Dr. Francesco Graziano
Medical Oncology Hospital of Pesaro

Farmacogenetica nel paziente oncologico Quali Implicazioni Cliniche?

GSEC - GENETIC SUSCEPTIBILITY TO ENVIRONMENTAL CARCINOGENS
UNIVERSITY OF PITTSBURGH

Sixth Framework Programme

European Commette for Genetic Cancer Research

Terapia dei tumori

Stadi precoci

chirurgia

↓

+/- chemioterapia precauzionale (adiuvante)

↓

guarigione

Stadi avanzati

Chemioterapia della malattia metastatica

↓

prolungamento della sopravvivenza

palliazione

Pazienti con carcinoma del colon metastatico e caratteristiche cliniche e di malattia comparabili

chemioterapia comprendente Irinotecan (CPT-11) usando la medesima dose (180 mg/m2)

Osservazione clinica

Paziente 1		Paziente 2
+	Mucosite	+
+	Diarrea	+++
+	tossicità ematologica	+++
=	Risposta	+

Differenze inter-individuali per risposta e tossictà

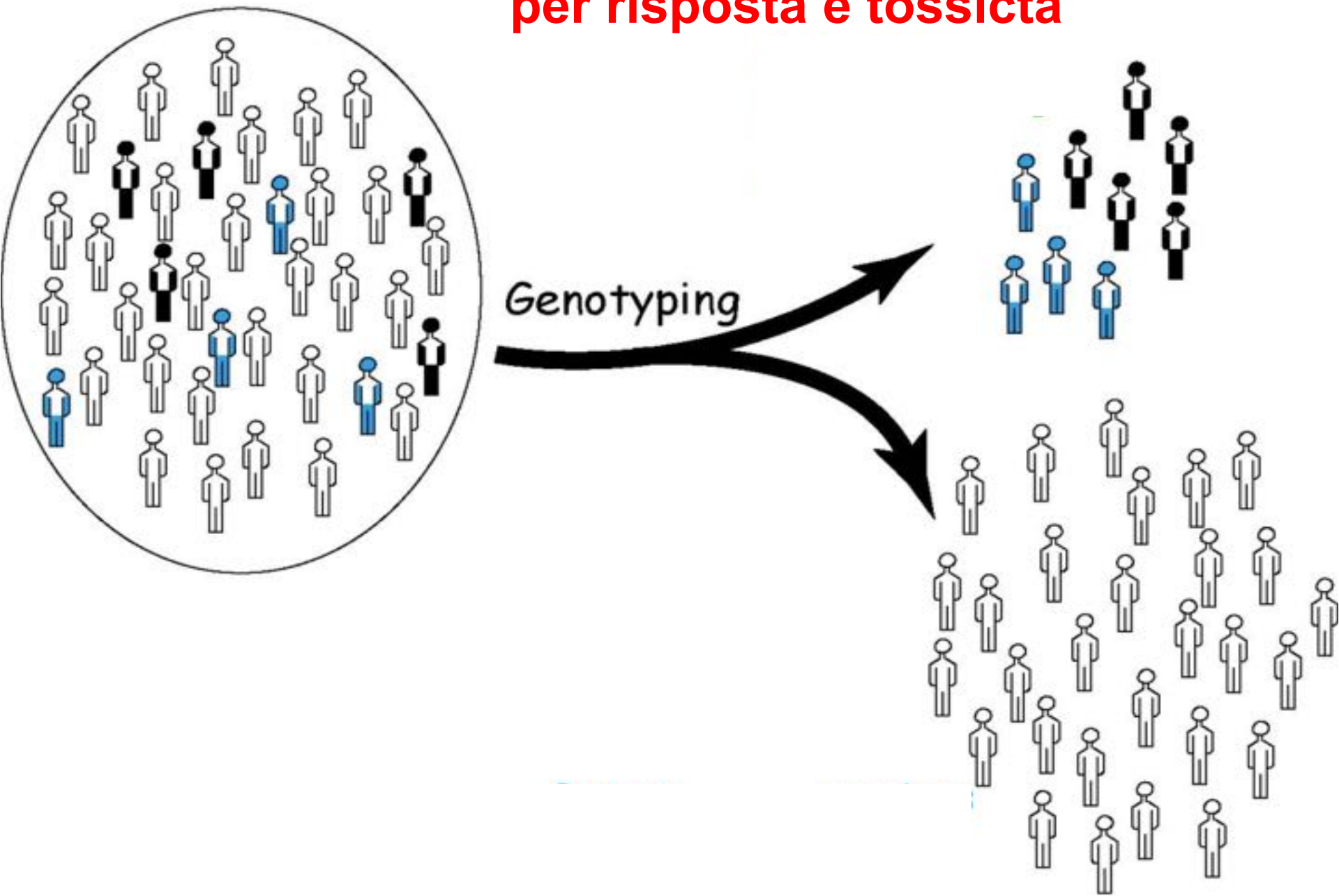
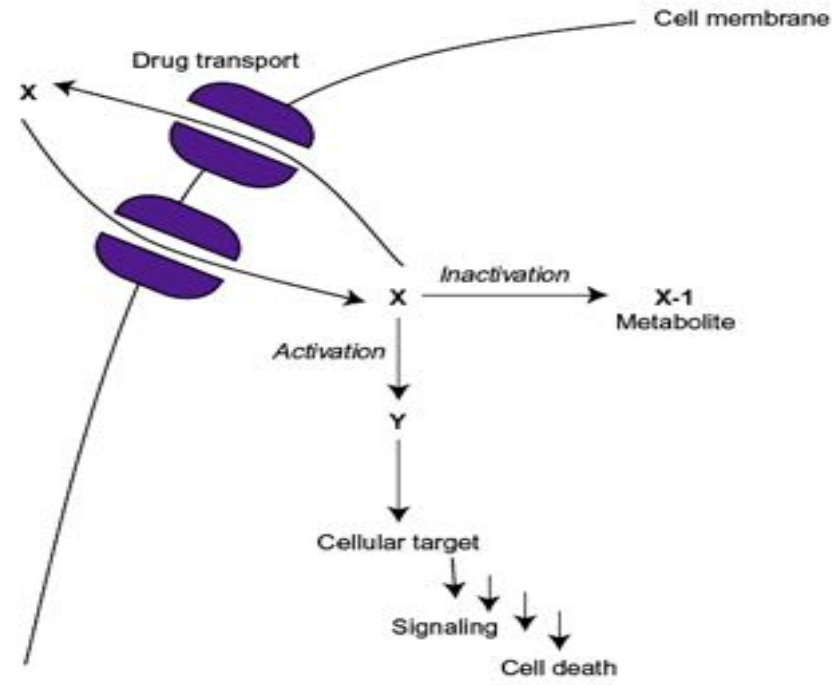


Figure 1. Schematic of the cellular fate of an administered drug, depicting some of the major sources of variation in drug effect.



Tossicità

Risposta

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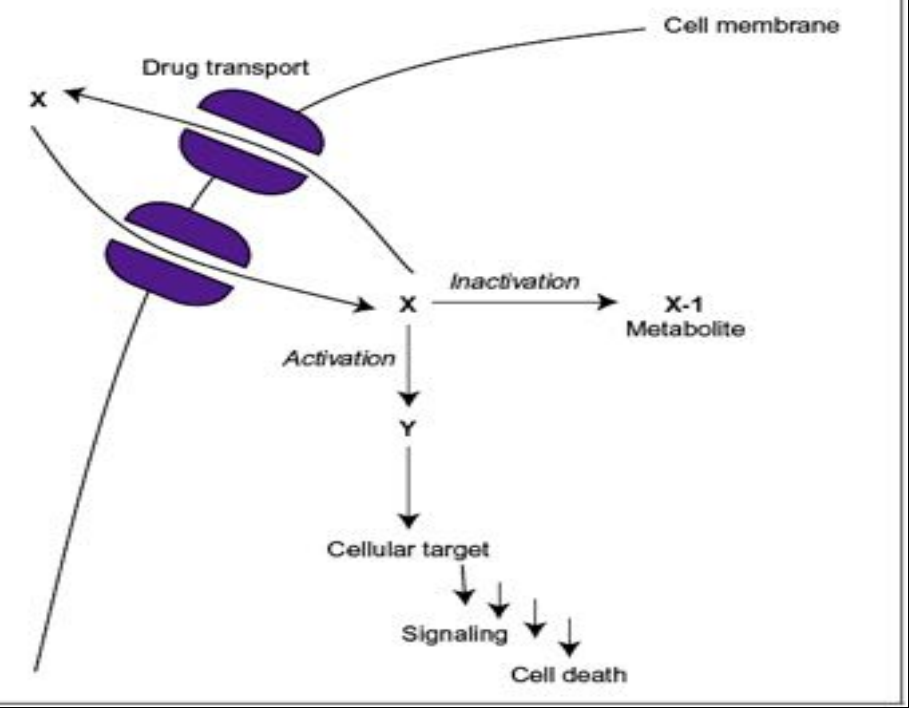


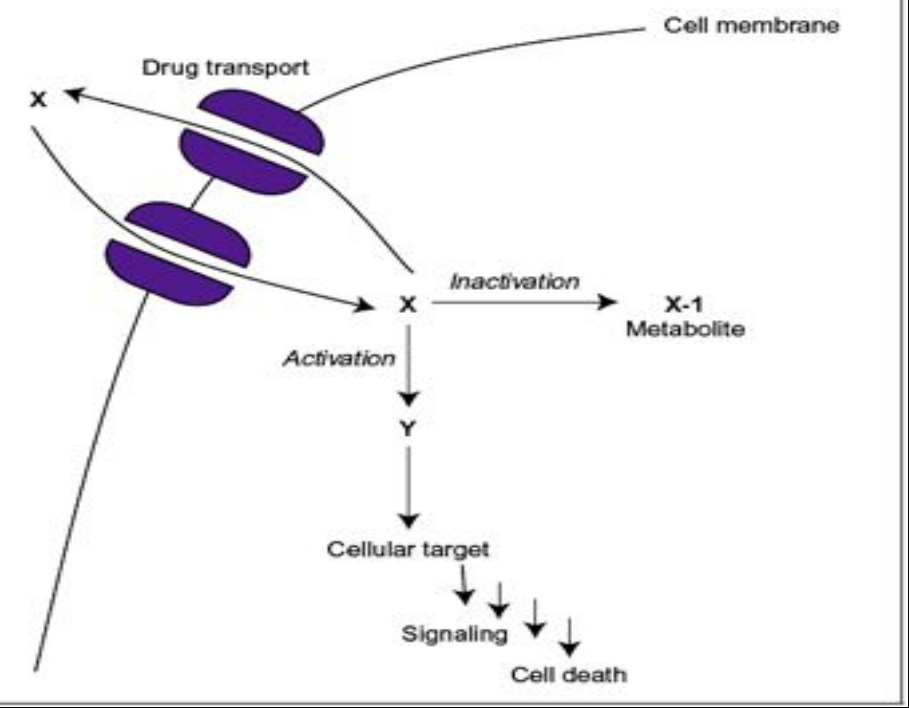
Tossicità

Attivazione
Detossificazione
Escrezione

Risposta

Modificazione del bersaglio
Riparazione del danno

Figure 1. Schematic of the cellular fate of an administered drug, depicting some of the major sources of variation in drug effect.



Tossicità

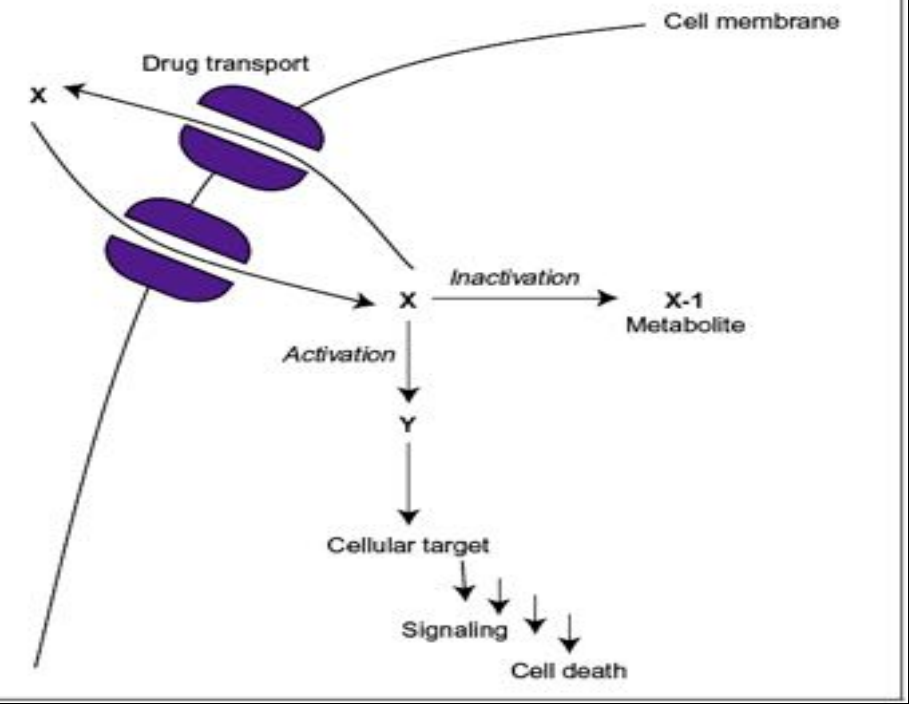
Attivazione
Detossificazione
Escrezione

biodisponibilità del farmaco

Risposta

Modificazione del bersaglio
Riparazione del danno

Figure 1. Schematic of the cellular fate of an administered drug, depicting some of the major sources of variation in drug effect.



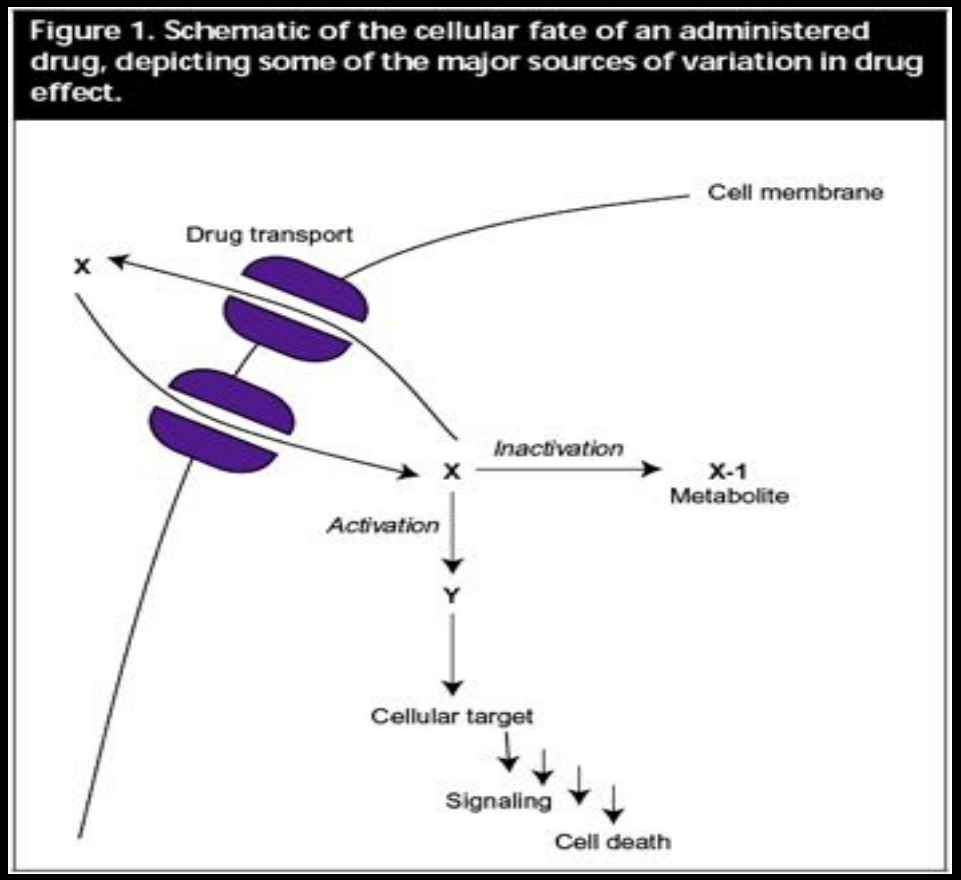
Tossicità

Attivazione
Detossificazione
Escrezione

Attività enzimatiche geneticamente determinate

Risposta

Modificazione del bersaglio
Riparazione del danno



Tossicità

Attivazione
Detossificazione
Escrezione

polimorfismi

frequenza nella popolazione >1%

Risposta

Modificazione del bersaglio
Riparazione del danno

Variazioni genetiche che possono determinanare un effetto quantitativo/qualitativo delle attività enzimatiche


JANUARY 15, 2001
TIME
SPECIAL ISSUE
DRUGS
OF THE
FUTURE
Amazing
new medicines
will be based on
DNA
Find out how they will change
YOUR LIFE

