UNIVERSITÉ PARIS DESCARTES

HEGP

Instituts thématiques Inserm

Institut national de la santé et de la recherche médicale

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

QuickTime™ et un décompresseur TIFF (non compressé) sont requis pour visionner cette image.

Recherche translationnelle

La pharmacogénétique:

une réalité hospitalière!

Ph. Beaune

European Medicines Agency

Definitions

Pharmacogénomique:

La recherche des variations caracteristiques de l'ADN et de l'ARN en relation avec la réponse aux médicaments

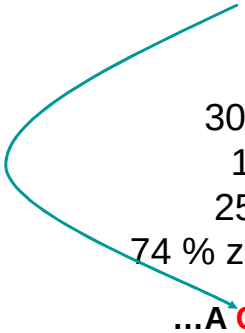
Pharmacogénétique:

L'infuence des variations de séquence en ADN sur la réponse aux médicaments

Réponse aux médicaments PK and PD

Séquençage du génome humain : 2003

...A T C G G A C T ...



3 10^9 pb
30 000 gènes
1 % exons
25 % introns
74 % zones répétitives

...A C C G G A C T ...

10 à 20 10^6 SNPs
Soit environ 1 SNP/1000 bases

Toxicité

Effets indésirables des médicaments

☛ **Question de santé publique**

USA:

- ~ 100 000 morts / an (4ème à 6ème cause, Lazarou 1998)

- Coût : 2 to 50 Milliards $

France:

- 3, 2 % hospitalizations

- Coût: 320 M€

☞ **50 % mauvaise utilisation**

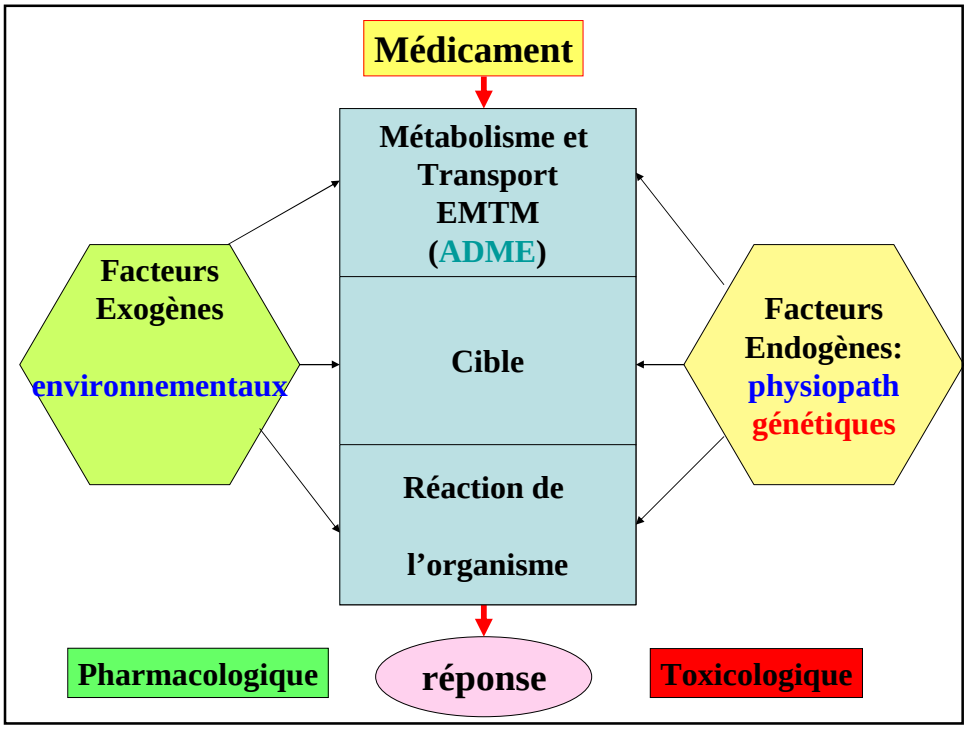
Efficacité des médicaments

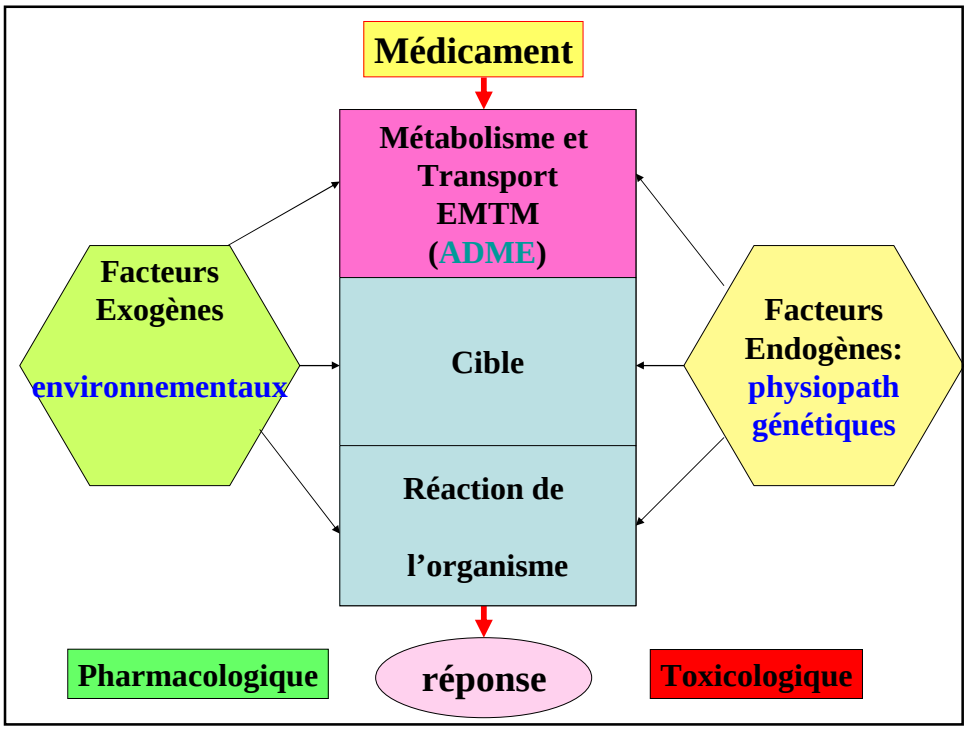
- très variable

- dose / PK (métabolisme et transport)

- charactérisation de la maladie et/ou de la cible ---> strategie thérapeutique

- ???





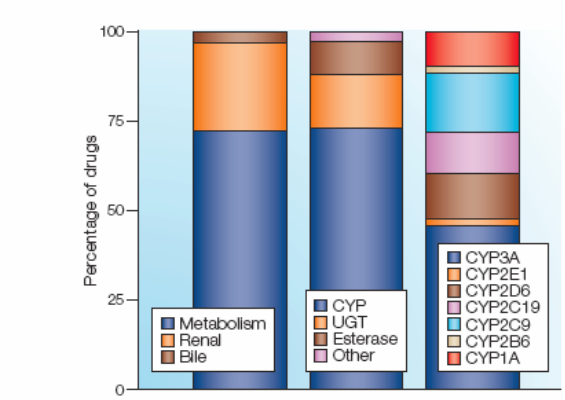
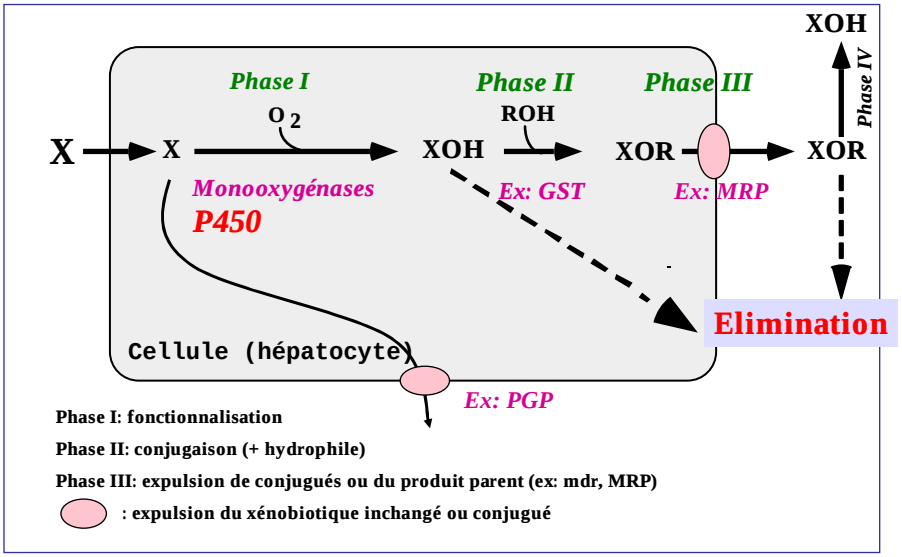


Figure 1 | **Routes of elimination of the top 200 most prescribed drugs in 2002.** Metabolism represents the listed clearance mechanism for ~73% of the top 200 drugs. Of the drugs cleared via metabolism, about three-quarters are metabolized by members of the cytochrome P450 (CYP) superfamily. For the CYP-mediated clearance mechanisms, the majority of drug oxidations (46%) were carried out by members of the CYP3A family; followed by 16% by CYP2C9; 12% for both CYP2C19 and CYP2D6; 9% for members of the CYP1A family; and 2% for both CYP2B6 and CYP2E1 (REF. 9). UGT, uridine diphosphate glucuronyl transferase.

