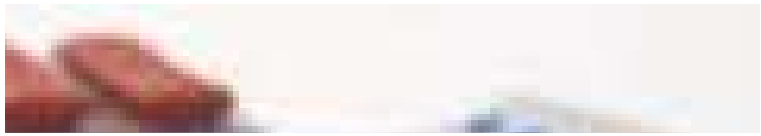
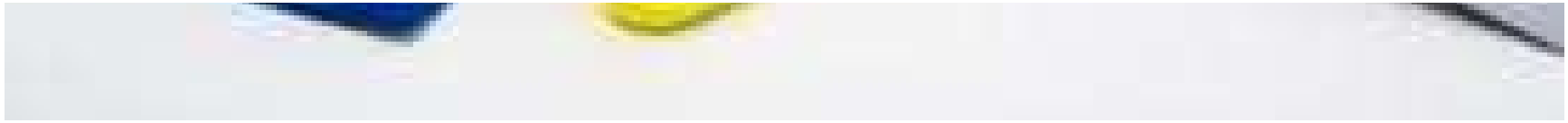


FARMACOGENETICA

dei farmaci antitumorali



Farmaci antitumorali

AGENTI CHEMIOTERAPICI CITOTOSSICI DIRETTI

- AGENTI ALCHILANTI
- COMPOSTI A BASE DI PLATINO
- ANTIMETABOLITI
  - *Analoghi dell'acido folico*
  - *Analoghi pirimidinici*
  - *Analoghi purinici*
- ANTIBIOTICI ANTITUMORALI
- INIBITORI MITOTICI
- INIBITORI TOPOISOMERASI
- ALTRO

AGENTI «NON CITOTOSSICI» DIRETTI

- TERAPIE ORMONALI
- IMMUNOTERAPIE
- TERAPIE TARGET
- ALTRO

Farmaci antitumorali

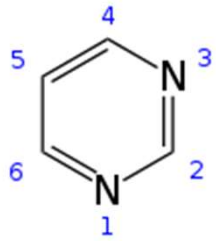
AGENTI CHEMIOTERAPICI CITOTOSSICI DIRETTI

- AGENTI ALCHILANTI
- COMPOSTI A BASE DI PLATINO
- ANTIMETABOLITI
  - *Analoghi dell'acido folico*
  - *Analoghi pirimidinici (fluoropirimidine)*
  - *Analoghi purinici (tiopurine)*
- ANTIBIOTICI ANTITUMORALI
- INIBITORI MITOTICI
- INIBITORI TOPOISOMERASI *(irinotecano)*
- ALTRO