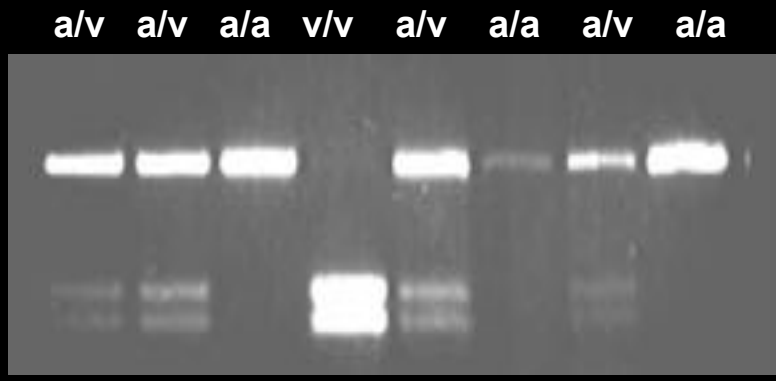
Single nucleotide polymorphism (SNP):
variazione di singolo nucleotide (A,T,C,G)

Normal MTHFR allele

Gene sequence	…GCG	GGA	GCC	GAT…
Protein Sequence	… Ala	Gly	Ala	Asp…

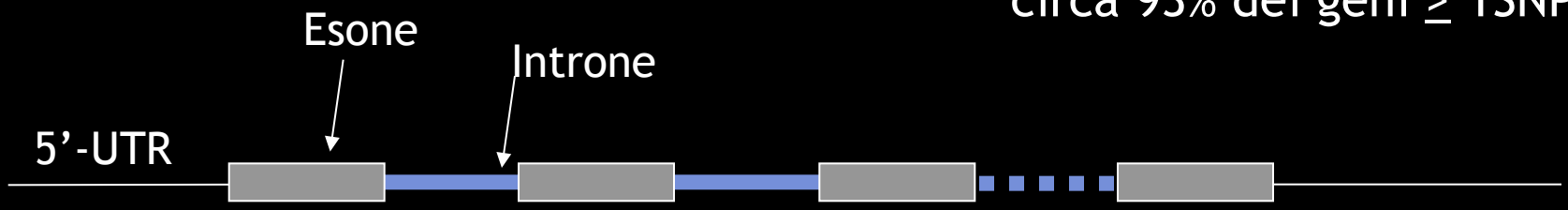
MTHFR 677C/T allele

Gene Sequence	…GCG	GGA	GTC	GAT…
Protein Sequence	…Ala	Gly	Val	Asp …

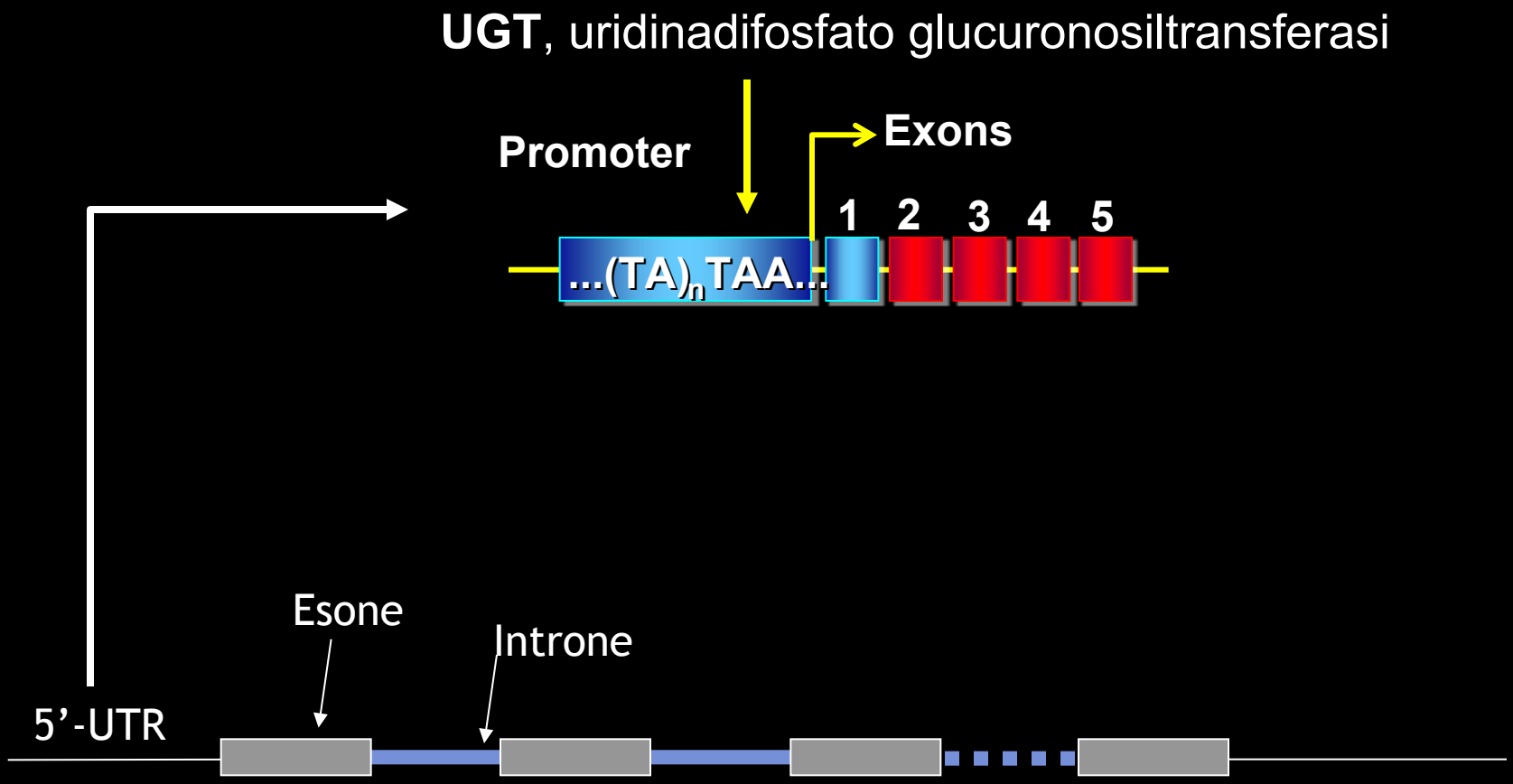


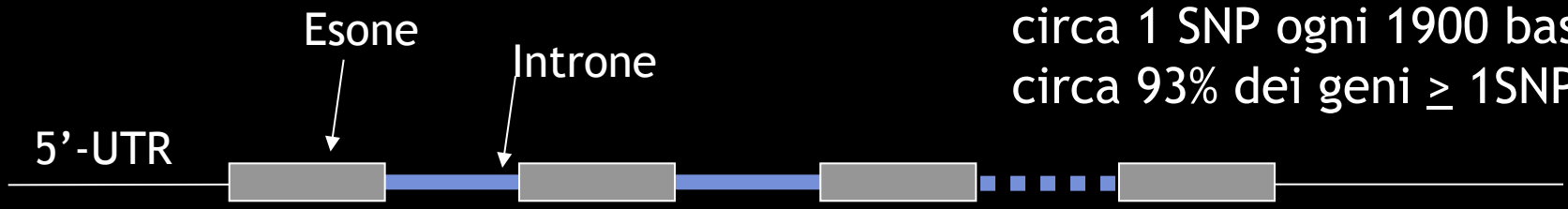
circa 1 SNP ogni 1900 basi

circa 93% dei geni ≥ 1SNP



Variable number of tandem repeats (VNTR):
numero variabile di ripetizioni dinucleotidiche





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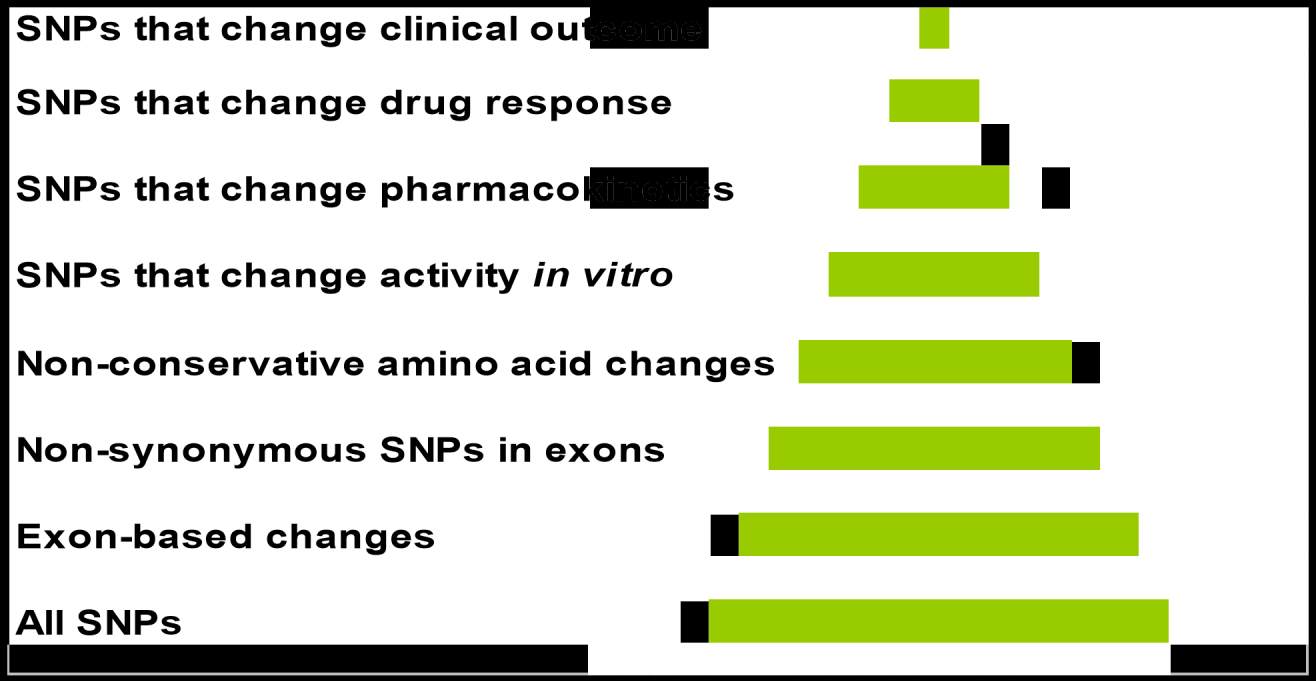


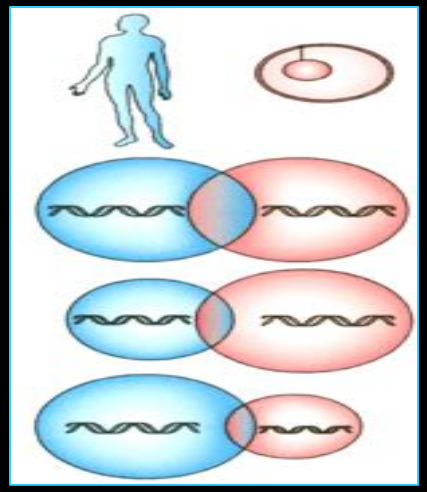
1 Prelievo di sangue periferico

2 estrazione e amplificazione del DNA

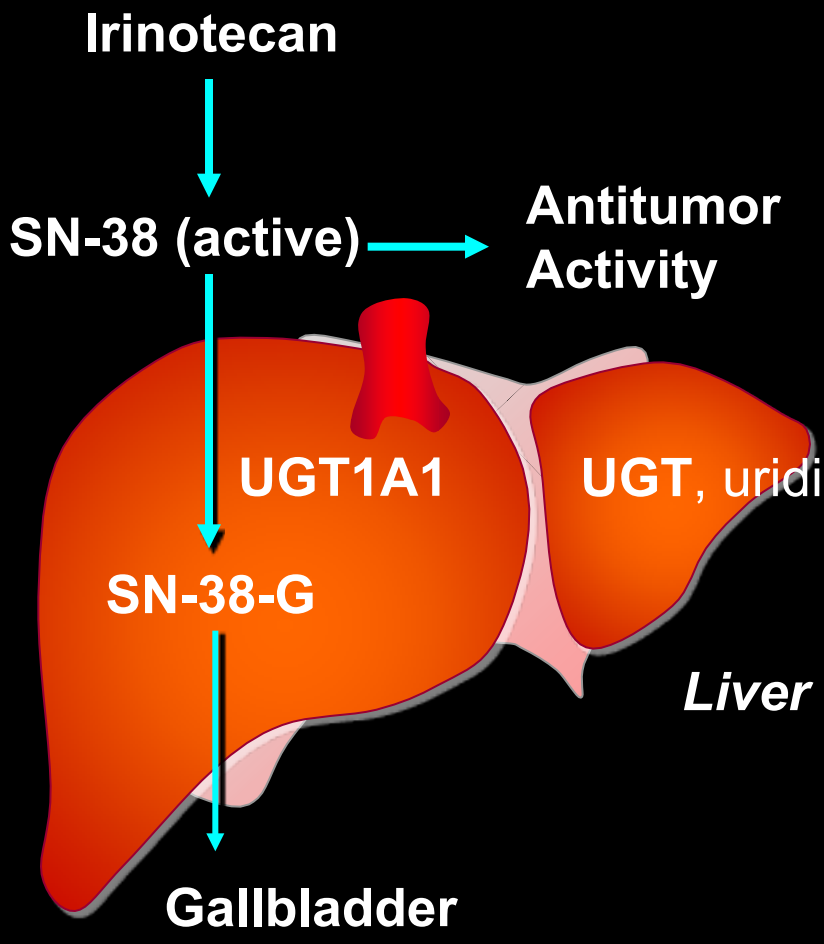
3 Sonde che distinguono una variante genetica

4 Definizione di Genotipo

DNA “genomico” (patrimonio di tutte le cellule dell’organismo)



Irinotecan (CPT-11)

