

Pharmacogenetics and pharmacogenomics

**Vincent Bours
Genetics Center
CHU / University of Liège**

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Pharmacogenetics

- **Study of genetic differences between individuals that influence the clinical response to a drug**
- **Genetic factors predictive of the response to a specific drug**
- **Choice of the best medicine for an individual patient**

**Personnalized medicine
Precision medicine**

2

Pharmacogenomics

- **Study the interactions between drugs and the genome**
- **Global approach / drug discovery / genomic markers**

3

Pharmacogenetics

- **Genetic factors predictive of the response to a specific drug**
 - **Probability of a clinical response**
 - **Risk of severe side effects**
- **Drug prescription: method by « try and error »**

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- **USA: adverse reactions to prescription drugs:**
 - **2 million people each year**
 - **100 000 deaths/year**
 - **7% of hospital admissions**
 - **Cost: > 30 billion \$**

- **Causes:**
 - **Environmental: drug interactions**
 - **Co-morbidity**
 - **Genetic factors**

- **Pharmacogenetics: Could genetic factors be anticipated?**

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If it were not for the great variability among individuals, medicine might as well be a science and not an art.

Sir William Osler, 1892

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

GENOMIC MEDICINE
 Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D., *Editors*

Inheritance and Drug Response
 Richard Weinshilboum, M.D.

REVIEW ARTICLE


DRUG THERAPY
 Alastair J.J. Wood, M.D., *Editor*

**Pharmacogenomics — Drug Disposition,
 Drug Targets, and Side Effects**
 William E. Evans, Pharm.D., and Howard L. McLeod, Pharm.D.

N ENGL J MED 348:6 WWW.NEJM.ORG FEBRUARY 6, 2003

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**With your genes? Take one
 of these, three times a day**

 Truly 'personalized' medicine remains a distant goal. But researchers are now thinking about how to use genomic data to avoid prescribing drugs that may kill, or won't work. NATURE | VOL 425 | 23 OCTOBER 2003

Pharmacogenomics and Drug Toxicity
 Yusuke Nakamura, M.D., Ph.D.

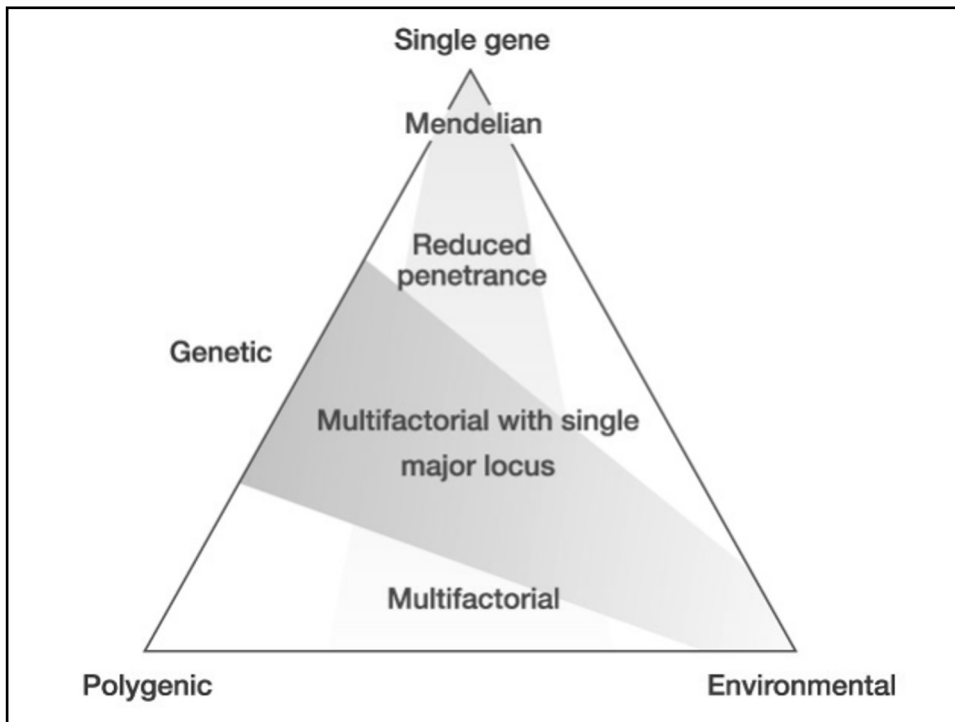
N ENGL J MED 359:8 WWW.NEJM.ORG AUGUST 21, 2008

