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PHARMACOGENETICS

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OBJECTIVES

- Describe the main variations across the human genome and their functional consequences.
- Understand how to utilize genotypes to infer phenotypes using activity scores.
- Discuss examples of drug-gene pairs where pharmacogenetic testing can be utilized to inform drug dosing.
- Describe the impact of drug-gene interaction on phenotype derivation.

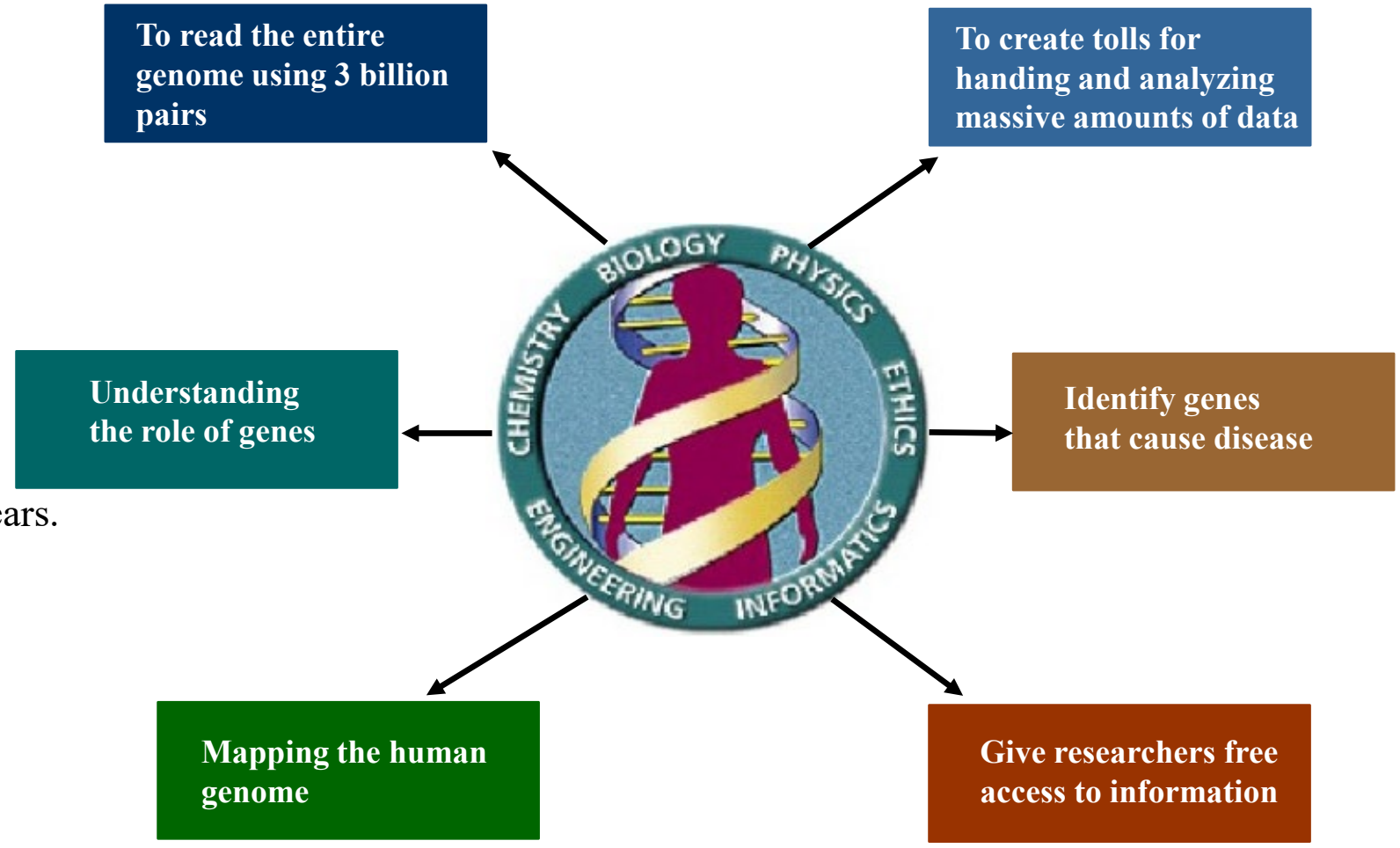
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HUMAN GENOME PROJECT

- **Main goals of project:**
  - Sequence the entire human genome
  - Map and identify all genes in human DNA
  - Store information in databases

- **Project:**
  - Collaborative effort involving 20 groups.
  - Began in 1990 and was completed after 13 years.

- **Lessons learned:**
  - Genome contains 3 billion nucleotide bases
  - Average size of gene is about 3000 bases
  - Less than 2% codes for proteins
  - 99.9% of nucleotide sequence is the same



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DEFINITIONS/TERMINOLOGY

- **Pharmacogenetics:** "**PHARMACOLOGY**" + "**GENETICS**"; genetic variation that affects response/toxicity to medications.

- **Pharmacogenomics**: Broader term; studies how all the genes (human genome) affect response/toxicity.

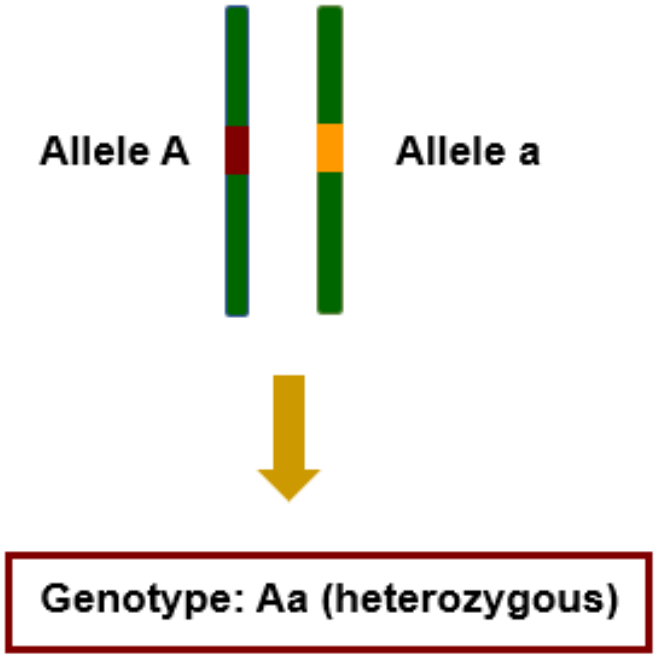
- **Precision medicine**: application of pharmacogenetics i.e. utilize this information to tailor or individualize therapy.

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DEFINITIONS/TERMINOLOGY

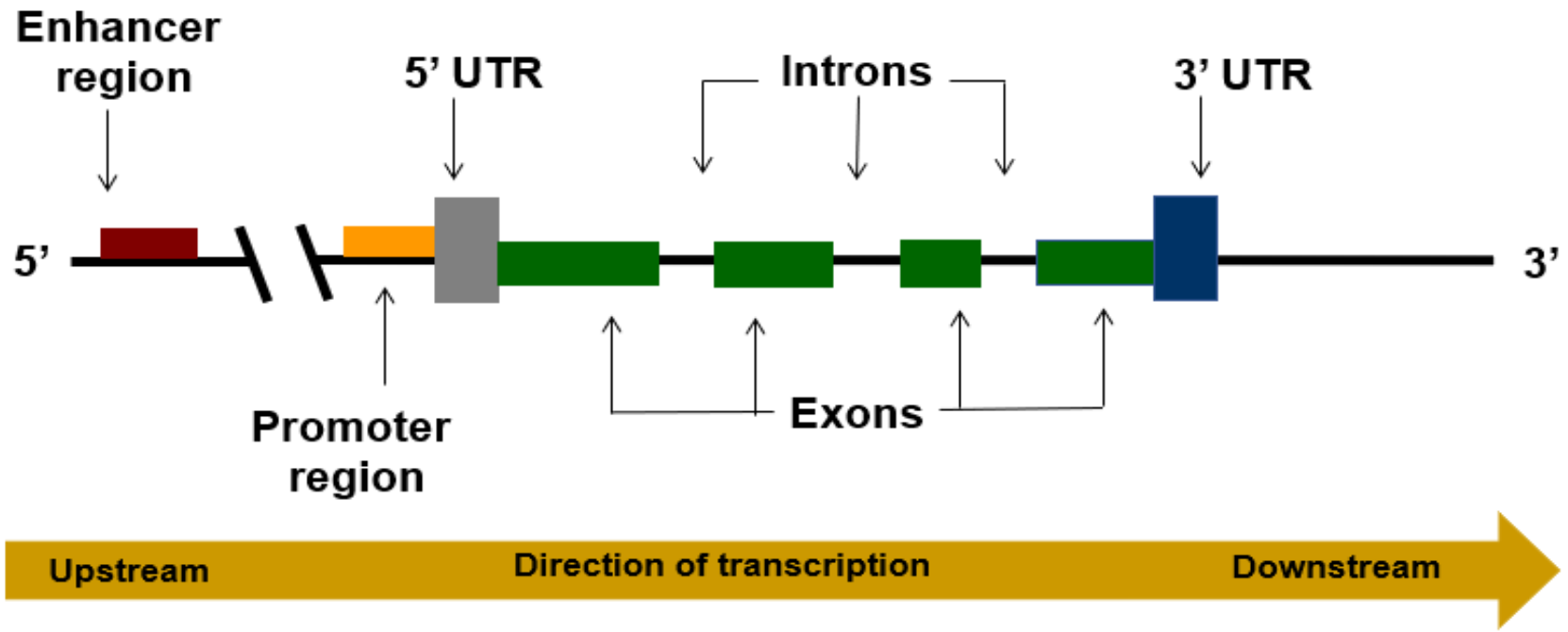
- **Allele**: one of two versions of a genetic sequence at a particular location in the genome.

- **Genotype**: two alleles inherited for a particular gene at a particular location in the genome.
  - *Identical alleles* → ***Homozygous***
  - *Different alleles* → ***Heterozygous***



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BACK TO BASICS: GENE STRUCTURE



- **Exon**: Part of the gene are ultimately translated into protein (coding region)
- **Intron:** Part of the gene that is transcribed into RNA, but removed during splicing (non-coding)

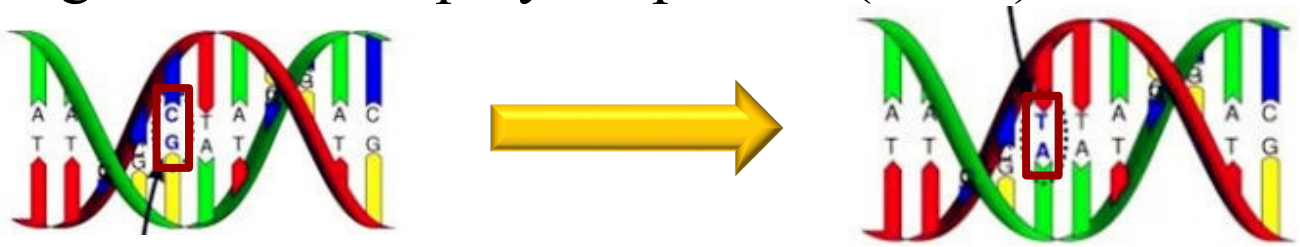
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TYPES OF VARIATIONS ACROSS HUMAN GENOME

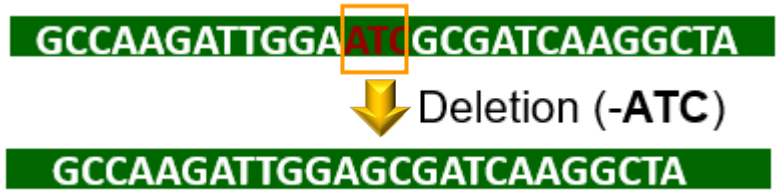
- Variation in **nucleotide sequence** ; occur at **frequency** of > 1% across populations

- **Types of polymorphisms:**

  - Single nucleotide polymorphisms (SNPs)



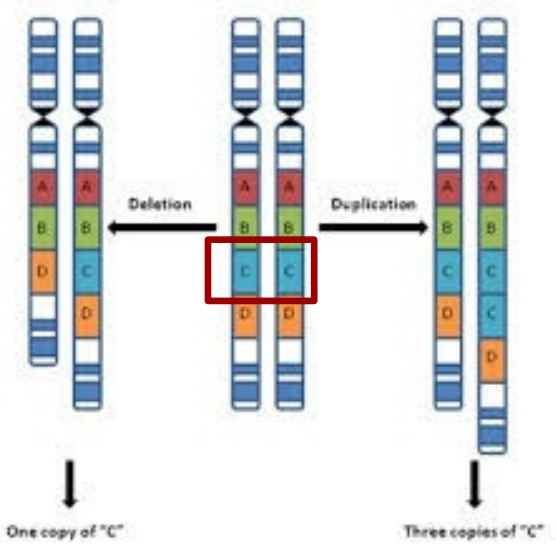
  - Insertions/deletions (Indels)



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TYPES OF VARIATIONS ACROSS HUMAN GENOME

- **Copy number variations (CNVs)**: Deletions, duplications/multiplications



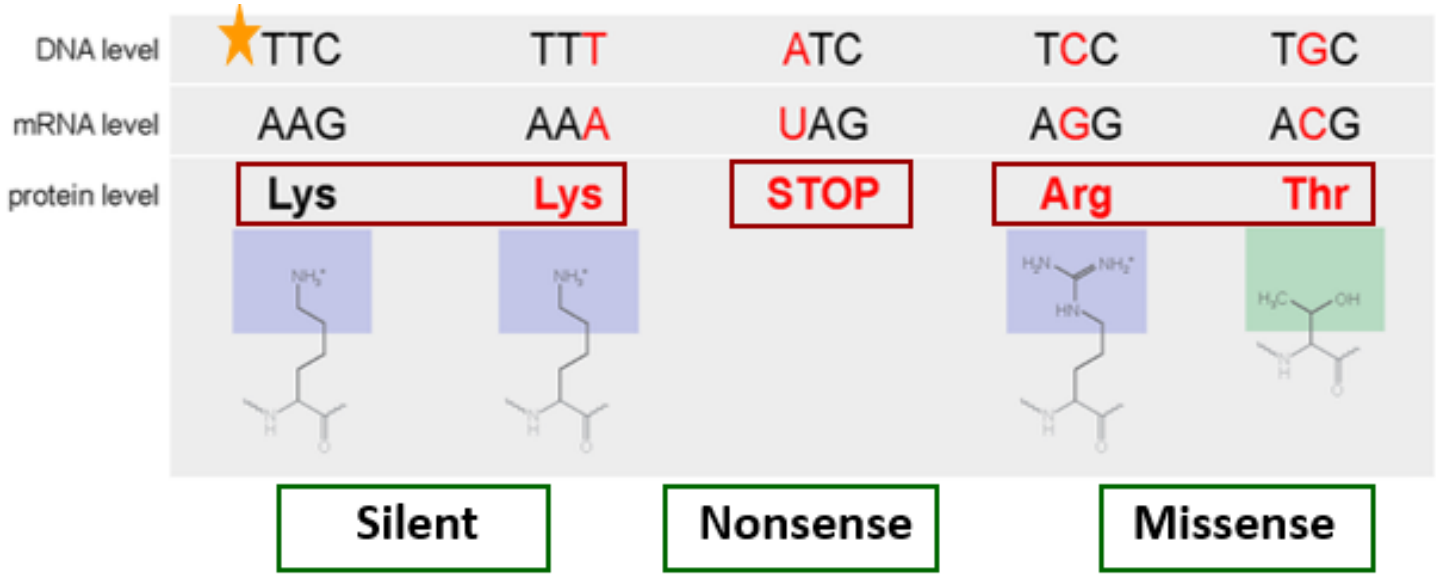
- **Tandem repeats**: 1 or more nucleotides are **repeated** (adjacent)
  - **Microsatellite:** nucleotide sequence (motif) of 1-6 base pairs repeated about 5-50 times
  - **Minisatellite:** nucleotide sequence (motif) of 10-60 base pairs repeated about 5-50 times



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CONSEQUENCES OF POLYMORPHISMS