From Wienkers and Heath 2008

Métabolisme des xénobiotiques



Les enzymes du métabolisme et du transport des médicaments (EMTM)

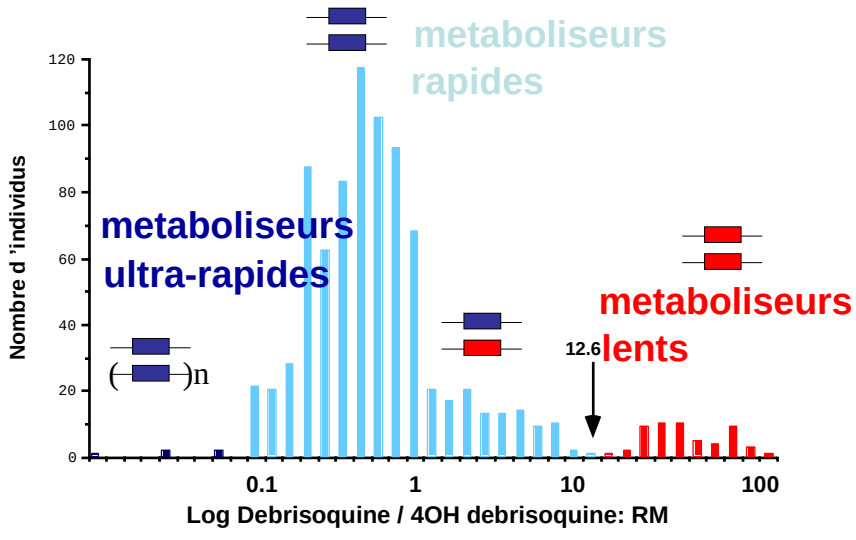
Propriétés communes:

- nombreuses isoformes
  spécificité relative et chevauchante
  redondantes
- peu efficace
- variabilité d'expression extrême
- polymorphismes génétiques fonctionnels avec fréquence élevée (%)
- substrats exogènes et endogènes

☞ importance dans réponse aux médicaments

REDONDANCE,

INTERACTIONS MEDICAMENTEUSES



Bertilsson and Dahl 1996

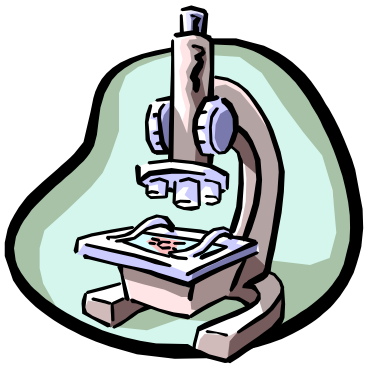
Phénotype:

- activité réelle
- quantifiable
- mise en oeuvre plus difficile
- variations (xénobiotiques, pathologies)
- pas permanent

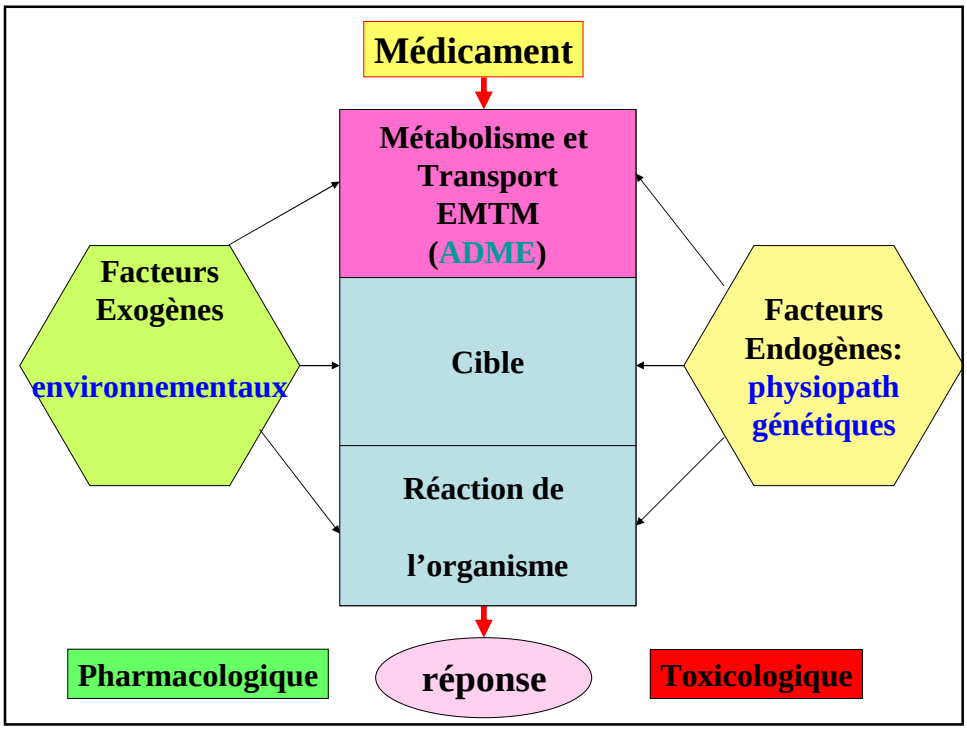
Génotype:

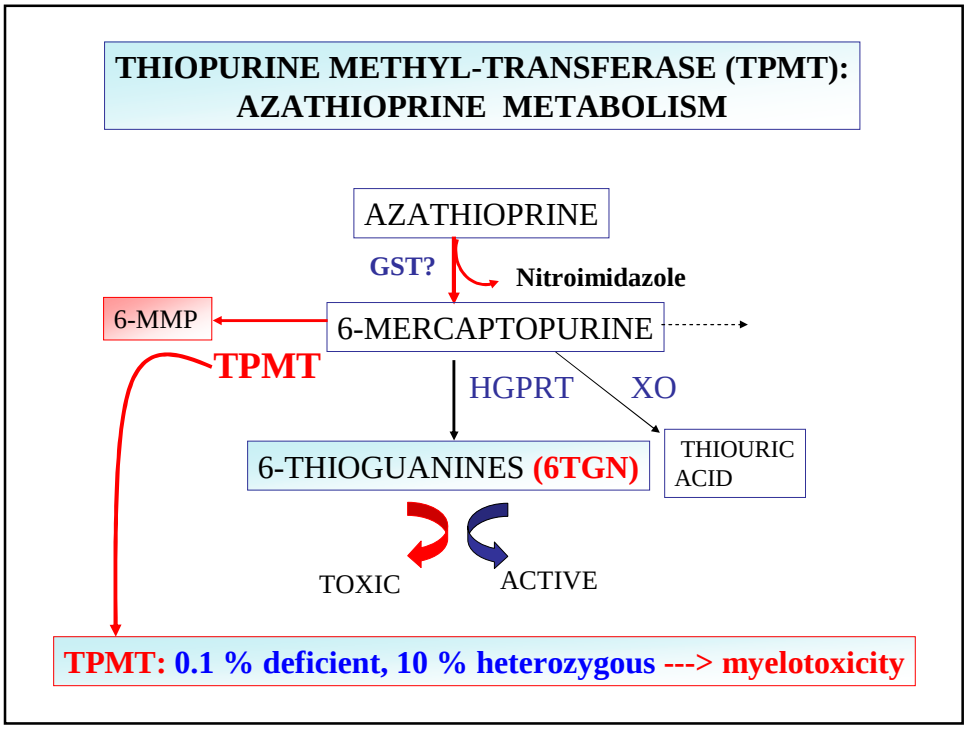
- facile
- permanent
- pas quantifiable
- pas activité réelle

Conséquences cliniques ??



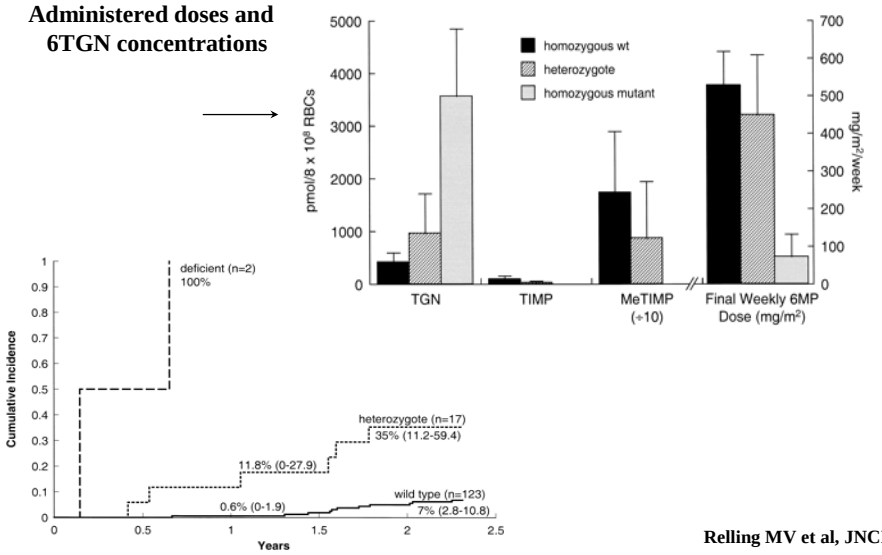
ou


Médicament
Métabolisme et Transport EMTM (ADME)
Facteurs Exogènes environnementaux
Cible
Facteurs Endogènes: physiopath génétiques
Réaction de l'organisme
Pharmacologique
réponse
Toxicologique

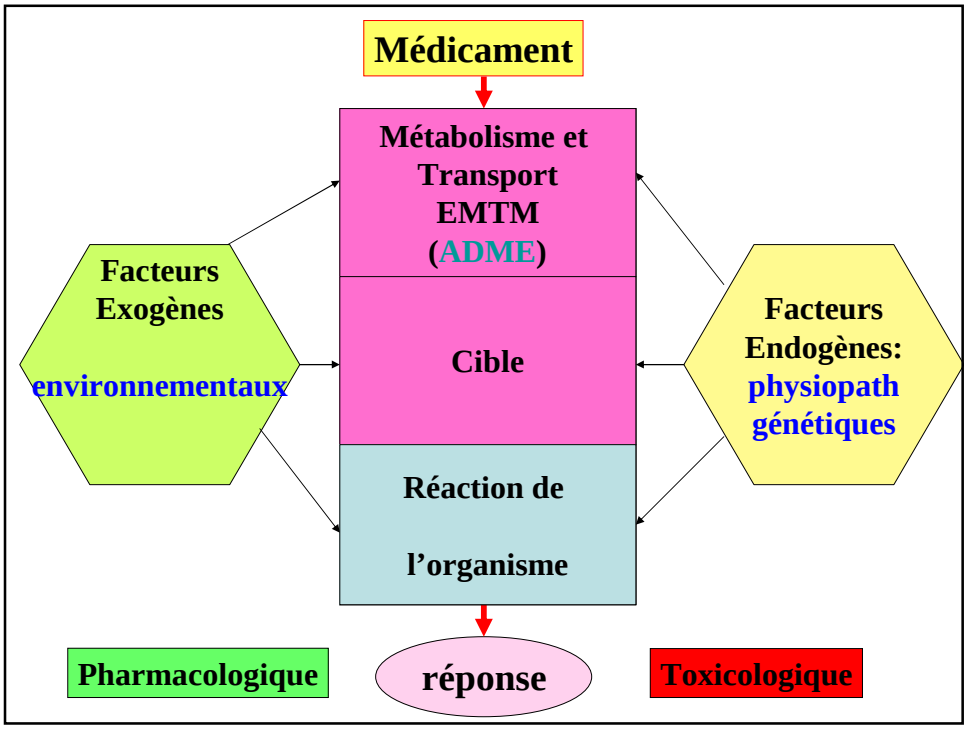

THIOPURINE METHYL-TRANSFERASE (TPMT): AZATHIOPRINE METABOLISM
AZATHIOPRINE
GST?
Nitroimidazole
6-MMP
6-MERCAPTOPURINE
TPMT
HGPRT
XO
6-THIOGUANINES (6TGN)
THIOURIC ACID
TOXIC
ACTIVE
TPMT: 0.1 % deficient, 10 % heterozygous ---> myelotoxicity