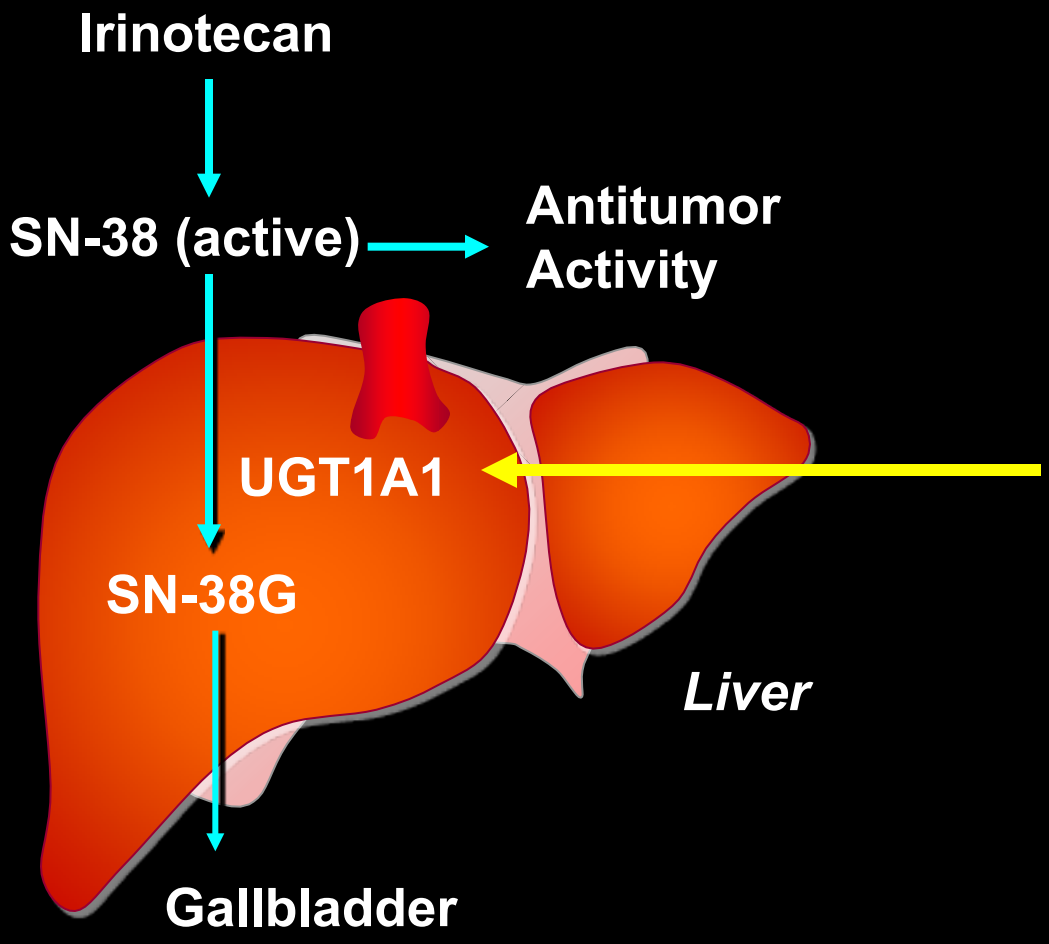


UGT, uridinadifosfato glucuronosiltransferasi

Carcioma del colon
Carcinoma gastrico

MV Relling. Nat Cancer Rev 2001

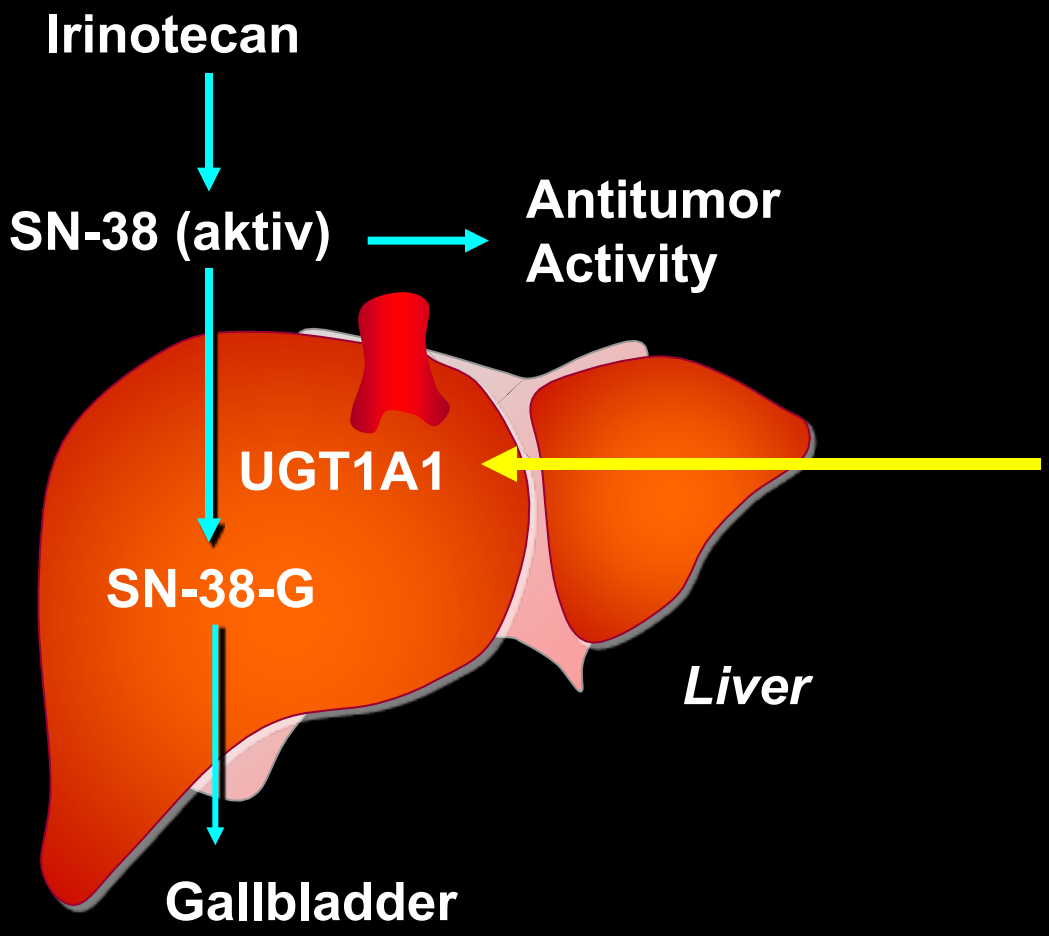
Irinotecan (CPT-11)



La variabiltià dell'attività enzimatica può comportare differenti livelli del metabolita attivo (SN-38) o inattivato (SN-38G)

MV Relling. Nat Cancer Rev 2001

Irinotecan (CPT-11)

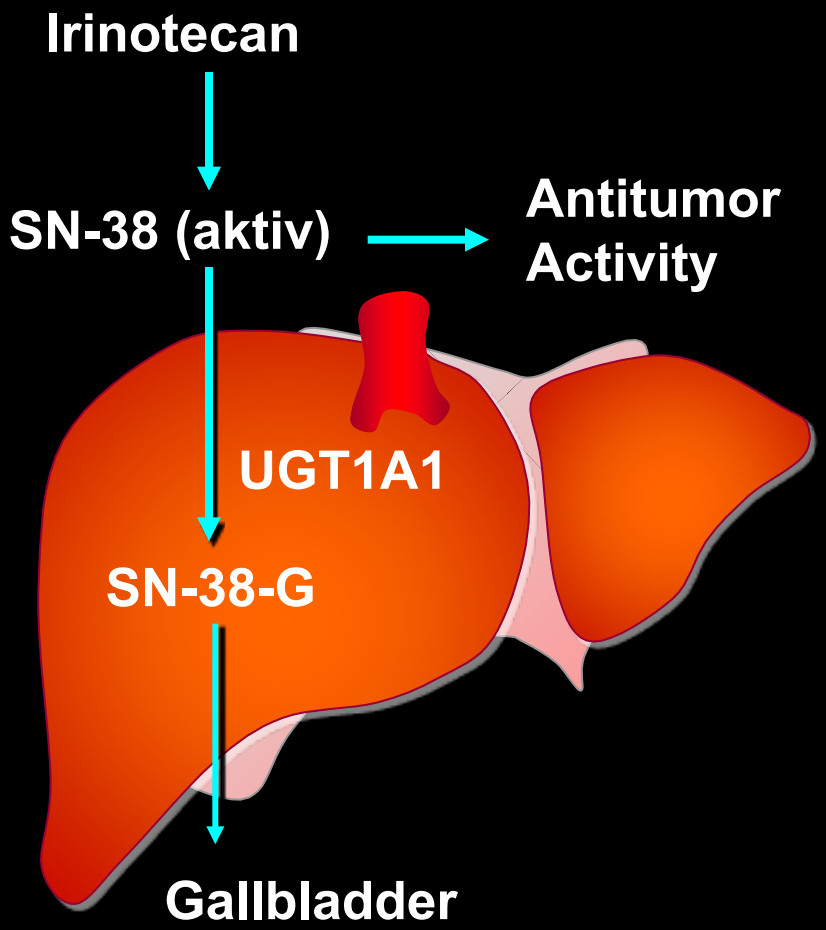


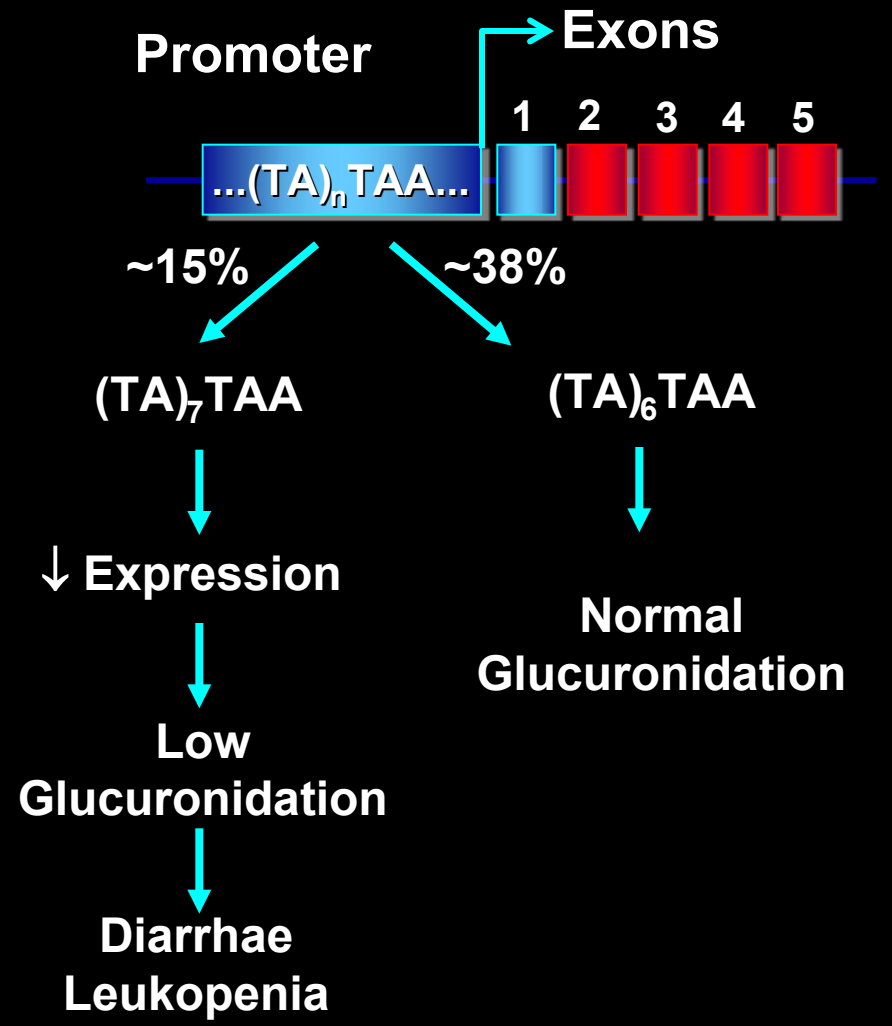
La variabiltià dell'attività enzimatica può comportare differenti livelli del metabolita attivo (SN-38) o inattivato (SN-38-G)

Può essere geneticamente determinata

MV Relling. Nat Cancer Rev 2001

Variable number of tandem repeats (VNTR): numero variabile di ripetizioni dinucleotidiche





MV Relling. Nat Cancer Rev 2001

Genotipo UGT e tollerabilità a irinotecano

Rischio di neutropenia grave: 7/7 vs 6/6 + 6/7 genotypes

Author	n/N (%)		Est. Odds Ratio	95% CI
	7/7	6/6 + 6/7		
Innocenti	3/6 (50%)	3/53 (6%)	16.7	2.3 - 120.6
Rouits	4/7 (57%)	10/66 (15%)	7.5	1.4 - 38.5
Marcuello[a]	4/10 (40%)	18/85 (21%)	2.5	0.6 - 9.7
Ando[b]	4/7 (57%)	22/111 (20%)	5.4	1.1 - 25.9
Ruzzo	12/15 (80%)	22/131 (18%)	4.8	1.44-9.8
Toffoli*	3/19 (16%)	9/228 (4%)	8.6*	1.31-56.5

*rischio significativo di neutropenia G3-G4 solo per il primo ciclo di terapia

Revised Camptosar® label

population is homozygous for the UGT1A1*28 allele. In a prospective study, in which irinotecan was administered as a single-agent on a once-every-3-week schedule, patients

Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A1*28 allele (see DOSAGE AND ADMINISTRATION). Heterozygous patients (carriers of one variant allele and one wild-type allele which results in intermediate UGT1A1 activity) may be at increased risk for neutropenia; however, clinical results have been variable and such patients have been shown to tolerate normal starting doses.

A reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele (See CLINICAL PHARMACOLOGY and WARNINGS). The appropriate dose reduction in this patient population is not known.

Carl has metastatic colorectal cancer.
Now Genzyme can help you determine his risk of serious adverse effects

before

he starts therapy.

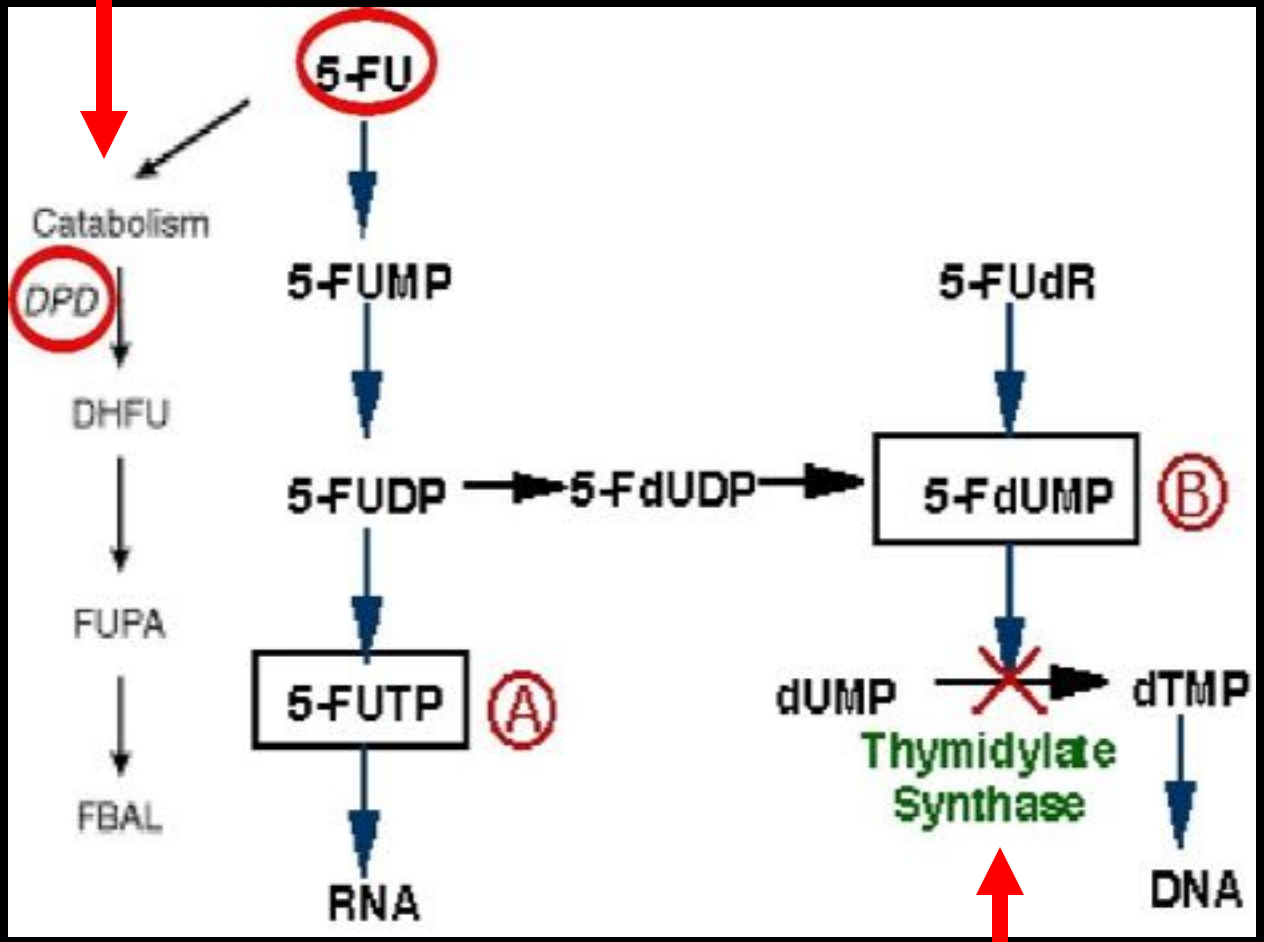
Genzyme now offers the Invader® UGT1A1 Molecular Assay, an FDA-cleared innovative screening test designed to help you identify patients who are at increased risk for severe toxicity when treated with irinotecan. This simple blood test will assist you in making adjustments in your patient's therapy before adverse effects occur.