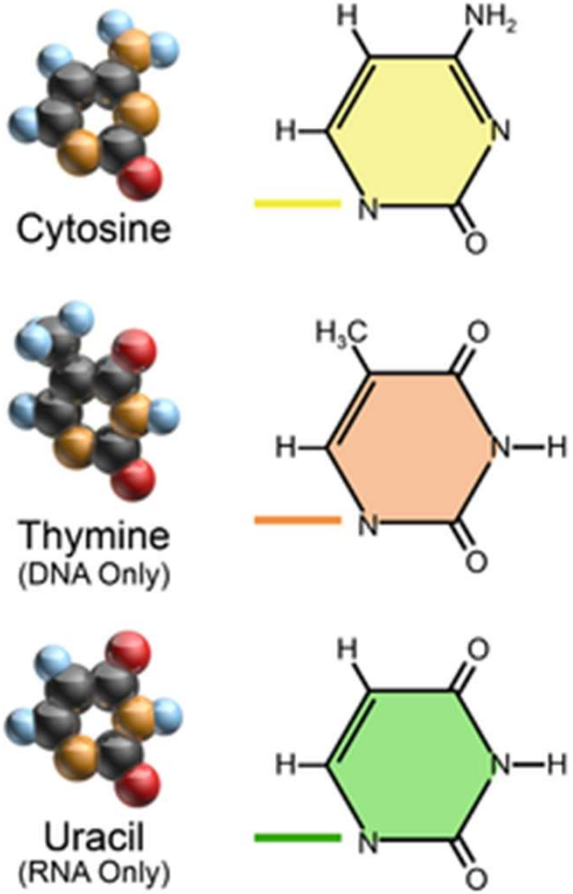
AGENTI «NON CITOTOSSICI» DIRETTI

- TERAPIE ORMONALI *(tamoxifene)*
- IMMUNOTERAPIE
- TERAPIE TARGET
- ALTRO

FLUOROPIRIMIDINE



PIRIMIDINA

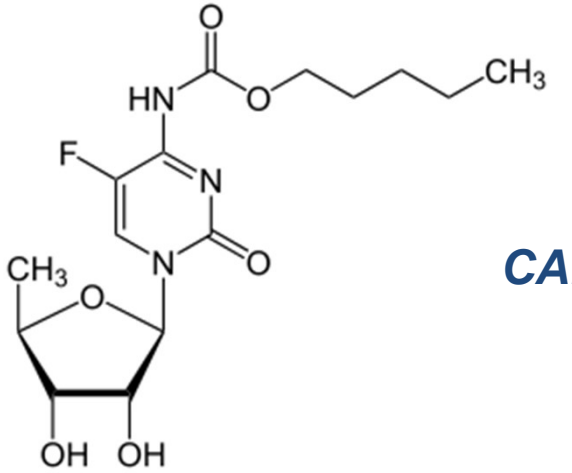


BASI PIRIMIDINICHE

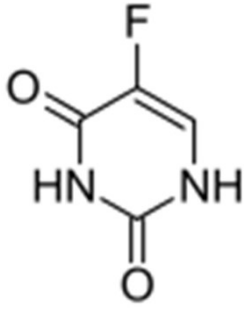
AGENTI CITOSSICI DIRETTI

ANTIMETABOLITI

ANALOGHI DELLE BASI PIRIMIDINICHE



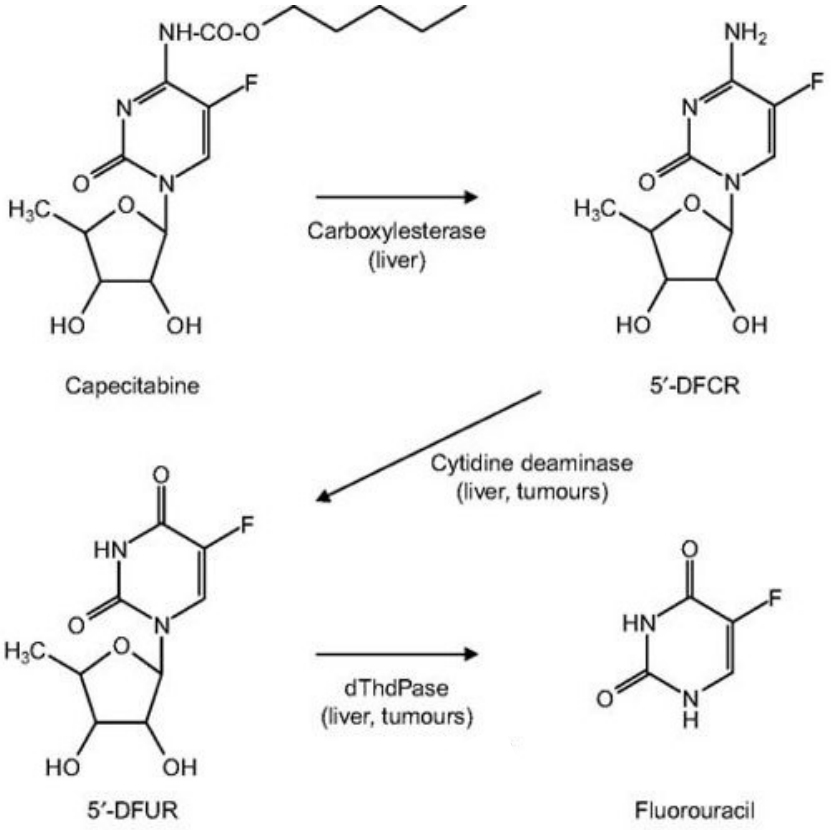
CAPECITABINA



5-FLUOROURACILE

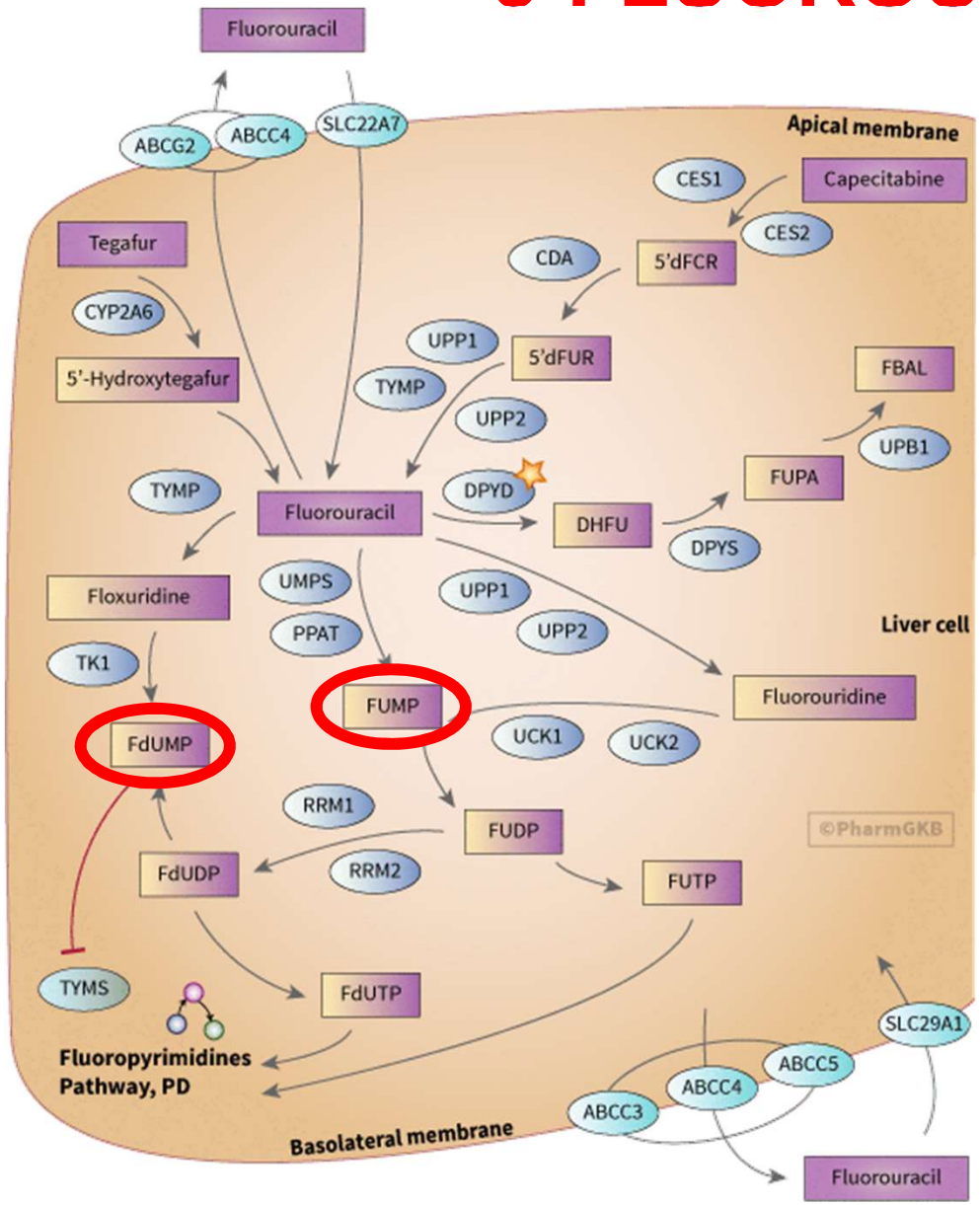
FLUOROPIRIMIDINE
CAPECITABINA

Fluoropirimidina carbamato (Profarmaco del 5-FU), Antimetabolita con attività citotossica solo dopo conversione metabolica in 5-FU



- 5’-DFCR: 5'-deoxy-5-fluorocytidine
- 5’-DFUR: 5'-deoxy-5-fluorouridine

FLUOROPIRIMIDINE
5-FLUOROURACILE



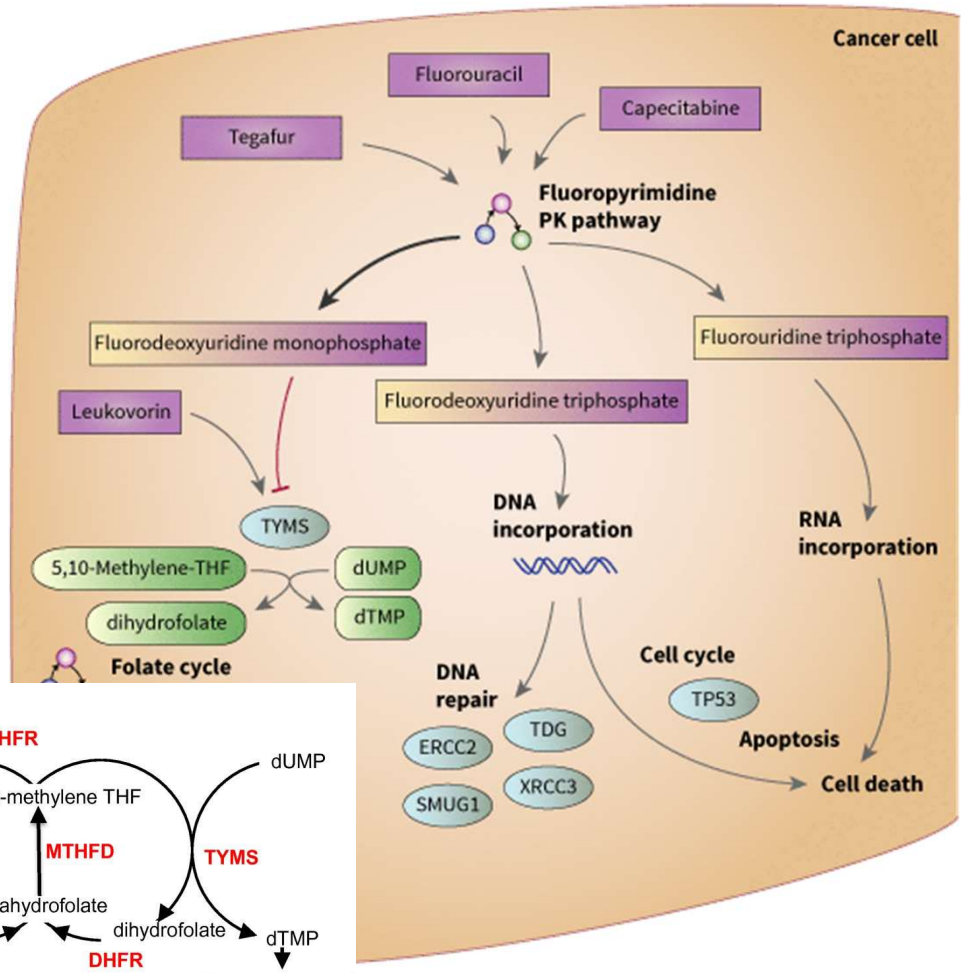
Analogo delle diidropirimidine: metabolita *inattivo* che deve essere convertito in nucleotide per dare l'azione citotossica

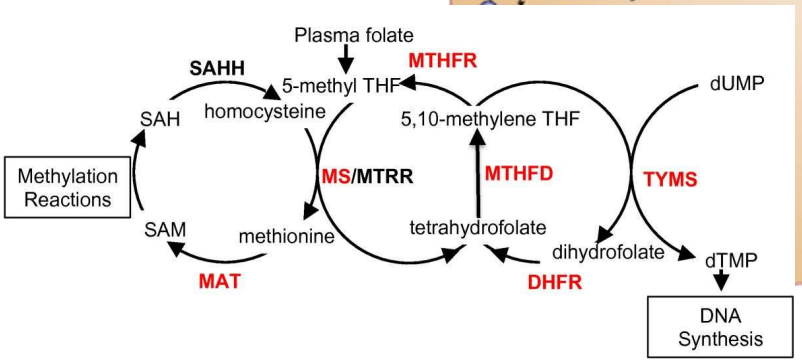
https://www.pharmgkb.org/pathway//PA150653776

FLUOROPIRIMIDINE
5-FLUOROURACILE

FdUMP

INIBIZIONE IRREVERSIBILE della TIMIDILATO SINTASI (TYMS)





FdUTP e FUTP

INIBIZIONE SINTESI del DNA ALTERAZIONE RNA

INDUZIONE DEI PROCESSI APOPTOTICI

https://www.pharmgkb.org/pathway/PA165291507

FLUOROPIRIMIDINE

- utilizzate come **chemioterapici** nel trattamento di tumori solidi e aggressivi
  - tumore colorettale metastatico
  - tumore al colon ed al retto (come adiuvante)
  - tumore gastrico avanzato
  - tumore pancreatico avanzato
  - tumore esofageo avanzato,
  - -tumore mammario avanzato o metastatico o tumore mammario primario operabile (come adiuvante)
  - nel trattamento del carcinoma a cellule squamose della testa e del collo non operabile, ricorrente o metastatico

- utilizzate in associazione con altri chemioterapici

- somministrato generalmente per infusione. 5-FU ha un indice terapeutico ristretto. L'80% della dose viene degradata e il resto viene eliminato con l'urina. L'emivita media di eliminazione dal plasma è di circa 16 minuti, con un range di 8-20 minuti

- 10-40% dei pazienti trattati con fluorouracile sviluppa tossicità severe (grado ≥ 3)

REAZIONI AVVERSE AI FARMACI

Classificazione per severità

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

REAZIONI AVVERSE AI FARMACI

CTC-AE

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

REAZIONI AVVERSE AI FARMACI CTCAE v5

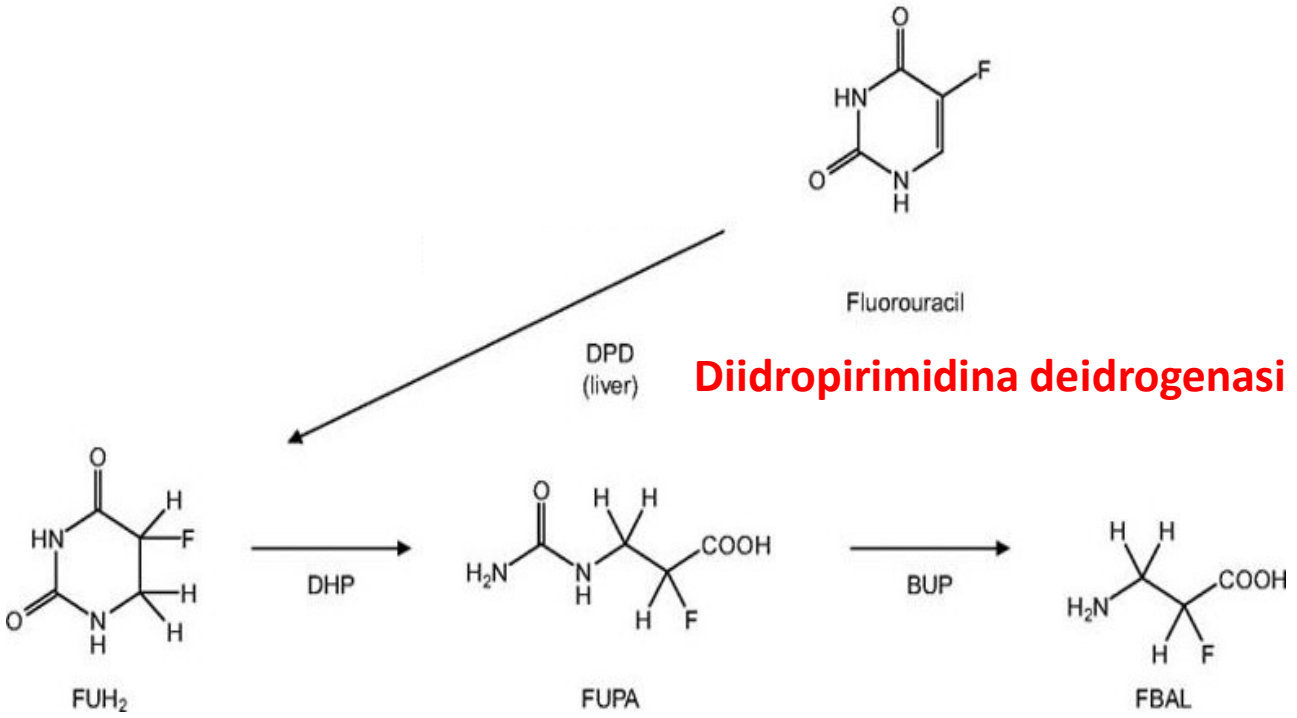
REAZIONI AVVERSE AI FARMACI
CTCAE v5: esempi