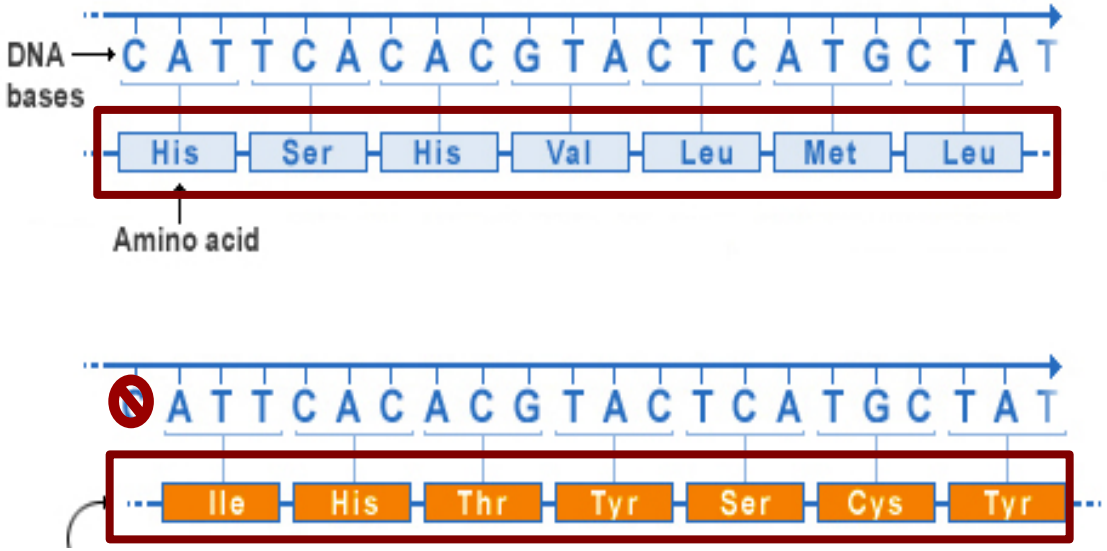
- **SNPs in exons** (coding regions of a gene):
  - **Synonymous**: does not alter amino acid sequence (silent)
  - **Non-synonymous**:
    i) missense: substitution of different amino acid
    ii) nonsense: premature protein termination→ **stop codon**



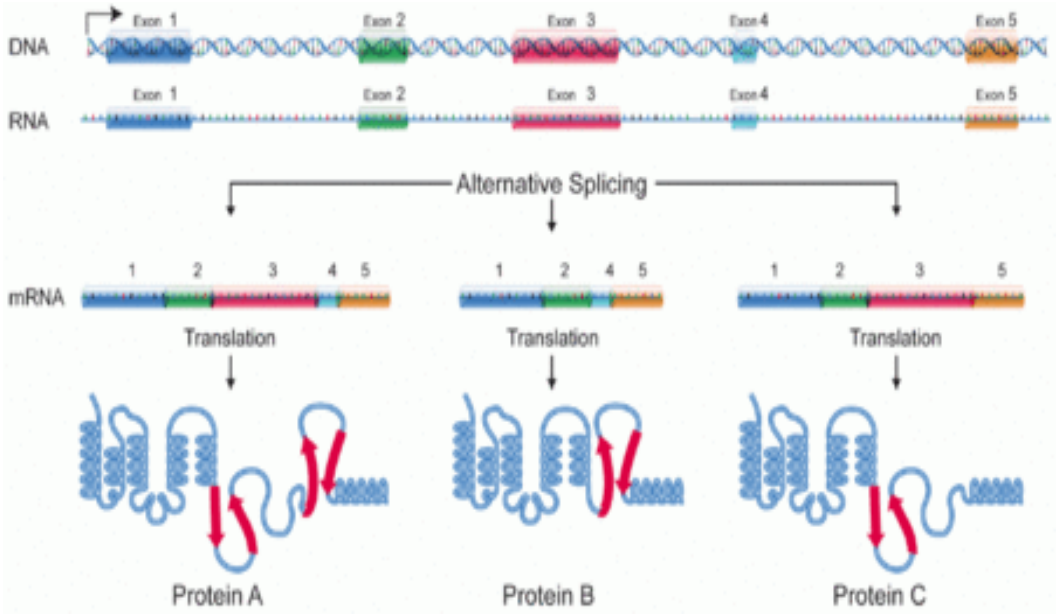
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CONSEQUENCES OF POLYMORPHISMS

- **INDELS (if in coding regions):**
  - Not a multiple of 3: frame shift mutation
  - Multiples of 3: addition or deletion of amino acid



- **SNPs in introns**: alter splicing (exon skipping), affect expression or could be silent.



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SOMATIC VS. GERMLINE MUTATIONS

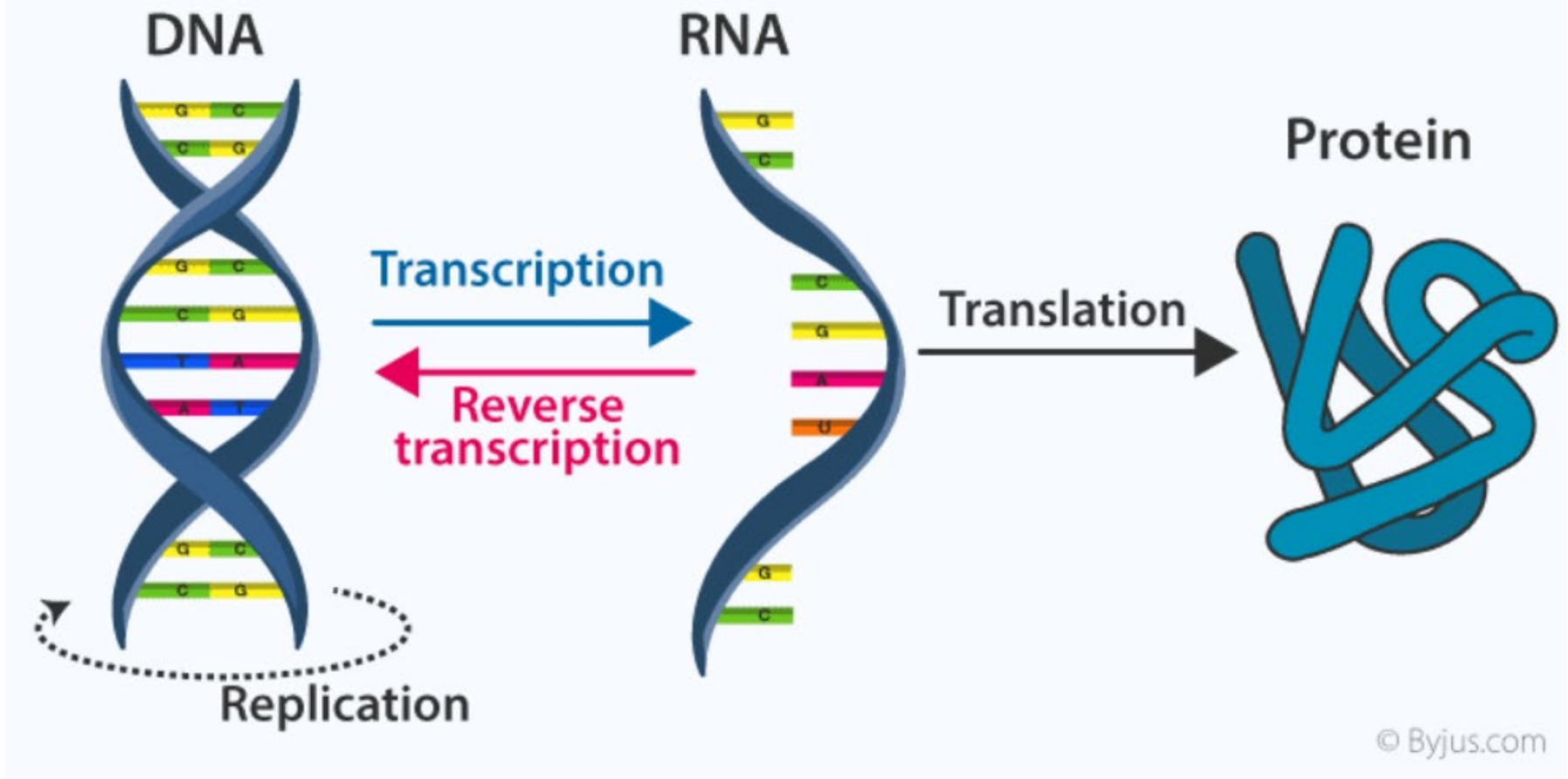
Germline
- Inherited and present in all cells
- Can be detected in blood and saliva
- Will be present in tumor

Somatic
- Acquired mutations (after birth) and are only present in tumor
- Detected by testing tumor or tissue

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CENTRAL DOGMA OF MOLECULAR BIOLOGY

Genome | **Transcriptome** | **Proteome**

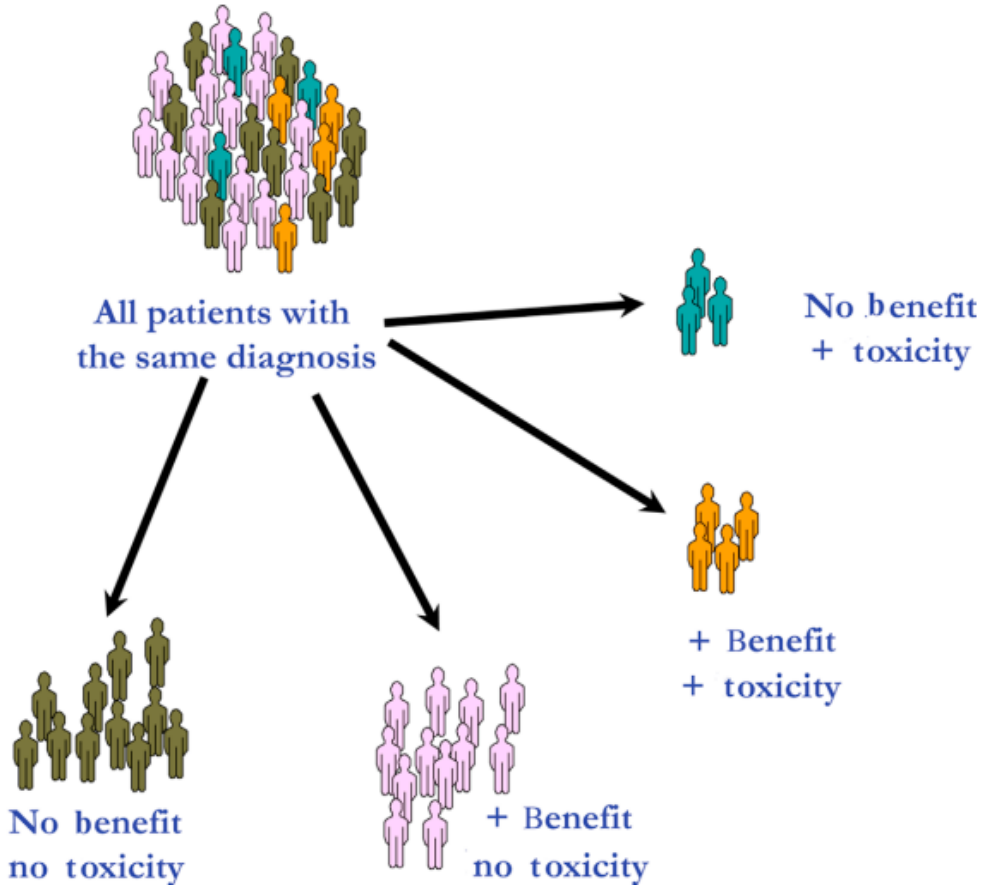


Metabolome

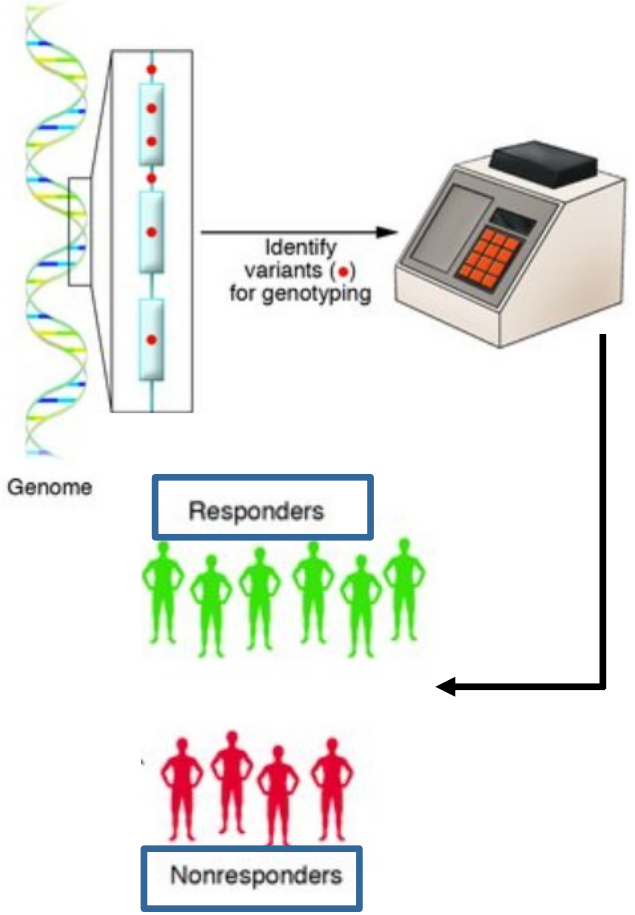
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DIVERSITY IN DRUG RESPONSE

Traditional Medicine



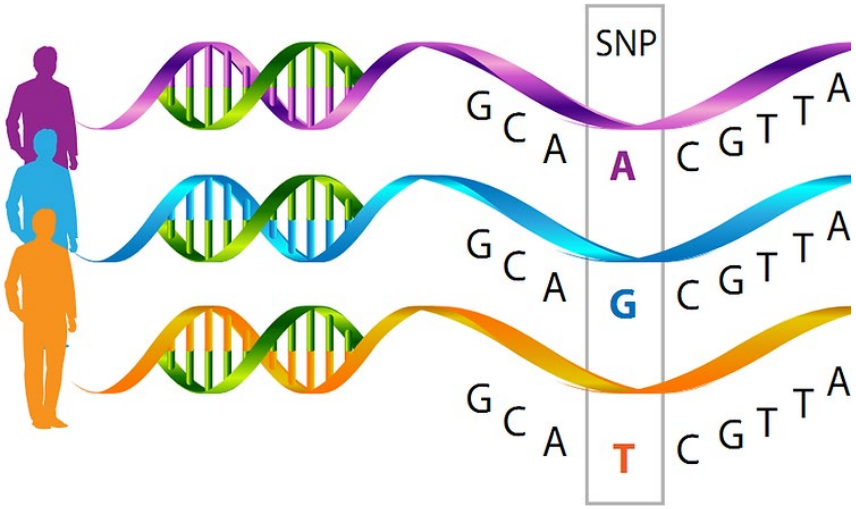
Precision Medicine

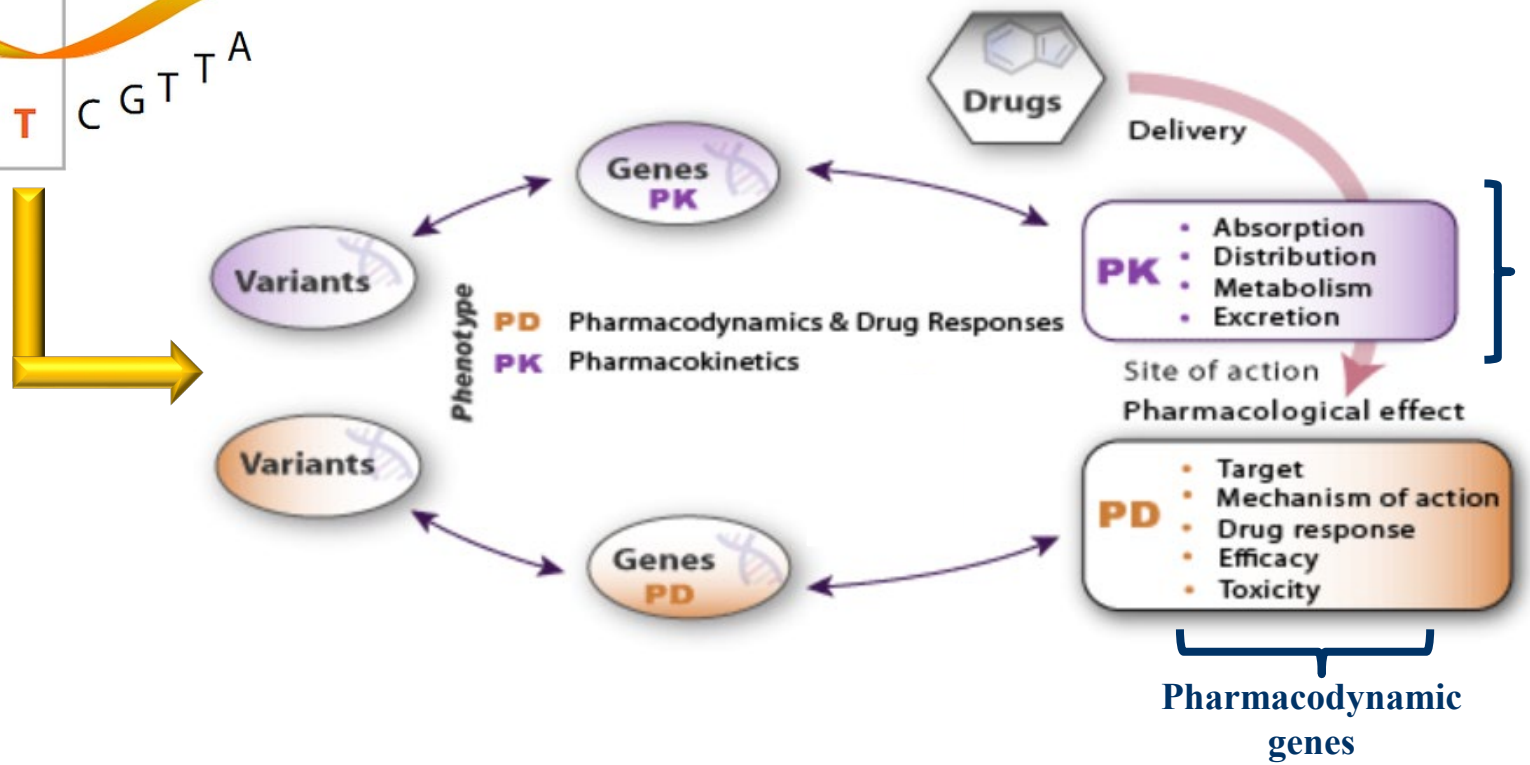


Reitman ML, et al. *J Clin Invest.* 2007; 117(5):1226-1229

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GENETIC VARIANTS AND PK/PD PATHWAYS