Dose Adjustment as a function of TPMT genotype

Administered doses and 6TGN concentrations



Relling MV et al, JNCI, 1999



AVK

600 000 patients traités

1ère cause de **iatrogénie médicamenteuse**

17 000 hospitalisations / an
et 4 800 décès

Réel problème de santé publique

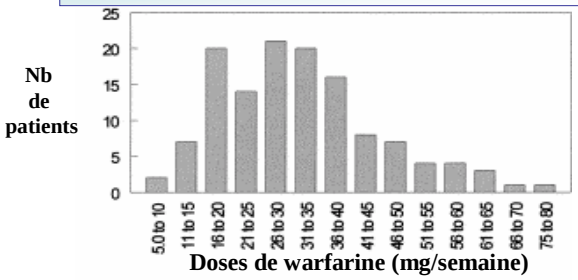
Patients âgés

Augmentation incidence des maladies TE

Vieillissement de la population

Données Afssaps, 2001

VARIABILITE DANS LA REPONSE



Observance du traitement

Alimentation (vit. K)

Situation physiopathologique

Interactions médicamenteuses

Facteurs génétiques

Risque hémorragique

HYPERSENSIBILITE

Risque thrombotique

RESISTANCE

VARIABILITE DE LA REPONSE

Apports en vitamine K

Apports moyens : 1 à 2,5 µg/kg/j
soit 50 à 250 µg/j (variations saisonnières**)**

Effet controversé alimentation/ traitement AVK

MANGER EQUILIBRE

Apports en vitamine K
Etat physiopathologique
Interactions médicamenteuses
Facteurs génétiques

VARIABILITE DE LA REPONSE

Etat physiopathologique

Diminution de 10% de la dose / décennie
(Redwood *et al*,1991 ; Siguret 2005)

Influence des comorbidités
(Penning-van Beest, Thromb Haemost, 2001)

Apports en vitamine K
Etat physiopathologique
Interactions médicamenteuses
Facteurs génétiques

VARIABILITE DE LA REPONSE
AVK et facteurs démographiques

Posologie à l'équilibre pour la warfarine

- **6 mg** chez les trentenaires
- **4 mg** chez les sujets de 70 ans (Redwood *et al*,1991)
- **3,5 mg** chez les patients de 85 ans (Siguret 2005)

Variable	Variation dose (%) 95% IC	p
Age (par décennie)	-8 (-5 à 11)	< 0,0001
Surface corporelle	+ 13 (+8 à +18)	< 0,0001
Sexe féminin	-7 (+1 à -15)	0,10

VARIABILITE DE LA REPONSE

Interactions médicamenteuses

Médicaments potentialisateurs : amiodarone, aspirine, antibiotiques

Médicaments inhibiteurs : rifampicine, phénobarbital, millepertuis

(Holbrook Arch Intern Med 2005)

Apports en vitamine K

Etat physiopathologique

Interactions médicamenteuses

Facteurs génétiques

VARIABILITE DE LA REPONSE

Facteurs génétiques

Cible pharmacologique

Métabolisme

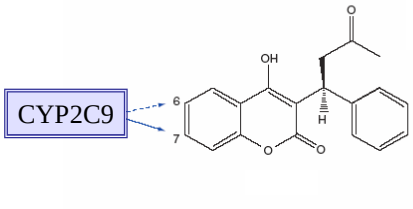
Apports en vitamine K

Etat physiopathologique

Interactions médicamenteuses

Facteurs génétiques

WARFARINE : Métabolisme et cible pharmacologique



Métabolisme hépatique

warfarine

VKORC1 = Vitamine K époxyde réductase (sous unité 1)

VKORC1

AVK

GGC=γ- glutamyl carboxylase

Vitamine K réduite

Cycle de la vitamine K

Vitamine K oxydée

Facteurs Vit K dépendants immatures

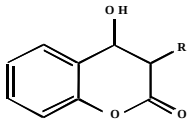
II VII IX X

GGC

Facteurs Vit K dépendants matures

METABOLISME DE LA WARFARINE

- métabolisme hépatique: voie des cytochromes P450 (CYP)
- warfarine: énantiomères R et S à activités différentes
- rôle majeur de l'isoforme CYP2C9: métabolites hydroxylés inactifs

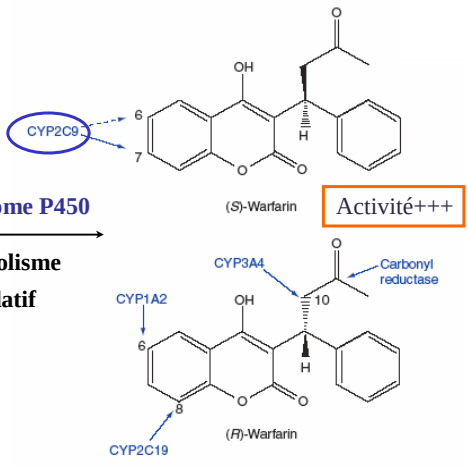


Anticoagulants Coumariniques

warfarine
acénocoumarol
phenprocoumone

cytochrome P450

Métabolisme oxydatif



VARIABILITE DE LA REPONSE AVK et facteurs génétiques

Métabolisme : CYP2C9

Variants alléliques	Fréquence Allélique	Activité
CYP2C9*1	0,79-0,86	100 %
CYP2C9*2 (Cys144Arg)	0,08-0,19	12 %
CYP2C9*3 (Leu359Ileu)	0,06-0,1	5 %

Populations caucasiennes

CYP2C9 et risque hémorragique

Allèle CYP2C9*2 et/ou CYP2C9*3 augmente le risque hémorragique

Génotype CYP2C9 ⟹ Facteur de risque pour la survenue de **complications hémorragiques**

CONSEQUENCES CLINIQUES DES POLYMORPHISMES GENETIQUES DU CYP2C9 LORS D'UN TRAITEMENT PAR AVK

(1) ➔ Risque hémorragique

Etude rétrospective incluant 185 patients traités au long cours par la warfarine

HR de saignement = **3.94;** IC 95%,1.29-12.04

Chez les sujets porteurs d'au moins un allèle variant (CYP2C9*2 or *3)

Higashi et al. JAMA 2002; 287:1690-1698

HR : Hazard ratio, calculé pendant la phase d'initiation (90 jours)

CYP2C9 et posologie à l'équilibre

Etude	Effectif (n)	CYP2C9 *1/*1	CYP2C9 *1/*2	CYP2C9 *2/*2	CYP2C9 *1/*3	CYP2C9 *2/*3	CYP2C9 *3/*3
Furuya (1995)	94	4,7mg	3,8mg *(-19%)*	nd	nr	nr	nr
Aithal (1999)	52	4,25mg	3,5mg *(-18%)*	3,5mg *(-18%)*	2,5mg *(-40%)*	nd	nd
Margaglione (2000)	180	6,7mg	5,2mg *(-22%)*	5,2mg *(-22%)*	3,8mg *(-43%)*	1,8mg *(-73%)*	nd
Taube (2000)	561	5,01mg	4,31mg *(-14%)*	3,04mg *(-40%)*	3,97mg *(-21%)*	4,09mg *(-18%)*	nd
Higashi (2002)	185	5,6mg	4,9mg *(-13%)*	4,07mg *(-27%)*	3,3mg *(-41%)*	2,03mg *(-59%)*	1,06mg *(-71%)*
Loebstein (2001)	156	6,5mg	5,2mg *(-20%)*	nd	3,3mg *(-49%)*	3,3mg *(-49%)*	nd
Sconce (2005)	297	4,1 mg	3,6 mg *(-12%)*	1,9 mg *(-54%)*	2,7 mg *(-34%)*	1,6 mg *(-61%)*	1,6 mg *(-61%)*

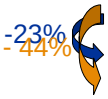
FACTEURS DE VARIABILITE DE LA REPONSE

Cible pharmacologique : VKORC1

« A polymorphism in VKORC1 gene is associated with an inter individual variability in the dose-anticoagulant effect of warfarin »

D'Andrea, Blood. 2004

Relation entre SNP 1173C>T (intron 1) et dose de warfarine à l'équilibre



VKORC1	DOSE	95% CI	p	n PATIENTS
CC	**6,2**	5-7,3	Ref	54
CT	**4,8**	3,8-5,9	0,002	69
TT	**3,5**	2,2-4,8	0,001	24

CYP2C9 **explique 21% de la variabilité**
VKORC1 **explique 13% de la variabilité**

ANALYSE HAPLOTYPIQUE DE VKORC1 EN RELATION AVEC LA REPONSE PHARMACOLOGIQUE A L'ACENOCOUMAROL

- Etude de 220 **volontaires sains** : prise unique de **4 mg d'acénocoumarol**
- Mesure de la **variation du facteur VII** J0 et 24H après
- Base de données => SNPs : reconstruction des haplotypes

SNPs						Effet haplotypique	
-4931T> C	-4451C> A	-2659G>C	-1639G>A	497T>G	Fréquence	Variation du Factor VII (%) (95% CI)	
C	C	G	**A**	G	0.27	**18.9 (16.7-21.1)**	**18.9 (16.9-20.9)**
C	C	G	**A**	T	0.12	**18.6 (14.0-23.2)**	
T	C	G	**A**	G	0.019	**19.2 (7.5-30.9)**	
T	C	G	**G**	T	0.23	34.3 (32.4-37.2)	36.0 (34.2-37.8)
T	A	C	**G**	T	0.21	36.8 (33.6-39.9)	
T	A	G	**G**	T	0.11	37.6 (32.8-42.3)	
C	C	G	**G**	T	0.017	41.5 (22.3-60.7)	

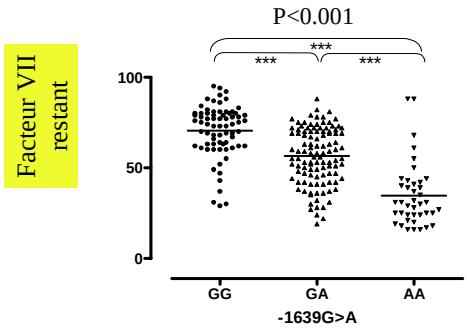
7 haplotypes: SNP -**1639G>A** =« marqueur des haplotypes »

Collaboration avec Pr Laurent Becquemont, CIC Saint-Antoine

FACTEURS GENETIQUES CYP2C9 ET VKORC1 ET REPONSE PHARMACOLOGIQUE A L'ACENOCOUMAROL

Etude chez 220 volontaires sains recevant une dose orale unique d'AC (4mg):
Mesure de la variation du facteur VII avant et 24H après la prise

Identification d'un polymorphisme VKORC1 modulant la réponse



Génotype VKORC1

Part de la variabilité génétique: **50%**

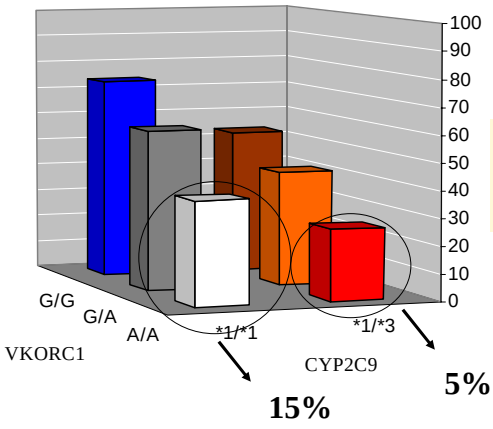
CYP2C9: 13%

VKORC1: 37%

Bodin L et al, Blood 2005

http://www.warfarindosing.org

EFFET ADDITIF DE VKORC1 –1639G>A ET CYP2C9*3 SUR LA REPONSE A L'ACENOCOUMAROL



Variation Facteur VII (%)

Les sujets d'origine Asiatique sont plus sensibles aux AVK

Du fait d'une fréquence double du polymorphisme VKORC1

	Chinois n=390	Occidentaux n=222
- 1639 allèle A	0,92 (0,89-0,95)	0.42 (0,35-0,49)
- 1639 allèle G	0,08 (0,05-0,11)	0,58 (0,51-0,55)

Laramendi, B Clin Pharm Tox 2006

Risque surdosage avec OA VKORC1 et CYP2C9

	VKORC1 + CYP2C9
RR	12
Sensibilité	33 %
Spécificité	92 %
PPV	80 %
NPV	58 %

Quteinieh et coll. 2005 Thromb Haem.