Blood and lymphatic system disorders					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death

Gastrointestinal disorders					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the stomach					
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the oral mucosal.					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-

FLUOROPIRIMIDINE

Catabolismo del 5-FU

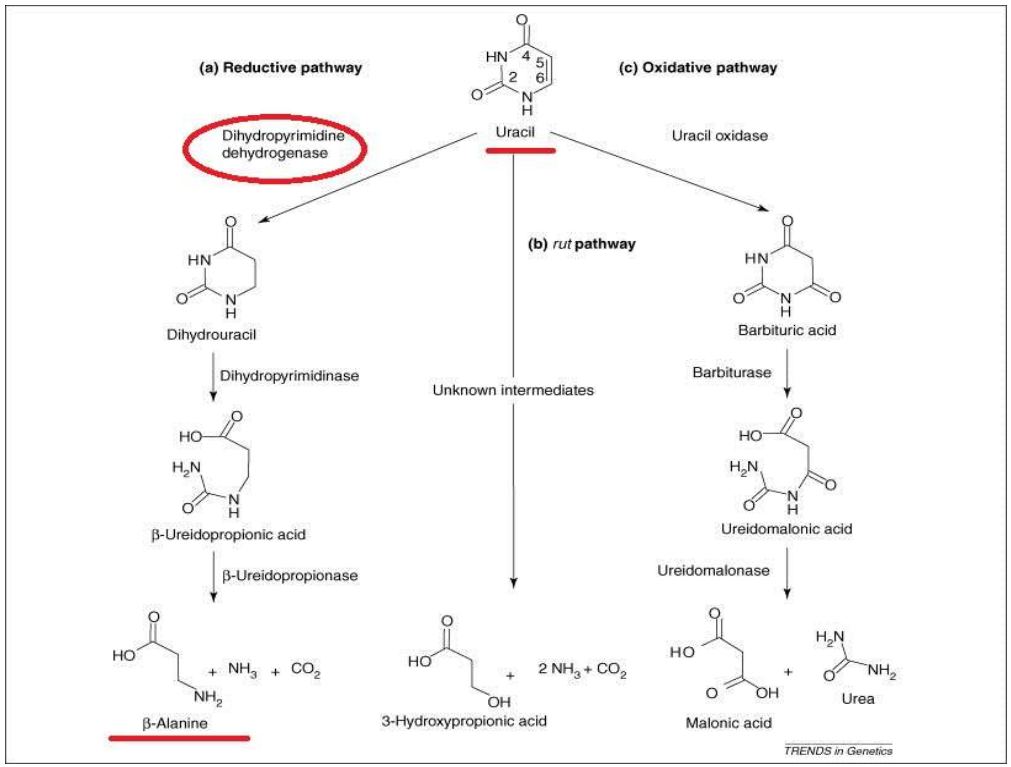


DPD è un **enzima citosolico ubiquitario espresso principalmente a livello epatico**; agisce riducendo il doppio legame dell'anello pirimidinico e formando il *5-fluoro-5,6-diidrouracile (5-FDHU), un composto instabile* convertito in *acido fluoroureidopropionico (FUPA)* dall'enzima diidropirimidinasi e successivamente in *5-alfa-fluoro-beta-alanina (FBAL)*, il principale metabolita urinario del 5-FU.

Diidropirimidina deidrogenasi (DPD o DPYD)

Localizzato sul cromosoma 1, in posizione 1p22
4399 nucleotidi, 950kb
23 esoni

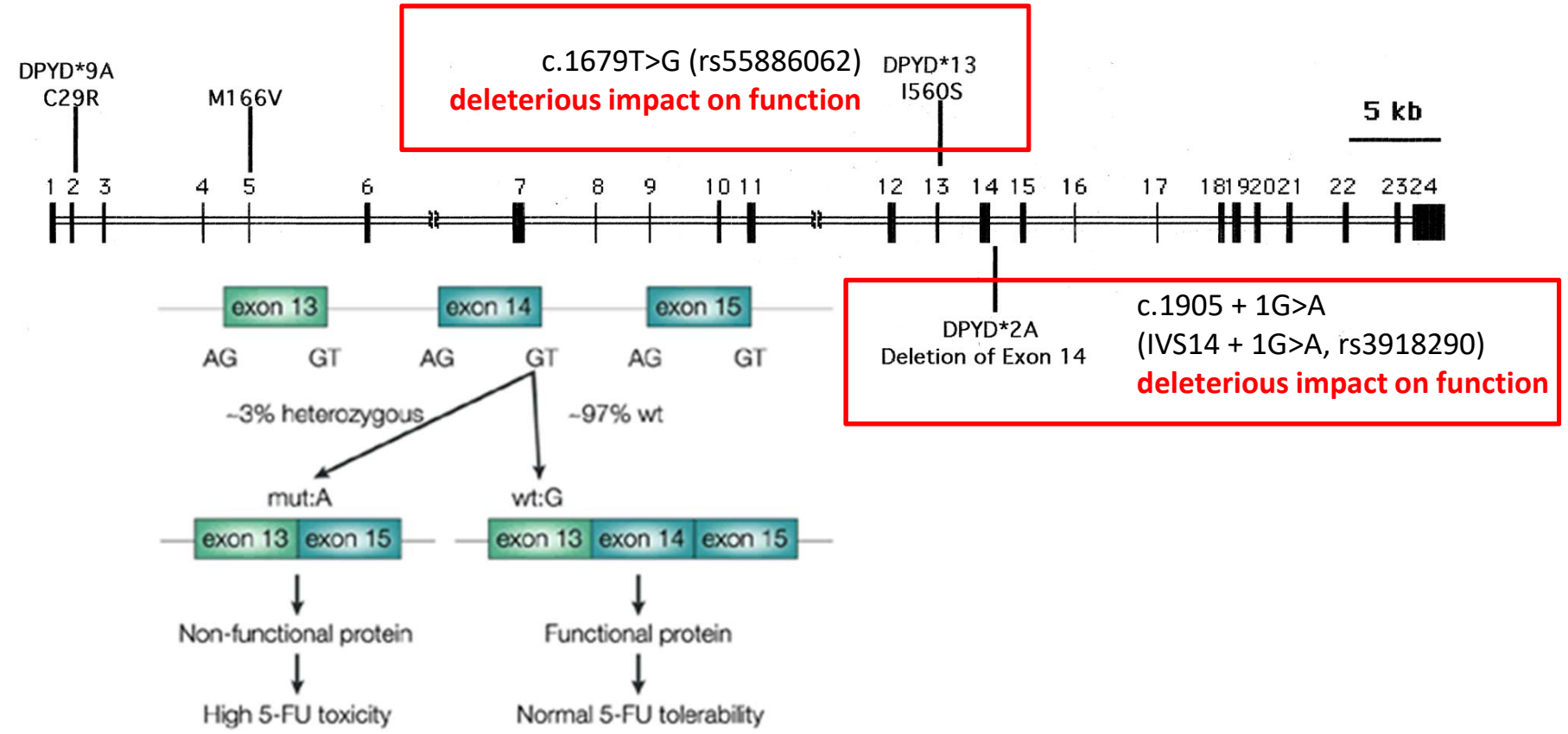
I substrati fisiologici sono le pirimidine: uracile e timina e vengono degradati formando β-alanina. La reazione enzimatica di catalisi delle pirimidine è NADPH-dipendente



Diidropirimidina deidrogenasi (DPD o DPYD)

Localizzato sul cromosoma 1, in posizione 1p22
4399 nucleotidi, 950kb
23 esoni

DPYD è **altamente polimorfico (frequenza variabile in base al gruppo etnico)**



Diidropirimidina deidrogenasi (DPD o DPYD)

Impatto deleterio sulla funzione enzimatica di DPD

c.1905+1G>A (rs3918290, also known as *DPYD**2A**, DPYD:IVS14 + 1G>A), is located at the intron boundary of exon 14 and results in skipping of the entire exon and a nonfunctional protein

c.1679T>G (rs55886062, *DPYD**13**, p.I560S)

Impatto modesto sulla funzione enzimatica di DPD

c.2846A>T (rs67376798, **p.D949V**)

c.1129–5923C>G (rs75017182, **HapB3**) «located deep in intron 10, introduces a cryptic splice site and the partial production of a nonfunctional transcript. The SNP is the likely underlying causal variant of a DPYD haplotype (HapB3) spanning intron 5 to exon 11. LD con synonymous variant c.1236G>A (rs56038477) thus a proxy for this variant in Europeans”

Diidropirimidina deidrogenasi (DPD o DPYD)

Supplemental Table S3. Frequencies[1] of alleles in major race[2] groups				
Allele	Caucasian	Asian	African-American or Black	Middle Eastern
*2A	0.00862	0.0015	0	0
*3	0	0	0	0
*4	0.0194	0.001	0.00237	0.0293
*5	0.147	0.268	0.177	0.119
*6	0.0412	0.015	0.0451	0.092
*7	0.00122	0	n/a	n/a
*9A	0.182	0.0315	0.137	n/a
*11	n/a	0.0015	n/a	n/a
*12	0	0	n/a	n/a
*13	0.001	0	n/a	n/a
IVS10-15T>C	n/a	0.018	0.042	n/a
rs75017182	0.0155	n/a	n/a	n/a
rs67376798	0.0111	n/a	n/a	n/a

Considering all four variants combined, 7% of Europeans carry at least one decreased function DPYD variant.

The decreased function variant **c.557A>G (rs115232898, p.Y186C)** is unique to individuals of **African ancestry and is relatively common (3–5% carrier frequency) in this population.** DPD activity was 46% lower in carriers as compared with non-carriers. relatively common (3–5% carrier frequency). Most other DPYD variants of phenotypic consequence are very rare

Tossicità da fluoropirimidine

Pazienti con bassa attività enzimatica per la DPD
non sono in grado di inattivare con efficienza il 5-FU:

⟶ **↓ clearance del farmaco (↑ $t_{1/2}$)**

⟶ **elevata tossicità**

- Mielosoppressione (neutropenia)
- Mucosite, nausea, vomito, diarrea
- sindrome mani-piedi-bocca (MMPB)
- attacchi epilettici e neurotossicità (2% pazienti presenta: sonnolenza atassia e disfunzioni piramidali),
- possibili microcefalie e ritardo mentale in età pediatrica,

LINEE GUIDA CPIC
DPYD e Fluoropirimidine

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update

Ursula Amstutz[1], Linda M. Henricks[2], Steven M. Offer[3], Julia Barbarino[4], Jan H.M. Schellens[2,5], Jesse J. Swen[6], Teri E. Klein[4], Howard L. McLeod[7], Kelly E. Caudle[8], Robert B. Diasio[3,9] and Matthias Schwab[10,11,12]

Clin Pharmacol Ther. 2018 Feb;103(2):210-216.