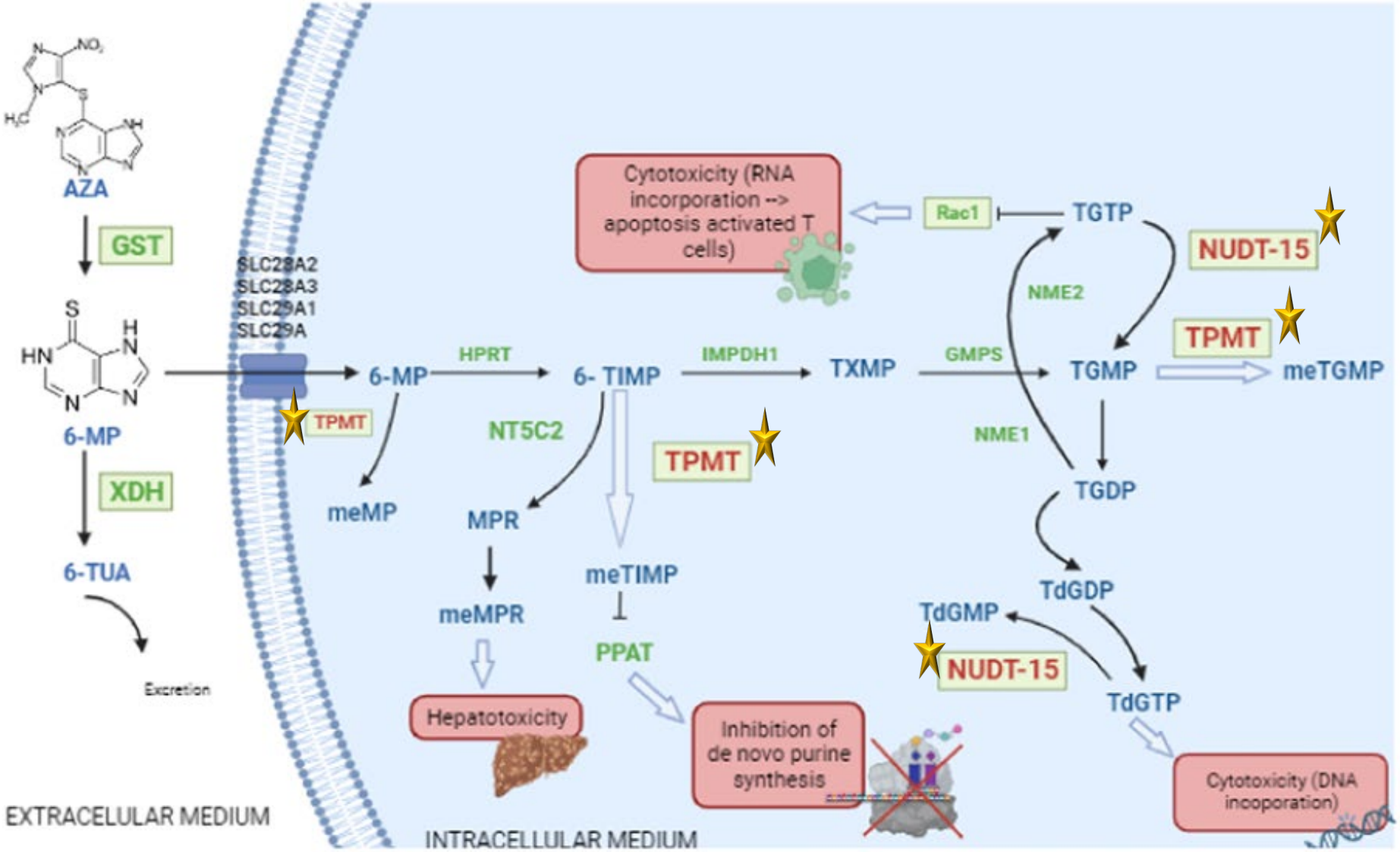


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Pharmacokinetic Genes

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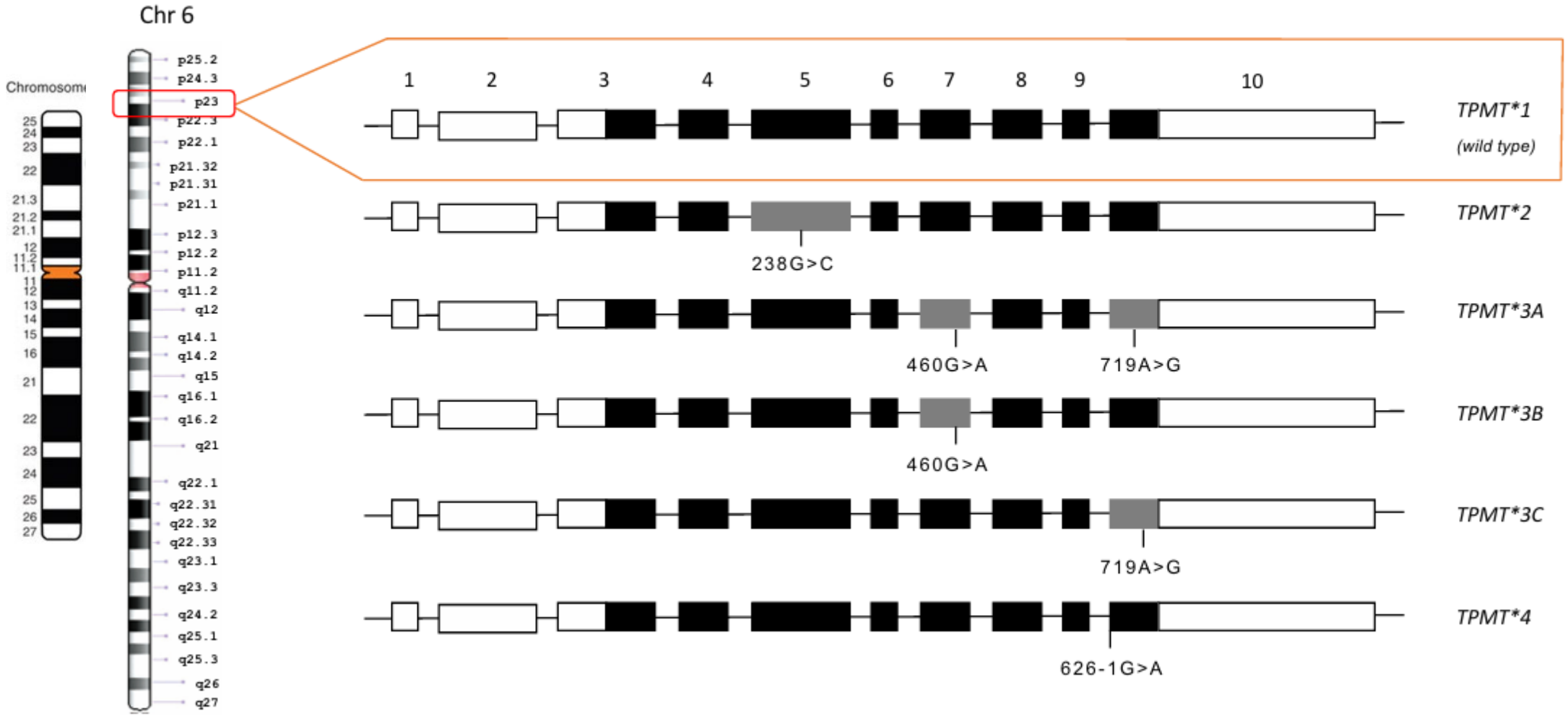
METABOLISM OF MERCAPTOPURINES



Villamarin XD, et al. *Biomedicine and Pharmacotherapy*. 2023;168: 1-10.

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TPMT GENE AND RELATED SNPS



Saito YA, et al. *Am J Gastroenterol*. 2009;104(10): 2583-2587

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FREQUENCIES OF TPMT VARIANTS

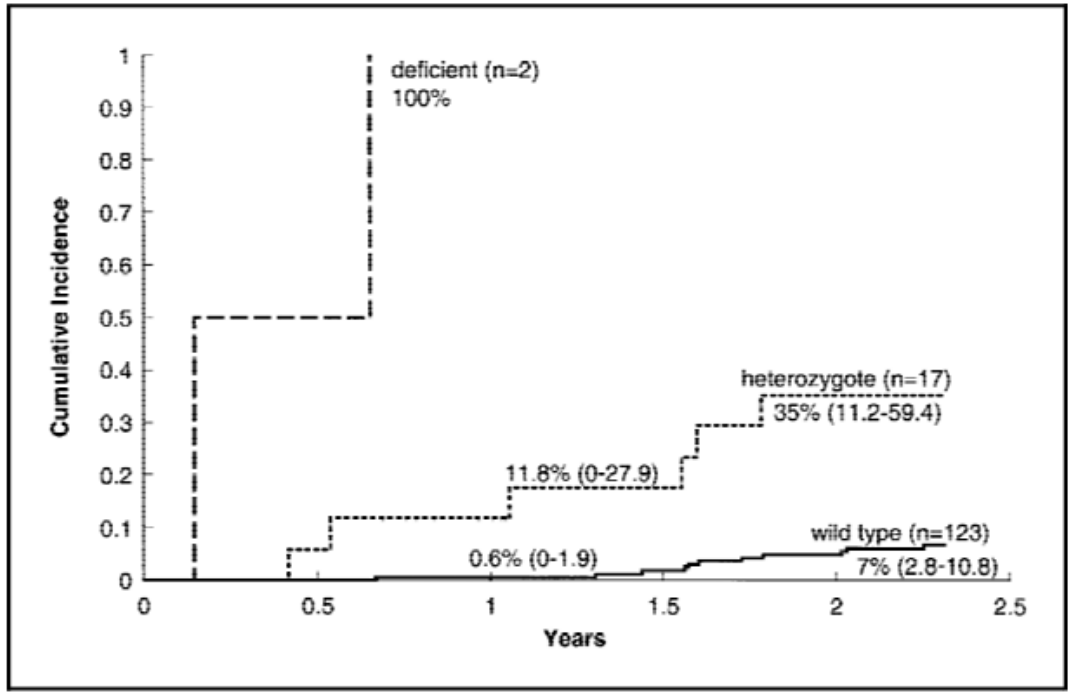
	n	*wt/wt %*	*wt/mut* %*	*mut/mut* %*	*TPMT*2 %*	*TPMT*3A %*	*TPMT*3C %*
British Caucasians (Ameyaw *et al*, 1999)	199	89.9	9.6	0.5	0.5	4.5	0.3
French Caucasians (de la Moureyere *et al*, 1998)	191	85.9	13.6	0.5	0.5	5.7	0.8
American Caucasian (Yates *et al*, 1997)	cal.	92.5	7.4	0.14	0.2	3.2	0.2
African–American (Hon *et al*, 1999)	cal.	90.7	9.2	0.2	0.4	0.8	2.4
Kenyan (McLeod *et al*, 1999)	101	89.1	10.9	0	0	0	5.4
Ghanaian (Ameyaw *et al*, 1999)	217	85.3	14.4	0.5	0	0	7.6
Chinese (Collie-Duguid *et al*, 1999)	192	95.3	4.7	0	0	0	2.3
Japanese (Kumagai *et al*, in press)	553	97.3	2.4	0.4	0	0	1.5
Southwest Asian (Collie-Duguid *et al*, 1999)	99	98	2	0	0	1	0

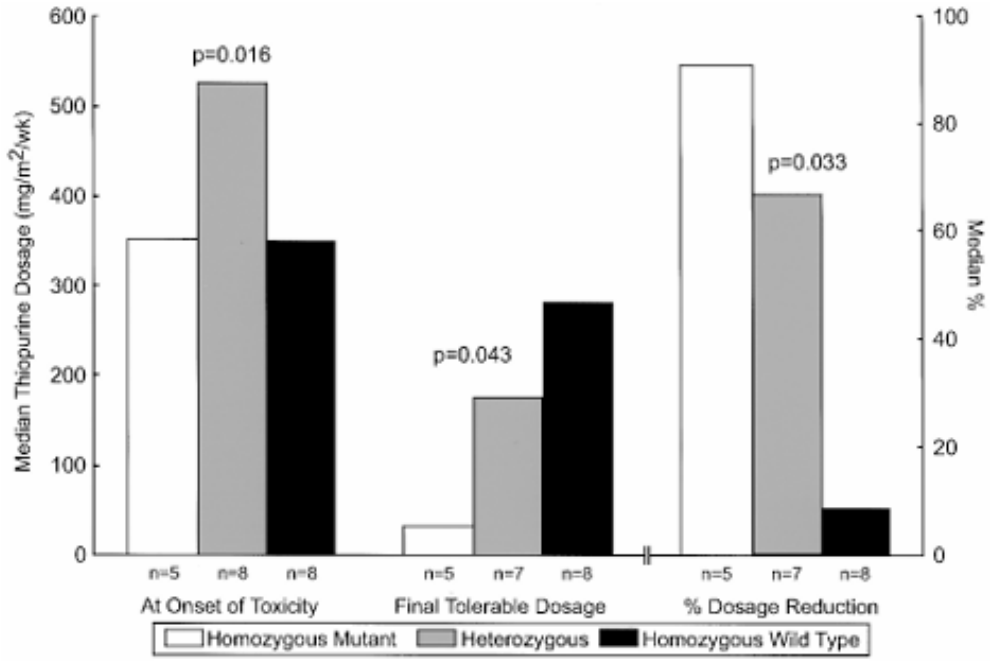


Mcleod HA, et al. *Leukemia*. 2000;14: 567-572

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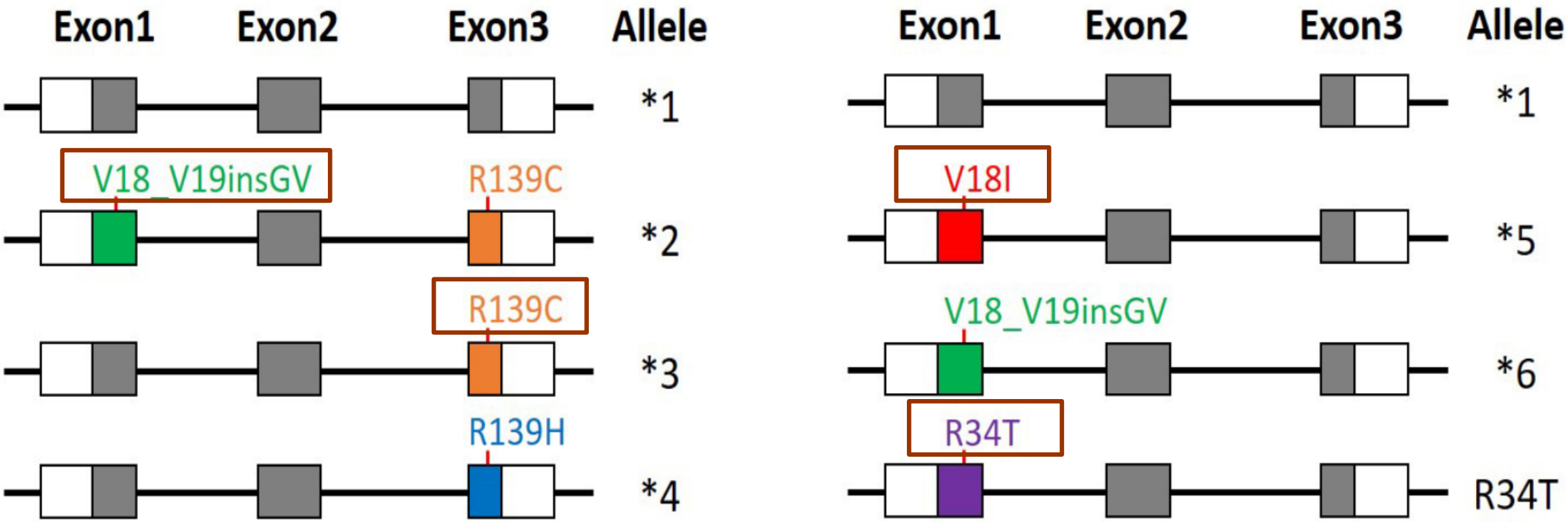
TOXICITIES WITH STANDARD DOSING OF 6-MP