The NEW ENGLAND
 JOURNAL of MEDICINE

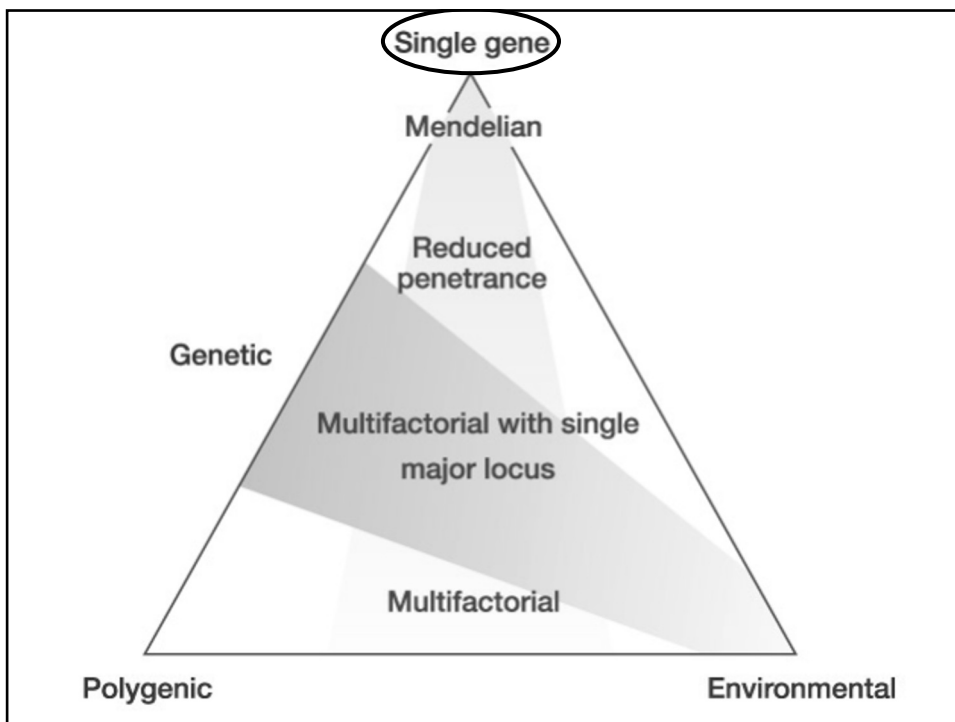
ESTABLISHED IN 1812 FEBRUARY 19, 2009 VOL. 360 NO. 8

**Estimation of the Warfarin Dose with Clinical
 and Pharmacogenetic Data**
 The International Warfarin Pharmacogenetics Consortium*

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9



10

Alcohol

Several genes are involved in alcohol metabolism.