LINEE GUIDA CPIC
DPYD e Fluoropirimidine

For each variant allele, an activity score was applied:

1: normal function,

0.5: decreased function (c.2846A>T; 1129-5923C>G)

0: no function or minimal function variants (c1905+1G>A(*2A); c1679T>G(*13))

Table 1 Assignment of likely DPD phenotypes based on *DPYD* genotypes

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]

[a]Calculated as the sum of the two lowest individual variant activity scores. See text for further information. [b]Allele definitions, assignment of allele function and references can be found on the CPIC website (*DPYD* Allele Functionality Table available at [ref 4]) [c]HGVS nomenclature using the reference sequence NM_000110.3 [d]Likely HapB3 causal variant. See *DPYD* Allele Functionality Table available at [ref 4] for other HapB3 proxy SNPs.

Clin Pharmacol Ther. 2018 Feb;103(2):210-216.

LINEE GUIDA CPIC
DPYD e Fluoropirimidine

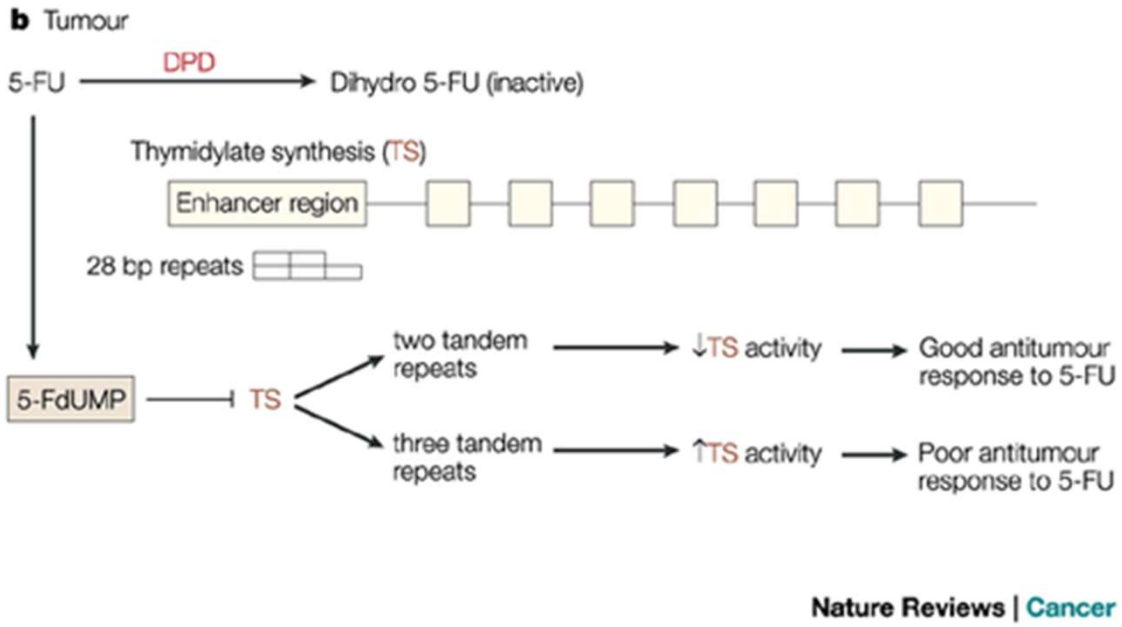
Table 2 Recommended dosing of fluoropyrimidines[a] by DPD phenotype

Phenotype	Implications for phenotypic measures	Dosing recommendations	Classification of recommendations[b]
DPYD normal metabolizer ***DPYD-AS: 2***	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 ***DPYD-AS: 1 o 1.5***	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.	***CPIC ONLINE UPDATE (2018)*** DPYD Intermediate Metabolizers should receive a 50% dose reduction from the full standard starting dose, whether the activity score is 1 or 1.5 followed by dose titration, based on clinical judgement and ideally therapeutic drug monitoring.	
DPYD poor metabolizer ***DPYD-AS: 0 o 0.5***	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

[a]5-fluorouracil or capecitabine. [b]Rating scheme described in Supplement. [c]Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities. [d]If available, a phenotyping test (see main text for further details) should be considered to estimate the starting dose. In the absence of phenotyping data, a dose of <25% of the normal starting dose is estimated assuming additive effects of alleles on 5-FU clearance. [e]Therapeutic drug monitoring should be done at the earliest timepoint possible (e.g., minimum timepoint in steady state) in order to immediately discontinue therapy if the drug level is too high.

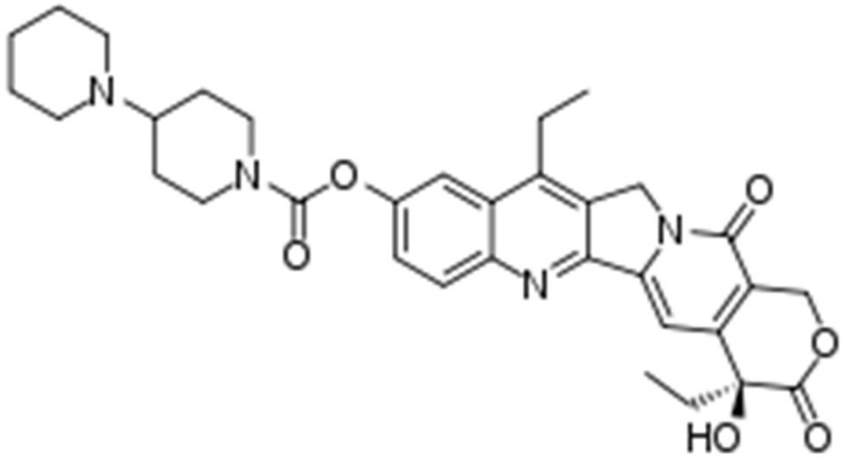
Clin Pharmacol Ther. 2018 Feb;103(2):210-216.

FLUOROPIRIMIDINE
Resistenza al trattamento



b. Polimorfismo del gene TYMS, se presente una ripetizione di 28bp nella regione enhancer l'attività della TS varia

IRINOTECANO



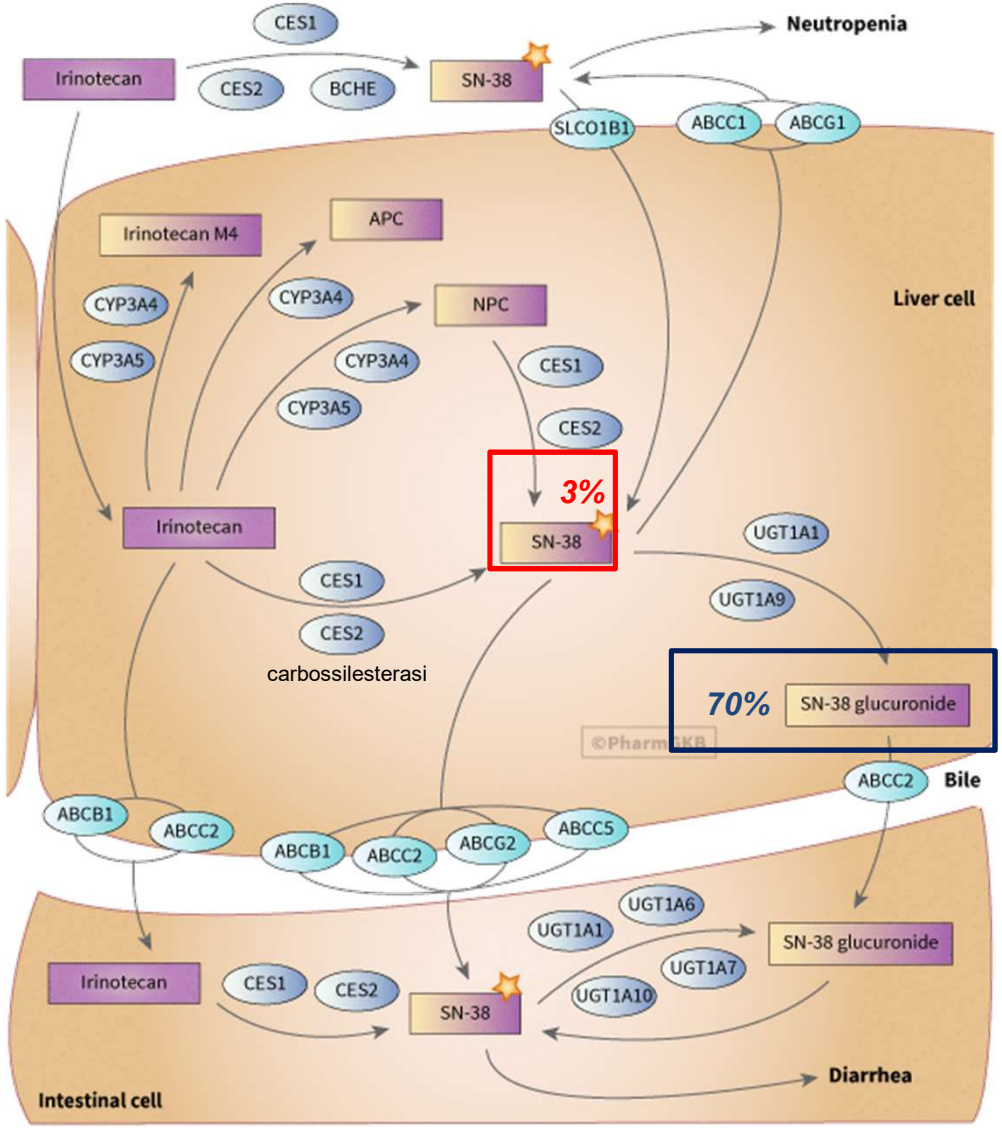
AGENTI CITOSSICI DIRETTI

INIBITORI delle TOPISOMERASI

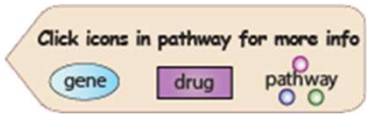
- Alcaloide citotossico
- Classe delle ***camptotecine***: molecole estratte dalla corteccia della *Camptotheca Acuminata* con proprietà antitumorali
- Chemioterapico, citotossico e anti-proliferativo
- Utilizzato nel cancro colon-rettale metastatico (mCRC)