Blood Cells, Molecules, and Diseases
journal homepage: www.elsevier.com/locate/ybcmd

Influence of CYP2C9 and VKORC1 on warfarin response during initiation of therapy☆

N.A. Limdi [a,□], H. Wiener [b], J.A. Goldstein [c], R.T. Acton [d], T.M. Beasley [e]
[a] Department of Neurology, University of Alabama at Birmingham, 1719 6thAvenue South, CIRC-312, Birmingham AL 35294-0021, USA
[b] Department of Epidemiology, University of Alabama at Birmingham, AL, USA
[c] Laboratory of Pharmacology and Chemistry, National Institute of Environmental Health Sciences, University of Alabama at Birmingham, AL, USA
[d] Department of Microbiology, University of Alabama at Birmingham, AL, USA
[e] Department of Biostatistics, Section on Statistical Genetics, University of Alabama at Birmingham, AL, USA

Possession of variant VKORC1 (± variant CYP2C9) genotype was associated with a more rapid attainment of target INR and higher frequency of dose adjustments. Patients possessing variant genotypes spent less time in target range. However adjustment for rate of INR increase rendered the association non-significant. European Americans (but not African Americans) possessing variant VKORC1 (± variant CYP2C9) genotype had a higher risk of over-anticoagulation. Neither CYP2C9 nor VKORC1 influenced the risk of minor hemorrhage. CYP2C9 and VKORC1 explained 6.3% of the variance in dose change over the first 30 days of therapy demonstrating that the usefulness of genotype-guided dosing may extend beyond first day of therapy.
Conclusion: The benefit of genotype-based dose prediction may extend beyond first few days of therapy. Whether genotype-guided dosing will decrease the risk of over-anticoagulation, improve anticoagulation control and most importantly improve outcomes for chronic warfarin users remains to be proven.

The new england journal of medicine
established in 1812 february 19, 2009 vol. 360 no. 8

Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data

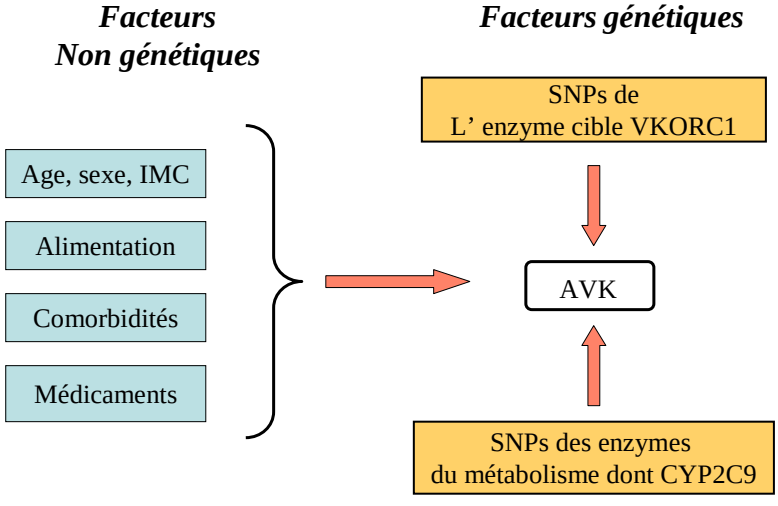
The International Warfarin Pharmacogenetics Consortium*

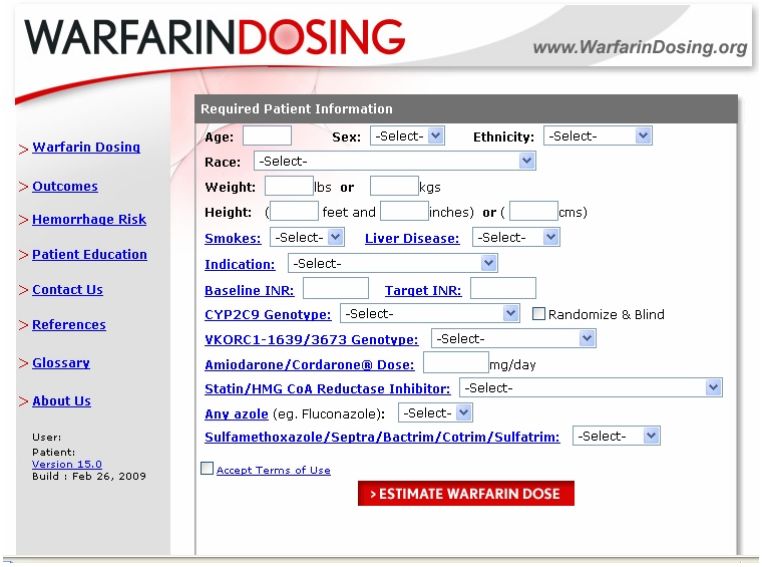
The use of a pharmacogenetic algorithm for estimating the appropriate initial dose of warfarin produces recommendations that are significantly closer to the required stable therapeutic dose than those derived from a clinical algorithm or a fixed-dose approach. The greatest benefits were observed in the 46.2% of the population that required 21 mg or less of warfarin per week or 49 mg or more per week for therapeutic anticoagulation.

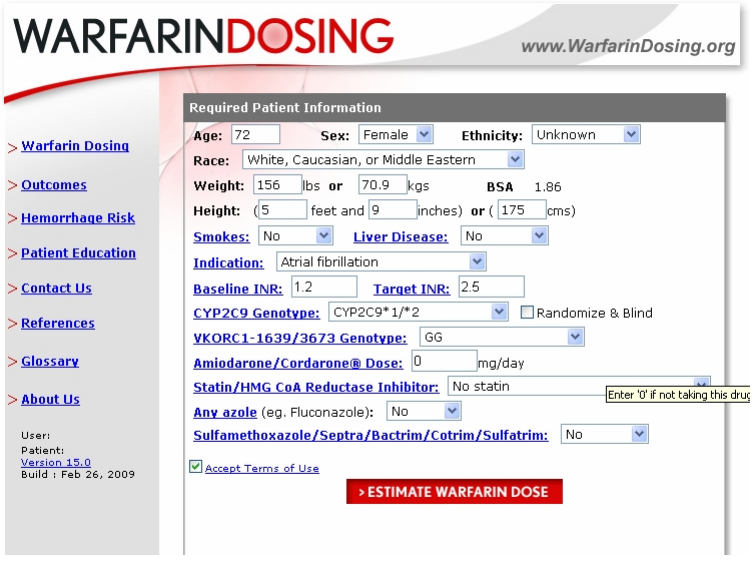
Conclusion

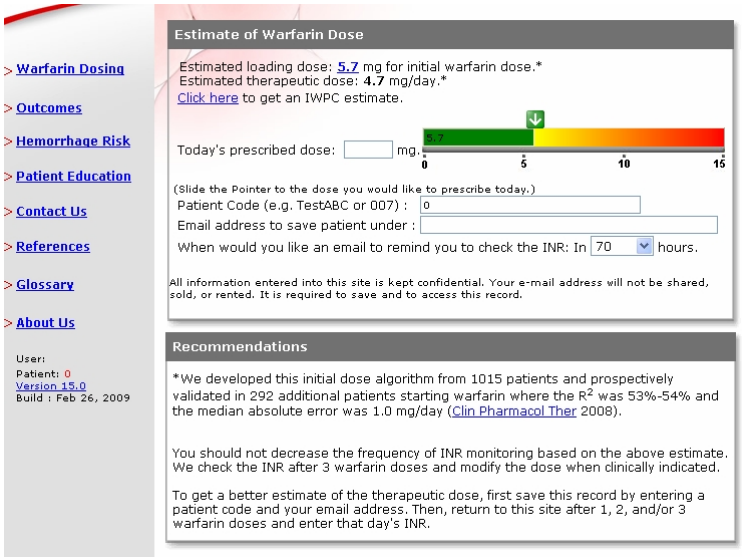
The use of a pharmacogenetic algorithm for estimating the appropriate initial dose of warfarin produces recommendations that are significantly closer to the required stable therapeutic dose than those derived from a clinical algorithm or a fixed-dose approach. The greatest benefits were observed in the 46.2% of the population that required 21 mg or less of warfarin per week or 49 mg or more per week for therapeutic anticoagulation.