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COMMON SNPS IN *NUDT15* GENE

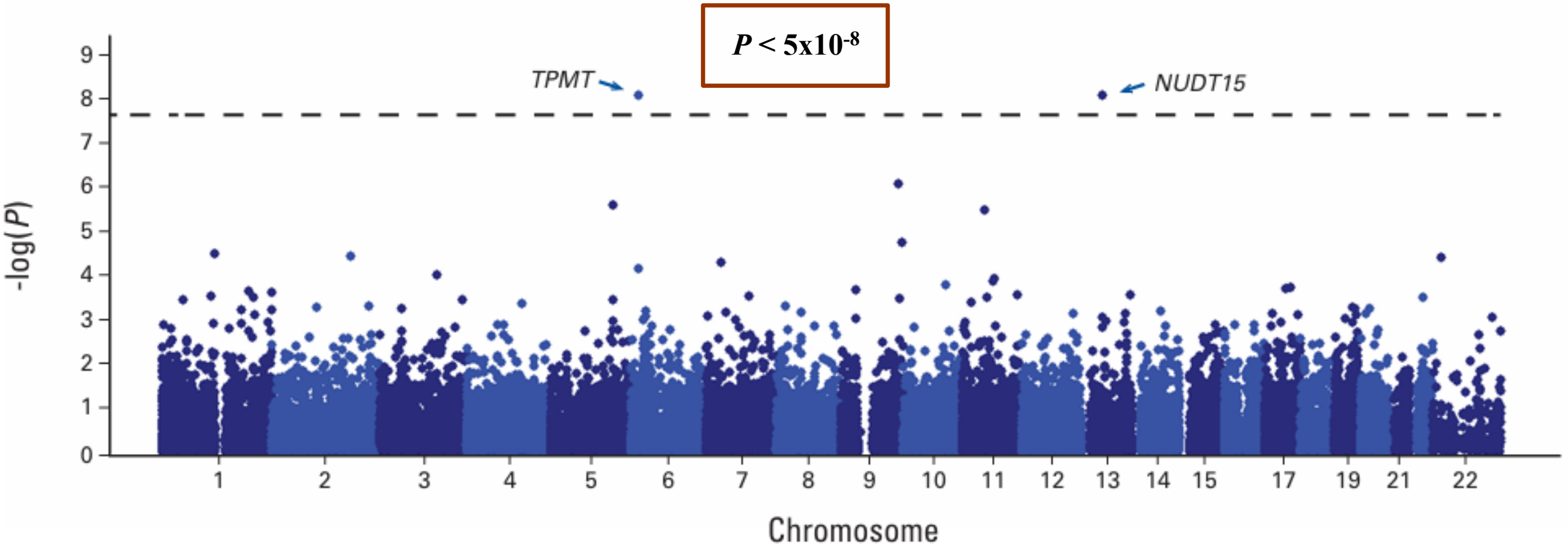


5 Coding SNPs representing 6 different alleles/ haplotypes of *NUDT15*

Yu CH, et al. *Scientific Report*. 2020;10:1-8

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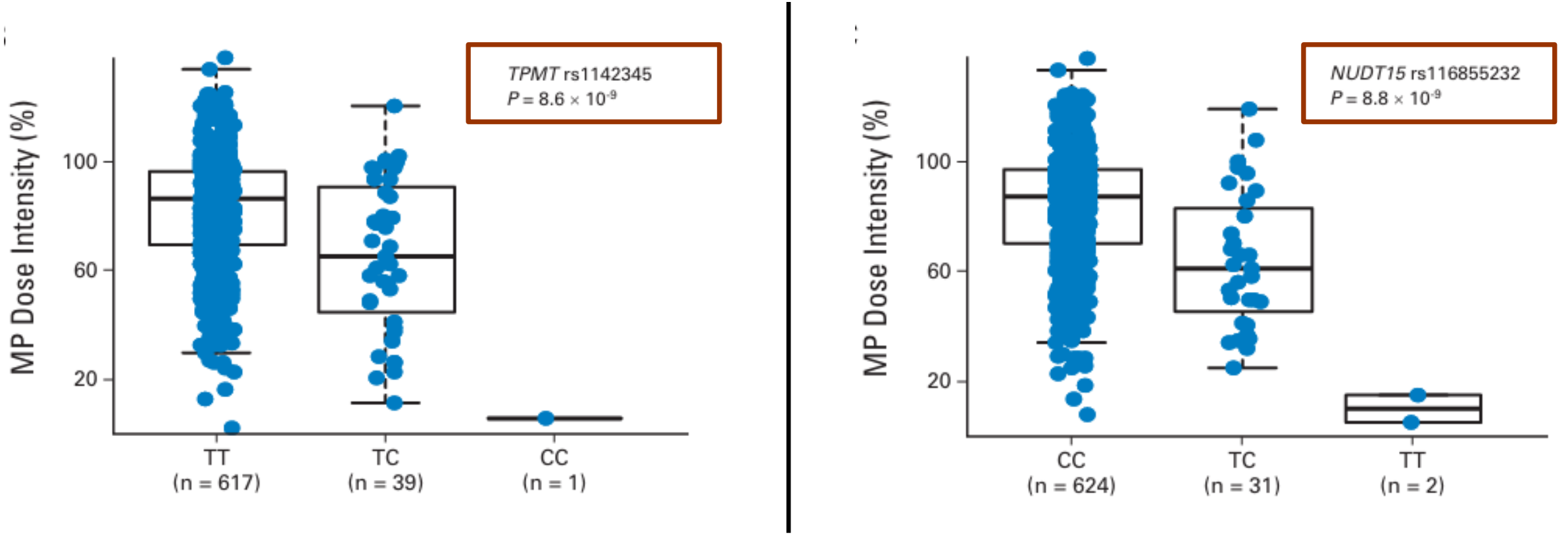
GWAS STUDIES IDENTIFYING VARIANTS LINKED TO 6-MP DOSE INTENSITY



Yang JJ, et al. *J Clin Oncol*. 2015;33(11): 1235-1242.

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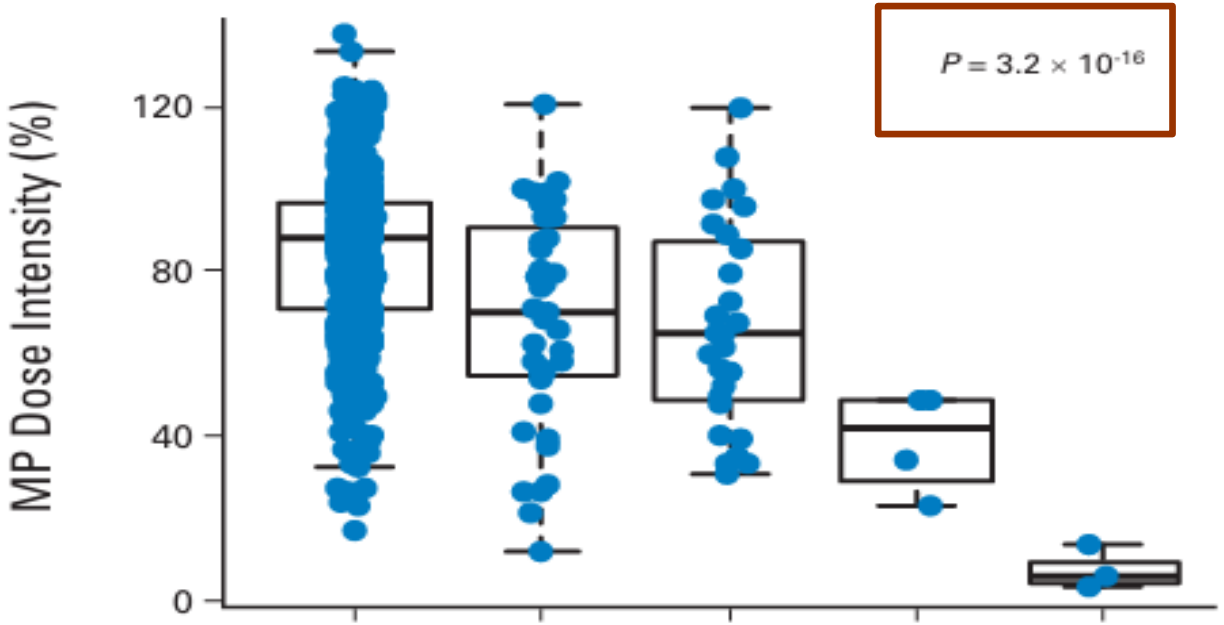
TPMT AND *NUDT15* POLYMORPHISMS AND 6-MP DOSE INTENSITY



Yang JJ, et al. *J Clin Oncol*. 2015;33(11): 1235-1242.

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COMBINED EFFECT OF *TPMT* AND *NUDT15*



Genetic Risk Score	0	1	1	2	2
n =	589	40	27	4	3
Median (%)	87.7	70.0	65.1	41.5	6.0
25th percentile (%)	70.8	54.4	48.9	31.6	4.5
75th percentile (%)	96.7	90.7	87.1	48.6	9.7

Yang JJ, et al. *J Clin Oncol*. 2015;33(11): 1235-1242.

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TPMT: PHENOTYPE DERIVATION TO INFORM DOSING

Likely phenotype[a]	Genotypes	Examples of diplotypes
Assignment of likely TPMT phenotypes based on genotypes		
Normal metabolizer	An individual carrying two normal function alleles	*1/*1
Intermediate metabolizer	An individual carrying one normal function allele PLUS one no function allele	*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4
Possible intermediate metabolizer	An individual carrying one uncertain/unknown function allele PLUS one no function allele	*2/*8, *3A/*7
Poor metabolizer	An individual carrying two no function alleles	*3A/*3A, *2/*3A, *3A/*3C, *3C/*4, *2/*3C, *3A/*4
Indeterminate	An individual carrying two uncertain/unknown function alleles OR one normal function allele plus one uncertain allele function allele	*6/*8 *1/*8

Relling MV, et al. *Clin Pharmacol Ther*. 2019;105(5): 1096-1105

NUDT15: PHENOTYPE DERIVATION TO INFORM DOSING

Assignment of likely NUDT15 phenotypes based on genotypes

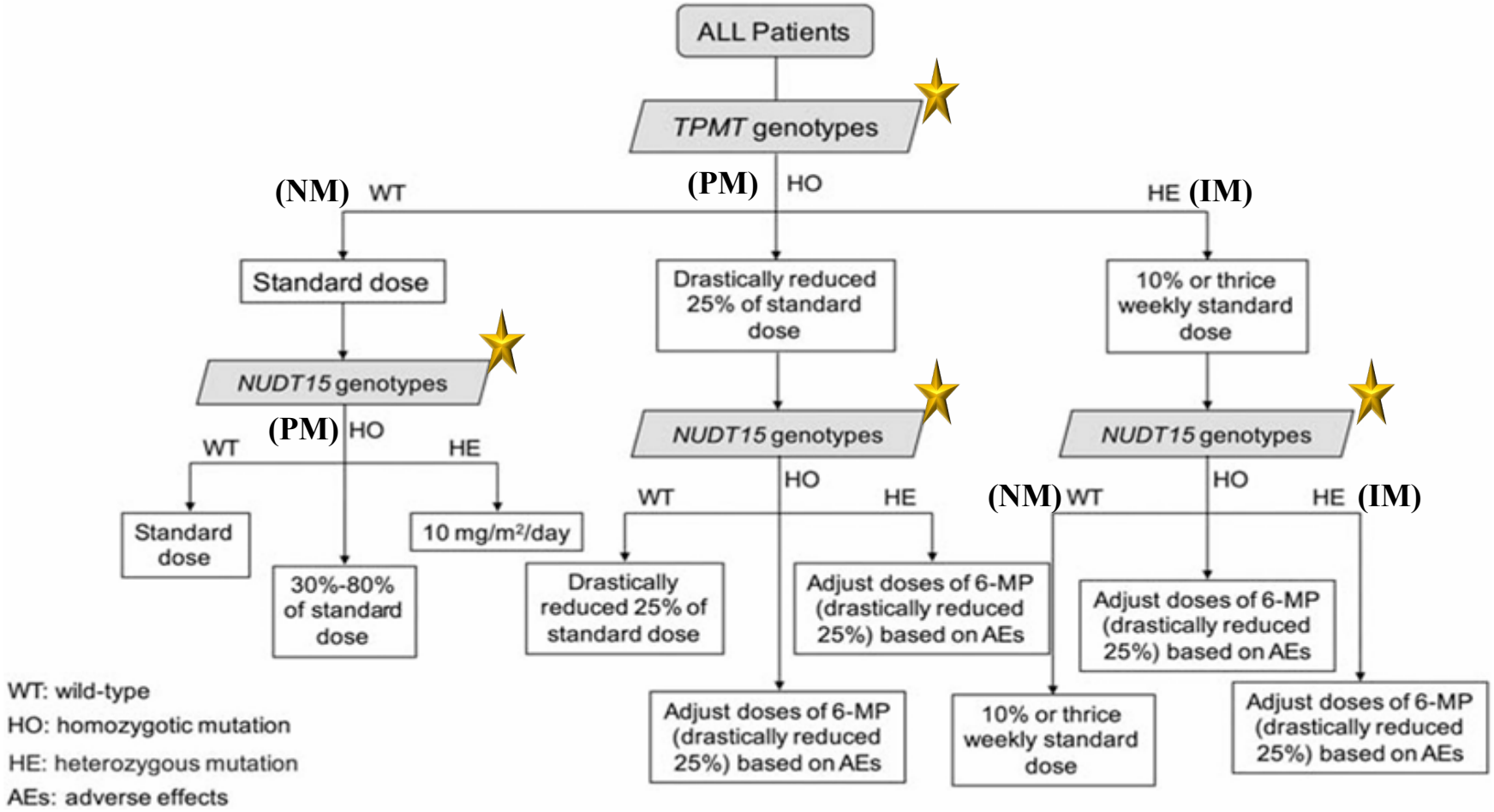
Normal metabolizer	An individual carrying two normal function alleles	*1/*1
Intermediate metabolizer	An individual carrying one normal function allele PLUS one no function allele	*1/*2, *1/*3
Possible intermediate metabolizer	An individual carrying one uncertain function allele PLUS one no function allele	*2/*5, *3/*6
Poor metabolizer	An individual carrying two no function alleles	*2/*2, *2/*3, *3/*3
Indeterminate	An individual carrying two uncertain function alleles OR one normal function allele plus one uncertain function allele	*1/*4, *1/*5 *4/*5, *5/*6



Relling MV, et al. *Clin Pharmacol Ther*. 2019;105(5): 1096-1105

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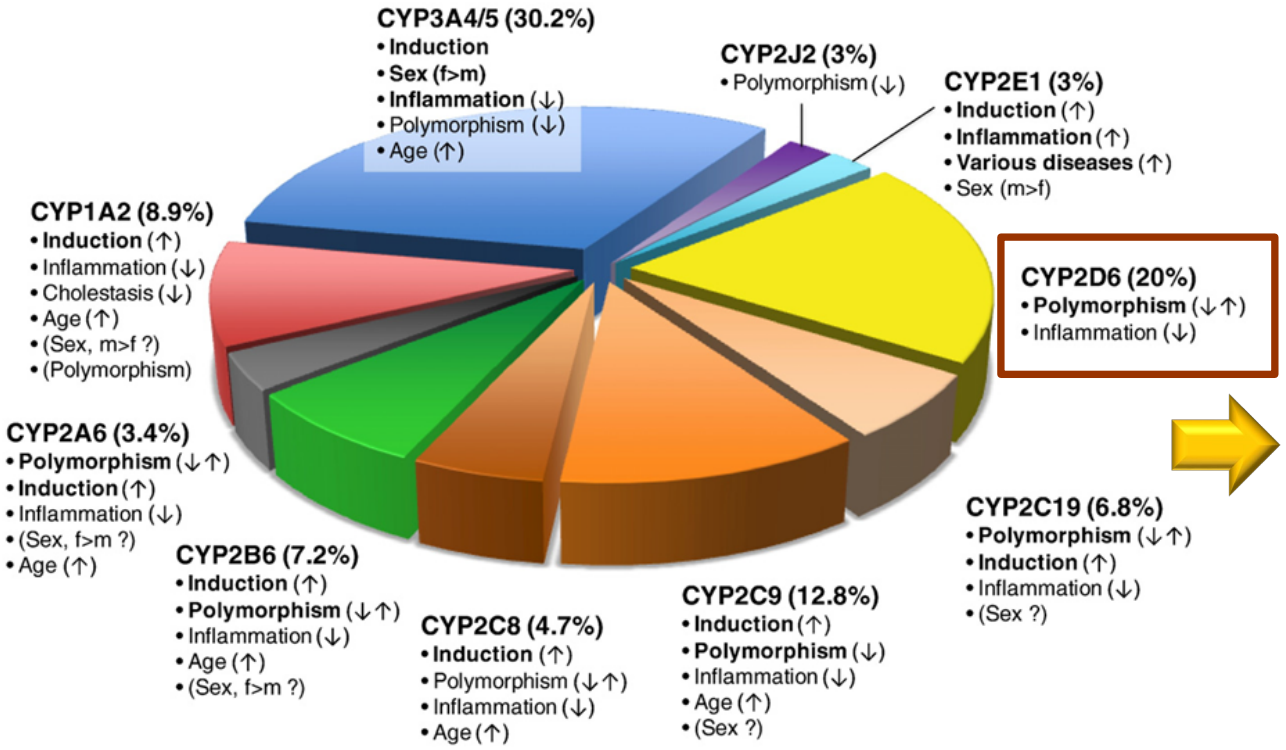
DOSE ADJUSTMENTS OF MERCAPTOPURINES



Zhou Y, et al. *Br J Clin Pharmacol*. 2020;86:1519-1527.