IRINOTECANO: farmacocinetica

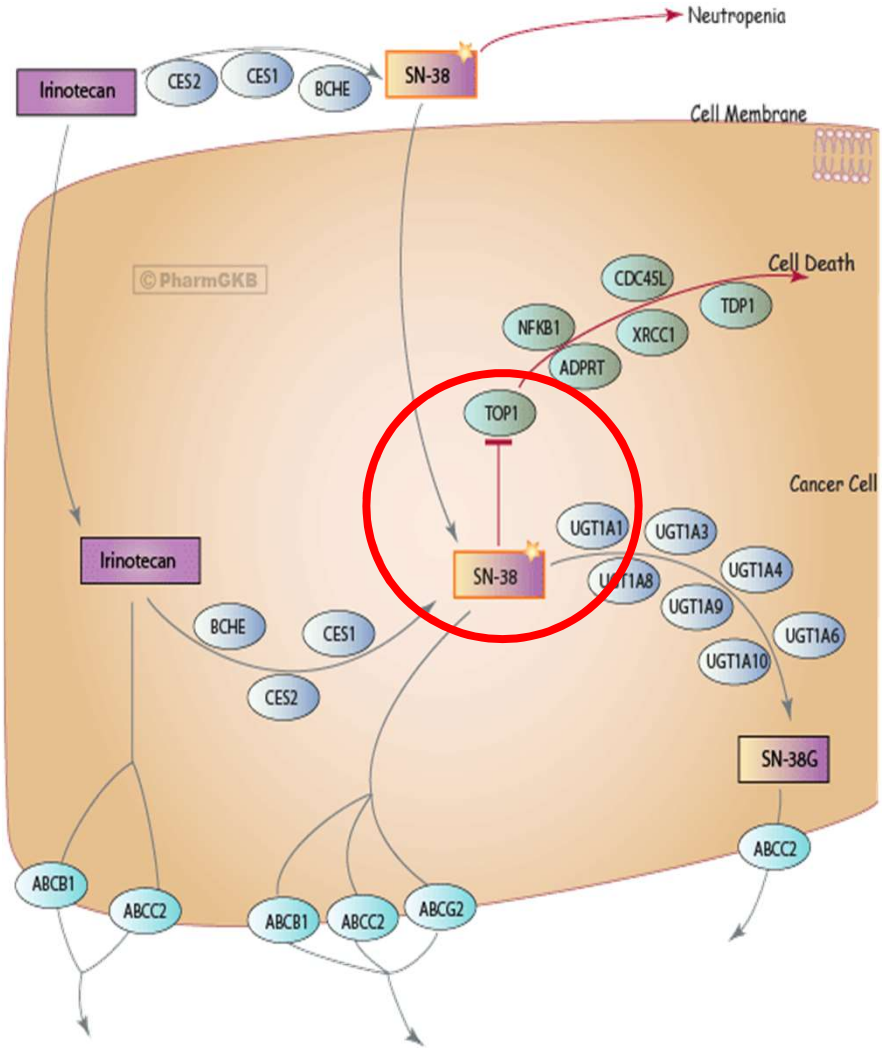
PROFARMACO



SN-38: Metabolita attivo *(ATTIVITa' DA 100 A 1000 volte maggiore dell'irinotecano*



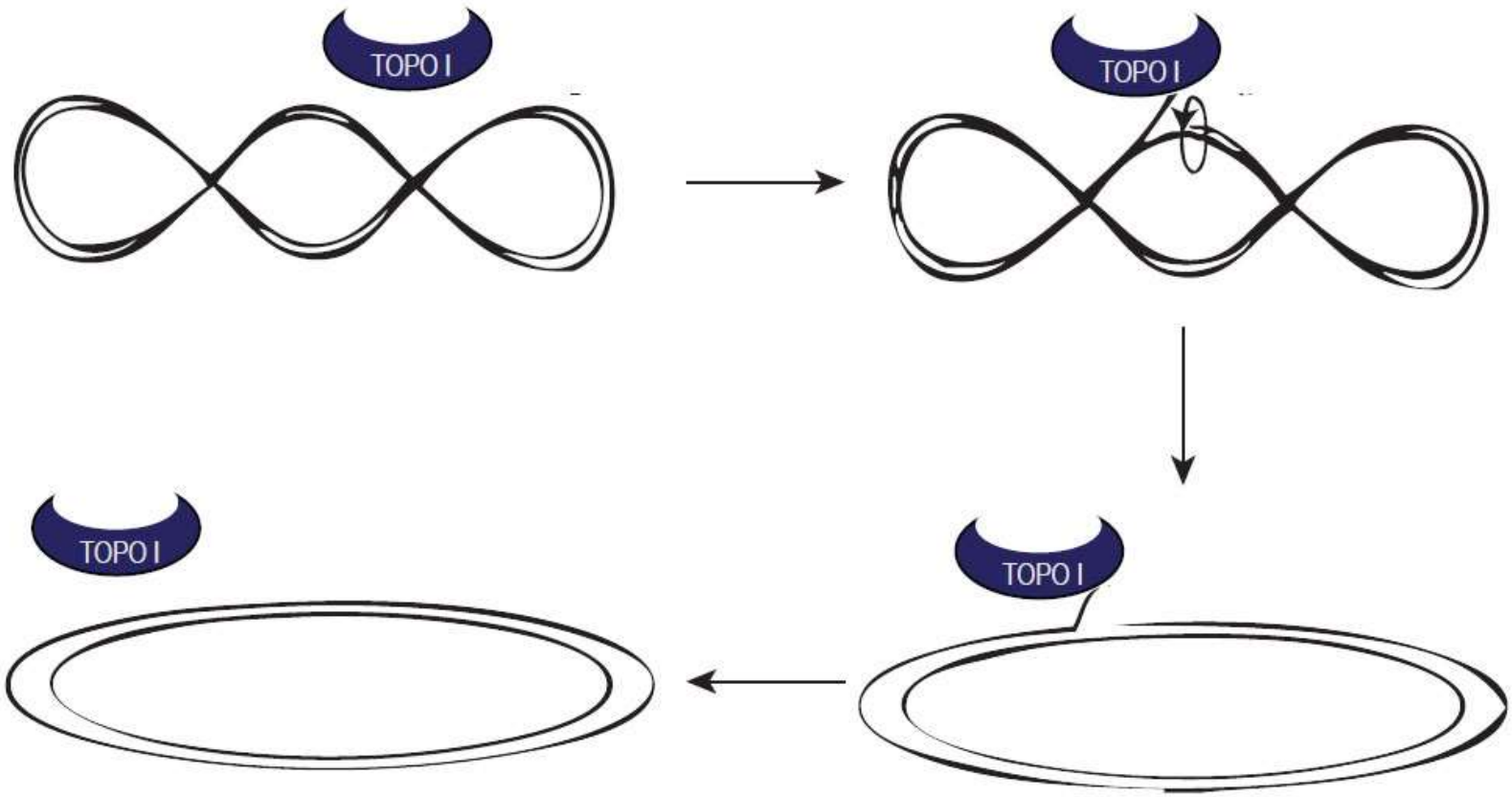
IRINOTECANO: farmacodinamica



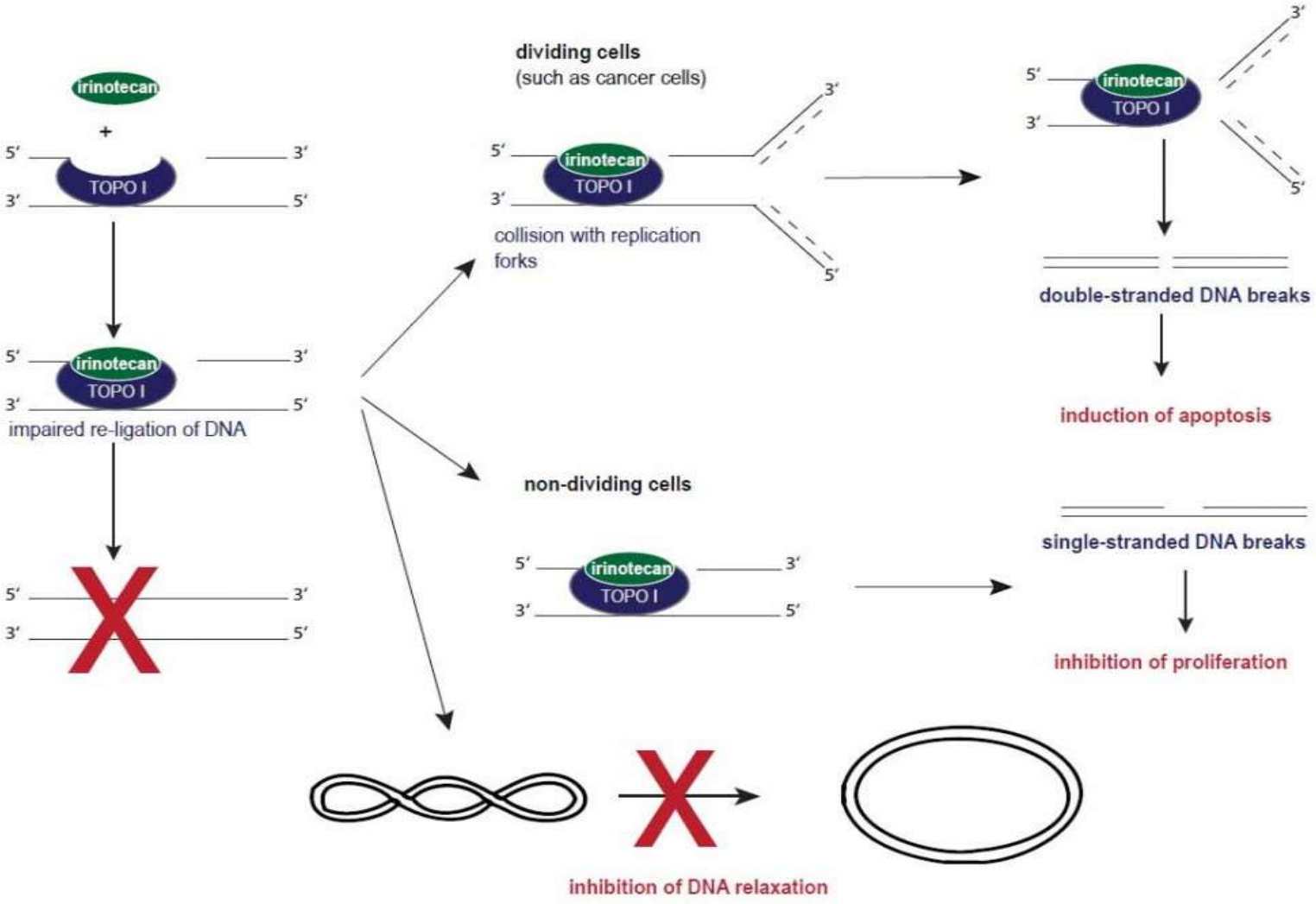
Bersaglio molecolare di SN38 : Topoisomerasi