For more information about Genzyme's cancer testing services, including our menu of innovative tests that can help physicians understand a patient's response to cancer therapy, visit **www.genzymegenetics.com** or call **(800) 447-5816.**

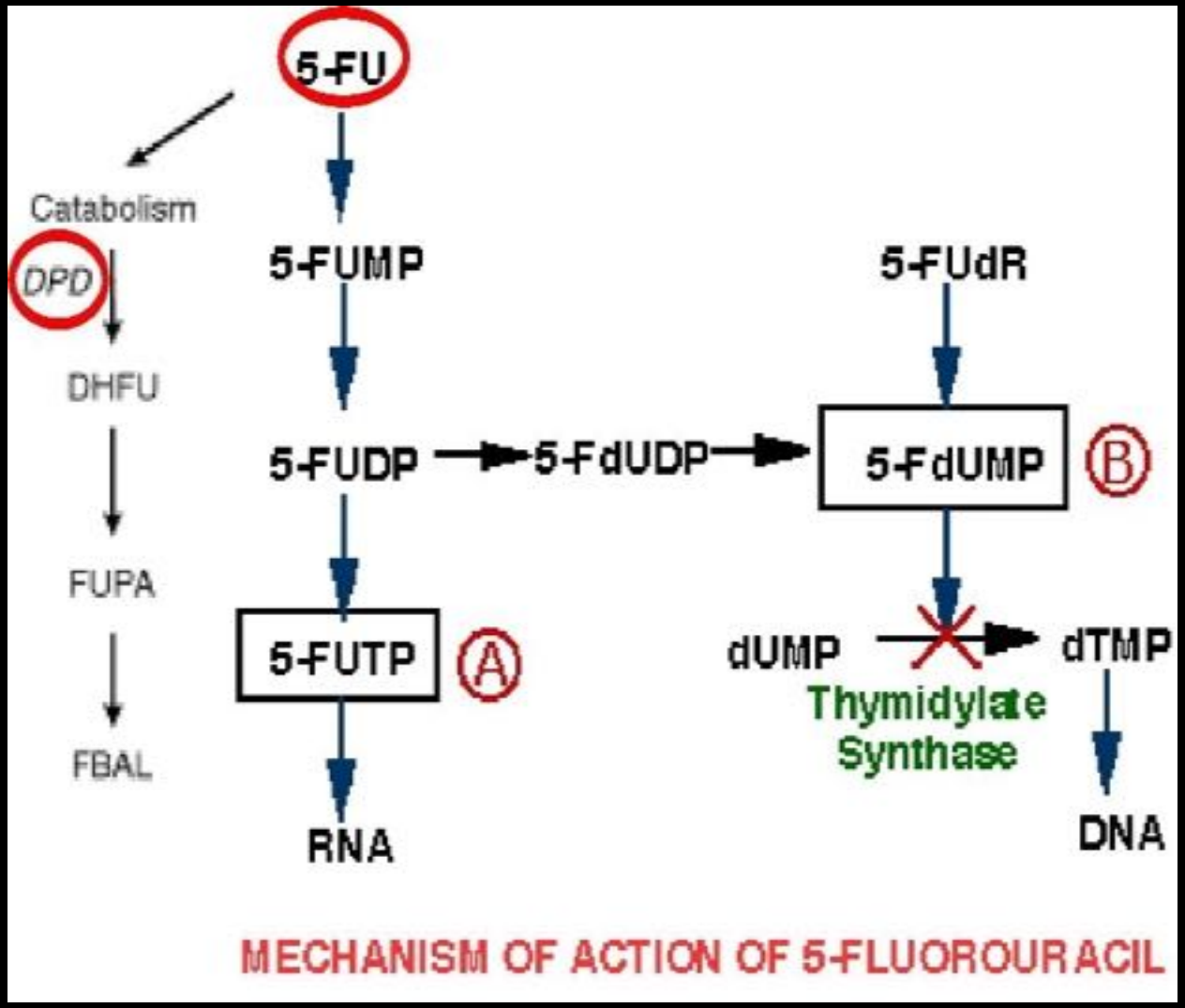
Experience Tomorrow's Cancer Testing Laboratory Today.

genzyme

5-fluorouracil



Mechanism of 5-fluorouracil



Carcinoma:

colon-retto

gastrico

esofageo

testa-collo

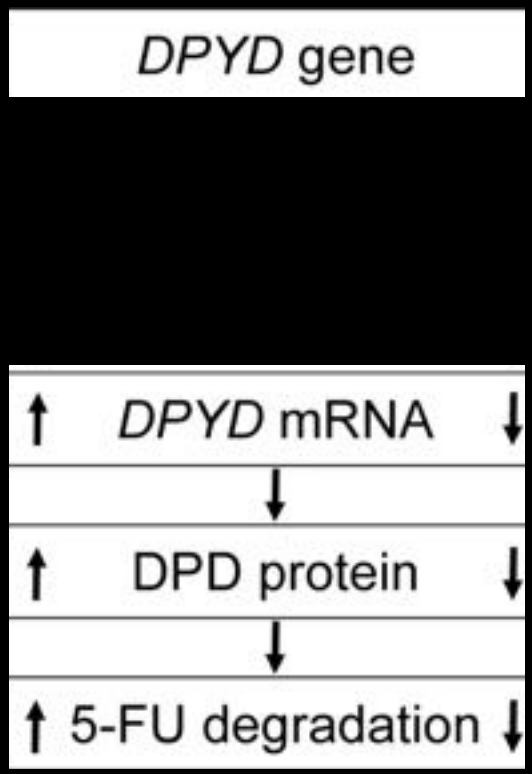
mammario

Effetti collaterali del 5-fluorouracile

- Stomatitis, diarrhea, dermatitis, nausea, hair loss, fever, leukopenia, thrombocytopenia, myelosuppression, neurotoxicity, and cardiotoxicity.
- In some instances, these side effects will culminate in death.




Catabolismo



Noguchi, T. et al. Clin Cancer Res 2004;10:7100-7107

Catabolismo

DPYD gene

↑ *DPYD* mRNA ↓

↓

↑ DPD protein ↓

↓

↑ 5-FU degradation ↓

TOSSICITA'!

Noguchi, T. et al. Clin Cancer Res 2004;10:7100-7107

Clinical Cancer Research

Diidropirimidina deidrogenasi (DPD) e tossicità da fluoropirimidine

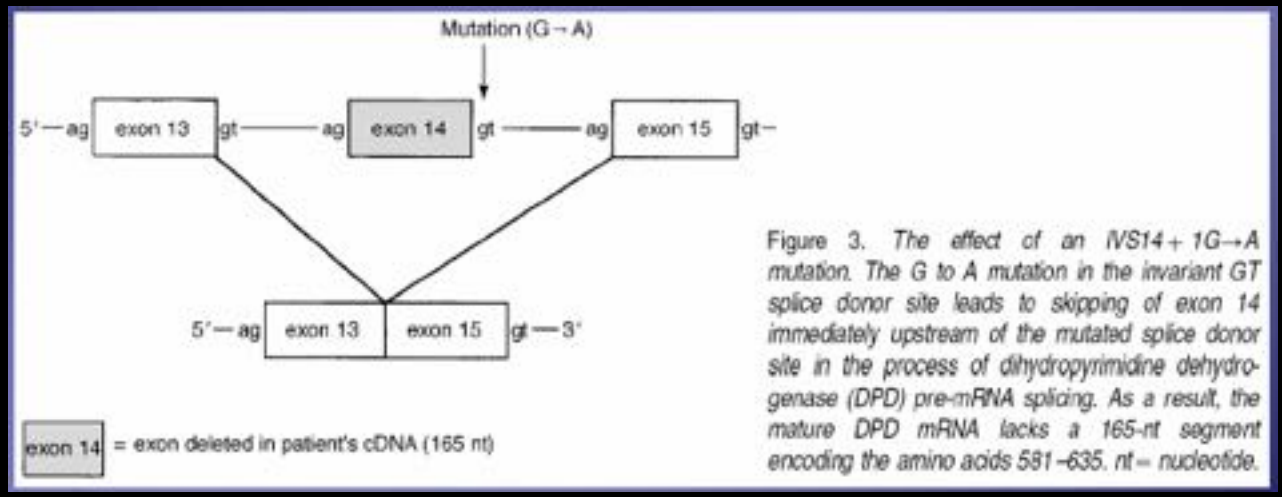
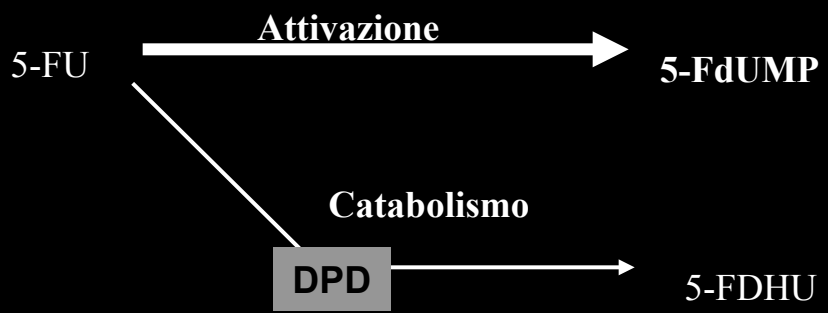
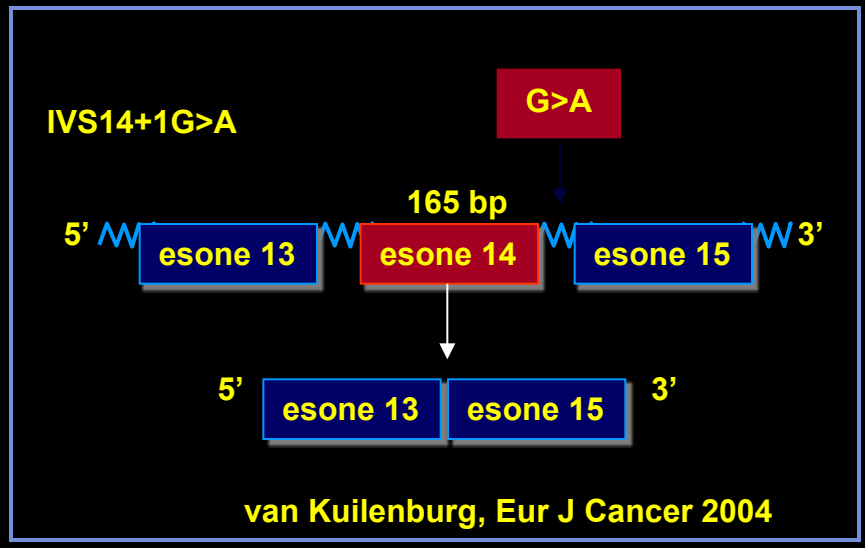


Figure 3. *The effect of an IVS14+1G→A mutation. The G to A mutation in the invariant GT splice donor site leads to skipping of exon 14 immediately upstream of the mutated splice donor site in the process of dihydropyrimidine dehydrogenase (DPD) pre-mRNA splicing. As a result, the mature DPD mRNA lacks a 165-nt segment encoding the amino acids 581–635. nt = nucleotide.*



Deficit enzimatico



van Kuilenburg, Eur J Cancer 2004

- Doctors initiate treatment with 5-FU for approx. 100,000 patients annually.

- 1/3 of all patients with a toxicity 4 after 5-FU treatment are carriers of the Exon-14 Skipper Mutation (*DPYD*2*)

N	Mutation carrier	Prevalence	Source
60	17	28%	van Kuilenburg, Pharmacogenetics 2002
25	6	24%	Oncoscreen/Raida Clin.Canc.Res.2001
8	2	25%	Oncoscreen, unpubliziert
93	25	27%	* Total

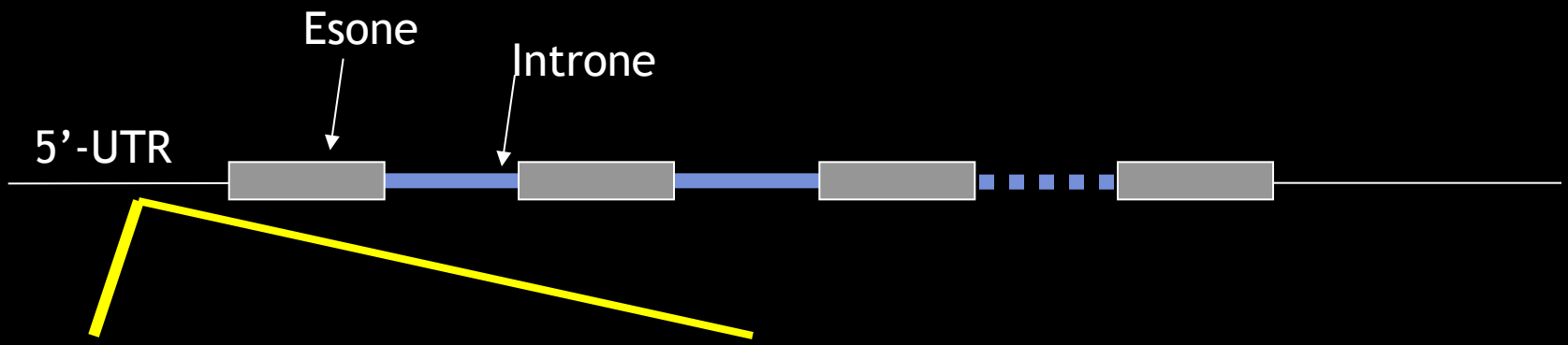
Thymidylate Synthase (TS) in Cancer Patients