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CYP2D6 AND DRUG METABOLISM



Classes of drugs as CYP2D6 substrates:

- *Beta blockers*: metoprolol, timolol

- *Antiarrhythmics*: amiodarone, propafenone

- *Opioids*: tramadol, oxycodone, hydrocodone

- *Antiemetics*: ondansetron

- *Antipsychotics*: haloperidol, risperidone

- *Antidepressants*: amitriptyline, fluoxetine, trazodone.

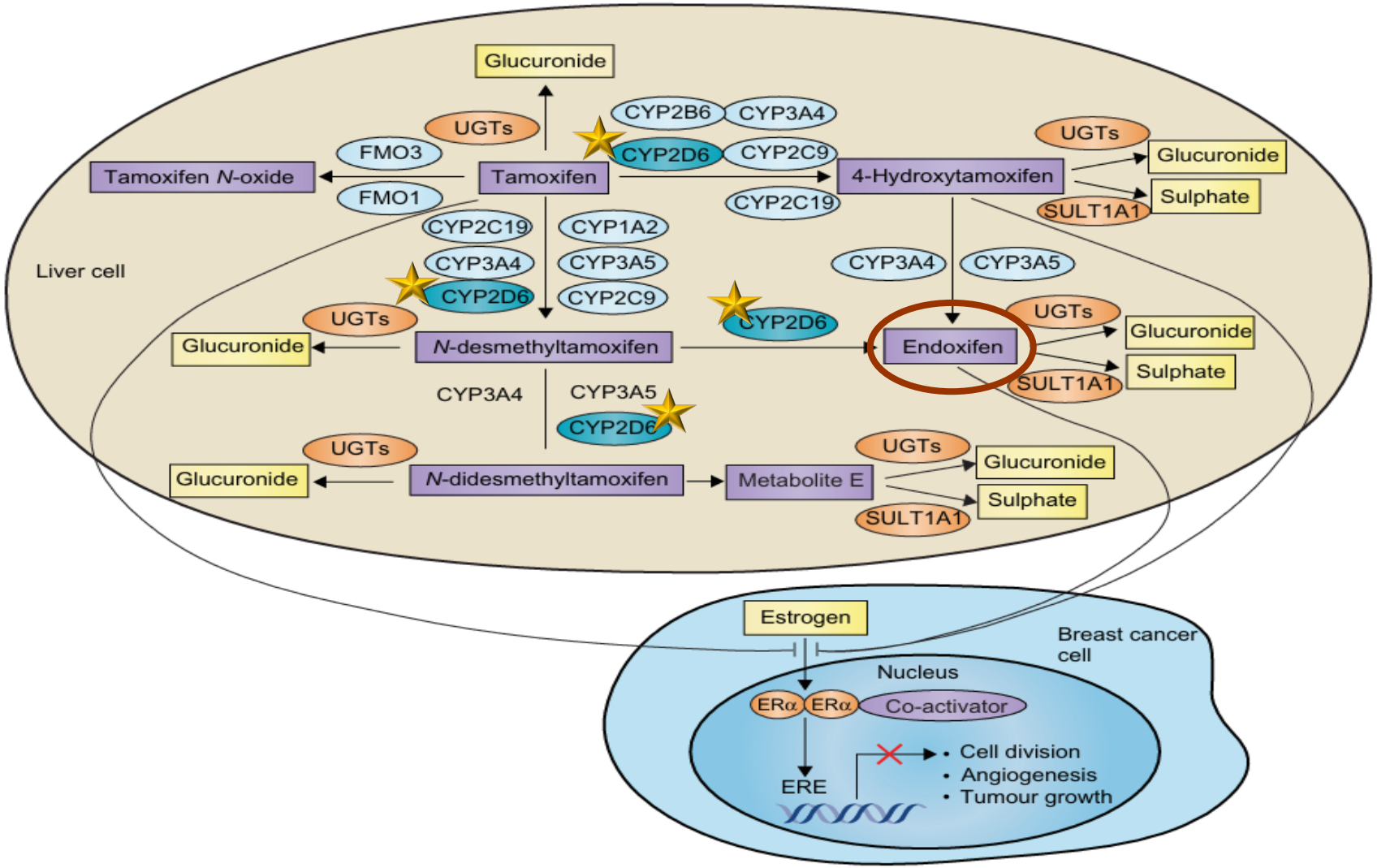
- *Cancer drugs*: tamoxifen



Ulrich MZ, et al. Pharmacology and Therapeutics. 2013;138: 103-141

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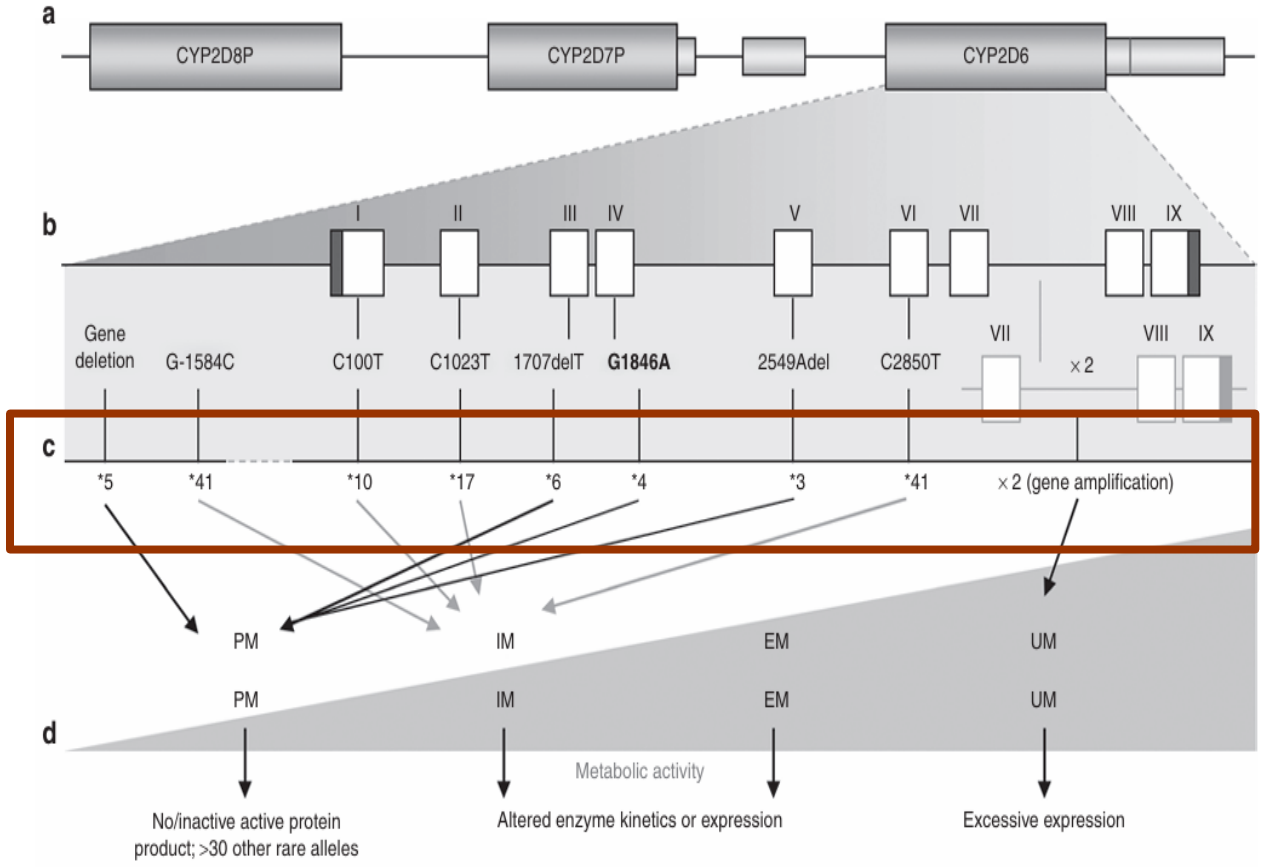
TAMOXIFEN METABOLIC PATHWAY

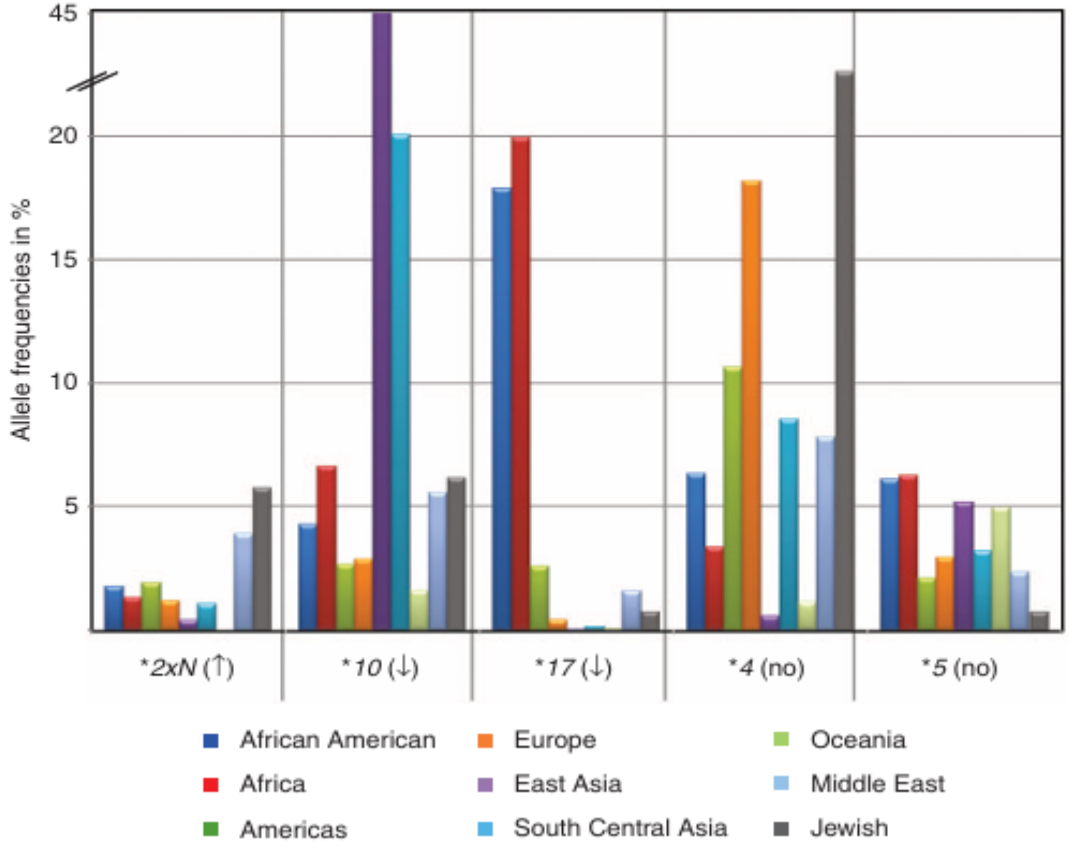


Li J, et al. *Pharmacogenomics and Personalized Medicine*. 2011;4: 11-33.

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CYP2D6 AND RELATED SNPS



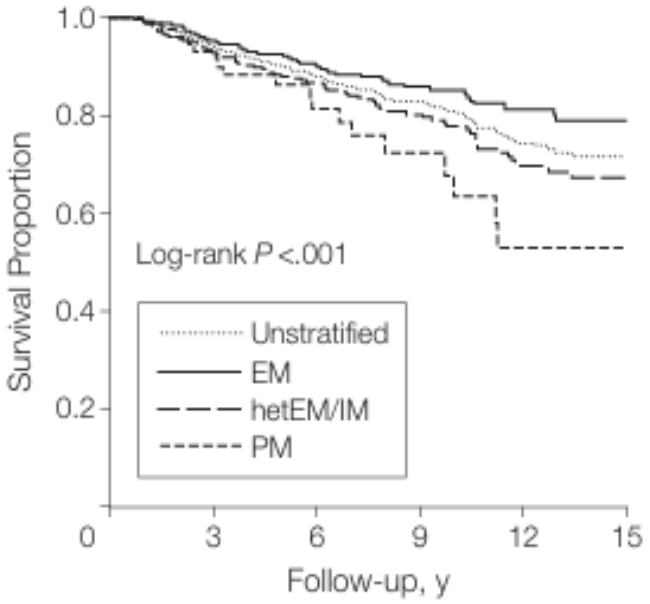


Goetz M, et al. *Clin Pharmacol Ther.* 2017;10: 1-8. Gaedigk A, et al. *Genetics in Medicine.* 2017;19(1): 69-76.

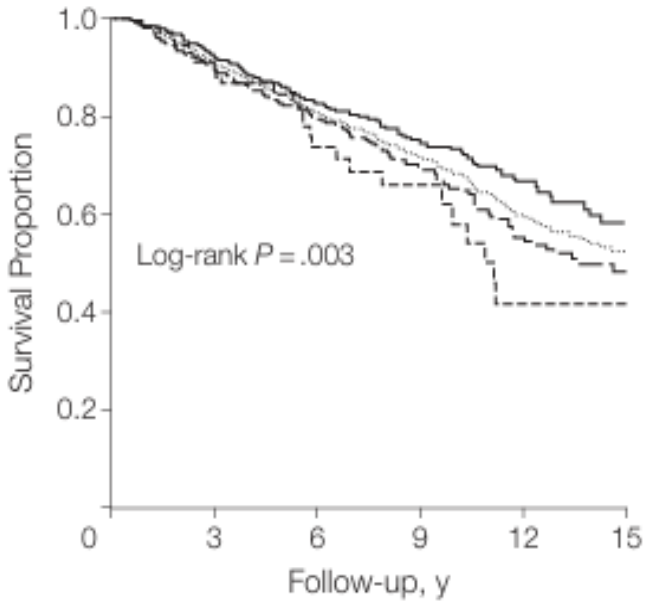
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TAMOXIFEN: IMPACT OF *CYP2D6* POLYMORPHISMS ON PATIENT OUTCOME

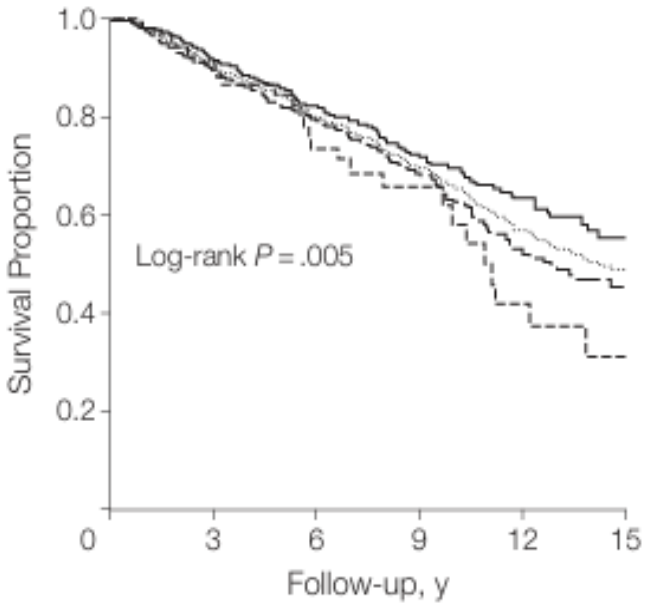
Time to recurrence



Event-free survival



Disease-free survival



Breast cancer patients with *CYP2D6* poor metabolizer phenotype who received adjuvant tamoxifen for breast cancer had inferior outcomes

Schroth W, et al. *JAMA.* 2009;302(13): 1429-1436

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ACTIVITY SCORE FOR INFERING *CYP2D6* PHENOTYPES

Phenotype[a]		Genotype	Examples of *CYP2D6* diplotypes[b]
Metabolizer	Activity score		
CYP2D6 ultrarapid metabolizer	> 2.0	An individual carrying duplications of functional alleles	**1/*1xN, *1/*2xN, *2/*2xN*[c]
CYP2D6 normal metabolizer	1.5 and 2.0	An individual carrying two normal function alleles or one normal function and one decreased function allele	**1/*1, *1/*2, *1/*9, *1/*41, *2/*2,*
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[d]	1.0	An individual carrying two decreased function alleles or one normal function and one no function allele. *An activity score (AS) of 1.0 is associated with decreased tamoxifen metabolism to endoxifen compared to those with an AS of 1.5 or 2.*	**1/*4, *1/*5, *41/*41*
CYP2D6 intermediate metabolizer	0.5	An individual carrying one decreased function and one no function allele	**4/*10,*4/*41, *5/*9*
CYP2D6 poor metabolizer	0	An individual carrying only no functional alleles	**3/*4,*4/*4, *5/*5, *5/*6*

Goetz M, et al. *Clin Pharmacol Ther.* 2017;10: 1-8.