SN38 lega e inibisce il complesso Topoisomerasi I-DNA → rottura irreversibile della doppia elica di DNA → morte cellulare

TOPOISOMERASI I

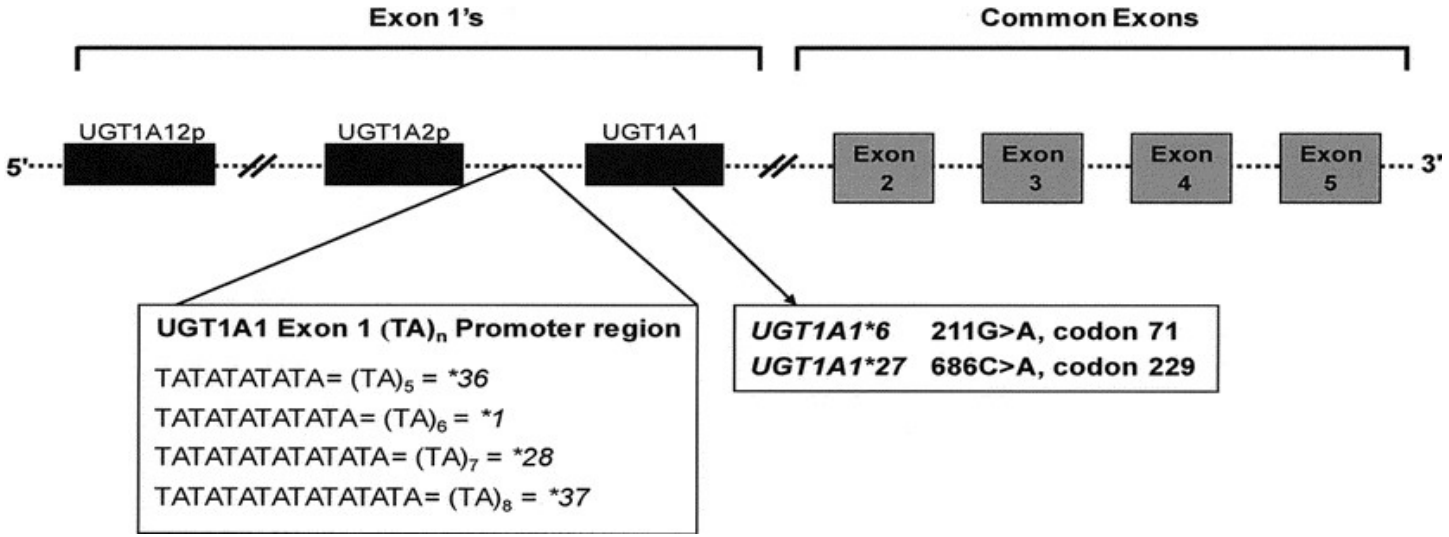


IRINOTECANO: meccanismo d'azione



UDP glucuronosyltransferase famiglia 1 A

Located on chromosome 2q37



At least 113 variants in *UGT1A1*

*UGT1A1*1* (wt) → 6 ripetizioni di Timina-Adenina (TA) nel promotore

***UGT1A1*28* (rs8175347)→ 7 ripetizioni TA**

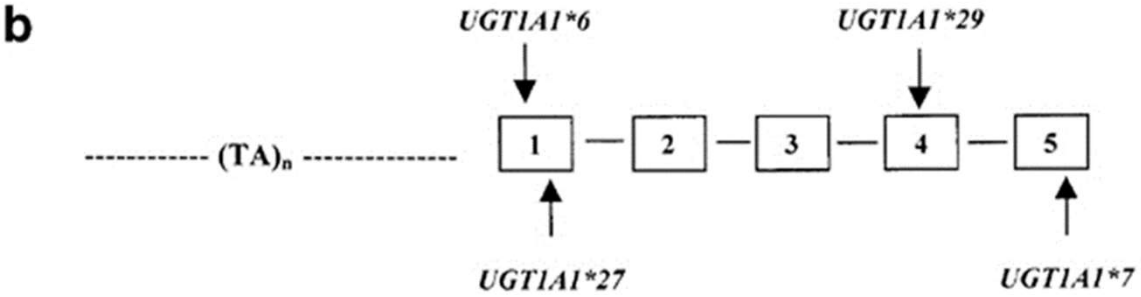
Allele mutato più frequente: 45% hz (*1/*28), 15% mut (*28/*28)

porta a riduzione dell'attività dell'enzima di circa il 30% rispetto al wt

UDP glucuronosyltransferase famiglia 1 membro A1 (UGT1A1)

CAUCASICI

AFRO-AMERICANI



ASIATICI

SNP nell'esone 1:

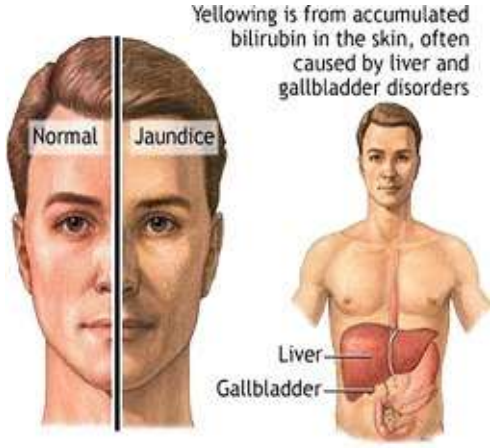
*UGT1A1*6* ((Arg71Gly; 211 G>A; rs4148323) → G>A causa riduzione dell'attività enzimatica di circa il 30%

*UGT1A1*27* → C>A causa completa abolizione dell'attività enzimatica

UGT1A1 e suscettibilità alle malattie

Denomination	Expression level	Enzymatic activity	Clinical consequence	Ref
*UGT1A1*1*	100%	100%	None	
*UGT1A1*6*	Unchanged	Reduced	Gilbert's syndrome	[26]
*UGT1A1*27*	Unchanged	Reduced	Gilbert's syndrome	[26]
*UGT1A1*28*	Reduced	Reduced	Gilbert's syndrome	[27]
*UGT1A1*36*	Increased	Unchanged	None	[24]
*UGT1A1*37*	Reduced	Unchanged	Gilbert's syndrome	[24]
*UGT1A1*60*	Reduced	Unchanged	Gilbert's syndrome	[26]
*UGT1A1*93*	Reduced	Unchanged	Gilbert's syndrome	[19]

Table II Biologic impact of UGT1A1 variants described in Table I.



UGT1A1 e irinotecano

I pazienti omo ed eterozigoti per *28, mostrano un livello sistemico di SN38 significativamente più elevato con maggiore severità di effetti avversi, tra cui diarrea e neutropenia, rispetto a pazienti wt.

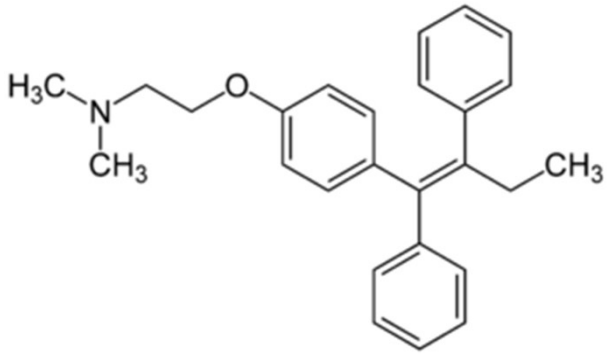
LINEE GUIDA DPWG 2011
UGT1A1 e irinotecano

PHENOTYPE (GENOTYPE)	THERAPEUTIC DOSE RECOMMENDATION	LEVEL OF EVIDENCE	CLINICAL RELEVANCE
*1/*28	None.	Published controlled studies of moderate quality* relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints..	Clinical effect (S): death; arrhythmia; unanticipated myelosuppression.
*28/*28	Dose >250mg/m^2: reduce initial dose by 30%. Increase dose in response to neutrophil count. Dose <=250mg/m^2: no dose adjustment.	Published controlled studies of moderate quality* relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints.	Clinical effect (S): Failure of lifesaving therapy e.g. anticipated myelosuppression; prevention of breast cancer relapse; arrhythmia; neutropenia < 0.5x10^9/l; leucopenia < 1.0x10^9/l; thrombocytopenia < 25x10^9/l; life-threatening complications from diarrhea.