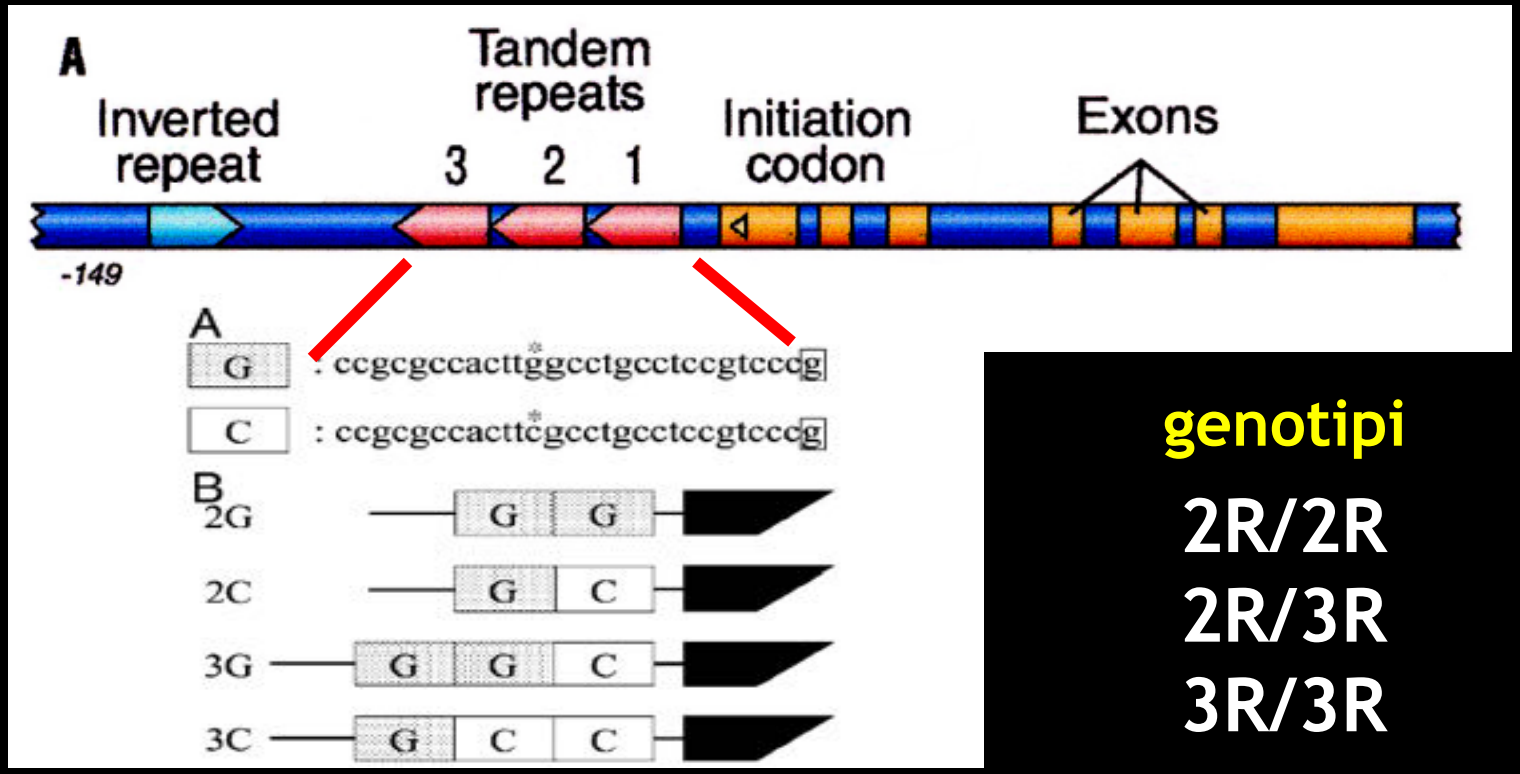
High TS levels

5-fluorouracil

Chemoresistance

Polymorphisms in the *TS* 5'-UTR



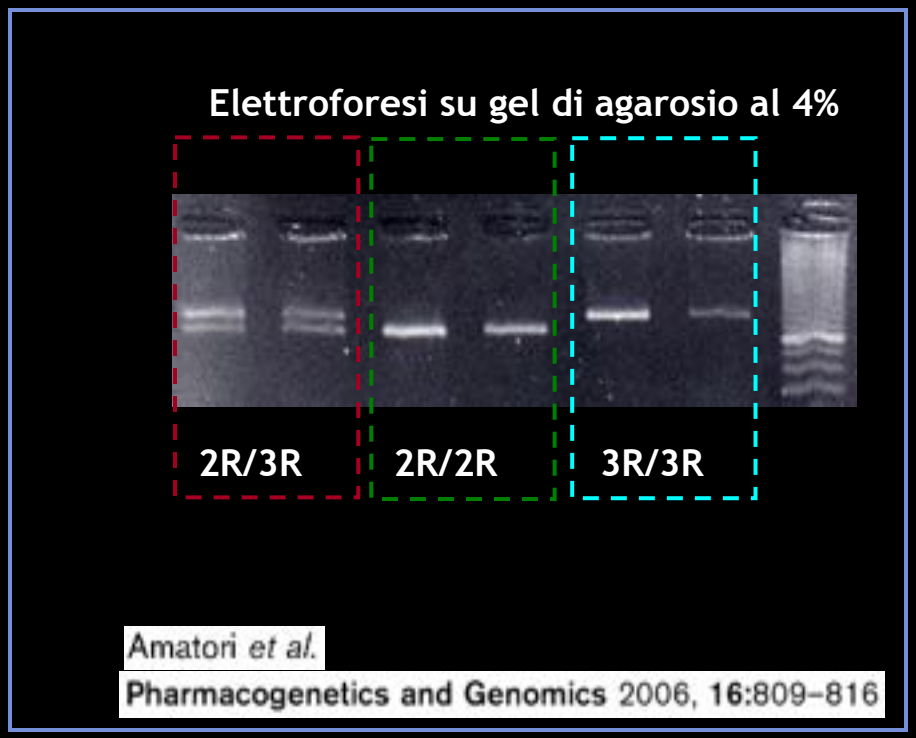


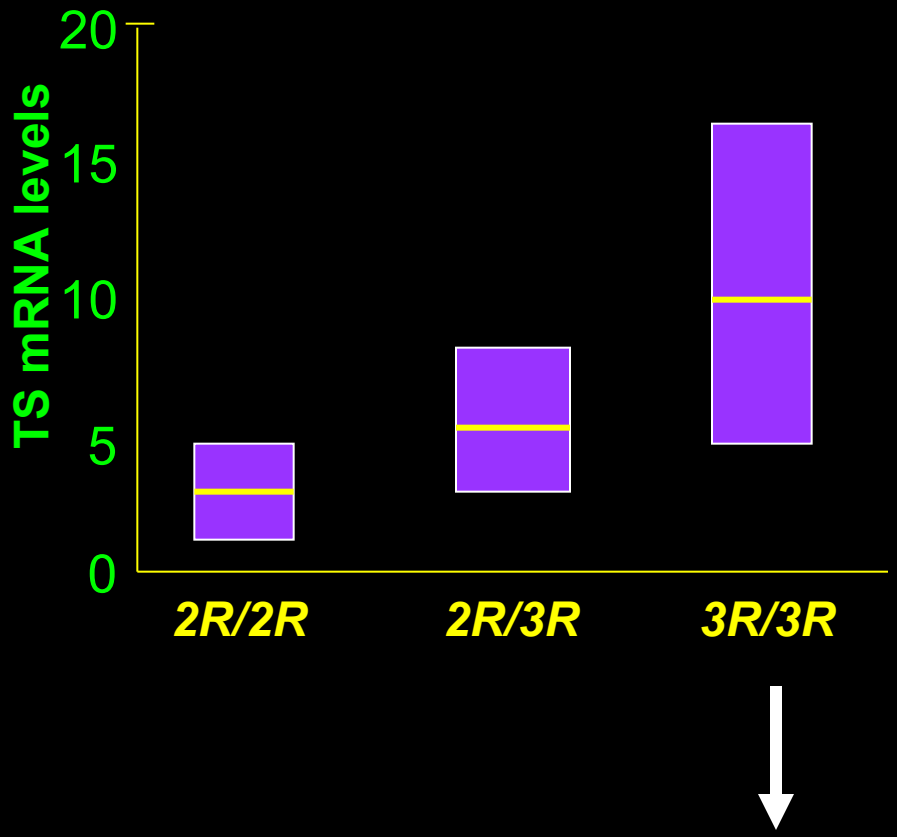
genotipi

2R/2R

2R/3R

3R/3R





High TS levels

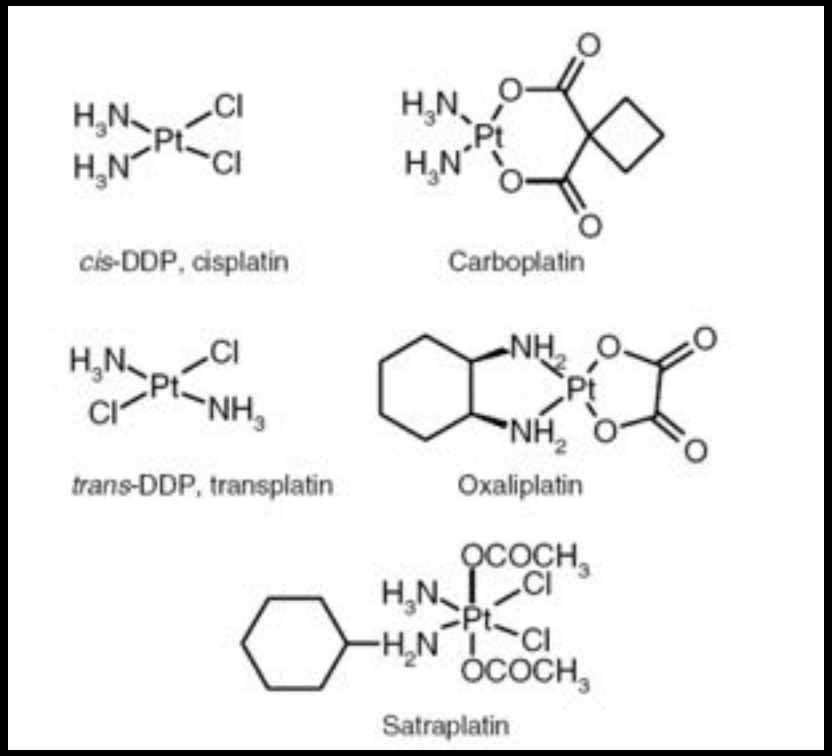
Chemoresistance

Polimorfismi di Timidilato Sintetasi e chemioterapia con 5-fluorouracile nel CCR

			5'-UTR
Dotor E, et al. *J Clin oncol 2006*	129 paz.	adiuvante	*3R/3R*
Hitre E, et al. *Pharmacogen 2005*	166 paz.	adiuvante	*3R/3R*
Jakobsen, et al. *J Clin Oncol 2005*	88 paz.	palliativa	*3R/3R*
Marcuello C, et al. *Int J Cancer 2004*	89 paz.	palliativa	*3R/3R*
Iacopetta B, et al. *BJC 2001*	221 paz.	adiuvante	*3R/3R*
Villafranca E, et al *J Clin Oncol 2001*	55 paz.	pre-op retto	*3R/3R*
Tsui T, et al *Clin Cancer Res 2001*	135 paz.	adiuante	*3R/3R*

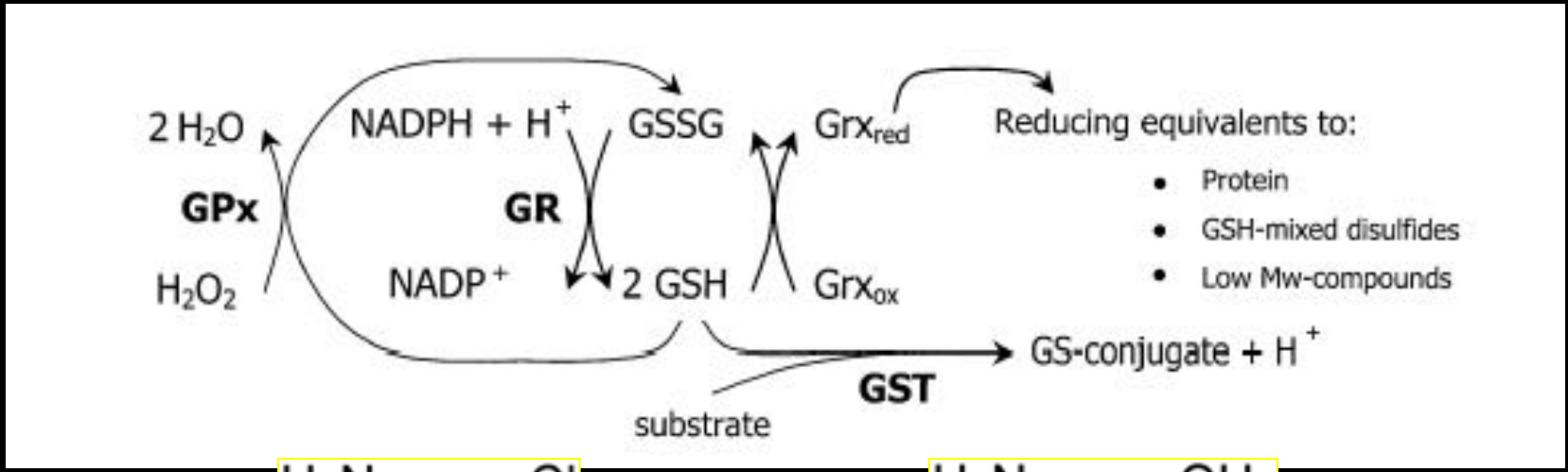
Platinum compounds

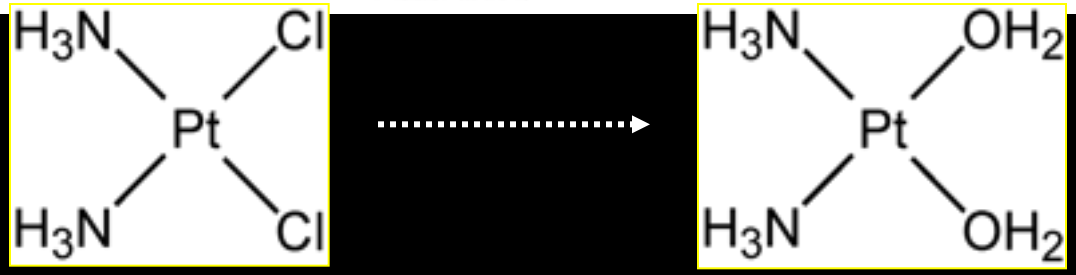
- Cisplatin
- Carboplatin
- Oxaliplatin



carcinoma polmonare
carcinomi testa-collo
carcinoma gastrico
carcinoma ovarico

GST (Glutathione-S-transferases) catalyze the conjugation of GSH with other molecules, and serve as an intermediate in detoxification processes.





La neurotossicità è un effetto collaterale caratteristico di oxaliplatino/cisplatino

GST pi (GSTP1)

Located on chromosome 11q13

A G-->A transition in exon 5 produces Ile→Val change

ile/ile homozygote wild type,
ile/val heterozygote,
val/val homozygote variant.

→ altered enzyme activity

VOLUME 25 · NUMBER 6 · FEBRUARY 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cisplatin-Induced Long-Term Hearing Impairment Is Associated With Specific Glutathione S-Transferase Genotypes in Testicular Cancer Survivors

Jan Oldenburg, Sigrid M. Kraggerud, Miladis Cvancarova, Ragnhild A. Lothe, and Sophie D. Fosså

GST pi (GSTP1)

Located on chromosome 11q13

A G-->A transition in exon 5 produces Ile→Val change

ile/ile homozygote wild type,
ile/val heterozygote,
val/val homozygote variant.

→

altered enzyme activity

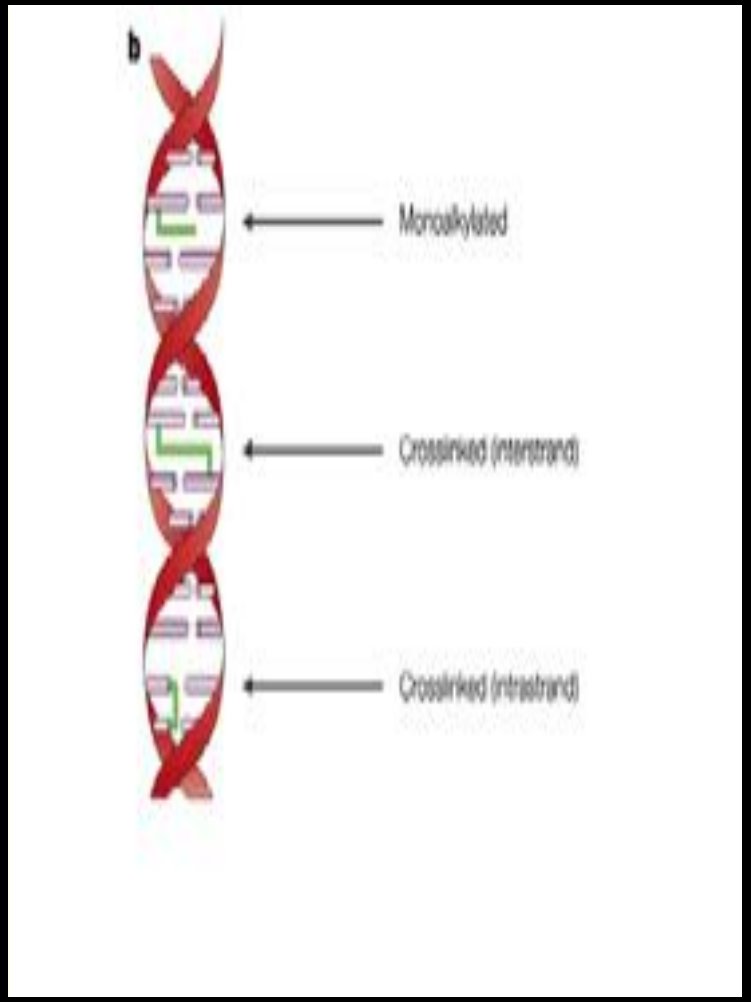
Imaging, Diagnosis, Prognosis Clin Cancer Res 2006;12(10) May 15, 2006

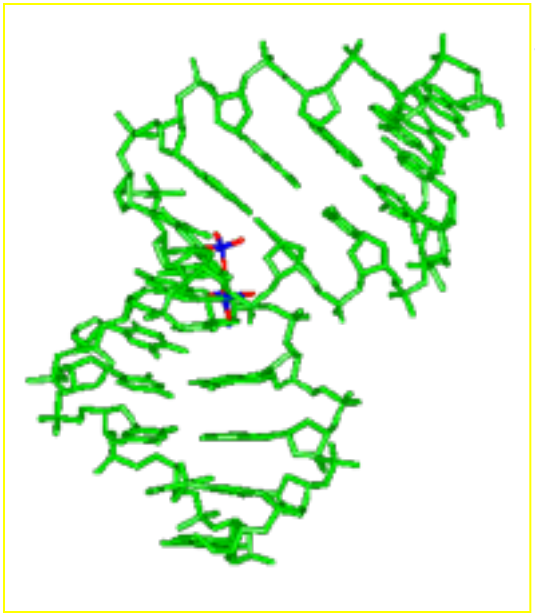
Glutathione *S*-Transferase P1 Polymorphism (Ile^{105}Val) Predicts Cumulative Neuropathy in Patients Receiving Oxaliplatin-Based Chemotherapy

Thierry Lecomte,[1,3] Bruno Landi,[1] Philippe Beaune,[2,3] Pierre Laurent-Puig,[2,3] and Marie-Anne Loriot[2,3]

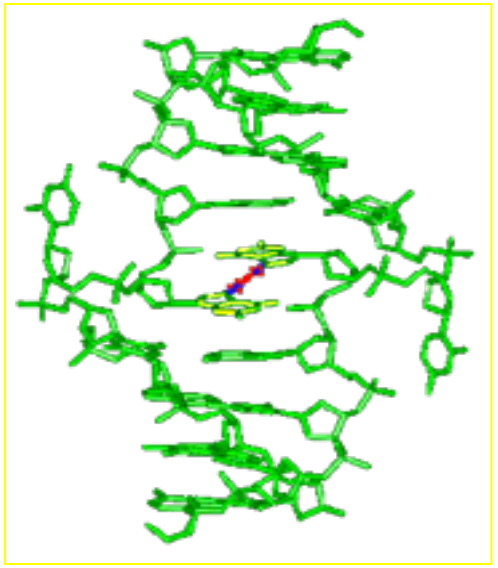
Platinum compounds and DNA damage

- DNA damage is the primary mechanism of platinum cytotoxicity
  - Monoadducts
  - interstrand crosslinks
  - intrastrand crosslinks

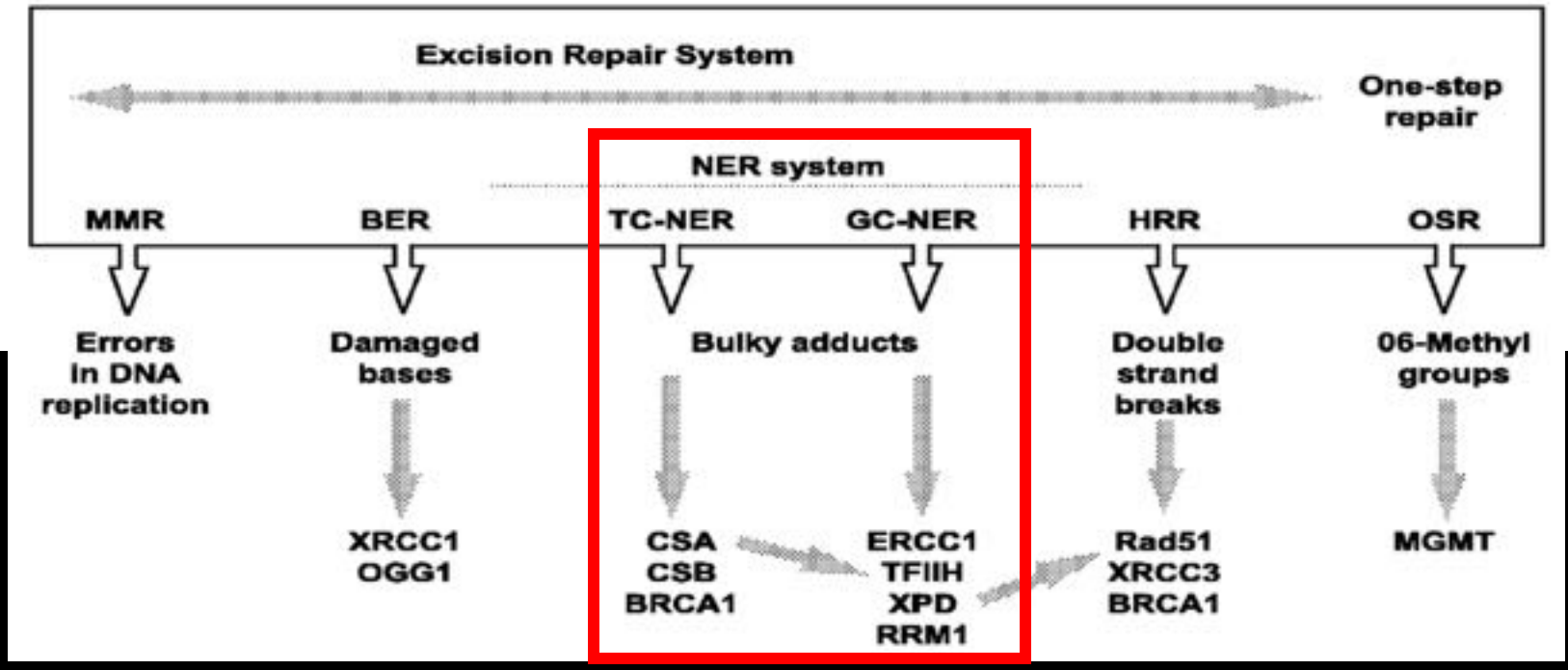




1,2-Intrastrand Crosslink



1,2-Interstrand Crosslink



Polimorfismi e riparazione DNA (cisplatino/oxaliplatino)

Genes	R. enzyme	Polymorphism	Putative effect
ERCC1 118	MaeII	*C/T, Asn118Asn* (exon 4)	Enhanced *ERCC* mRNA levels and DNA repair in *Asn* allele carriers.
XRCC1 194	PvuII	*C/T, Arg194Trp* (exon 6)	Diminished DNA repair efficiency in *Trp* allele carriers.
XRCC3 241	NcoI	*T/C, Thr241Met* (exon 7)	Defective DNA repair in *Met* allele carriers.
XRCC1 399	NciI	*G/A, Arg399Gln* exon 10)	Diminished DNA repair efficiency in *Gln* allele carriers.
XPD (ERCC2) 312	StyI	*G/A, Asp312Asn* (exon 10)	Diminished DNA repair efficiency in *Asn* allele carriers.
XPD (ERCC2) 751	MboII	*A/C, Lys751Gln* (exon 23)	Diminished DNA repair efficiency in *Lys* allele carriers.