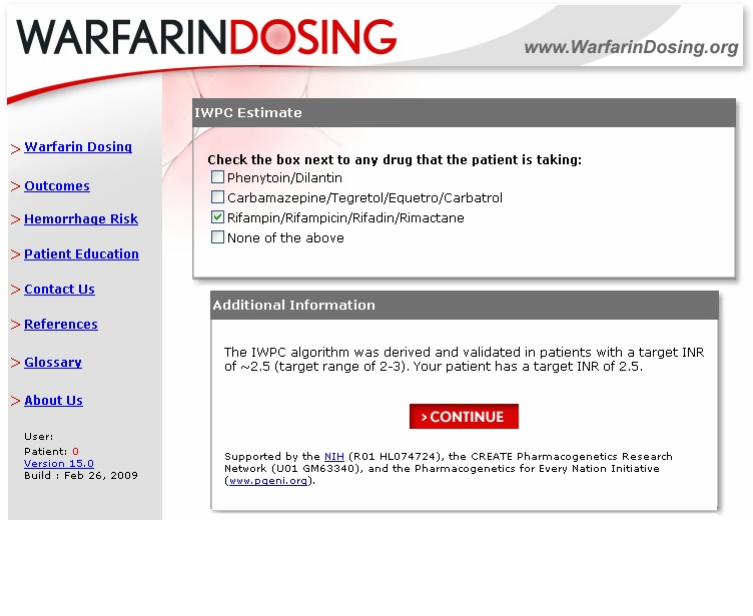
VARIABILITE DE LA REPONSE

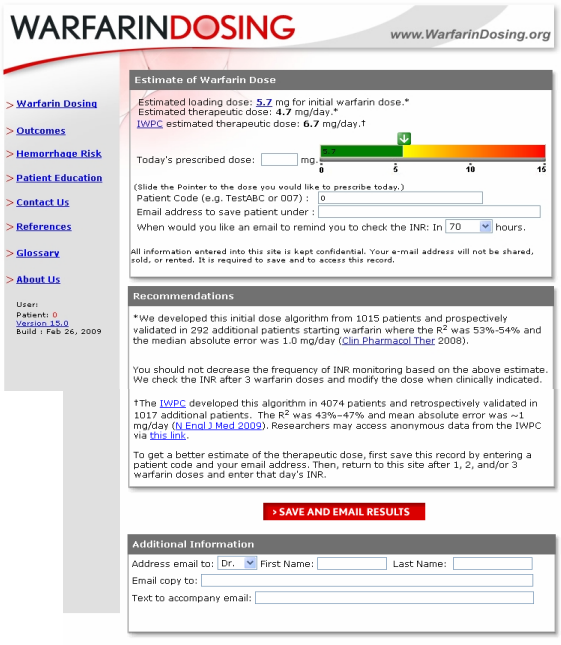



WARFARINDOSING
www.WarfarinDosing.org
Warfarin Dosing
Outcomes
Hemorrhage Risk
Patient Education
Contact Us
References
Glossary
About Us
User:
Patient:
Version 15.0
Build : Feb 26, 2009
Required Patient Information
Age:
Sex: -Select-
Ethnicity: -Select-
Race: -Select-
Weight: lbs or kgs
Height: (feet and inches) or (cms)
Smokes: -Select-
Liver Disease: -Select-
Indication: -Select-
Baseline INR:
Target INR:
CYP2C9 Genotype: -Select-
Randomize & Blind
VKORC1-1639/3673 Genotype: -Select-
Amiodarone/Cordarone® Dose: mg/day
Statin/HMG CoA Reductase Inhibitor: -Select-
Any azole (eg. Fluconazole): -Select-
Sulfamethoxazole/Septra/Bactrim/Cotrim/Sulfatrim: -Select-
Accept Terms of Use
> ESTIMATE WARFARIN DOSE


WARFARINDOSING
www.WarfarinDosing.org
Warfarin Dosing
Outcomes
Hemorrhage Risk
Patient Education
Contact Us
References
Glossary
About Us
User:
Patient:
Version 15.0
Build : Feb 26, 2009
Required Patient Information
Age: 72
Sex: Female
Ethnicity: Unknown
Race: White, Caucasian, or Middle Eastern
Weight: 156 lbs or 70.9 kgs BSA 1.86
Height: (5 feet and 9 inches) or (175 cms)
Smokes: No
Liver Disease: No
Indication: Atrial fibrillation
Baseline INR: 1.2
Target INR: 2.5
CYP2C9 Genotype: CYP2C9*1/*2
Randomize & Blind
VKORC1-1639/3673 Genotype: GG
Amiodarone/Cordarone® Dose: 0 mg/day
Statin/HMG CoA Reductase Inhibitor: No statin
Enter '0' if not taking this drug
Any azole (eg. Fluconazole): No
Sulfamethoxazole/Septra/Bactrim/Cotrim/Sulfatrim: No
Accept Terms of Use
> ESTIMATE WARFARIN DOSE


> Warfarin Dosing
> Outcomes
> Hemorrhage Risk
> Patient Education
> Contact Us
> References
> Glossary
> About Us
User:
Patient: 0
Version 15.0
Build : Feb 26, 2009
Estimate of Warfarin Dose
Estimated loading dose: 5.7 mg for initial warfarin dose.*
Estimated therapeutic dose: 4.7 mg/day.*
Click here to get an IWPC estimate.
Today's prescribed dose: mg.
5.7
0
5
10
15
(Slide the Pointer to the dose you would like to prescribe today.)
Patient Code (e.g. TestABC or 007) :
0
Email address to save patient under :
When would you like an email to remind you to check the INR: In 70 hours.
All information entered into this site is kept confidential. Your e-mail address will not be shared, sold, or rented. It is required to save and to access this record.
Recommendations
*We developed this initial dose algorithm from 1015 patients and prospectively validated in 292 additional patients starting warfarin where the R2 was 53%-54% and the median absolute error was 1.0 mg/day (Clin Pharmacol Ther 2008).
You should not decrease the frequency of INR monitoring based on the above estimate. We check the INR after 3 warfarin doses and modify the dose when clinically indicated.
To get a better estimate of the therapeutic dose, first save this record by entering a patient code and your email address. Then, return to this site after 1, 2, and/or 3 warfarin doses and enter that day's INR.


WARFARINDOSING
www.WarfarinDosing.org
> Warfarin Dosing
> Outcomes
> Hemorrhage Risk
> Patient Education
> Contact Us
> References
> Glossary
> About Us
User:
Patient: 0
Version 15.0
Build : Feb 26, 2009
IWPC Estimate
Check the box next to any drug that the patient is taking:
Phenytoin/Dilantin
Carbamazepine/Tegretol/Equetro/Carbatrol
Rifampin/Rifampicin/Rifadin/Rimactane
None of the above
Additional Information
The IWPC algorithm was derived and validated in patients with a target INR of ~2.5 (target range of 2-3). Your patient has a target INR of 2.5.
> CONTINUE
Supported by the NIH (R01 HL074724), the CREATE Pharmacogenetics Research Network (U01 GM63340), and the Pharmacogenetics for Every Nation Initiative (www.pgeni.org).



RESISTANCE ET AVK

Mutations VKORC1 et « résistance » aux AVK

- INR cible atteint ou non: posologies > 2-fois dose standard
- Traitements associés (interactions), questionnaire alimentaire

6/19 sujets porteurs de mutations VKORC1:

- 1 patient (50 mg warfarine/j, INR=1.2) : **Leu128 Arg** (exon 3)
- 2 patients (20 and 35 mg warfarine/j, INR=3) :**Val66Met** (exon 1)
- 1 patient (14 mg warfarine/j, INR=2**): Asp36Tyr** (exon 1)
- 1 patient (60 mg fluindione/j, INR=1.3): **Val54Leu** (exon 1)
- 1 patient (20 mg warfarine/j, INR=1.2) : **Ala26Pro** (exon 1)

mutations VKORC1 retrouvées dans 1/3 cas

Bodin et al, J Thromb Haemost 2005, 2008

Conclusion

Biomarqueur prédictif

- **dose équilibre**
- **temps équilibration**
- **stabilité**
- **INR hors cible**
- **limité, autres facteurs**
- **algorithme**
- **validation**

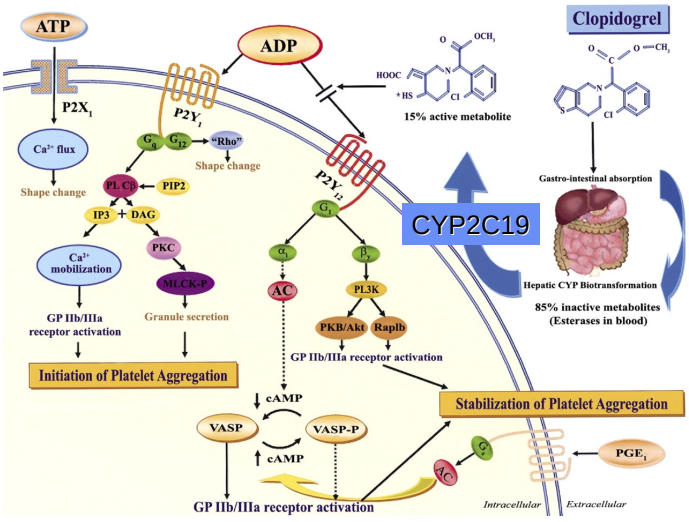
Biomarqueur explicatif

- **VKORC1 résistance**

Simple, peu coûteux, rapide, Consentement, remboursement

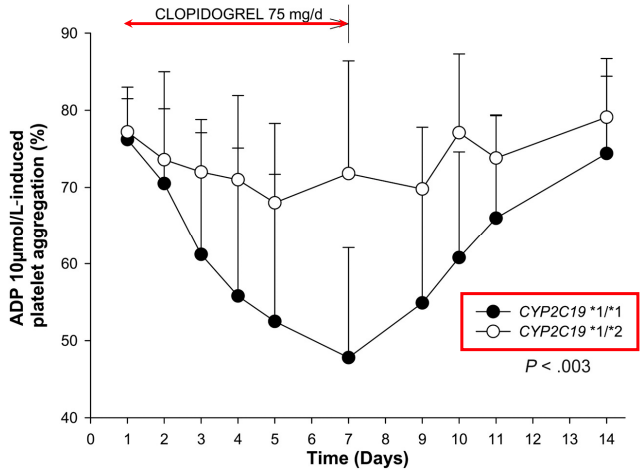
Pharmacogénétique du clopidogrel (PLAVIX®)

CLOPIDOGREL: mécanisme d'action



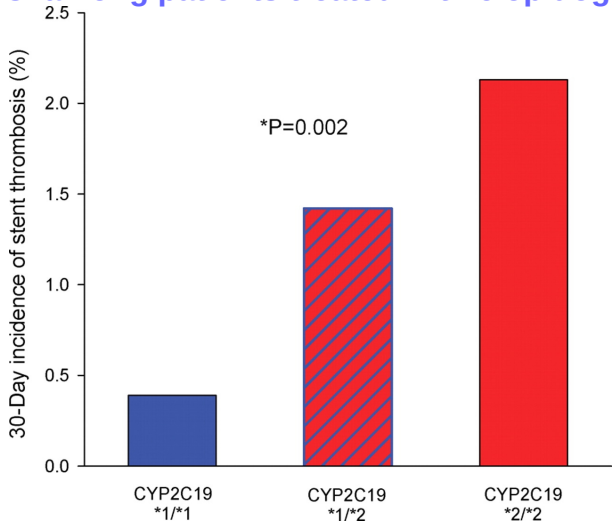
Angiolillo, D. J. et al. J Am Coll Cardiol 2007;49:1505-1516

Evolution de l'aggrégation plaquettaire *ex vivo* en réponse à 10 M ADP en fonction du génotype CYP2C19