LINEE GUIDA DPWG 2018
UGT1A1 e irinotecano

ALLELE/GENOTYPE/PHENOTYPE	DRUG	DESCRIPTION	RECOMMENDATION
UGT1A1 *1/*28	irinotecan	This genetic variation (*1/*28) is more common in Western populations than the wild-type (*1/*1). This means that treatment is largely geared to patients with this genetic variation. Adjustment of the treatment is therefore not useful.	NO action is needed for this gene-drug interaction
UGT1A1 *28/*28	irinotecan	Serious, life-threatening adverse events occur more often in patients with this genetic variation. The genetic variation reduces conversion of irinotecan to inactive metabolites.	Start with 70% of the standard dose If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.
UGT1A1 IM	irinotecan	This genetic variation (IM) is more common in Western populations than the wild-type (*1/*1). This means that treatment is largely geared to patients with this genetic variation. Adjustment of the treatment is therefore not useful.	NO action is needed for this gene-drug interaction.
UGT1A1 PM	irinotecan	Serious, life-threatening adverse events occur more often in patients with this genetic variation. The genetic variation reduces conversion of irinotecan to inactive metabolites.	Start with 70% of the standard dose If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

TAMOXIFENE



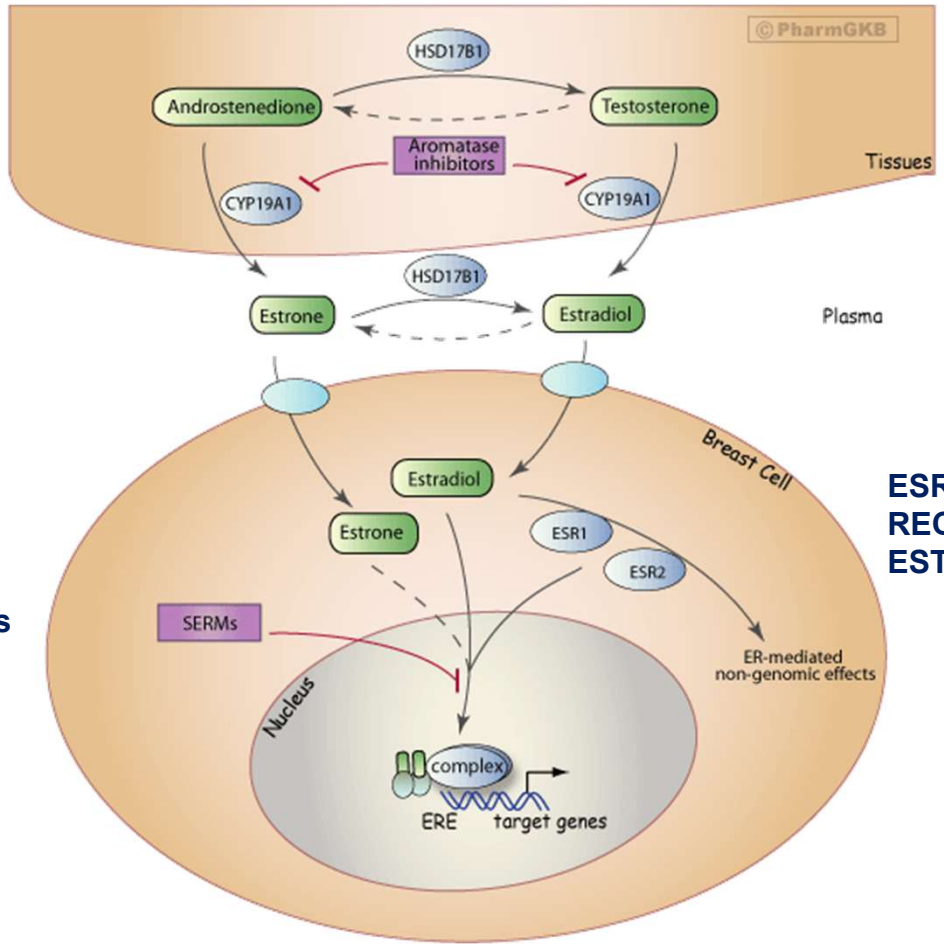
- modulatore selettivo dei recettori per gli estrogeni (ER)

- trattamento del tumore alla mammella ER+ (65-75%)

- primo ad essere impiegato nella chemioterapia adiuvante. Quando somministrato per 5 anni dopo l'asportazione chirurgica, riduce le ricadute annuali del 50% e la mortalità del 30%.
- Usato a scopo preventivo, per proteggere le pazienti ad alto rischio di carcinoma mammario familiare

- somministrato per via orale (60 mg/die), con picco plasmatico dopo poche ore e raggiunge lo steady state (plateau = concentrazione costante nel tempo) dopo circa 3 mesi

TAMOXIFENE: farmacodinamica



selective estrogen receptor modulators (ES: TAMOXIFENE)

ESR1, ESR2 RECETTORE ESTROGENI

Il tamoxifene lega ai recettori ER iperespressi in corso di carcinoma mammario, competendo con gli estrogeni (ligandi endogeni) bloccando così la trascrizione dei geni che sostengono la proliferazione cellulare → ↓effetto trofico e proliferativo sulle cellule neoplastiche di carcinoma mammario estrogeno dipendente

TAMOXIFENE: farmacocinetica

VIA METABOLICA CYP2D6 MEDIATA

Minore

Idrossilazione del tamoxifene

VIA METABOLICA CYP3A4 MEDIATA

Predominante (90%)

Demetilazione del tamoxifene

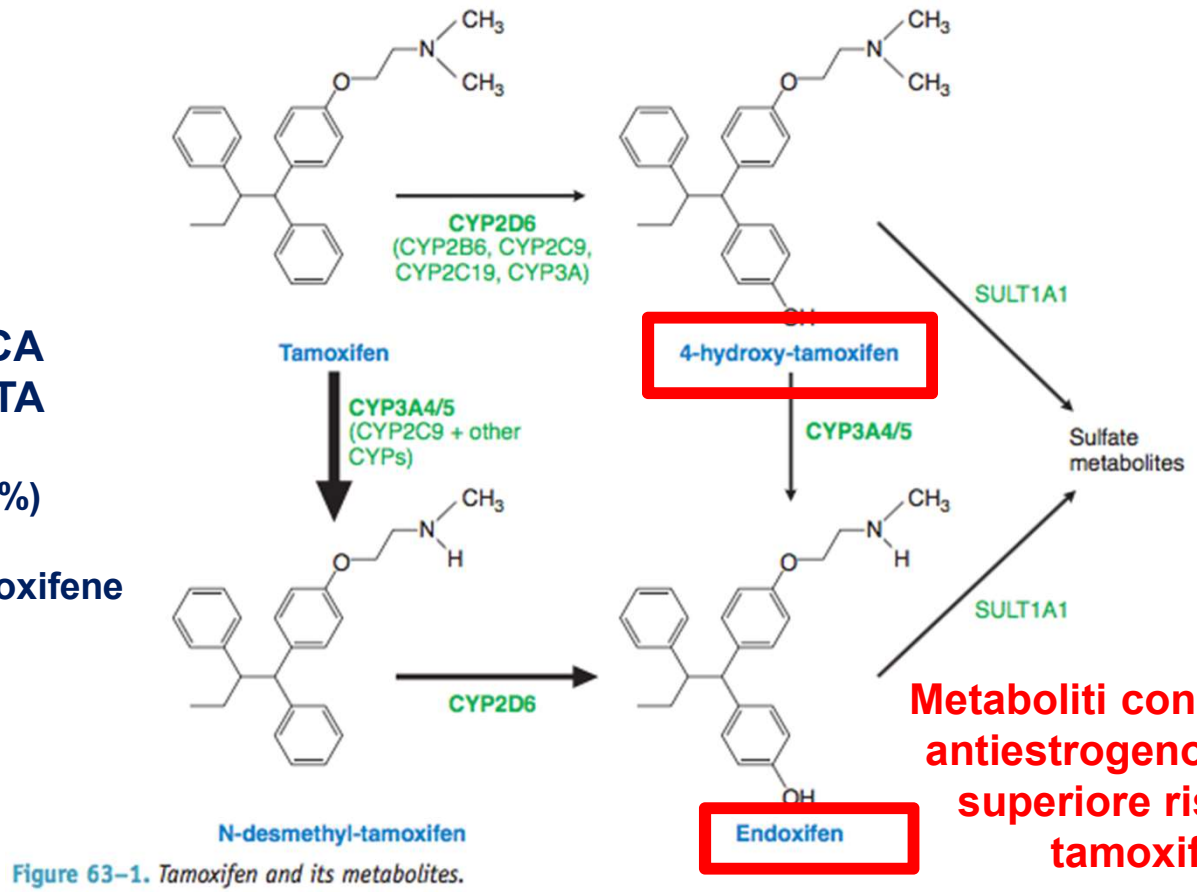


Figure 63–1. *Tamoxifen and its metabolites.*

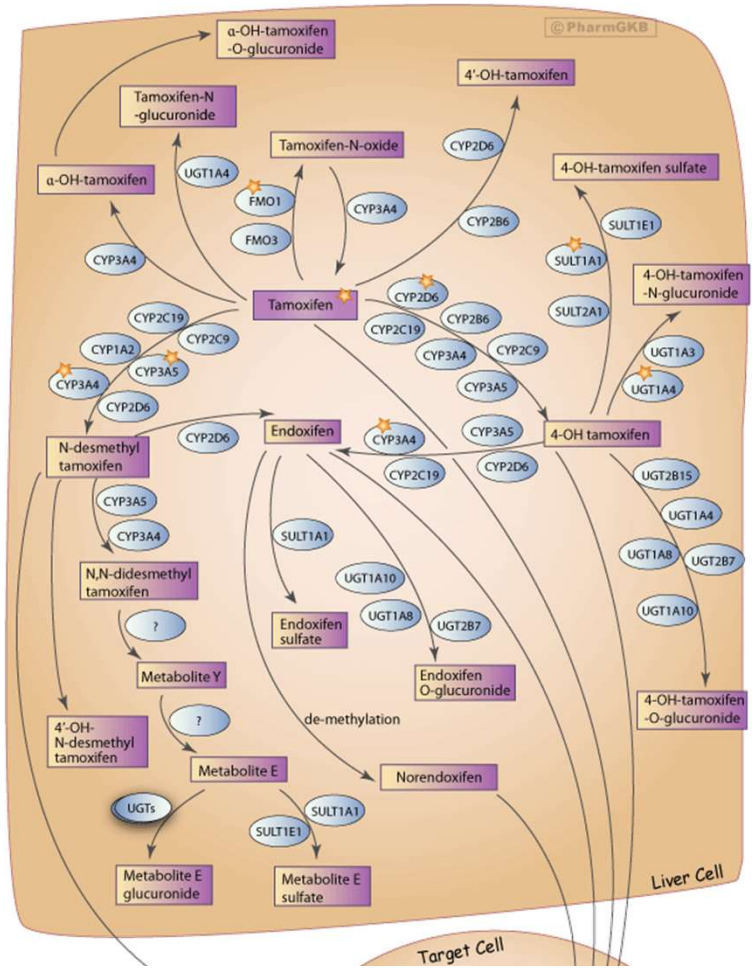
Metaboliti con potenziale antiestrogeno 100 volte superiore rispetto al tamoxifene

TAMOXIFENE: farmacocinetica

VIA METABOLICA CYP3A4 MEDIATA

Predominante (90%)