Polimorfismi e chemioterapia con Cisplatino nel NSCLC

Su D, et al. *Lung cancer 2007*	230 paz.	*ERCC-1 118 C/C*
Lu C, et al. *Cancer 2006*	424 paz.	*GSTP1 114 Val/Val*
Ryu T, et al. *Lung Cancer 2004*	109 paz.	*ERCC-1 118 C/C*
Zhou C, et al. *Clin Cancer Res 2004*	128 paz.	*ERCC-1 8092 C/A*
Zhang T, et al. *J Clin Obcol 2004*	103 paz.	XPD 312Asn and XRCC1Gly
Isla D, et al *Ann Oncol 2004*	62 paz.	*ERCC-1 118 C/C*
de Las Penas *Ann Oncol 2006*	135 paz.	*XRCC3 Met/Met*

Polimorfismi DNA repair e chemioterapia con Oxaliplatino nel CCR avanzato

Ruzzo A, et al. *J Clin oncol 2007*	166 paz.	12 varianti	*ERCC1-118 C/C* *XPD-751 C/C*
Park DJ, et al. *CAHO 2005*	106 paz.	1 variante	*ERCC1-118 C/C*
Viguier J, et al. *Clin Cancer Res 2005*	91 paz.	1 variante	*ERCC1-118 C/C*
Stoehlamcher J, et al. *BJC 2004*	106 paz.	7 varianti	*ERCC1-118 C/C* *XPD-751 C/C*
Stoehlamcher J, et al. *JNCI 2002*	107 paz.	3 varianti	*GSTP1 Val/Val*
Park DJ, et al *Cancer Res 2001*	73 paz.	2 varianti	*XPD-751 C/C*

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Pharmacogenetic Profiling in Patients With Advanced Colorectal Cancer Treated With First-Line FOLFOX-4 Chemotherapy

FOLFOX

terapia di combinazione con

5-fluorouracile
oxaliplatino

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Table 1. Characteristics of the Studied Polymorphisms With Primer Sequences and Restriction Enzymes

Site	Polymorphism	Genotype	Restriction Enzyme	Primers
*TS 5′-untranslated region (5′-UTR)**	VNTR* and SNP	*2R* or *3R* alleles, *C/G* SNP in *3R* carriers	HaeIII	*5′-AGG CGC GCG GAA GGG GTC CT 5′-TCC GAG CCG GCC ACA GGC AT*
TS 3′-untranslated region (3′-UTR)	6 bp insertion/deletion	*6+/6-*	DraI	*5′-CAA ATC TGA GGG AGC TGA GT 5′-CAG ATA AGT GGC AGT ACA GA*
MTHFR (exon 4)	SNP	*C/T, Ala677Val*	HinfI	*5′-TGA AGG AGA AGG TGT CTG CGG GA 5′-AGGACG GTG CGG TGA GAG TG*
MTHFR (exon 7)	SNP	*A/C, Glu1298 Ala*	MboII	*5′-CTT TGG GGA GCT GAA GGA CTA CTA 5′-CAC TTT GTG ACC ATT CCG GTT TG*
ERCC1(exon 4)	*SNP*	C/T, Asn118Asn	MaeII	*5′-GAG AGG GCT GAG CTG GAG ACA G 5′-CCA GCA CAT AGT CGG GAA TTA CGT C*
XRCC1 (exon 10)	SNP	G/A, Arg399Gln	NciI	*5′-CAA GTA CAG CCA GGT CCT AG 5′-CCT TCC CTC ATC TGG AGT AC*
XPD (exon 10)	SNP	*G/A, Asp312Asn*	StyI	*5′-CTG TTG GTG GGT GCC CGT ATC TGT TGG TCT 5′-TAA TAT CGG GGC TCA CCC TGC AGC ACT TCC T*
XPD (exon 23)	SNP	*A/C, Lys751Gln*	MboII	*5′-CAG GTG AGG GGG ACA TCT G 5′-CTC TCC CTT TCC TCT GTT C*
XRCC3 (exon 7)	SNP	T/C, Thr241Met	NcoI	*5′-GCC TGG TGG TCA TCG ACT C 5′-ACA GGG CTC TGG AAG GCA CTG CTC AGC TCA CGC ACC*
GSTP1 (exon 5)	SNP	*A/G, Ile105Val*	MspI	*5′-ACCCCAGGGCTCTATGGGAA 5′-TGAGGGCACAAGAAGCCCCT*
GSTM1	Deletion	±†	-	*5′-GAACTCCCTGAAAAGCTAAAGC 5′-GTTGGGCTCAAATATACGGTGG*
GSTT1	Deletion	±†	-	*5′-TTCCTTACTGGTCCTCACATCTC 5′-TCACCGGATCATGGCCAGCA*

Abbreviations: *TS*, thymidylate synthase; *UTR*, untranslated region; VNTR, variable number of tandem repeats; SNP, single nucleotide polymorphism; *MTHFR*, methylenetetrahydrofolate reductase; *ERCC1*, excision repair cross complementing group 1; *XRCC1*, x-ray cross complementing group 1; *XPD*, xeroderma pigmentosum group D; *XRCC3*, x-ray cross complementing protein 3; *GST*, glutathione S-transferase.

*The VNTR polymorphism is a two (*2R*) or three (*3R*) 28-bp tandem repeats sequence in *TS 5′-UTR*. A SNP in *3R* allele is a second polymorphism that distinguishes *3G* carriers (*2R/3G*, *3G/3G*, *3G/3C* genotypes) from non-*3G* carriers (*2R/2R*, *2R/3C*, and *3C/3C* genotypes).

†A genotype was defined as positive if at least one copy of the gene was present.

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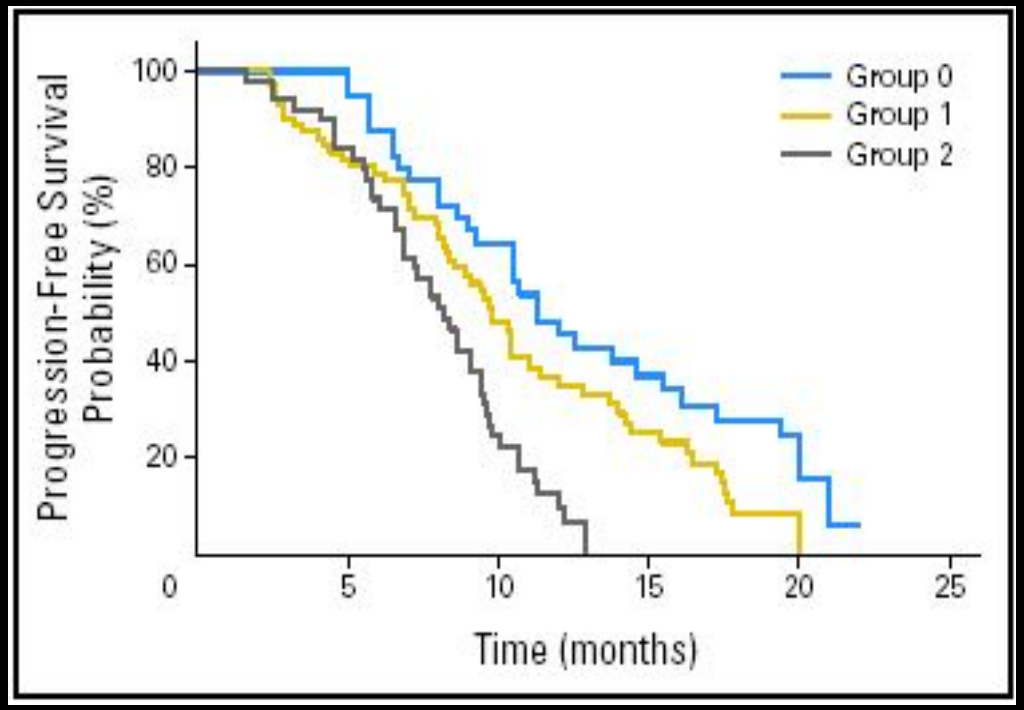
XPD 751 C/C

ERCC1 118 T/T



Polimorfismi in pazienti con Carcinoma Gastrico

	N° pazienti		
Liu B, et al. *EJMG 2007*	62	5-FU/Oxaliplatin	*XRCC-399 Gln/Gln*
Ott K, et al. *Int J Cancer 2006*	135	5-FU	*TS 5'-UTR 3R/3R*
Ruzzo A, et al. *J Clin Oncol 2006*	*175*	5-FU/Cisplatin	*TS 5'-UTR 3R/3R GSTP1 105 A/A*
Lu JW, et al. *J Hum Genet 2006*	106	5-FU	*TS 3'-UTR 6ins/6ins*
Goekkurt E, et al. *BJC 2006*	52	5-FU/Cisplatin	*TS 5'-UTR 3R/3R GSTP1 105 A/A*
Ishida J, et al *Anticancer Res 2002*	115	5-FU	*TS 5'-UTR 3R/3R*

Pharmacogenetic Profiling and Clinical Outcome of Patients With Advanced Gastric Cancer Treated With Palliative Chemotherapy

Annamaria Ruzzo, Francesco Graziano, Kazuyuki Kawakami, Go Watanabe, Daniele Santini, Vincenzo Catalano, Renato Bisonni, Emanuele Canestrari, Rita Ficarelli, Ettore Tito Menichetti, Davide Mari, Enrica Testa, Rosarita Silva, Bruno Vincenzi, Paolo Giordani, Stefano Cascinu, Lucio Giustini, Giuseppe Tonini, and Mauro Magnani

VOLUME 24 · NUMBER 12 · APRIL 20 2006

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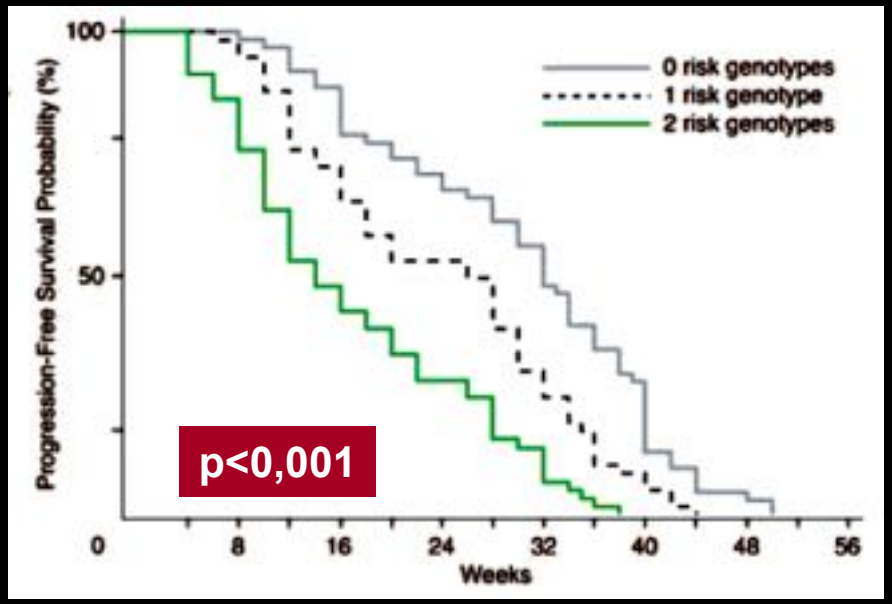
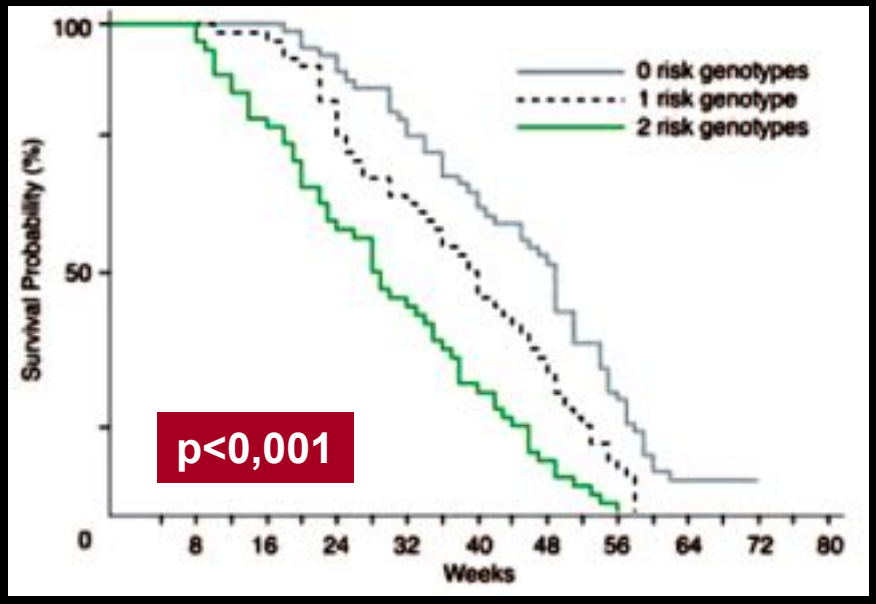
Pazienti affetti da carcinoma gastrico avanzato
Chemioterapia palliativa 5-FU e cisplatino
Studio dei polimorfismi di 9 geni

TS 5'-UTR 3R/3R
GSTPI 105A/A



Progression-free survival



Overall survival

Chemioterapici maggiormente studiati in farmacogenetica "in vivo"

Irinotecan (CPT-11)

5-Fluorouracile

Cisplatino

Oxaliplatino

Cetuximab (EGFR)

Bevacizumab (VEGF)

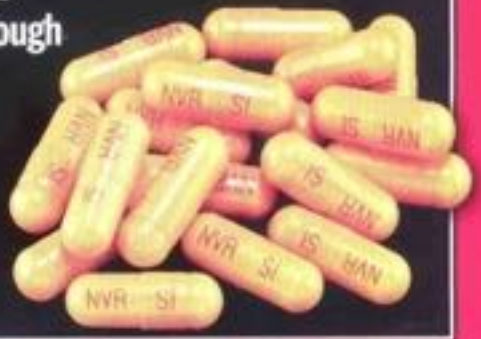
MAY 28, 2001 $4.95 (INCL. GST)