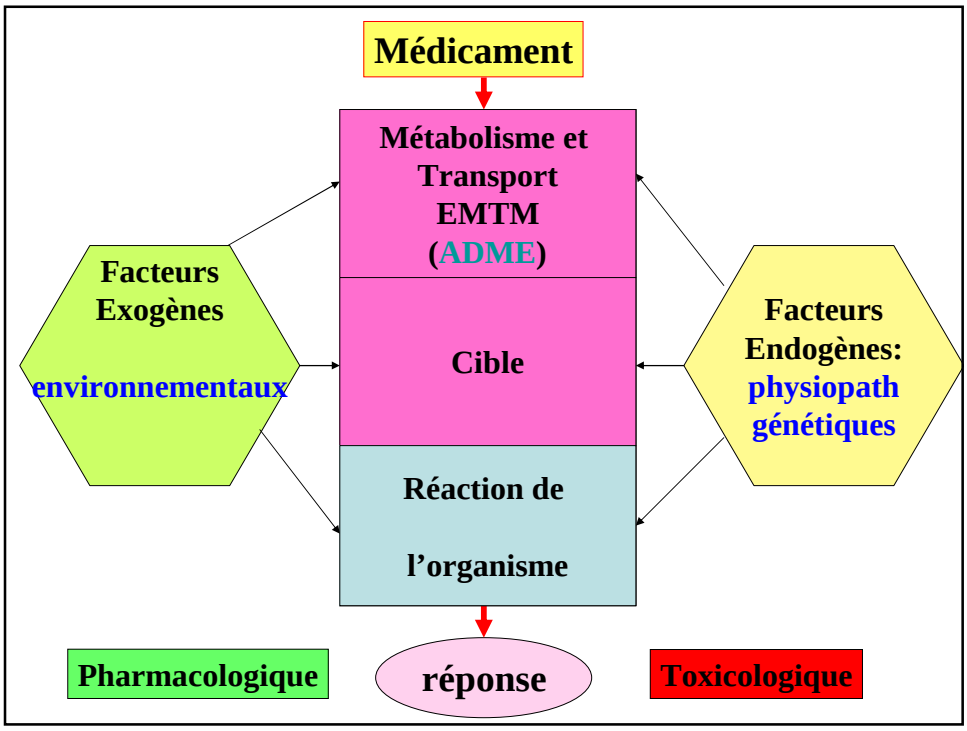
Hulot, J.-S. et al. Blood 2006;108:2244-2247

CYP2C19 genetic polymorphism and Stent thrombosis after PCI among patients treated with clopidogrel

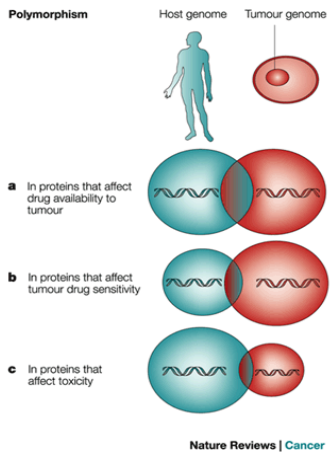


Sibbing, D. et al. Eur Heart J 2009 30:916-922; doi:10.1093/eurheartj/ehp041

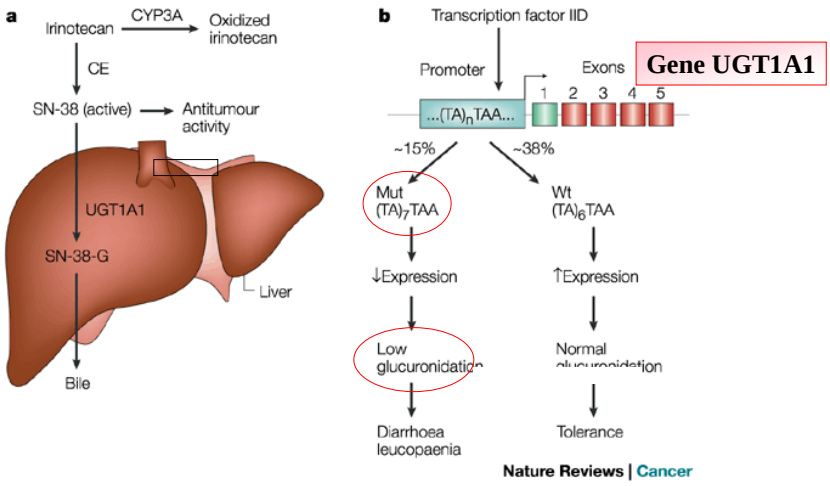
European Heart Journal



Variabilité génétique en cancérologie : 2 composantes « hôte et tumeur »

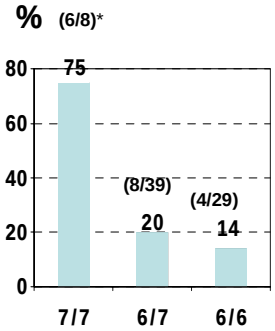


Irinotecan (CPT-11): Prédiction de la toxicité



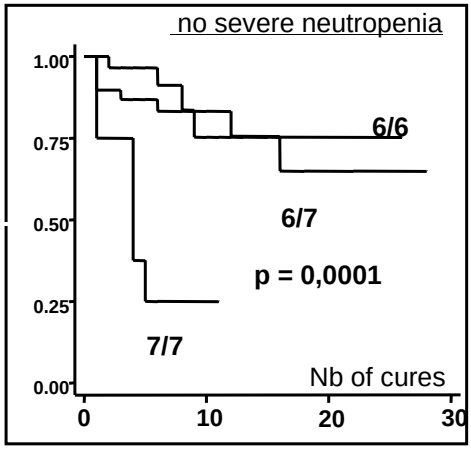
Neutropenia (5FU / Irinotecan) and *UGT1A1* genotype

N = 76 patients (HEGP)



p = 0,001

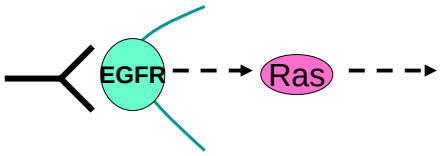
Neutropenia Grade 3/4



*: toxic death in a pt with a 7/7 génotype

Nb of cures median (7/7) : 4

KRAS STATUS AND RESPONSE TO CETUXIMAB

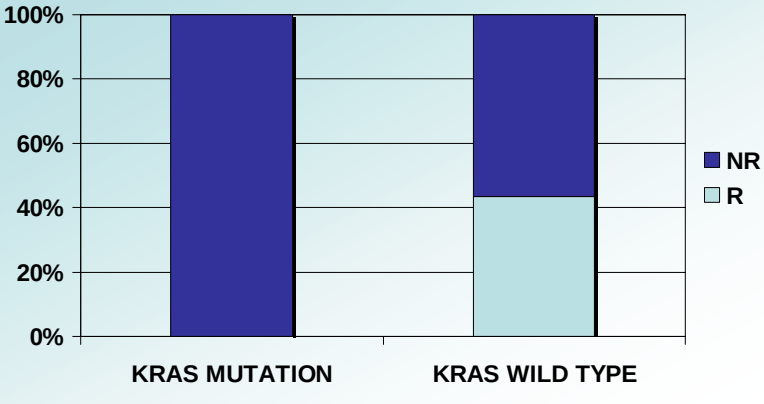


1st series
Lievre Cancer Res 2006
Among this series
25 was treated by Cetuximab according to French AMM

Validation series
89 patients
All treated by Cetuximab according to French AMM

Pooled series for mutivariate analysis

Results (Overall series - 114 cases)



(31.7% CI95% [22-40%]

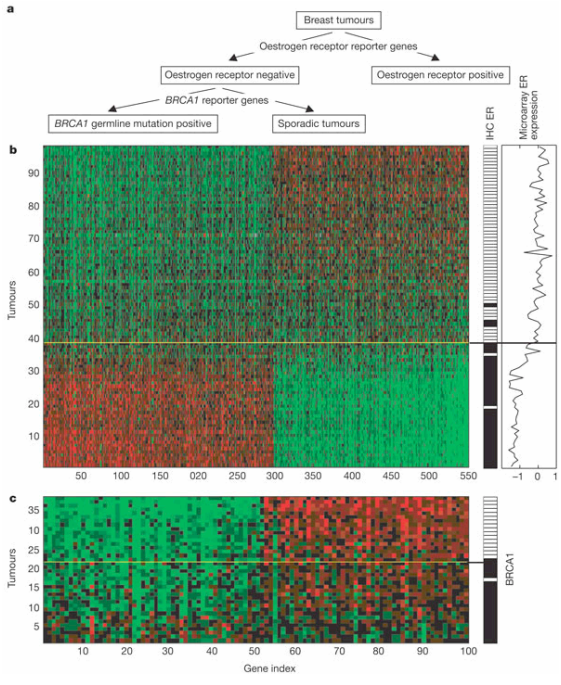
Pearson chi2(1) = 22.3615 Pr $<2.10^{-6}$

Transcriptome des cellules cancéreuses

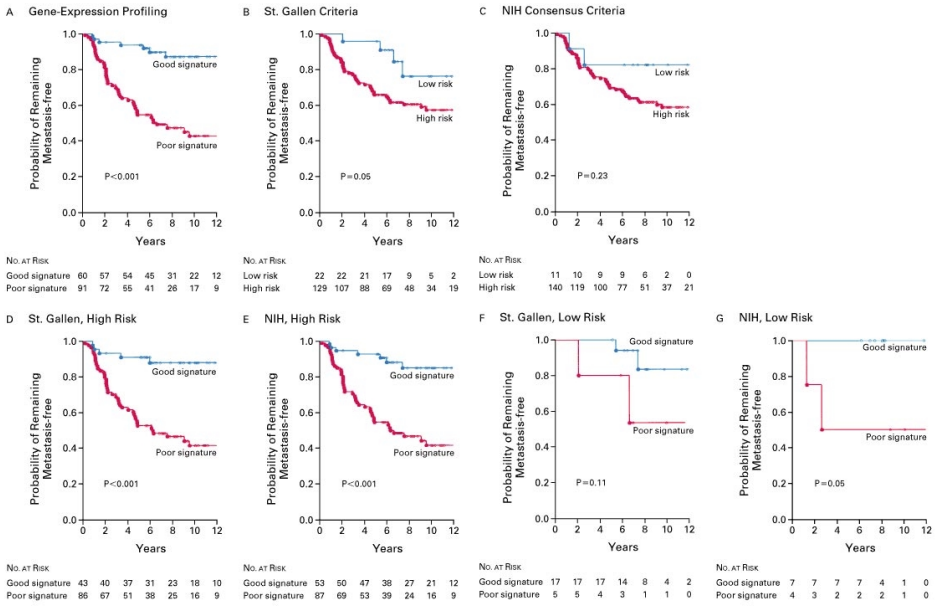
Ensembles des ARNm de la cellule: 30 000 gène soit <u>plusieurs milliers</u> d 'ARNm différents par cellule

