T	C	A	G	C	A	G	D	A	D	C	C	None
*17	A	G	T	C	G	A	T	C	A	G	C	D	A	D	A	D	C	C	Decreased
*18	G	C	T	C	G	A	T	C	A	G	C	D	G	G	A	D	C	C	None
*19	A	G	T	C	G	A	T	C	A	G	C	D	G	D	D	D	C	C	None
*20	A	G	T	C	G	A	T	C	A	G	C	D	G	D	A	C	C	C	None
*29	A	G	T	C	G	A	T	C	A	G	C	D	G	D	A	D	T	C	Decreased
*36	G	G	T	C	A	A	T	C	A	G	C	D	G	D	A	D	C	C	No function
*41	A	G	T	C	G	A	T	C	A	G	C	D	G	D	A	D	C	T	Decreased
*69	A	G	T	C	A	A	T	C	A	G	C	D	G	D	A	D	C	T	None

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Core star alleles and subtypes are provided on PharmVar website

PharmVar
Pharmacogene Variation Consortium

Allele Name	Legacy Label	PharmVar ID	Variants (rsIDs, Impact) **variant** = variants with dbSNP rsID	Allele Evidence Level	References
CYP2D6*4		PV00429	**1847G>A** (rs3892097, splice defect)		CPIC Clinical Function ✕
CYP2D6*4.001	CYP2D6*4A	PV00235	**-1426C>T** (rs28588594) **-1235A>G** (rs28735595) **-1000G>A** (rs1080989) **100C>T** (rs1065852, P34S) **310G>T** (rs28371699) **745C>G** (rs28371701) **842T>G** (rs28371702) **973C>A** (rs28371703, L91M) **983A>G** (rs28371704, H94R) **996C>G** (rs28371705) **1662G>C** (rs1058164) **1847G>A** (rs3892097, splice defect) **2098A>G** (rs2267447) **3385A>C** (rs1985842) **3583A>G** (rs2004511) **4181G>C** (rs1135840, S486T) **4402C>T** (rs28371738)	Def	deposited by Nofziger deposited by Gaedigk et al Gough et al. 1990 Hanioka et al. 1990 Kagimoto el al 1990
CYP2D6*4.002	CYP2D6*4B	PV00237	**100C>T** (rs1065852, P34S) **973C>A** (rs28371703, L91M) **983A>G** (rs28371704, H94R) **996C>G** (rs28371705) **1847G>A** (rs3892097, splice defect) **4181G>C** (rs1135840, S486T)	Lim	Kagimoto el al 1990
CYP2D6*4.003	CYP2D6*4C	PV00236	**100C>T** (rs1065852, P34S) **1662G>C** (rs1058164) **1847G>A** (rs3892097, splice defect) **3888T>C** (rs72549345) **4181G>C** (rs1135840, S486T)	Lim	Yokota et al. 1993
CYP2D6*4.004	CYP2D6*4D	PV00847	**-1426C>T** (rs28588594) **-1000G>A** (rs1080989) **100C>T** (rs1065852, P34S) **310G>T** (rs28371699) **842T>G** (rs28371702) **1038C>T** (rs1081003) **1662G>C** (rs1058164) **1847G>A** (rs3892097, splice defect) **2098A>G** (rs2267447) **3385A>C** (rs1985842) **3583A>G** (rs2004511) **4181G>C** (rs1135840, S486T) **4402C>T** (rs28371738)	Def	deposited by Gaedigk et al Marez et al. 1997 Liau et al. 2019

Core SNV

Challenges in the field

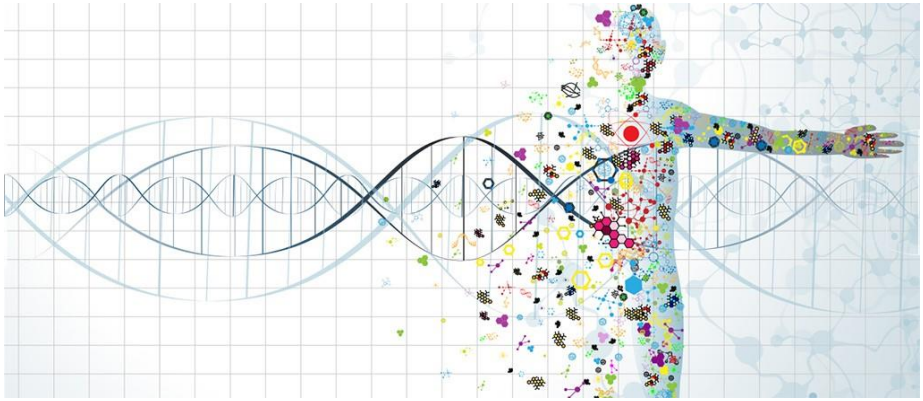
- Individual might be *1/*1 just because certain SNPs were not tested
- SNPs important to minority populations may not be known
- Previously reported gene-drug interactions may not be accurate
- Communicating clinical relevance to physicians and patients

CPIC®
Clinical Pharmacogenetics Implementation Consortium

PharmVar
Pharmacogene Variation Consortium

PGx is a Key Part of Precision Medicine

- PGx has implications for large portion of population throughout life
- Not always reimbursed because value might come years after testing
- PGx could help bring precision medicine to general population



Why be interested?

Cutting-edge genetics

- Multiple variants in a gene (haplotypes)
- Complex regions (*CYP2D6*)
- Novel multiplex assays

Social implications

- Population genetics
- International collaborations
- Precision medicine

References

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