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TAMOXIFEN DOSE ADJUSTMENTS

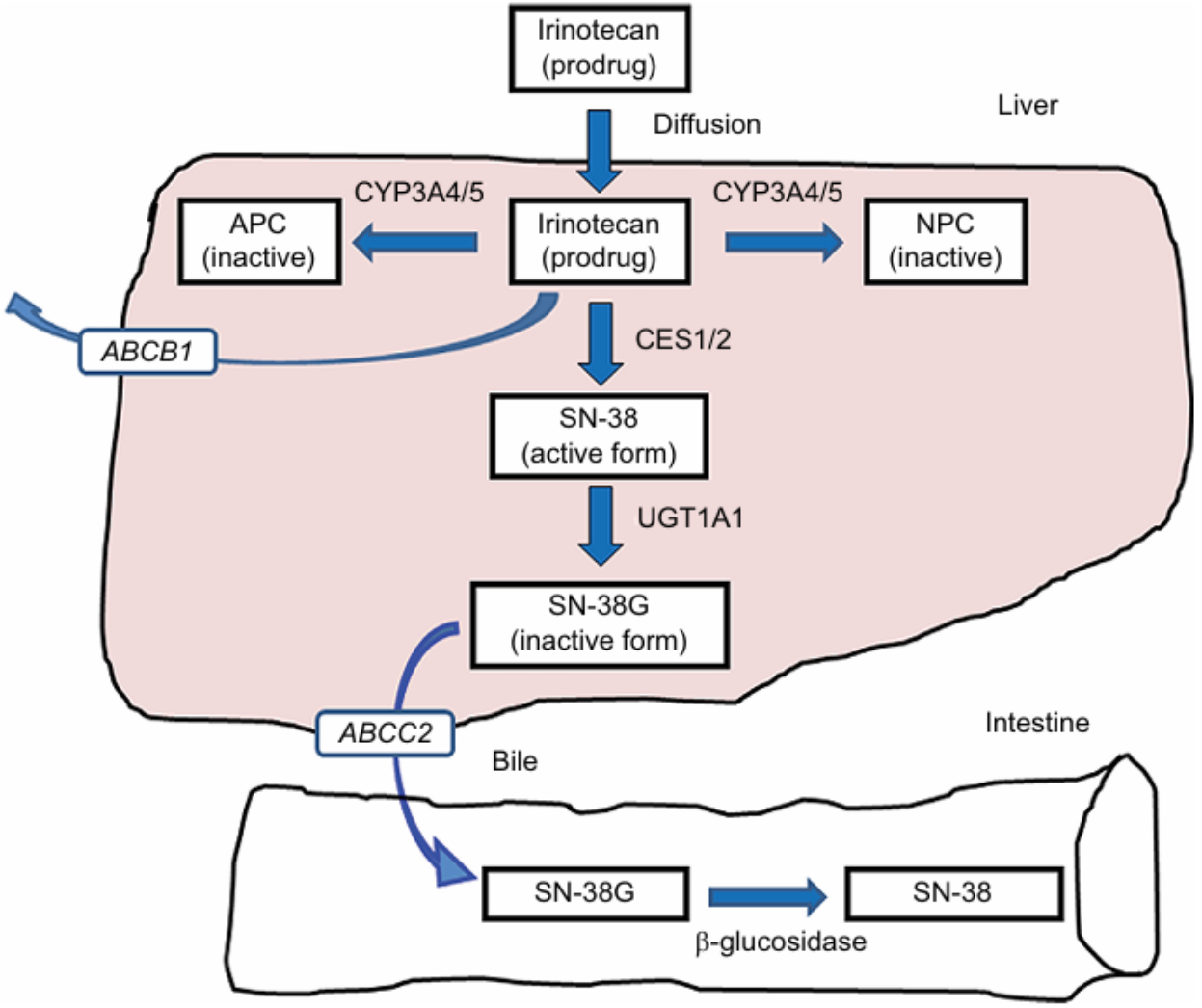
Phenotype		Therapeutic recommendation[b]
Metabolizer status	Activity score	
CYP2D6 ultrarapid metabolizer	>2.0	Avoid moderate and strong CYP2D6 inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).
CYP2D6 normal metabolizer	1.5 to 2.0	Avoid moderate and strong CYP2D6 inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[b]	1.0 (no *10 allele present)[b]	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype.[43] If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day).[45] Avoid CYP2D6 strong to weak inhibitors.
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[b]	1.0 (*10 allele present)[b]	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype.[43] If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day).[45] Avoid CYP2D6 strong to weak inhibitors.
CYP2D6 intermediate metabolizer	0.5	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype.[43] If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day).[45] Avoid CYP2D6 strong to weak inhibitors.
CYP2D6 poor metabolizer	0	Recommend alternative hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype[43] and based on knowledge that *CYP2D6* poor metabolizers switched from tamoxifen to anastrozole do not have an increased risk of recurrence.[38] Note, higher dose tamoxifen (40 mg/day) increases but does not normalize endoxifen concentrations and can be considered if there are contraindications to aromatase inhibitor therapy.[45,56]

Goetz M, et al. *Clin Pharmacol Ther.* 2017;10: 1-8.

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IRINOTECAN METABOLIC PATHWAY

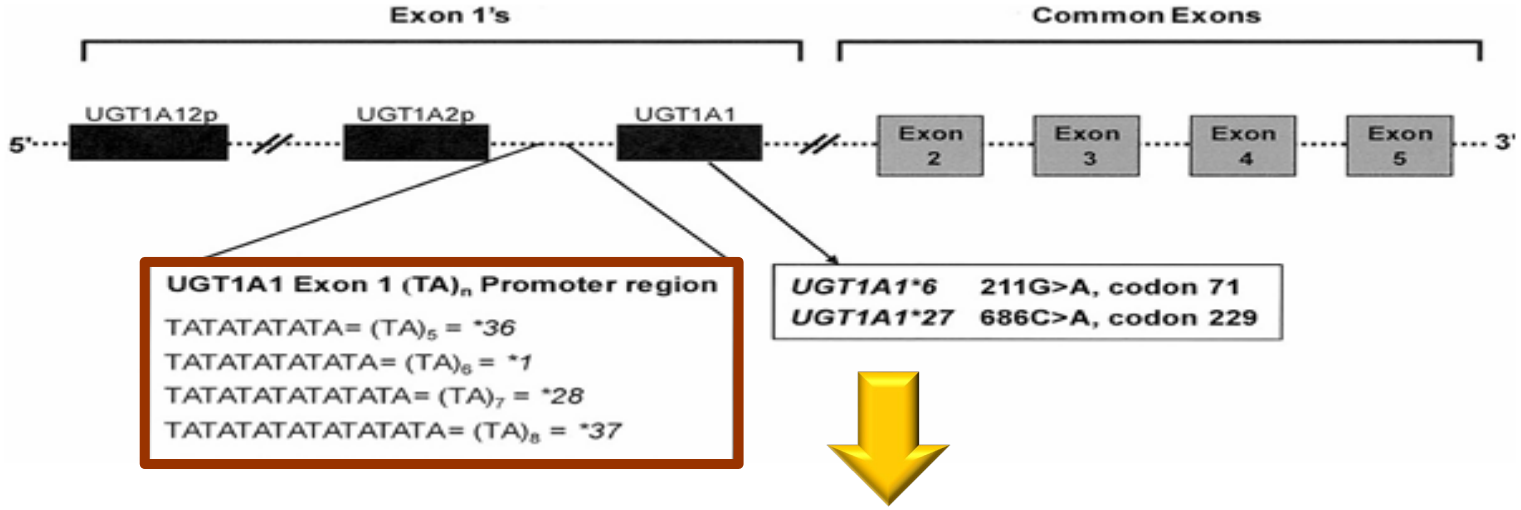
- Irinotecan is a topoisomerase I inhibitor
- It is used in combination with other drugs to treat colorectal cancer
- Irinotecan is a prodrug that is activated in the liver to cytotoxic agent SN-38
- Dose limiting toxicities include diarrhea and myelosuppression



Takano M, et al. *Pharmacogenomics and Personalized Medicine.* 2011;10:61-68.

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UGT1A1 POLYMORPHISMS

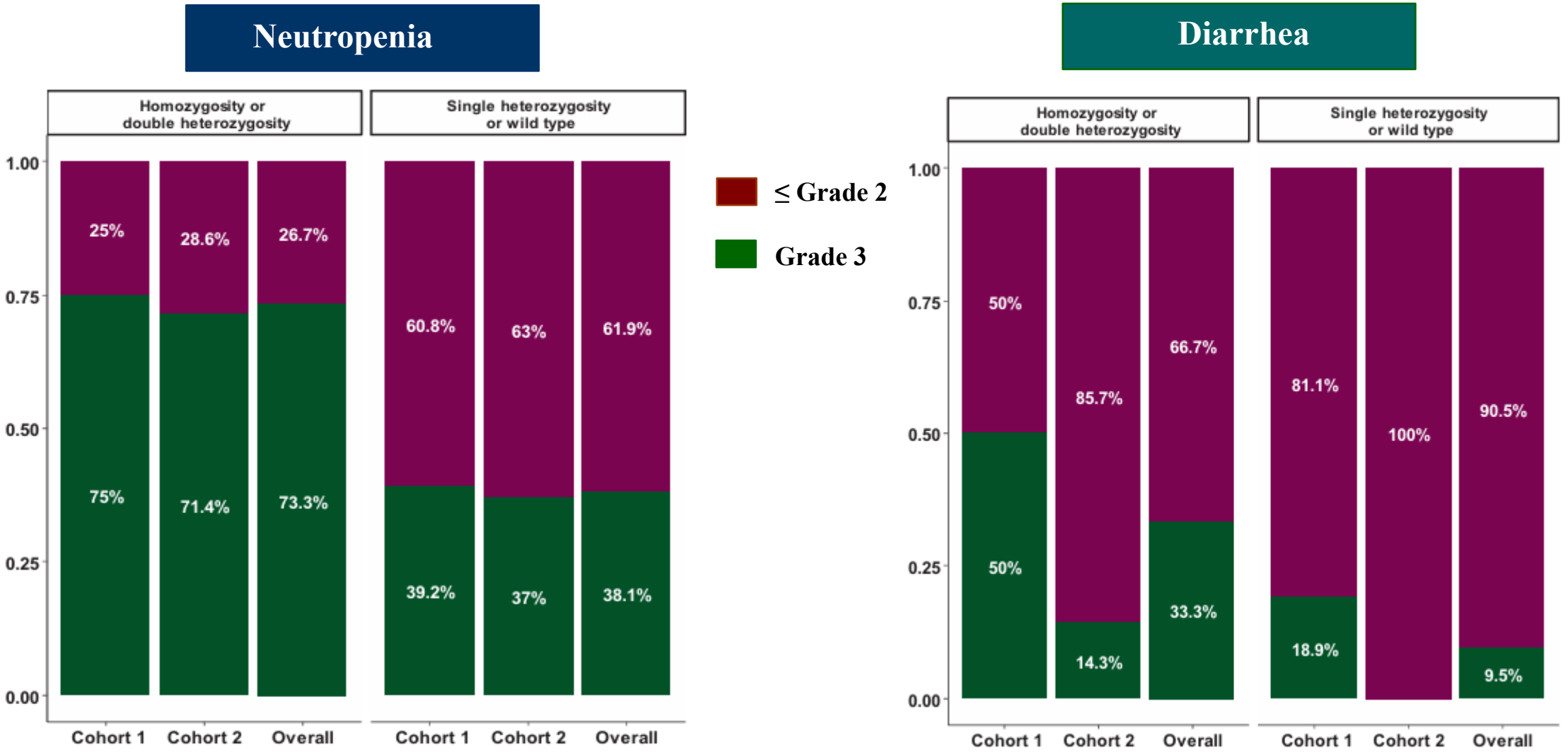


Denomination	Variants[14]	Allele frequency (ethnicity)[15,16]	Expression level	Enzymatic activity
*UGT1A1*1*	$(TA)_6TA$	Common allele	100%	100%
TATA box polymorphisms				
*UGT1A1*28*	c.–39_–40 ins TA: $(TA)_7TA$	29–45% (Caucasians); 42–51% (Africans); 16% (Asians)	Reduced	Reduced
Polymorphisms in the promoter region				
*UGT1A1*60*	c.–3279 T>G	23–39% (Caucasian); 15% (African Americans); 17% (Asians)	Reduced	Unchanged
Polymorphisms in exon 1				
*UGT1A1*6*	c.211 G>A p.Gly71Arg	15–20% (Asians)	Unchanged	Reduced
*UGT1A1*27*	c.686 C>A p.Pro229Gln	5–28% (Asians)	Unchanged	Reduced

Karas S, et al. *JCO Oncology Practice.* 2021;18(4): 270-277.

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UGT1A1 POLYMORPHISMS AND IRINOTECAN INDUCTED TOXICITIES



Su YY, et al. *ESMOOP.* 2022;8(1): 1-7.

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RECOMMENDATIONS BASED ON *UGT1A1* GENOTYPES

UGT1A1 Genotype	Effect on UGT1A1 Activity or Expression	Clinical Implication	Clinical Intervention
*1/*1	Normal	Average risk of irinotecan toxicity	Use standard starting dose[1,6,7] These patients may be able to tolerate irinotecan doses higher than the standard dose without compromising safety[5,45-48]
*1/*28	Reduced expression	Higher risk of irinotecan toxicity	Use standard starting dose[1,6,7]
*1/*6	Reduced activity		These patients may be able to tolerate irinotecan doses higher than the standard dose without compromising safety[5,45-48]
*28/*28	Further reduction in expression	Highest risk of irinotecan toxicity	Reduce the starting dose to at least one level lower than the standard dose.[1] For specific dosing recommendations, see Table 3 After cycle 1 at a reduced dose, upward titration at subsequent cycles can be considered, on the basis of individual tolerance[1,6,7]
*6/*6	Further reduction in activity		
*6/*28	Further reduction in activity and expression		

Karas S, et al. *JCO Oncology Practice.* 2021;18(4): 270-277.