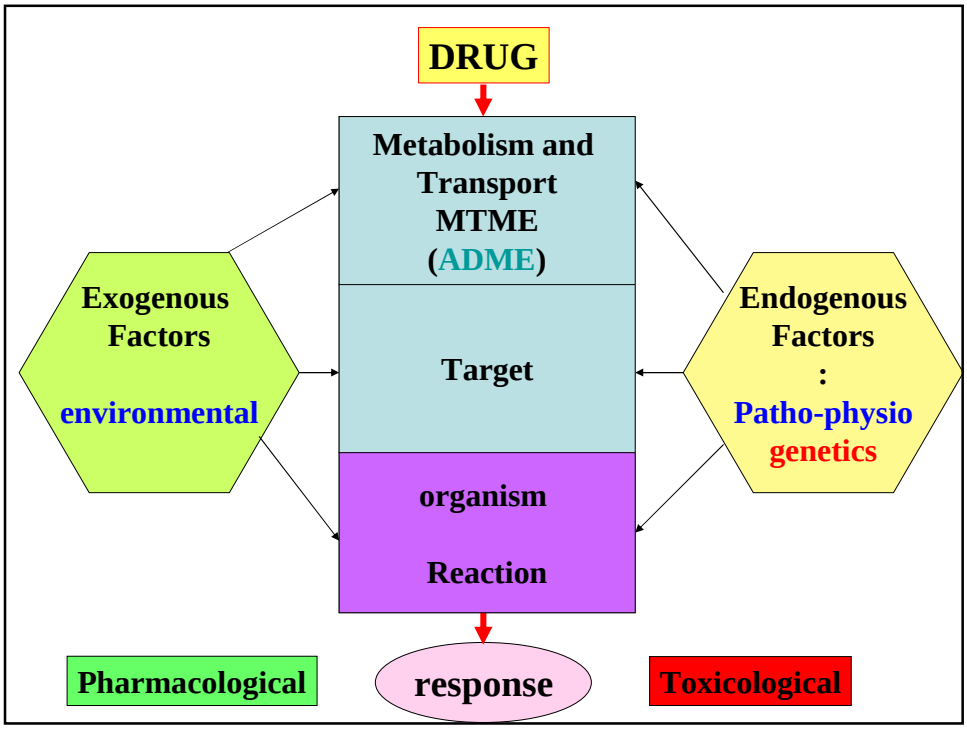
Caractérisation moléculaire <u>à grand échelle</u> de l 'expression des gènes d 'une tumeur

- **<u>Avantages</u>: L 'étude d 'un très grand nombre d 'ARNm permet une caractérisation plus fine d 'une tumeur, de son devenir, de sa sensibilité au traitement….**
- **<u>Inconvénients</u>: grande variabilité de l'expression d 'une tumeur à l 'autre; ARNm labiles**
- **Etudes publiées: lymphomes, sein, colon, foie**
- **Techniques d 'étude: Puces à ADN, SAGE ….**



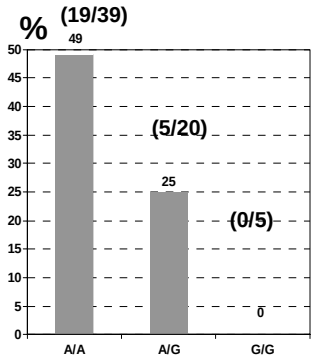
Comparaison avec les autres critères d'évaluation du risque métastatique





Neurotoxicité chronique à l'Oxaliplatine et polymorphisme de GST-P1

64 pts inclus et génotypés pour le polymorphisme de *GSTP1(Ile105Val)*
Dose cumulée min. de 500 mg/m^2



p = 0,04

Neuropathie chronique grade 3

Abacavir

Anti-HIV, non nucleoside analog (Ziagen®)

~ 5% hypersensitivity reactions (HSR) few cases → death

- HLA B5701, C4A6, -DR7, -DR3
67 % HSR have this haplotype
0% non HSR have this haplotype
OR = 117

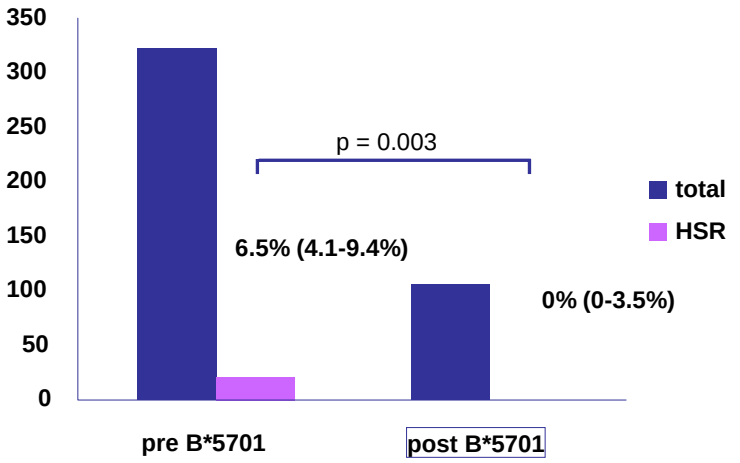
- HLA B5701
78 % HSR
2,4 % non HSR

Positive predictive value 100% and negative 97%

Haplotype Determination before treatment should allow to reduce 50%of HSR.

Mellal et coll. Lancet 2002, Hetherington et coll. Lancet 2002

Pharmacogenetics of Abacavir Hypersensitivity: Translation into Clinical Practice (Brighton Clinic)



Should be accompanied by clinical monitoring !!!!!!!

Reeves I, Churchill D and Fisher M, O19, Vol 7, Supplement 1, HIV Medicine, March 2006

Pharmacogenetics Odds ration for ADRs

SJS Asian carbamazepine : HLA-B*1502, OR=1023, Chung et al.
SJS Asian allopurinol : HLA-B*5801, OR=580, Hung et al.

Cholestasis flucloxacillin : HLA-B*5701, OR=80, Daly et al.
Neutropenia 6-mercaptopurine : TPMT, OR=49, Relling et al.
Hypersensitivity abacavir : HLA-B*5701, OR=36, Mallal et al.
Overdose oral anticoagulant : CYP2C9+VKORC1, OR=10, Quteineh et al.

Hepatitis isoniazid : NAT2, OR=7, Huang et al.
Cytolysis ximelagatran : HLA-DRB1*0701, OR=4, Kindmark et al.
Hepatitis NSAID : GSTM1+GSTT1, OR=9, Lucena et al.

FDA / EMEA Pharmacogenetics Labelling (SPC)

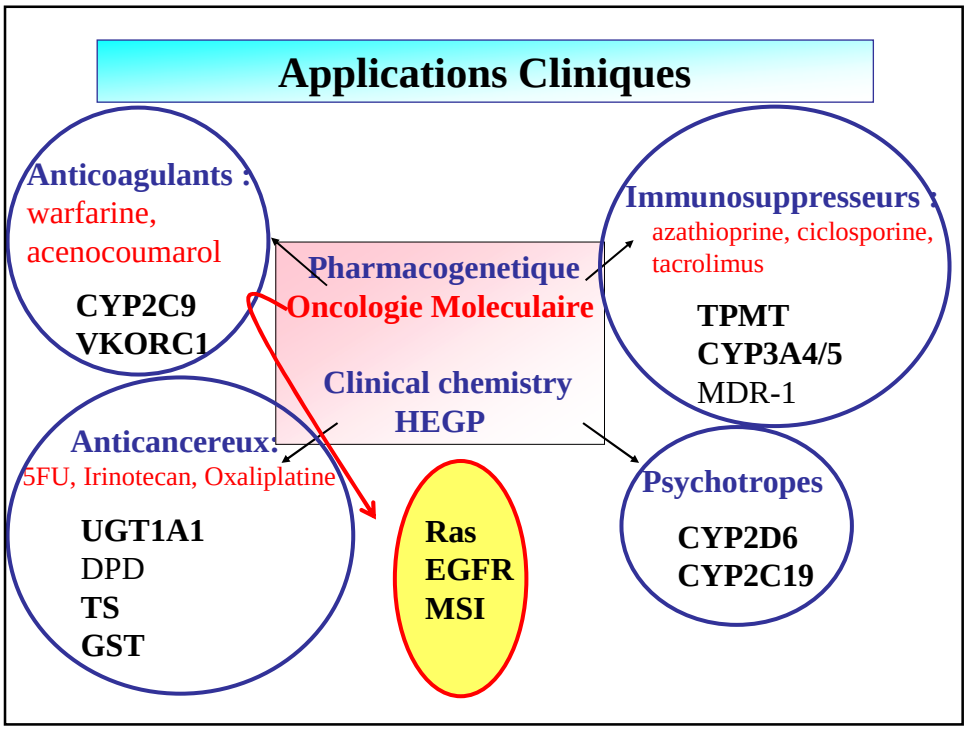
Constitutive genetic variants

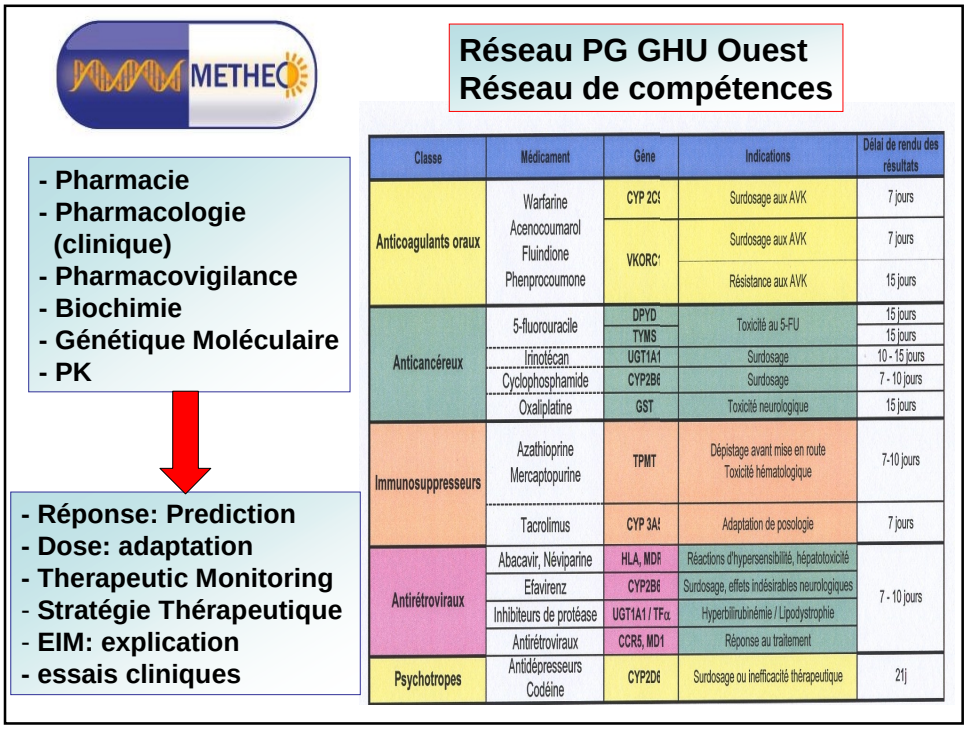
Drug	Gene target	Information	
Thioridazine	CYP2D6	ADRs : Test not required	QT prolongation : torsades de pointes
Codeine	CYP2D6	ADRs : Test not required	Apnea among children from breastfeeding mothers
Atomoxetine	CYP2D6	ADRs : Test not required	Dose reduction for PMs
Tamoxifene	CYP2D6-CYP2C19	*Lower response rate :* Test not required	Loss of efficacy among PMs and with CYP2D6 inhibitors
Voriconazole	CYP2C19	ADRs : Test not required	Hepatotoxicity
Warfarin	CYP2C9	ADRs : Test not required	Risk of bleeding
Warfarin	VKORC1	ADRs : Test not required	Risk of bleeding
Irinotecan	UGT1A1	ADRs : Test not required	Diarrhea, neutropenia
Azathioprine & 6-MP	TPMT	ADRs : Test not required	Neutropenia
Capecitabine	DPD	ADRs : Test not required	Oro digestive – neutropenia
Maraviroc	CCR5	*Non response* Test required	For CCR5 negative
Rasburicase	G6PD	ADRs : Test not required	Hemolysis in G6PD deficient patients
Carbamazepine	HLA-B*1502	ADRs : Test not required	Severe immunoallergic cutaneous
Abacavir	HLA-B*5701	ADRs : Test not required	Hypersensitivity reactions