TIME

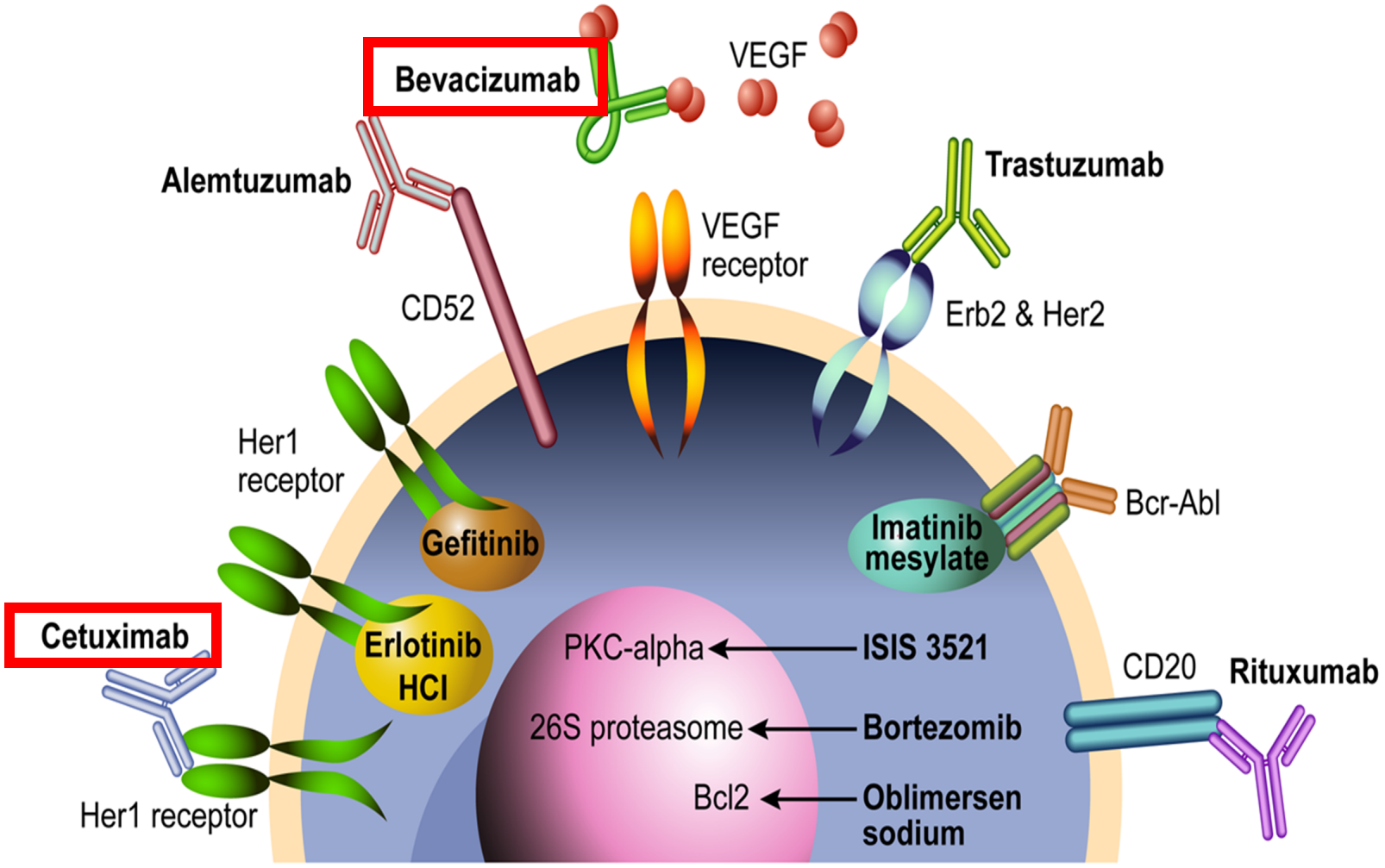
KILLER KIDS IN PRISON

THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.

Revolutionary new pills like GLIVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?



Targeted Therapies



Bersagli degli Anticorpi Monoclonali

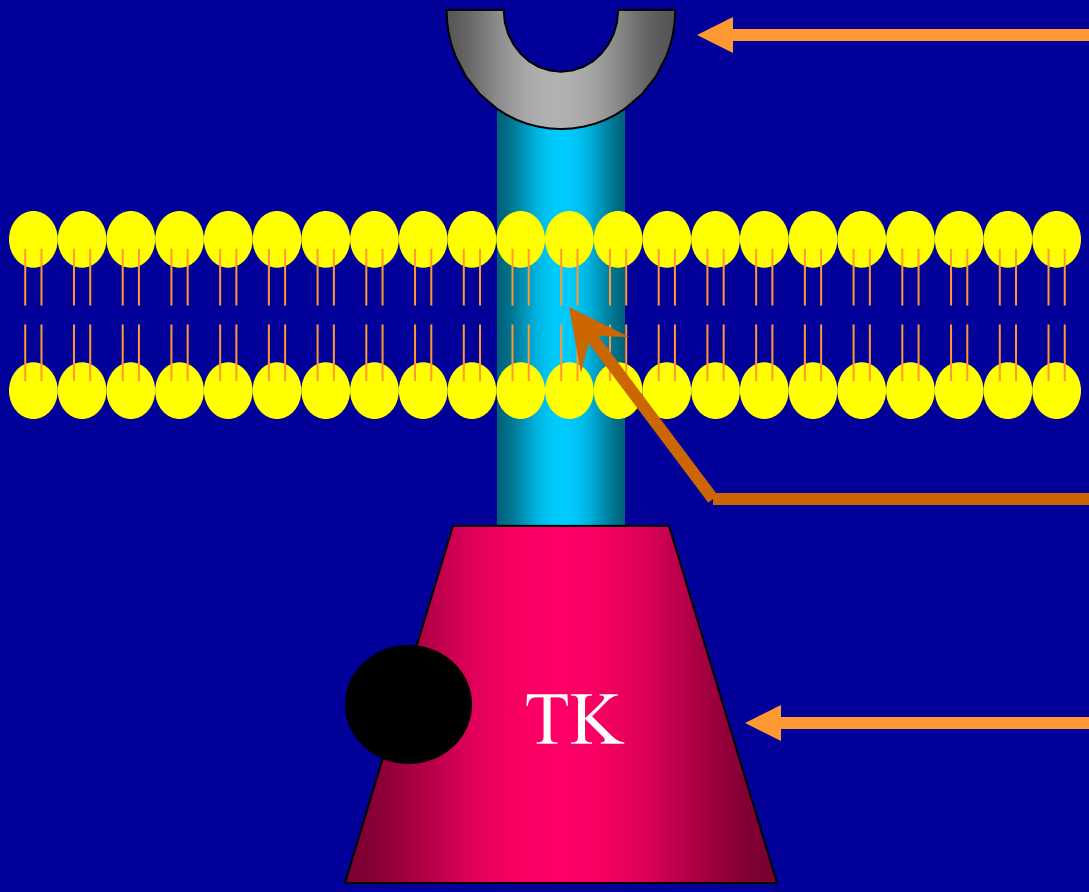
Erbitux (Cetuximab)

anti-Epidermal Growth Factor Receptor (EGFR)

Avastin (Bevacizumab)

anti-Vascular Endothelial Growth Factor (VEGF)

EGFR Structure

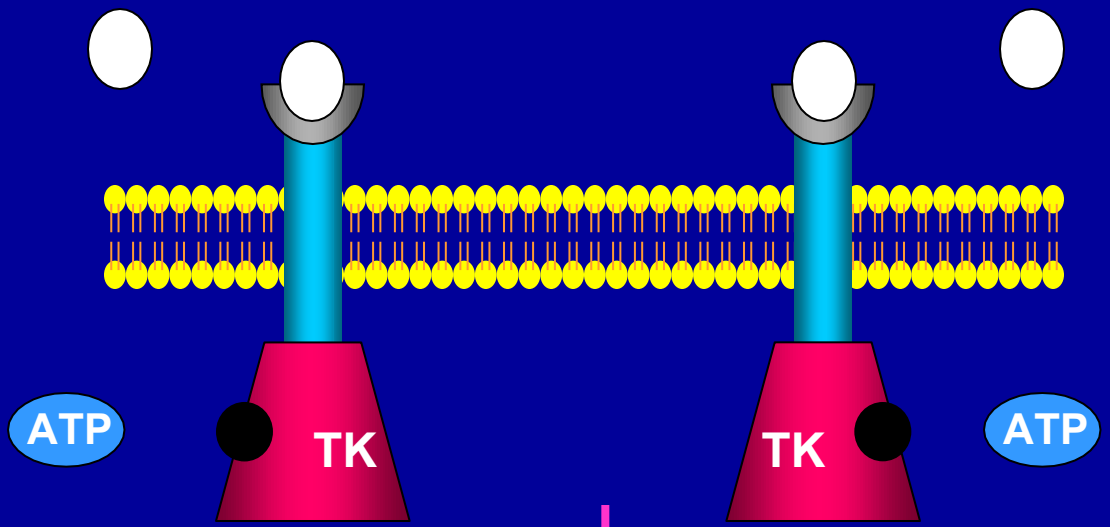


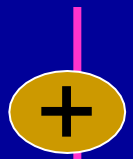
Extracellular Domain

Transmembrane Domain

Intracellular Domain

EGFR Function in Normal Cell





Gene Transcription

Cell Cycle Progression

Cell Proliferation

Antiapoptosis

Angiogenesis

Pazienti con carcinoma del colon metastatico e carattietistiche cliniche e di malattia comparabili

Osservazion clinica: terapia con anti-EGFR (cetuximab)

Paziente 1		Paziente 2
+	Mucosite	+
-	Diarrea	+
-	tossicià ematologica	-
-	tossicità cutanea	+++
+	Risposta	+++

Adverse skin effects after anti-EGFR treatment

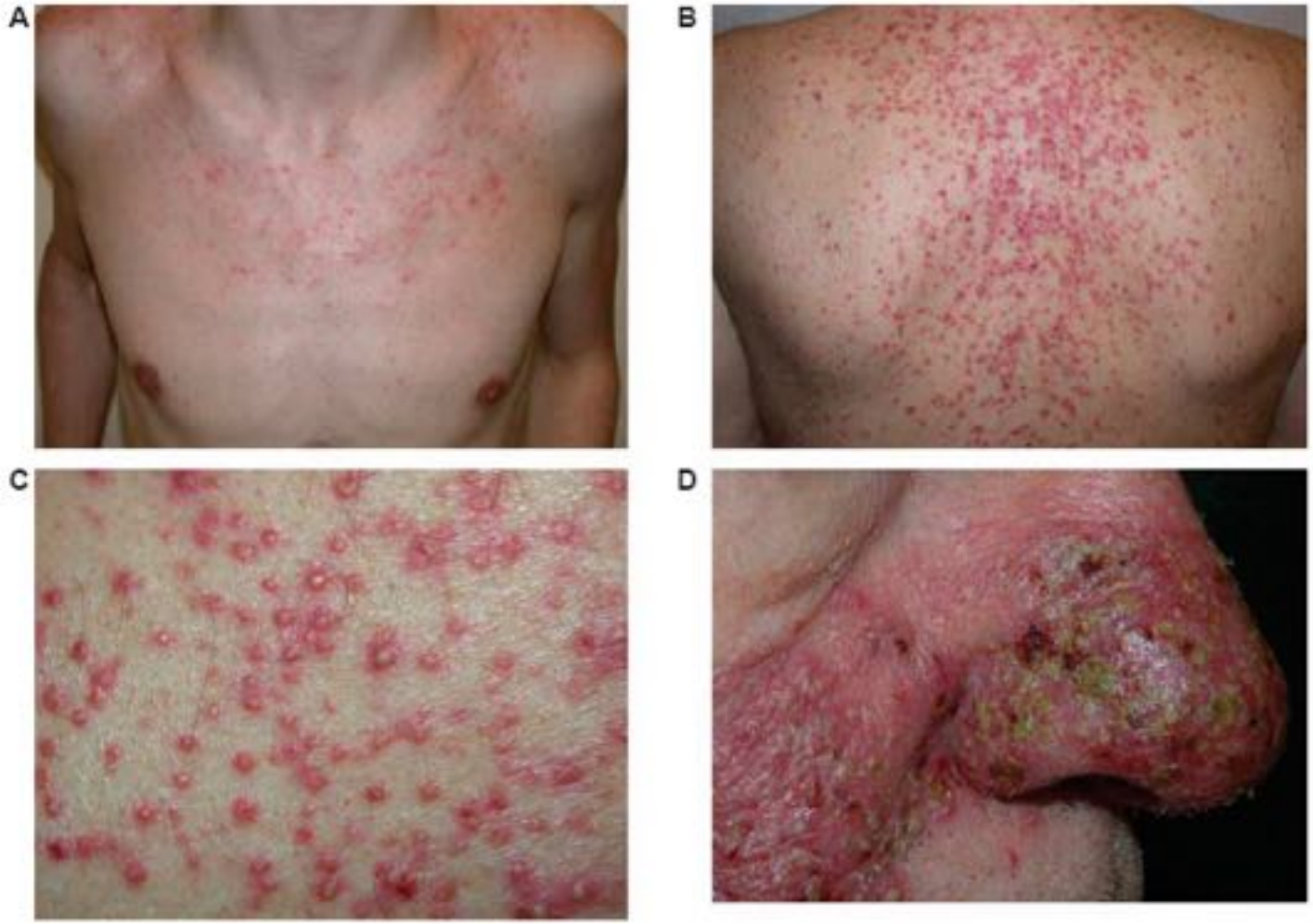
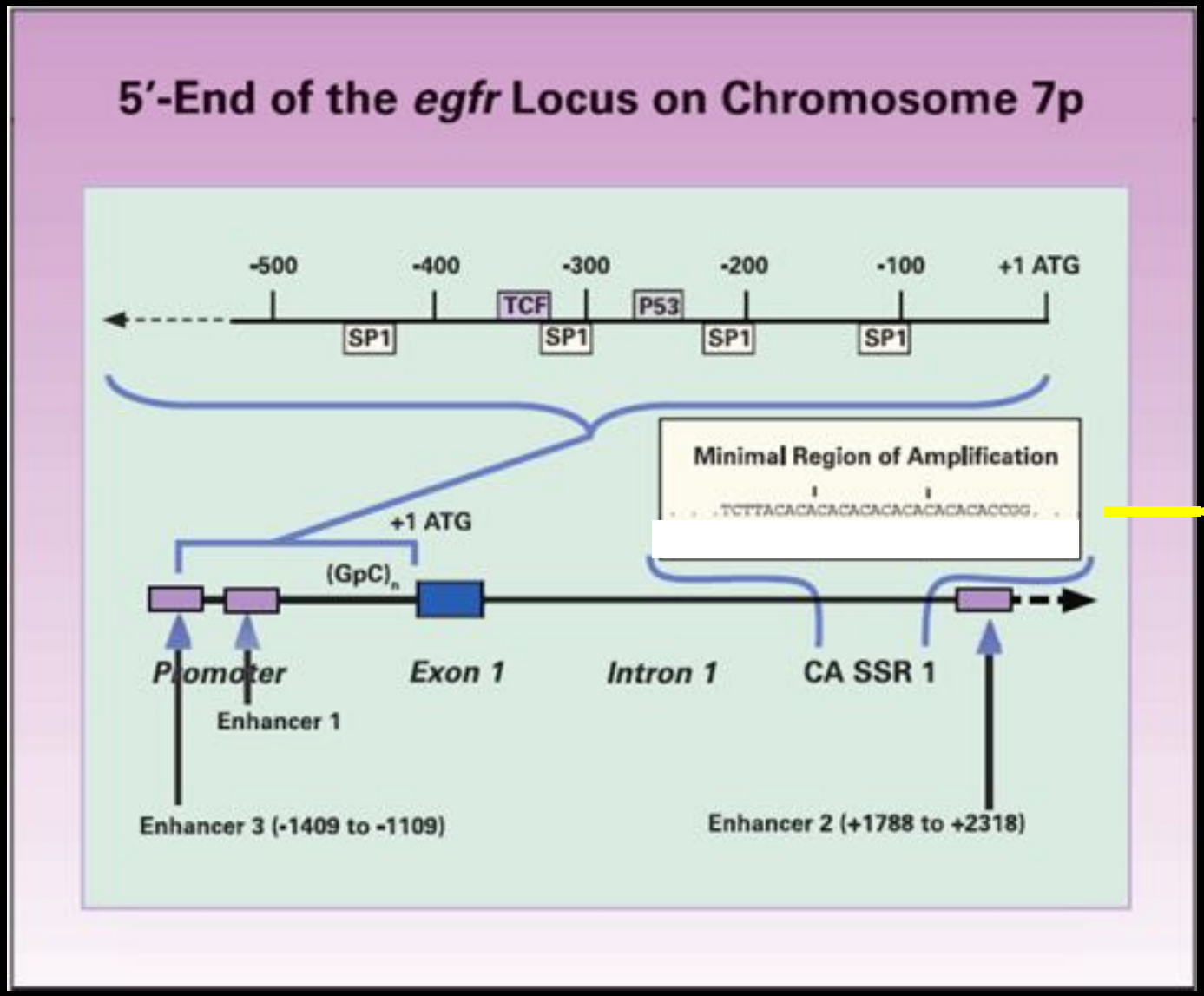


Figure 1. Acneiform eruption. (**A**) papular lesions on the chest, (**B**) V-shaped papulopustular eruption on the back, (**C**) close up of follicular pustules, (**D**) confluent pustules on the nose.