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DOSE MODIFICATIONS TO REDUCE TOXICITY

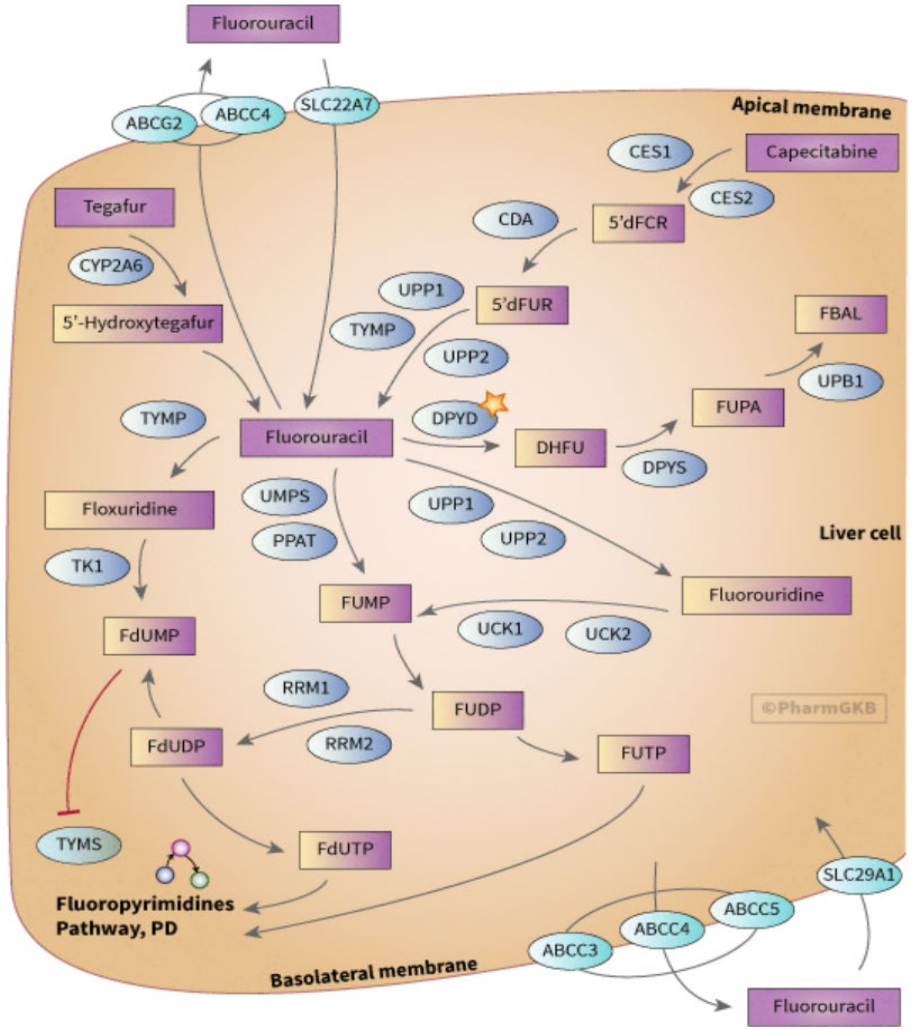
Formulation	Regimen	Standard Dose[1,6,7]	Reduced Dose	IV Infusion Duration[1,6,7]	Frequency[1,6,7]
Irinotecan HCl (Camptosar)	Single agent	350 mg/m^2	300 mg/m^2 [1]	90 minutes	Every 3 weeks
	FOLFIRI with or without bevacizumab	180 mg/m^2	150 mg/m^2 [1]	90 minutes	Every 2 weeks
	FOLFIRINOX with or without cetuximab	180 mg/m^2	150 mg/m^2 [67,68]	90 minutes	Every 2 weeks
	FOLFOXIRI with cetuximab or bevacizumab	165 mg/m^2	125 mg/m^2 [69,70]	60 minutes	Every 2 weeks
Irinotecan liposome (Onivyde)	With 5-FU, leucovorin	70 mg/m^2	50 mg/m^2 [6,71]	90 minutes	Every 2 weeks
Sacituzumab Govitecan-hziy (Trodelvy)	Single agent	10 mg/kg	7.5 mg/kg[72]	3 hours for the first infusion. 1-2 hours if prior infusions were tolerated	Days 1 and 8 of each 21-day cycle

Karas S, et al. *JCO Oncology Practice.* 2021;18(4): 270-277.

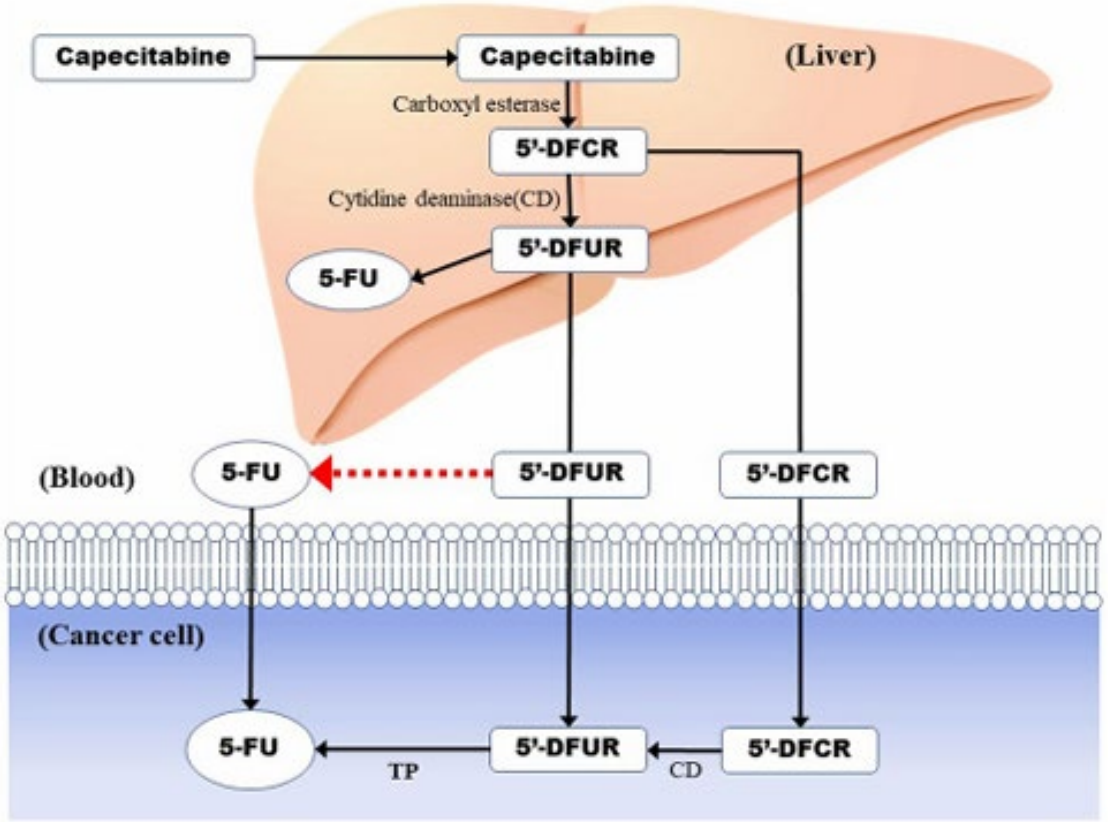
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METABOLIC PATHWAY OF 5-FU

5-Fluoro uracil



Capecitabine

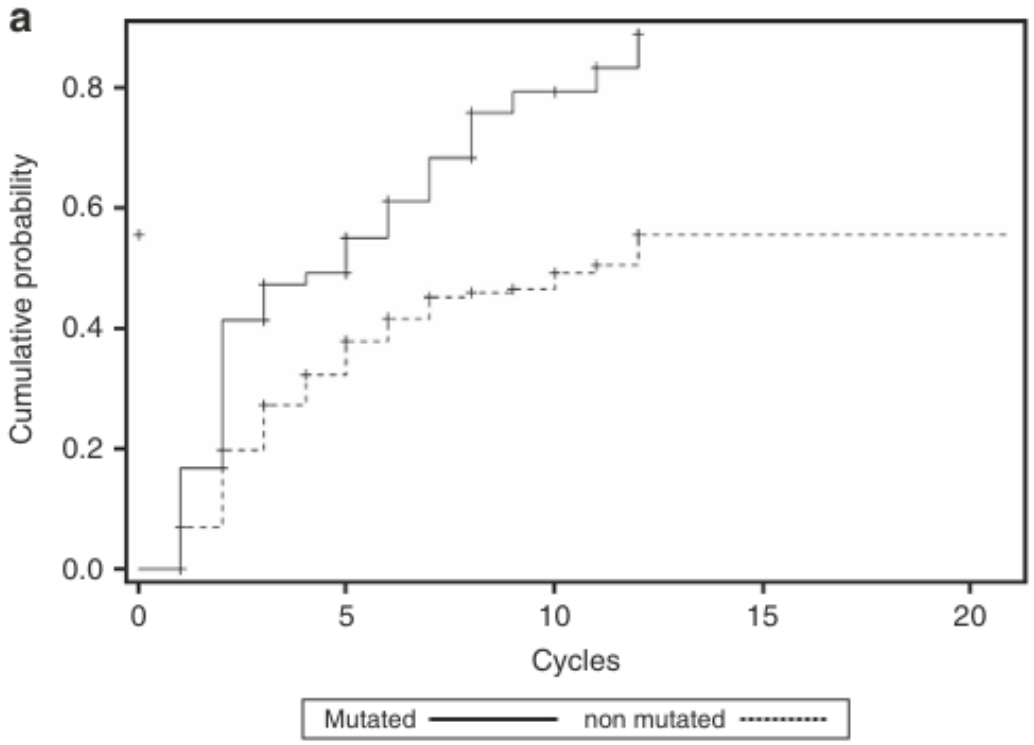


Amstutz U, et al. *Clin Pharmacol Ther*. 2017;11: 1-7.

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DPYD AND RELATED TOXICITIES

		Total n.	%	c.2194G/G no.	%	c.2194 (G/A)+(A/A) no.	%	*p*	OR	95% CI
All toxicities	NO	192	52	180	56	12	26			
	YES	174	48	140	44	34	74	**0.0001**	3.548	1.779–7.076
Haematological	NO	275	75	253	79	22	48			
	YES	91	25	67	21	24	52	**<0.0001**	4.090	2.161–7.741
Neutropenia	NO	276	75	253	79	23	50			
	YES	90	25	67	21	23	50	**<0.0001**	3.756	1.986–7.106
Intestinal	NO	299	82	260	81	39	85			
	YES	67	18	60	19	7	15	0.5624	0.817	0.354–1.889
Others	NO	335	92	293	92	42	91			
	YES	31	8	27	8	4	9	0.9531	1.130	0.393–3.253



***DPYD* mutations were associated with a higher likelihood of 5-FU related toxicities particularly hematological side effects.**

Lachetta F, et al. *British Journal of Cancer*. 2019;120: 834-839

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DPYD GENOTYPES

Allele	Activity value	Allele functional status
c.1905+1G>A (*2A)	0	No function
c. 1129-5923 C>G, c.1236 G>A (HapB3)	0.5	Decreased function
c. 2846 A>T	0.5	Decreased function
c.1679T>G (*13A)	0.5	Decreased function

Likely phenotype	Activity score[a]	Genotypes[b]	Examples of genotypes[c]
DPYD normal metabolizer	2	An individual carrying two normal function alleles.	c.[=];[=], c.[85T>C];[=], c.[1627A>G];[=]
DPYD intermediate metabolizer	1 or 1.5	An individual carrying one normal function allele plus one no function allele or one decreased function allele, or an individual carrying two decreased function alleles.	c.[1905+1G>A];[=], c.[1679T>G];[=], c.[2846A>T];[=]; c.[1129–5923C>G];[=][d]; c.[1129–5923C>G];[1129–5923C>G][d]; c.[2846A>T];[2846A>T]
DPYD poor metabolizer	0 or 0.5	An individual carrying two no function alleles or an individual carrying one no function plus one decreased function allele.	c.[1905+1G>A];[1905+1G>A], c.[1679T>G];[1679T>G], c.[1905+1G>A];[2846A>T] c.[1905+1G>A]; [1129-5923C>G]

Amstutz U, et al. *Clin Pharmacol Ther*. 2017;11: 1-7.

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DOSING RECOMMENDATIONS

Phenotype	Implications for phenotypic measures	Dosing recommendations	Classification of recommendations[b]
DPYD normal metabolizer	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity.	Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.	Strong
DPYD intermediate metabolizer	Decreased DPD activity (leukocyte DPD activity at 30% to 70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Reduce starting dose based on activity score followed by titration of dose based on toxicity[c] or therapeutic drug monitoring (if available). **Activity score 1:** Reduce dose by 50% **Activity score 1.5:** Reduce dose by 25% to 50%	**Activity score 1:** Strong **Activity score 1.5:** Moderate
DPYD poor metabolizer	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	**Activity score 0.5:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose[d] with early therapeutic drug monitoring.[e] **Activity score 0:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Strong

Amstutz U, et al. *Clin Pharmacol Ther*. 2017;11: 1-7.

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Drug-Gene Interactions

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DRUG-GENE INTERACTIONS

Term	Definition
Drug–Drug Interaction	When a drug in the individual's regimen affects that individual's ability to clear another drug.
Drug–Gene Interaction	When an individual's genetic phenotype affects that patient's ability to clear a drug.
Phenoconversion	Mismatch between the individual's genotype- based prediction of drug metabolism and true capacity to metabolize drugs due to non-genetic factos (e.g., inflamation, pregnancy, liver failure, GFR, smoking, gender, and comedication).
Victim Drug	Substrate of drug-metabolizing enzymes that are induced or inhibited in combination with a perpetrator drug (inhibitor or inducer). The serum levels of the vitim drug changes by this Drug–Drug-Interaction.
Perpetrator Drug	Inhibitor or inducer of drug-metabolizing enzymes that increases or decreases the serum levels of the victim drug. The serum level of the perpetrator drug does not change.



Hahn M, et al. *Pharmaceuticals*. 2021;14(487):1-15.

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DRUG-GENE INTERACTIONS

CYP	Known Phenotypes	Substrates	Phenoconversion
2C9	NM, IM, PM	losartan, NSAIDs, phenytoin, warfarin, glyburide	amiodarone, fluconazole, miconazole, rifampin
2C19	NM, IM, PM, RM, UM	clopidogrel, diazepam, proton pump inhibitors (PPI)	fluvoxamine, fluoxetine, fluconazole, omeprazole, ticlopidine, rifampin
2D6	NM, IM, PM, UM	antidepressants, betablockers, codeine, tramadol, tamoxifen, hydrocodone	bupropion, cimetidine, duloxetine, fluvoxamine, fluoxetine, paroxetine, quinidine, Note: there are no known inducers of CYP2D6.
3A4	normal function, decreased function, increased function	calcium channel blockers, macrolides, protease inhibitors, statins	azole antimycotics, boceprevir, cobicistat, danoprevir, grapefruit, ritonavir, telaprevir, verapamil, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort
3A5	NM, IM, PM Note: activity has major influence on CYP3A4 activity, if *1 is present	Tacrolimus, quetiapine	Ciprofloxacin, erythromycin, diltiazem, ketoconazole, verapamil



Hahn M, et al. *Pharmaceuticals*. 2021;14(487):1-15.

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PHENOCONVERSION AND CALCULATION OF ACTIVITY SCORE

Activity Score CYP2D6	Genetic Phenotype	Weak Inhibitor and Moderate Inhibitor	Strong Inhibitor
0	PM	Activity score × 0.5 = PM	Activity score × 0 = PM
> 0 < 1.25	IM	Activity score × 0.5 = IM	Activity score × 0 = PM
> 1.25 < 2.25	NM	Activity score × 0.5 = IM	Activity score × 0 = PM
>2.25	UM	Activity score × 0.5 = NM	Activity score × 0 = PM



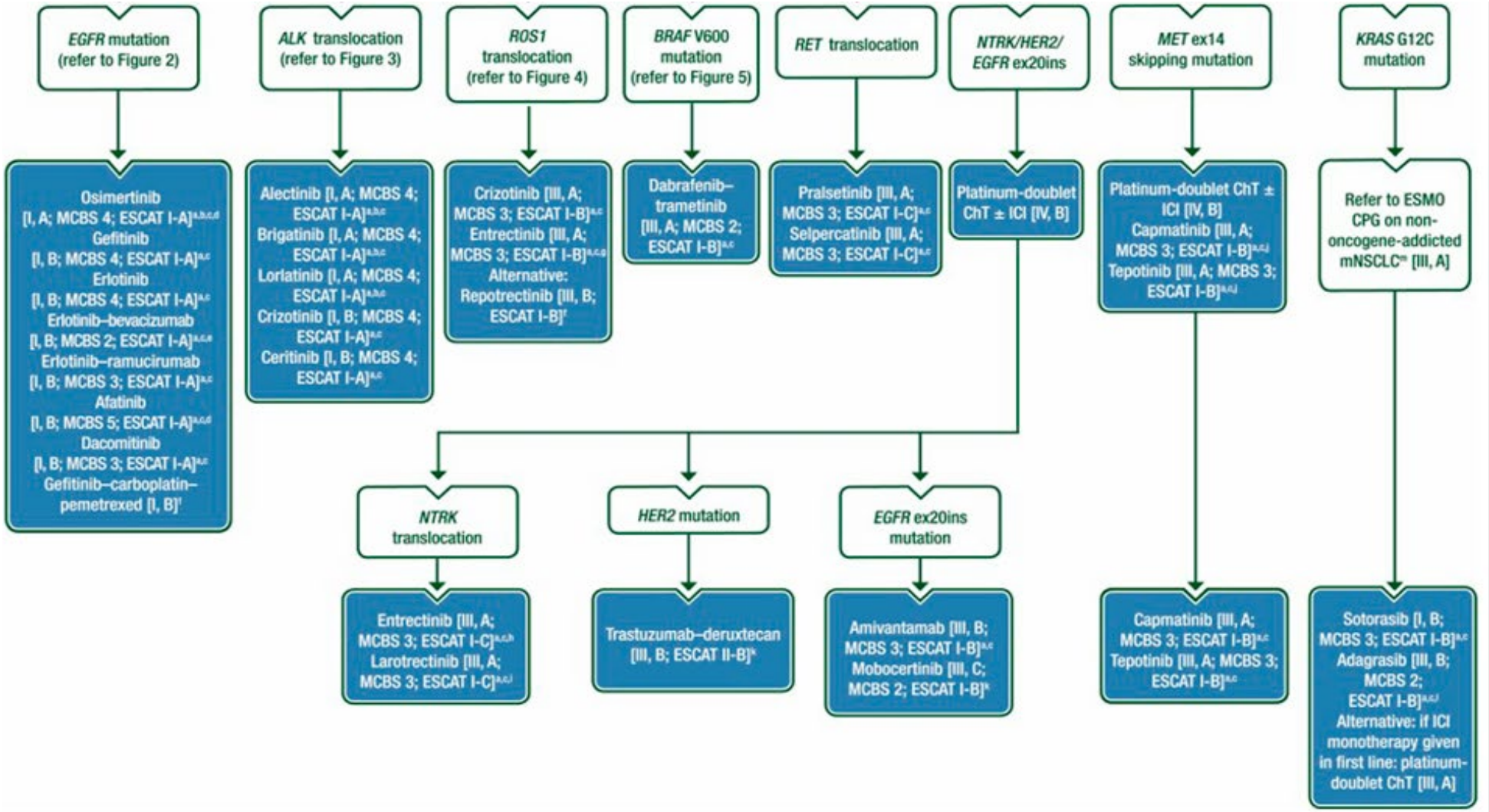
Hahn M, et al. *Pharmaceuticals*. 2021;14(487):1-15.