Demetilazione del tamoxifene successivamente trasformato a ENDOXIFENE



VIA METABOLICA CYP2D6 MEDIATA

Minore

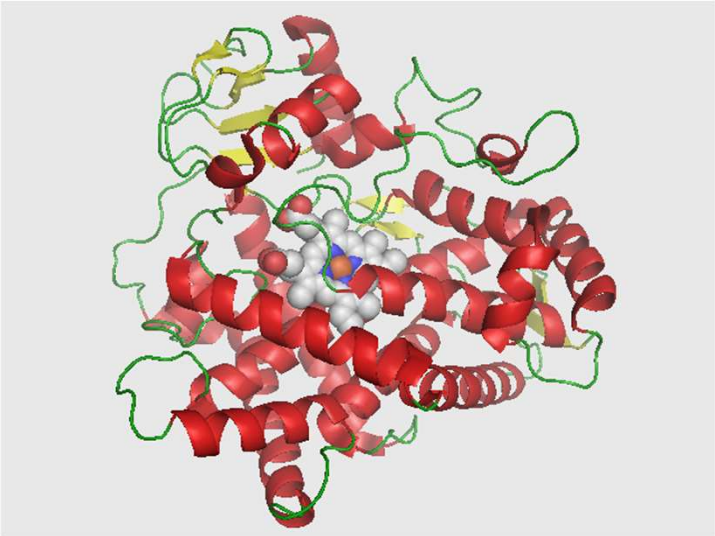
Idrossilazione del tamoxifene successivamente trasformato a ENDOXIFENE

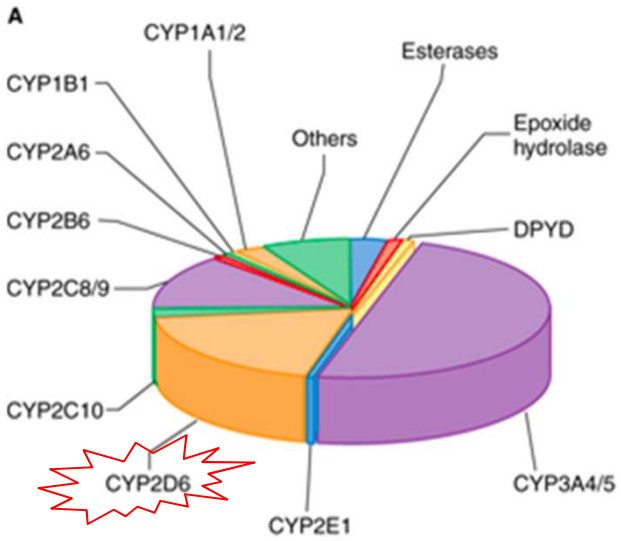
MOLTEPLICI METABOLITI con ATTIVITA' ANTIESTROGENA UGUALE, MINORE O AGGIORE RISPETTO AL TAMOXIFENE

GRANDE VARIABILITA' INTERINDIVIDUALE DI RISPOSTA AL FARMACO

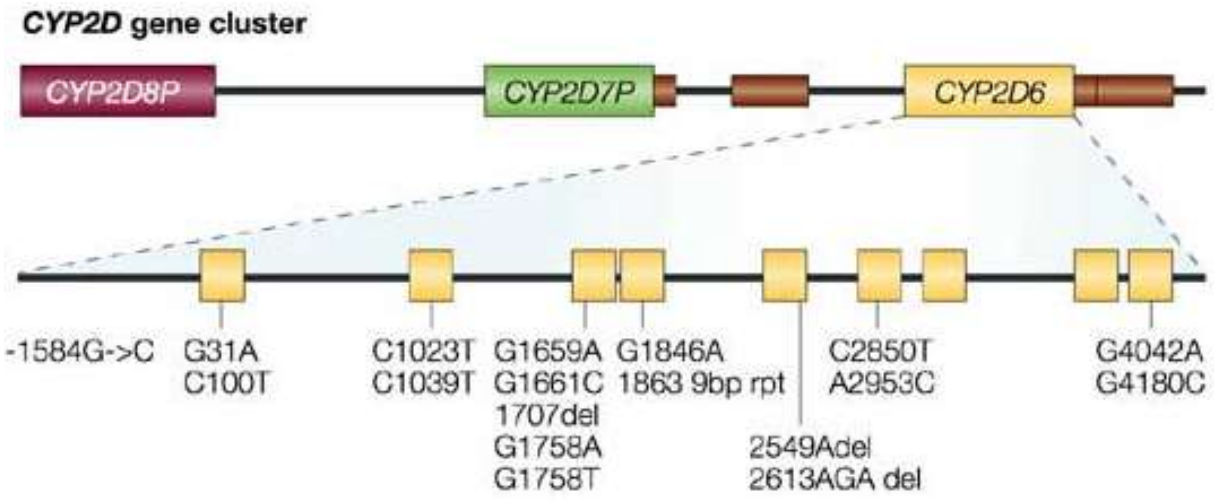
CYP2D6

- membro della famiglia citocromo P450
- si trova sul cromosoma 22q13.1
- coinvolto nel metabolismo del 15-25% dei farmaci, con attività ossido-riduttiva
- Gene altamente polimorfico: almeno 100 varianti conosciute

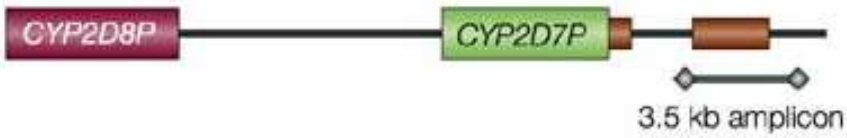




CYP2D6



- SNP
- deletions
- bp repeats



Gene deletions

Gene amplifications (xN)

Up to 13 copies

	Allele	Major nucleotide variation	SNV	Effect	
→	*1	Presumed	NA	Wild type	→ Attività enzimatica NORMALE
→	*2	2850C>G	rs16947	Arg296Cys	→ Attività enzimatica NORMALE
→	*3	2549delA	rs35742686	Frameshift	→ NO Attività enzimatica
→	*4	100C>T	rs1065852	Pro34Ser	→ NO Attività enzimatica
		1846G>A	s3892097	Splicing defect	
→	*6	1707delT	rs5030655	Frameshift	→ NO Attività enzimatica
	*7	2935A>C	rs5030867	His324Pro	
→	*9	2615_2617delAAG	rs5030656	Lys281del	→ Attività enzimatica RIDOTTA
→	*10	100C>T	rs1065852	Pro34Ser	→ Attività enzimatica RIDOTTA
	*12	124G>A	rs5030862	Gly42Arg	
	*14	1758G>A	rs5030865	Gly169Arg	
→	*17	1023C>T	rs28371706	Thr107Ile	→ Attività enzimatica RIDOTTA
		2850C>T	rs16947	Arg296Cys	
	*19	2539_2542delAACT	rs72549353	255Frameshift	
	*20	1973_1974insG	rs72549354	211Frameshift	
	*38	2587_2590delGACT	rs72549351	271Frameshift	
	*40	1863_1864insTTTCGCCCCX2	rs72549356	174_175insFRP × 2	
→	*41	2850C>T	rs16947	Arg296Cys	→ Attività enzimatica RIDOTTA
		2988G>A	rs38371725	Splicing defect	
	*42	3259_3260insGT	rs72549346	363Frameshift	
	*49	100C>T	rs1065852	Pro34Ser	
		1611T>A	rs1135822	Phe120Ile	

→ xN sono le CNV

→ Attività enzimatica AUMENTATA

LINEE GUIDA CPIC
CYP2D6 e Tamoxifene

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and Tamoxifen Therapy

Matthew P. Goetz[1], Katrin Sangkuhl[2], Henk-Jan Guchelaar[3], Matthias Schwab[4,5,6], Michael Province[7], Michelle Whirl-Carrillo[2], W. Fraser Symmans[8], Howard L. McLeod[9], Mark J. Ratain[10], Hitoshi Zembutsu[11], Andrea Gaedigk[12], Ron H. van Schaik[13,14], James N. Ingle[1], Kelly E. Caudle[15] and Teri E. Klein[2]

For each variant, an activity score was applied:

1: normal function,
0.5: decreased function
0: no function

Combination of allele is used to determine patient's diplotype. If an allele contains multiple copies of a functional gene, the value is multiplied by the number of copies present (0-3).

Clin Pharmacol Ther. 2018 May;103(5):770-777

LINEE GUIDA CPIC
CYP2D6 e Tamoxifene

Table 1 Assignment of likely CYP2D6 phenotypes based on genotypes

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*

[a]See the *CYP2D6* frequency table[1] for race-specific allele and phenotype frequencies. [b]For a complete list of *CYP2D6* diplotypes and resulting phenotypes, see the *CYP2D6* genotype to phenotype table.[1,6] Note that genotypes with an activity score of 1 are classified as NMs in the online *CYP2D6* genotype to phenotype table. [c]Where *xN* represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see supplemental data for additional information on how to translate diplotypes into phenotypes. [d]Patients with an activity score of 1.0 may be classified as intermediate metabolizers by some reference laboratories. A group of CYP2D6 experts are currently working to standardize the *CYP2D6* genotype to phenotype translation system. CPIC will update the CPIC website accordingly (*CYP2D6* genotype to phenotype table[1,6]).

LINEE GUIDA CPIC
CYP2D6 e Tamoxifene

Table 2 Dosing recommendations for tamoxifen based on *CYP2D6* phenotype

Phenotype		Implications	Therapeutic recommendation[b]	Classification of recommendation[a]
Metabolizer status	Activity score			
CYP2D6 ultrarapid metabolizer	>2.0	Therapeutic endoxifen concentrations	Avoid moderate and strong CYP2D6 inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).	Strong
CYP2D6 normal metabolizer	1.5 to 2.0	Therapeutic endoxifen concentrations	Avoid moderate and strong CYP2D6 inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).	Strong
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[b]	1.0 (no *10 allele present)[b]	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	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.	Optional[b]
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains)[b]	1.0 (*10 allele present)[b]	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	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.	Moderate[b]
CYP2D6 intermediate metabolizer	0.5	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	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.	Moderate
CYP2D6 poor metabolizer	0	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	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]	Strong

[a]Rating scheme described in the Supplement. [b]CPIC has generally classified patients with an activity score of 1 as a "normal metabolizer." However, in the case of tamoxifen, prescribing recommendations for those with an AS of 1.0 are allele dependent, based on the presence of the **10* allele. Those patients with an AS of 1.0 on the basis a **10* allele are provided a "moderate" recommendation. In contrast, prescribing recommendations for those with an activity score of 1 based on the presence of *CYP2D6* alleles other than *10 are graded as "optional" because the recommendations are primarily extrapolated from evidence generated from *10 individuals (i.e., limited data for clinical outcomes and pharmacokinetics for this group).