CA Simple Sequence Repeat 1



Short < 17 CA

Long ≥ 17 CA

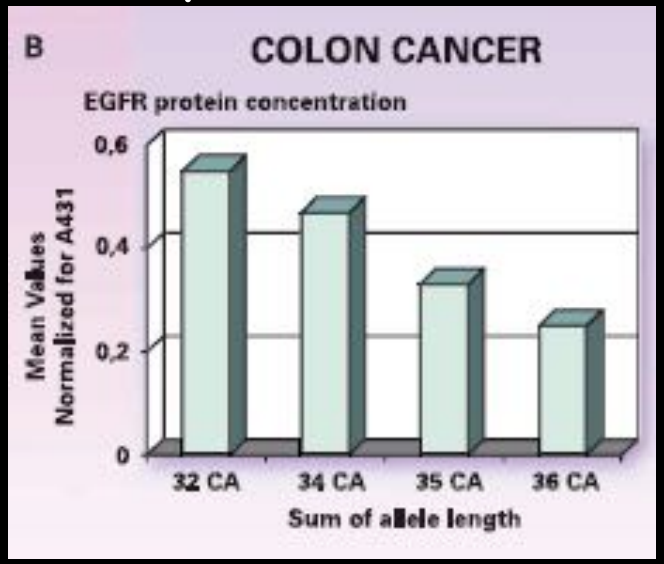
CA Simple Sequence Repeat 1

Minor numero di ripetiziomi CA: (Short < 17 CA)

⇧ EGFR gene trascription and EGFR expression

⇧ EGFR gene amplification

⇧ EGFR gene mutations



aumentata disponibilità del bersaglio

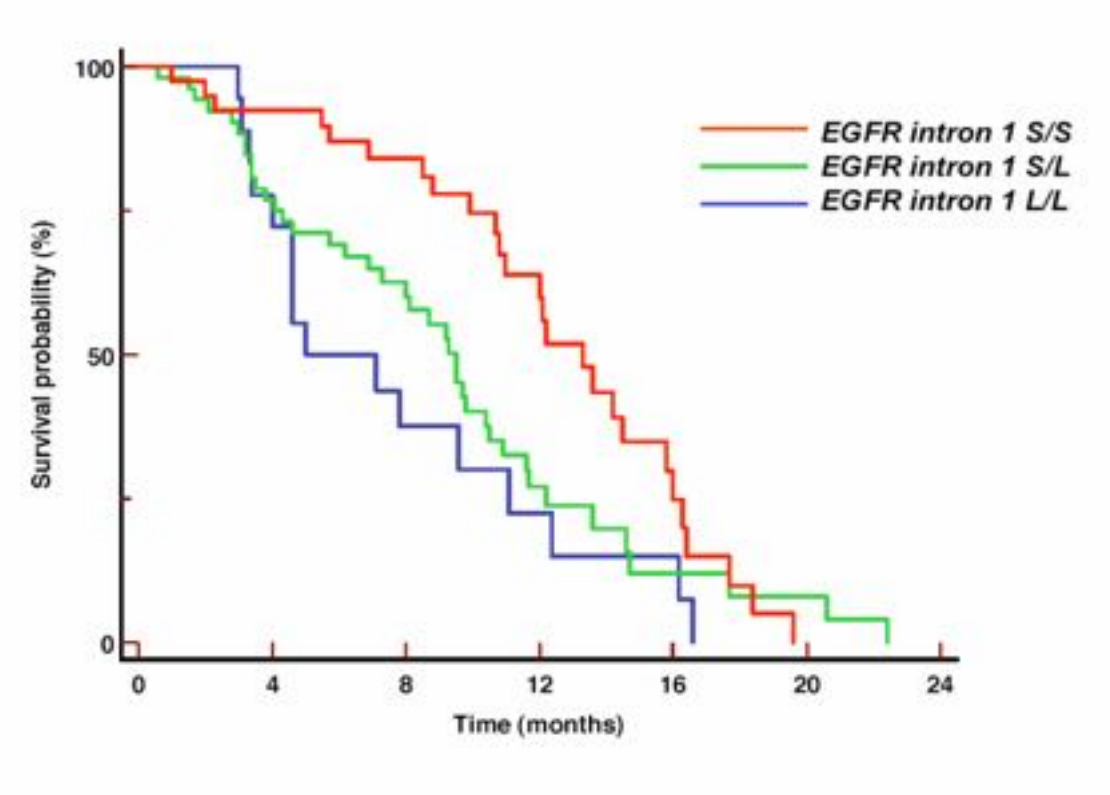
⇧ Response and Toxicity to EGFR-targeted therapy

VARIANTI GENETICHE CON POSSIBILE INFLUENZA SULL'ATTIVITA' DI FARMACI ANTI-EGFR

Site	Polymorphism	Effect
EGFR Intron 1	$(CA)_n$	The length of the $(CA)_n$ repeat variant $<(CA)_{17}$ or $\geq(CA)_{17}$ is used for classifying short (S) or long (L) alleles, respectively (see text). *EGFR* gene transcription activity declines with increasing number of CA repeats.
EGFR Exon 13	*497G>A*	The *497G>A* SNP causes attenuated functions in ligand binding, growth stimulation, TK activation, and induction of proto-oncogenes myc, fos, jun *in vitro*[5,10].
EGFR Promoter	*-216G>T*	The *-216G>T* SNP has been associated with variable EGFR expression *in vivo*
EGF 5'-UTR	*61A>G*	The *61A>G* SNP has been correlated with increased *in vitro* and *in vivo* EGF levels.
Cyclin-D1 Exon 4	*870A>G*	The *870 A>G* SNP influences *cyclin-D1* mRNA splicing, resulting in two different mRNA transcripts, *a* and *b*. The *A* allele preferentially encodes transcript *b*, which results in a longer cyclin-D1 half-life.
Fc-RIIa Exon 4	*131G>A*	The *131G>A* SNP was found to affect the receptors' affinities for the Fc of antibodies and probably ADCC efficiency.
Fc-RIIIa Exon 5	*158T>G*	The *158T>G* SNP was found affect the receptors' affinities for the Fc of antibodies and probably ADCC efficiency.

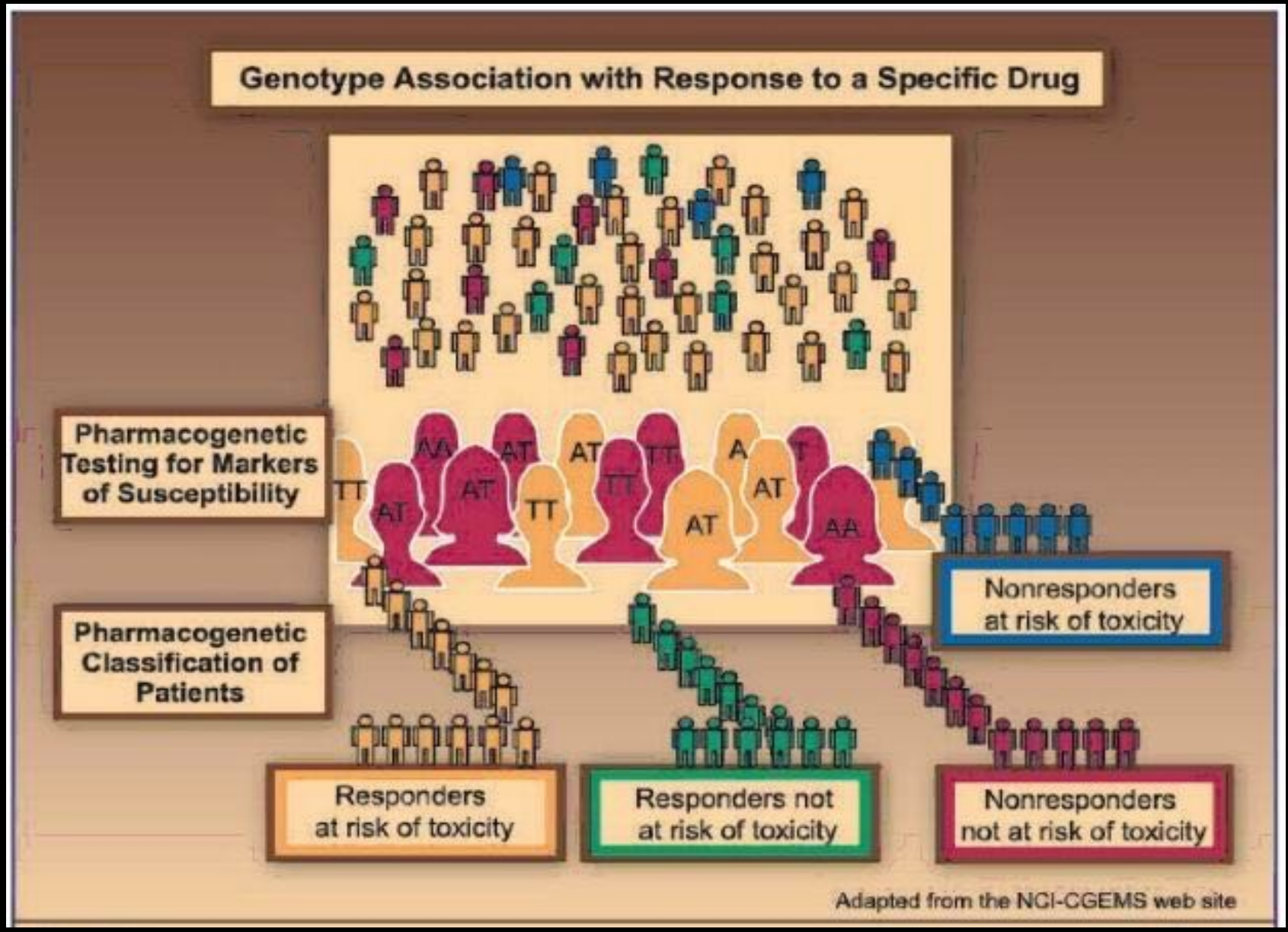
CA Simple Sequence Repeat 1

EGFR Intron 1	N patients	Skin toxicity G2-G3 (%)	CR and PR (%)	Median OS (months)
S/S	40	65	40	11.4
L/S	52	60	19	8.8
L/L	18	17	5	5.6

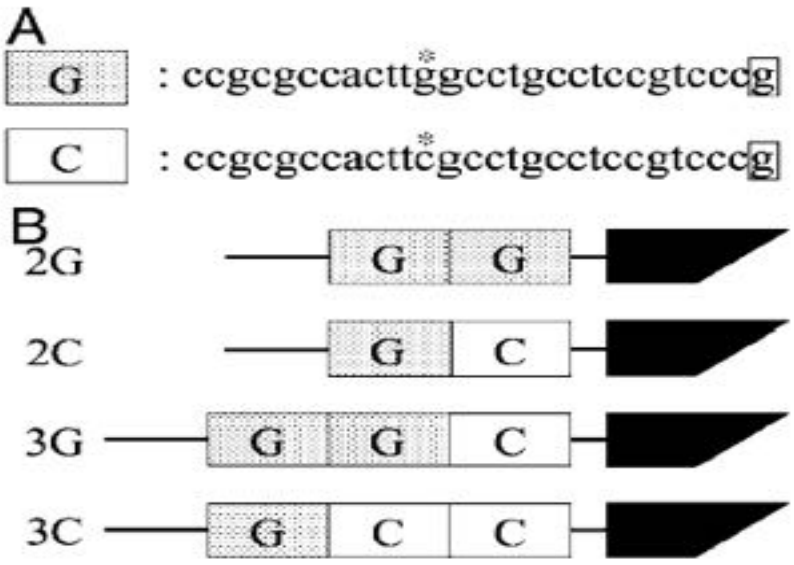


Short < 17 CA

Long ≥ 17 CA


Genotype Association with Response to a Specific Drug
Pharmacogenetic Testing for Markers of Susceptibility
Pharmacogenetic Classification of Patients
AA
AT
AT
AT
TT
TT
TT
AT
AT
TT
AT
A
T
AT
AA
Nonresponders at risk of toxicity
Responders at risk of toxicity
Responders not at risk of toxicity
Nonresponders not at risk of toxicity
Adapted from the NCI-CGEMS web site

Polimorfismi nella regione 5'-UTR di TS



3R allele associated with high mRNA translational efficiency

genotipi

2R/2R

2R/3R

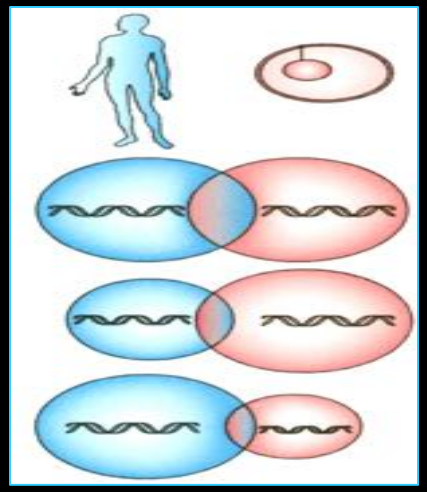
3R/3R

Effetto sfavorevole in un trattamento con 5-fluorouracile

1
Prelievo di sangue periferico

2
estrazione e amplificazione del DNA

DNA “genomico” (patrimonio di tutte le cellule dell’organismo)



e nella cellula tumorale?

TS 5’UTR 2R/3R

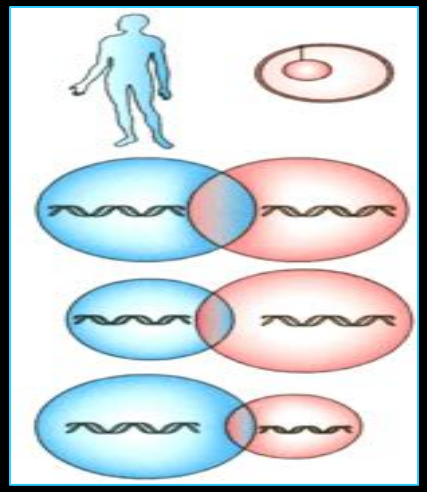
3
Sonde che distinguono una variante genetica

4
Definizione di Genotipo

1
Prelievo di sangue periferico

2
estrazione e amplificazione del DNA

DNA “genomico” (patrimonio di tutte le cellule dell’organismo)



TS 5’UTR 2R/3R

4
Definizione di Genotipo

3
Sonde che distinguono una variante genetica

e nella cellula tumorale?

mutazioni

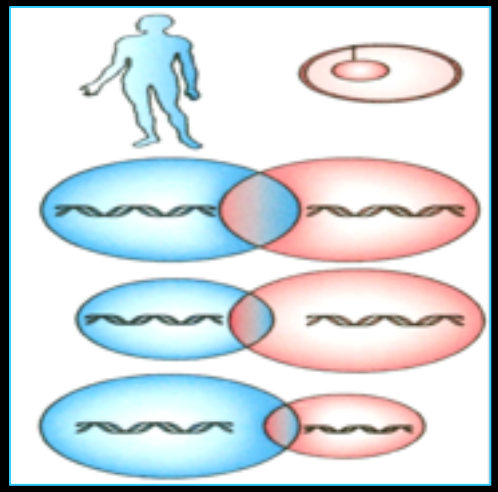
delezioni

fattori epigenetici

1 Prelievo di sangue periferico

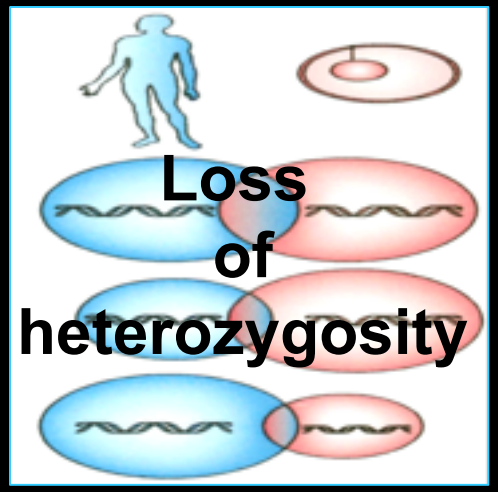
2 estrazione e amplificazione del DNA

DNA “genomico” (patrimonio di tutte le cellule dell’organismo)



TS 5’UTR 2R/3R

DNA “tumorale”



TS 5’UTR 2R/<u>null</u>

3 Sonde che distinguono una variante genetica

4 Definizione di Genotipo

Potenziale utilità dell'informazione farmacogenetica

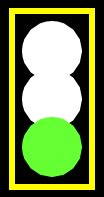
Predittività
di tossicità

Predittività
di efficacia

Potenziale utilità dell'informazione farmacogenetica

Predittività
di tossicità

Predittività
di efficacia



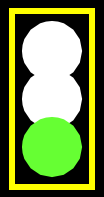
Influenza da fattori
genetici ed epigenetici
nel tumore

Mentre per la predizione di tossicità la determinazione di un genotico "costituzionale" da prelievo di sangue periferico può essere adeguata, per la predizione di risposta potrebbe essere opportuno lo studio con estrazione di DNA dal tumore

Potenziale utilità dell'informazione farmacogenetica

Predittività di tossicità

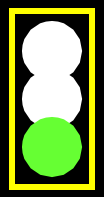
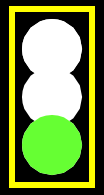
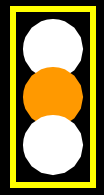
Predittività di efficacia



Influenza da fattori genetici ed epigenetici tumore-correlati

Conferme da studi prospettici con elevato numero di pazienti

Potenziale utilità dell'informazione farmacogenetica

Predittività di tossicità		Predittività di efficacia
	Influenza da fattori genetici ed epigenetici tumore-correlati	
	Conferme da studi prospettici con elevato numero di pazienti	
	Uso di combinazioni di chemioterapici	

Grazie per l'attenzione!!