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Pharmacodynamic Genes

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MAIN DRIVER/SOMATIC MUTATIONS IN ONCOLOGY



Galffy G, et al. *Pathology and Oncology Research*. 2024;10: 1-21.

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Questions?

TYPES OF VARIATIONS ACROSS HUMAN GENOME

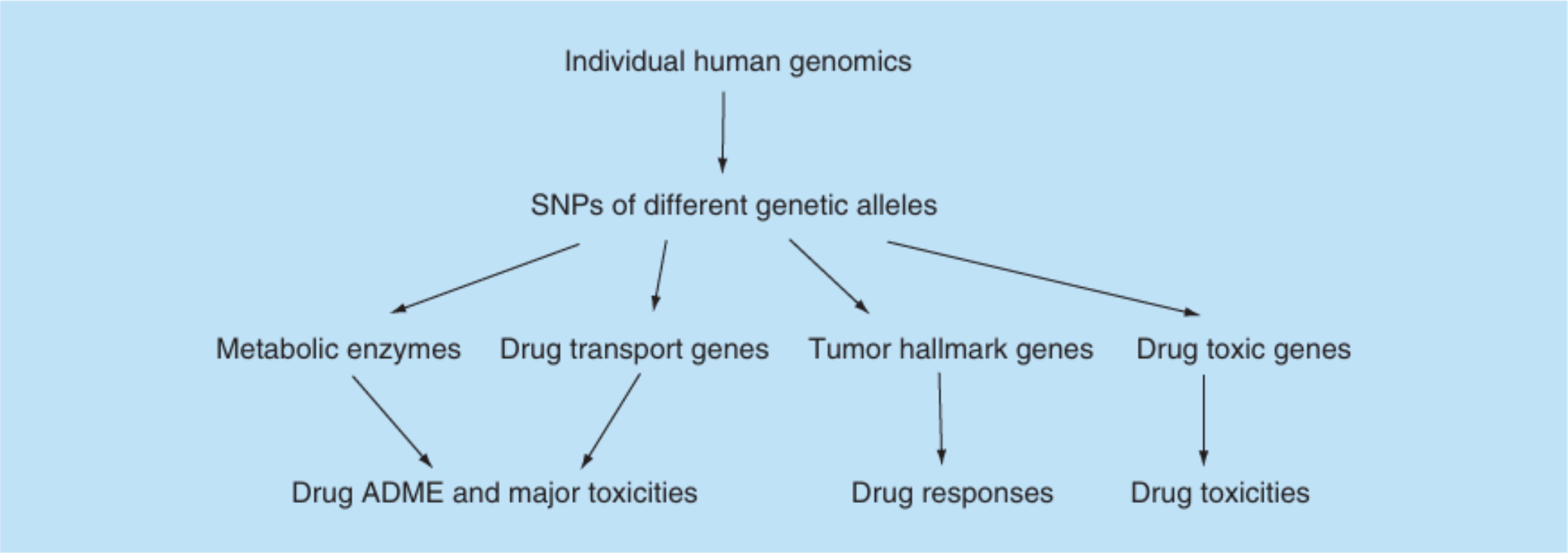
Human genome

Single nucleotide polymorphisms (SNPs)

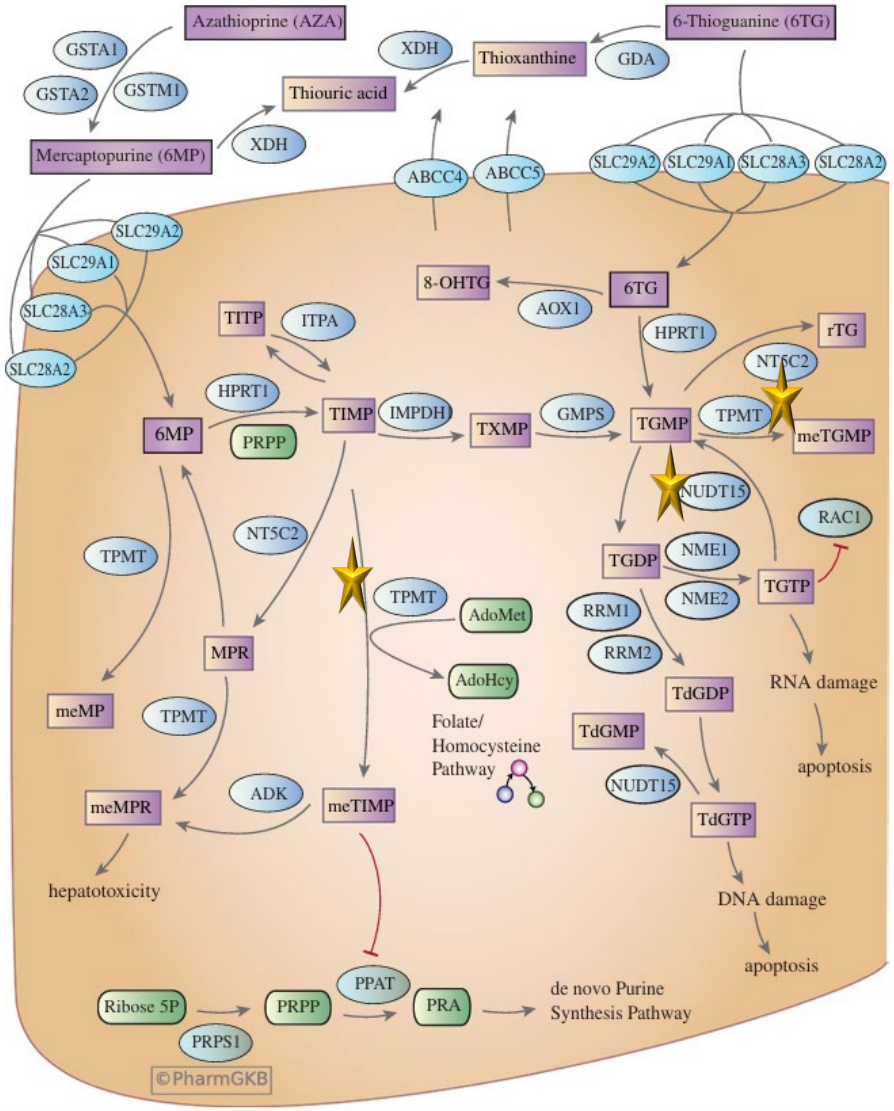
Insertion/deletion (Indels)

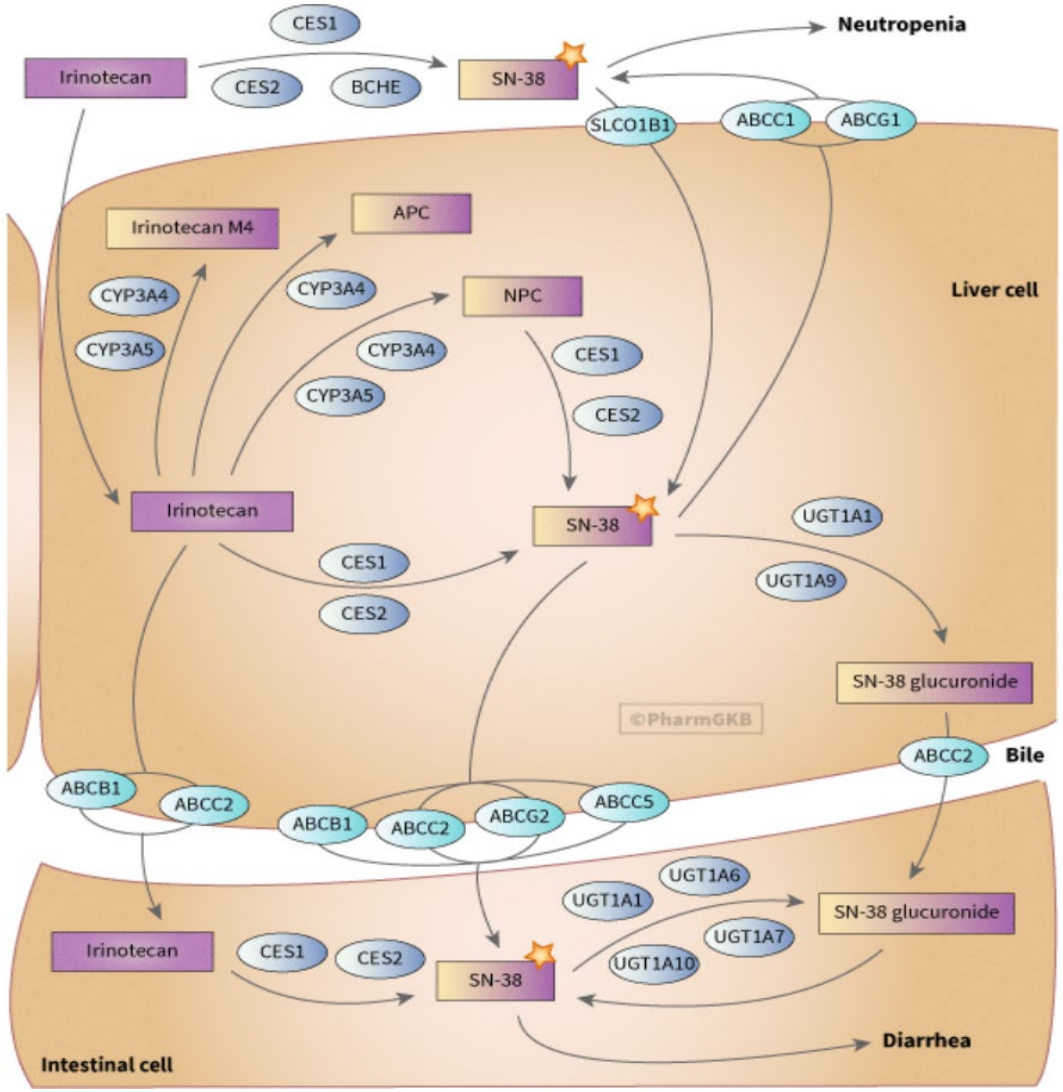
Structure variations

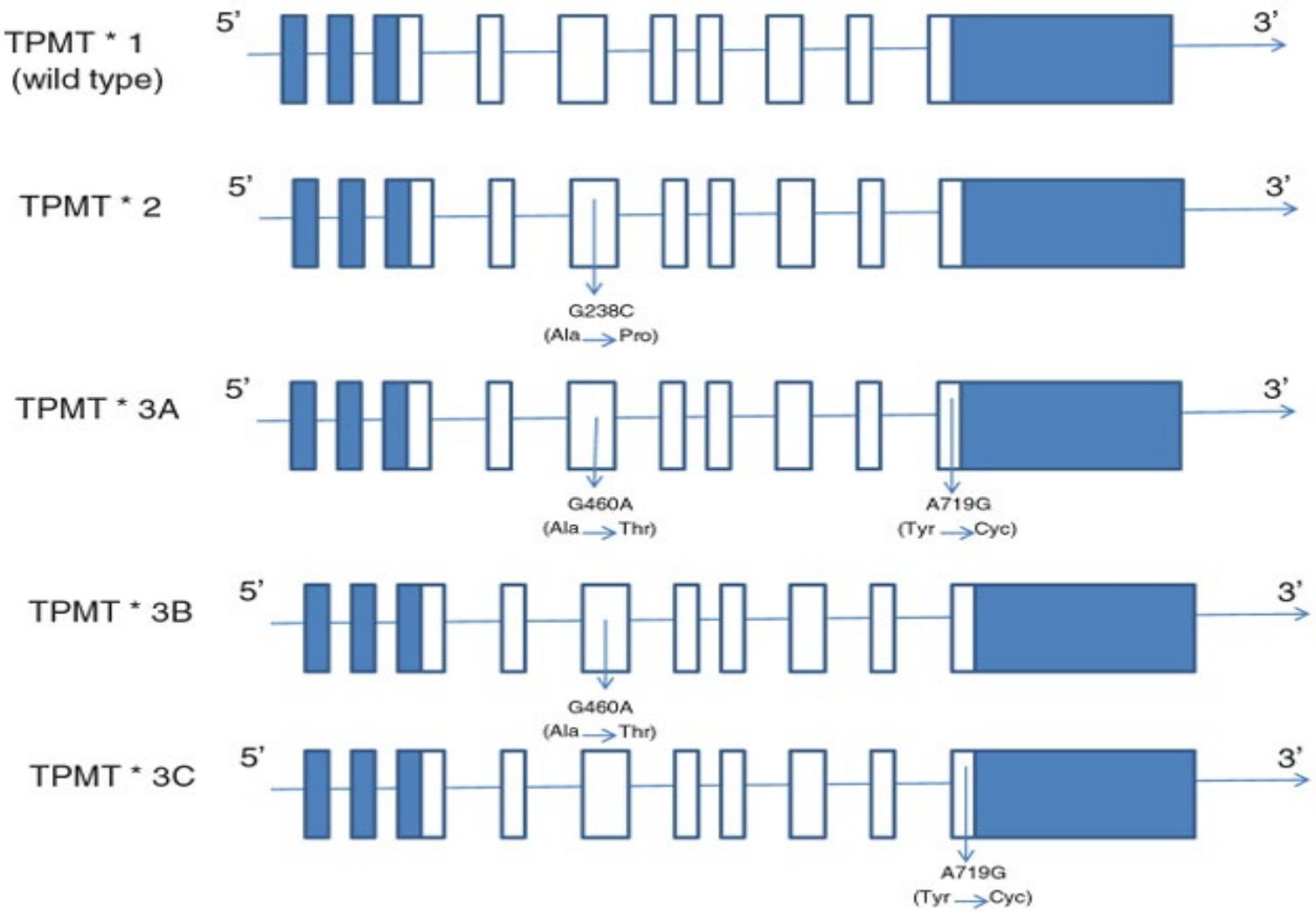
ONCOLOGY DRUGS PHARMCOGENETICS



METABOLISM OF MERCAPTOPURINES




CES1
Irinotecan
CES2
BCHE
SN-38
Neutropenia
SLCO1B1
ABCC1
ABCG1
Irinotecan M4
APC
CYP3A4
CYP3A5
CYP3A4
NPC
CYP3A4
CYP3A5
CES1
CES2
Liver cell
Irinotecan
SN-38
UGT1A1
UGT1A9
CES1
CES2
SN-38 glucuronide
©PharmGKB
ABCC2
Bile
ABCB1
ABCC2
ABCB1
ABCC2
ABCG2
ABCC5
UGT1A6
UGT1A1
SN-38 glucuronide
UGT1A7
UGT1A10
Irinotecan
CES1
CES2
SN-38
Diarrhea
Intestinal cell


TPMT * 1
(wild type)
5'
3'
TPMT * 2
5'
3'
G238C
(Ala → Pro)
TPMT * 3A
5'
3'
G460A
(Ala → Thr)
A719G
(Tyr → Cyc)
TPMT * 3B
5'
3'
G460A
(Ala → Thr)
TPMT * 3C
5'
3'
A719G
(Tyr → Cyc)