FDA / EMEA Pharmacogenetics Labelling (SPC)

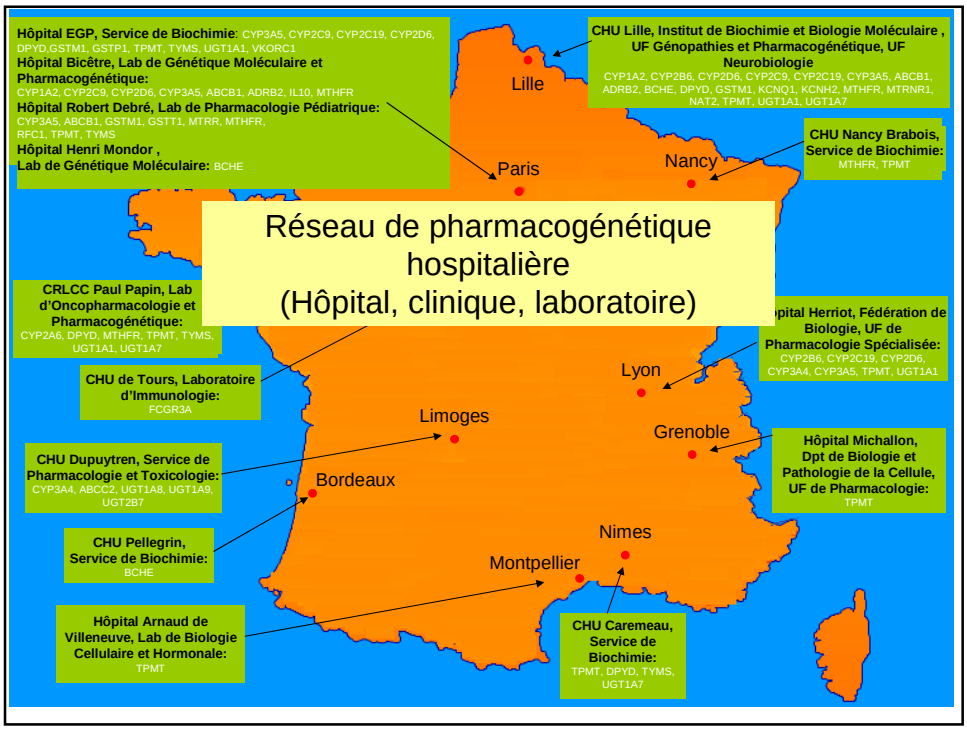
Tumoral genetics

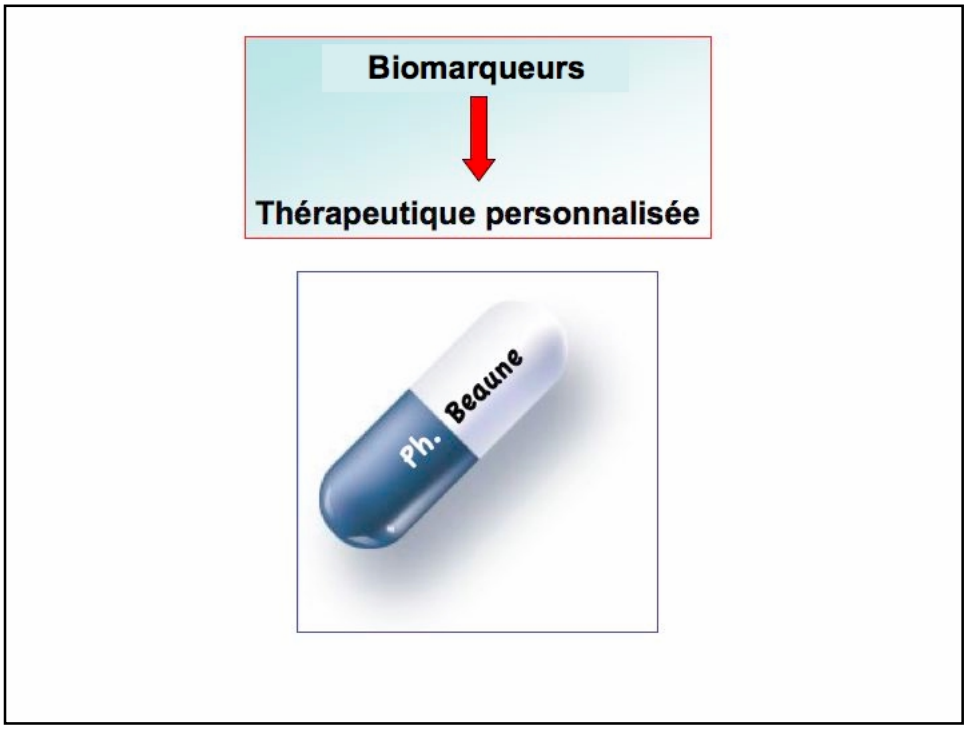
Drug	Gene target	Information	
Erlotinib	EGFR	None response Test no required	No tumoral EGFR expression
Cetuximab	EGFR	None response Test required	No tumoral EGFR expression
Panitumumab	EGFR	None response Test required	No tumoral EGFR expression
Trastuzumab	HER2	None response Test required	No tumoral HER2 expression
Tamoxifene	ER	None response Test required	No tumoral ER expression
Anastrozole	ER	None response Test required	No tumoral ER expression
Exemestane	ER	None response Test required	No tumoral ER expression
Letrozole	ER	None response Test required	No tumoral ER expression
Cetuximab	K-RAS	None response Test required	Tumoral K-RAS mutations
Panitumumab	K-RAS	None response Test required	Tumoral K-RAS mutations
Imatinib	C-Kit	None response Test required	Absence of activating tumoral c-Kit mutations





Classe	Médicament	Gène	Indications	Délai de rendu des résultats
Anticoagulants oraux	Warfarine Acenocoumarol Fluindione Phenprocoumone	CYP 2C9	Surdosage aux AVK	7 jours
		VKORC1	Surdosage aux AVK	7 jours
			Résistance aux AVK	15 jours
Anticancéreux	5-fluorouracile	DPYD	Toxicité au 5-FU	15 jours
		TYMS		15 jours
	Irinotecan	UGT1A1	Surdosage	10 - 15 jours
	Cyclophosphamide	CYP2B6	Surdosage	7 - 10 jours
	Oxaliplatine	GST	Toxicité neurologique	15 jours
Immunosuppresseurs	Azathioprine Mercaptopurine	TPMT	Dépistage avant mise en route Toxicité hématologique	7-10 jours
	Tacrolimus	CYP 3A4	Adaptation de posologie	7 jours
Antirétroviraux	Abacavir, Névirapine	HLA, MDR	Réactions d'hypersensibilité, hépatotoxicité	7 - 10 jours
	Efavirenz	CYP2B6	Surdosage, effets indésirables neurologiques	
	Inhibiteurs de protéase	UGT1A1 / TFα	Hyperbilirubinémie / Lipodystrophie	
	Antirétroviraux	CCR5, MD1	Réponse au traitement	
Psychotropes	Antidépresseurs Codéine	CYP2D6	Surdosage ou inefficacité thérapeutique	21j


Hôpital EGP, Service de Biochimie: CYP3A5, CYP2C9, CYP2C19, CYP2D6, DPYD,GSTM1, GSTP1, TPMT, TYMS, UGT1A1, VKORC1
Hôpital Bicêtre, Lab de Génétique Moléculaire et Pharmacogénétique: CYP1A2, CYP2C9, CYP2D6, CYP3A5, ABCB1, ADRB2, IL10, MTHFR
Hôpital Robert Debré, Lab de Pharmacologie Pédiatrique: CYP3A5, ABCB1, GSTM1, GSTT1, MTRR, MTHFR, RFC1, TPMT, TYMS
Hôpital Henri Mondor , Lab de Génétique Moléculaire: BCHE
CHU Lille, Institut de Biochimie et Biologie Moléculaire , UF Génopathies et Pharmacogénétique, UF Neurobiologie CYP1A2, CYP2B6, CYP2D6, CYP2C9, CYP2C19, CYP3A5, ABCB1, ADRB2, BCHE, DPYD, GSTM1, KCNQ1, KCNH2, MTHFR, MTRNR1, NAT2, TPMT, UGT1A1, UGT1A7
CHU Nancy Brabois, Service de Biochimie: MTHFR, TPMT
Lille
Paris
Nancy
Réseau de pharmacogénétique hospitalière (Hôpital, clinique, laboratoire)
CRLCC Paul Papin, Lab d'Oncopharmacologie et Pharmacogénétique: CYP2A6, DPYD, MTHFR, TPMT, TYMS, UGT1A1, UGT1A7
CHU de Tours, Laboratoire d'Immunologie: FCGR3A
pital Herriot, Fédération de Biologie, UF de Pharmacologie Spécialisée: CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, TPMT, UGT1A1
Lyon
Limoges
Grenoble
Hôpital Michallon, Dpt de Biologie et Pathologie de la Cellule, UF de Pharmacologie: TPMT
CHU Dupuytren, Service de Pharmacologie et Toxicologie: CYP3A4, ABCC2, UGT1A8, UGT1A9, UGT2B7
Bordeaux
CHU Pellegrin, Service de Biochimie: BCHE
Nimes
Montpellier
Hôpital Arnaud de Villeneuve, Lab de Biologie Cellulaire et Hormonale: TPMT
CHU Caremeau, Service de Biochimie: TPMT, DPYD, TYMS, UGT1A7


Biomarqueurs
Thérapeutique personnalisée
Ph. Beaune