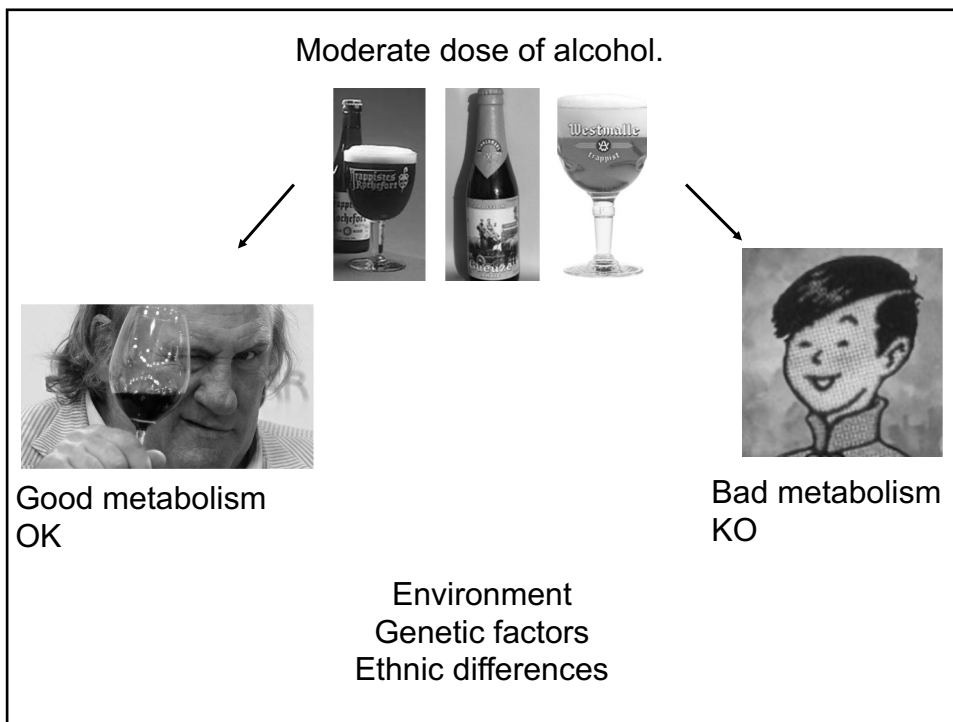


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ALDH2-2



12

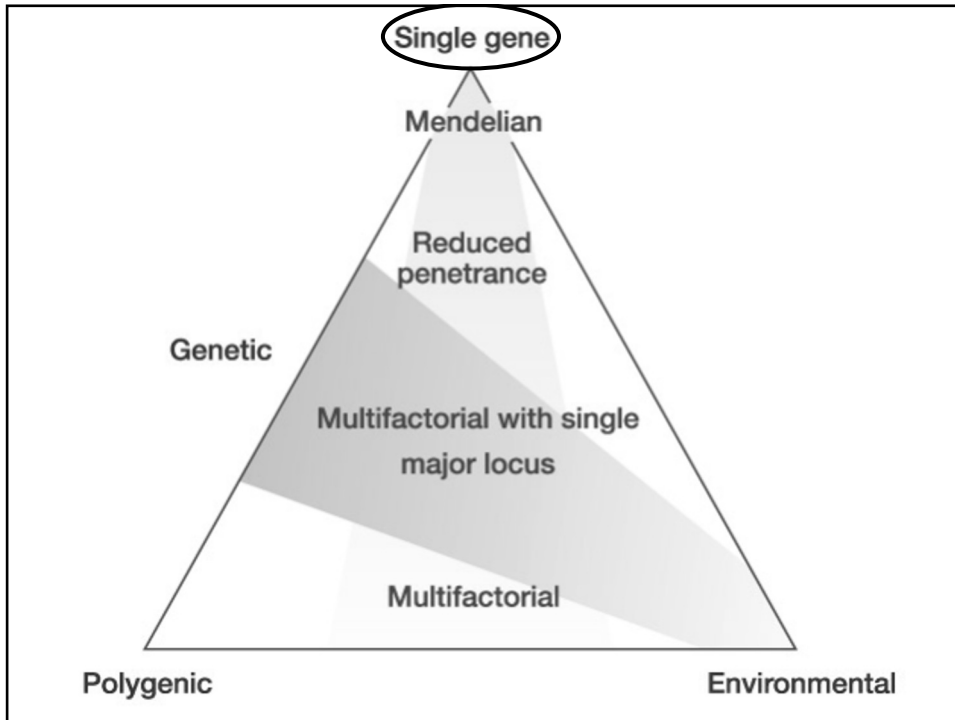


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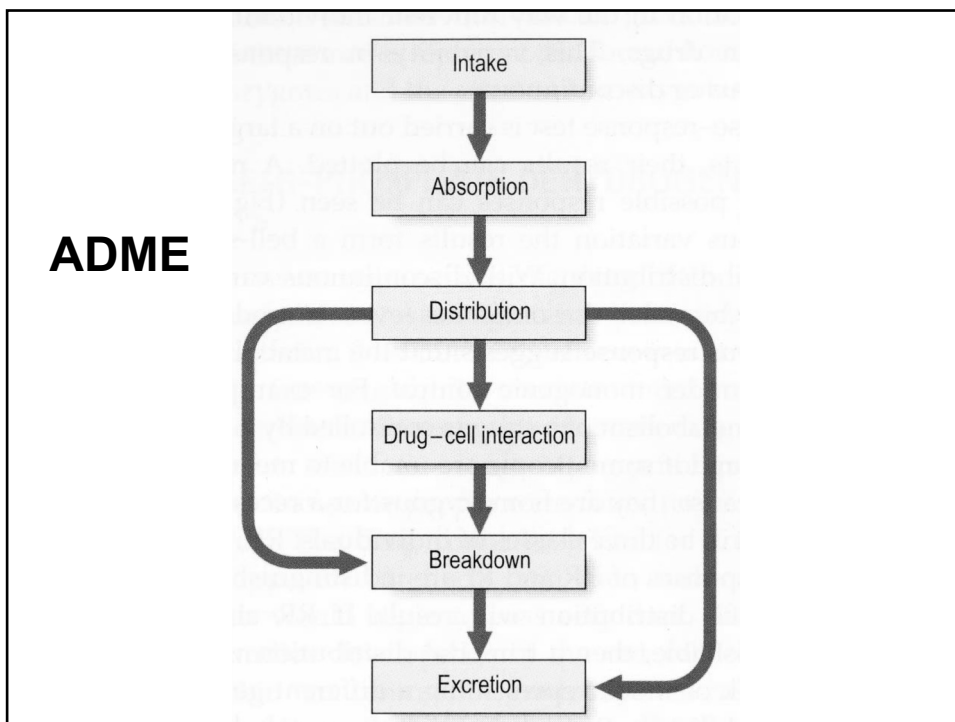
Table 11.1 Ethnic variations in some pharmacogenetic disorders

Disorder	Ethnic group	Frequency (%)
Slow acetylation	Europeans	50
	Orientals	10
Pseudocholinesterase variants	Europeans	<1
	Eskimos	1-2
	N. Europeans	<1
G6PD deficiency	S. Europeans	up to 25
	Afro-Caribbeans	10
	Europeans	5
Atypical ADH	Orientals	85

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Pharmacogenetics

1. Drug metabolism

- Phase I: CYP, ...
- Phase II: TPMT, NAT2, GST, ...

2. Transport

- MDR (ABC)

3. Targets

- Beta-adrenergic receptor

4. Unexpected side effects

- Long QT
- Deafness and aminoglycosids, ...

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Pharmacogenetics

1. Drug metabolism

- Phase I: CYP, ...
- Phase II: TPMT, NAT2, GST, ...

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1950s

Inherited traits: plasma or urine drug concentrations

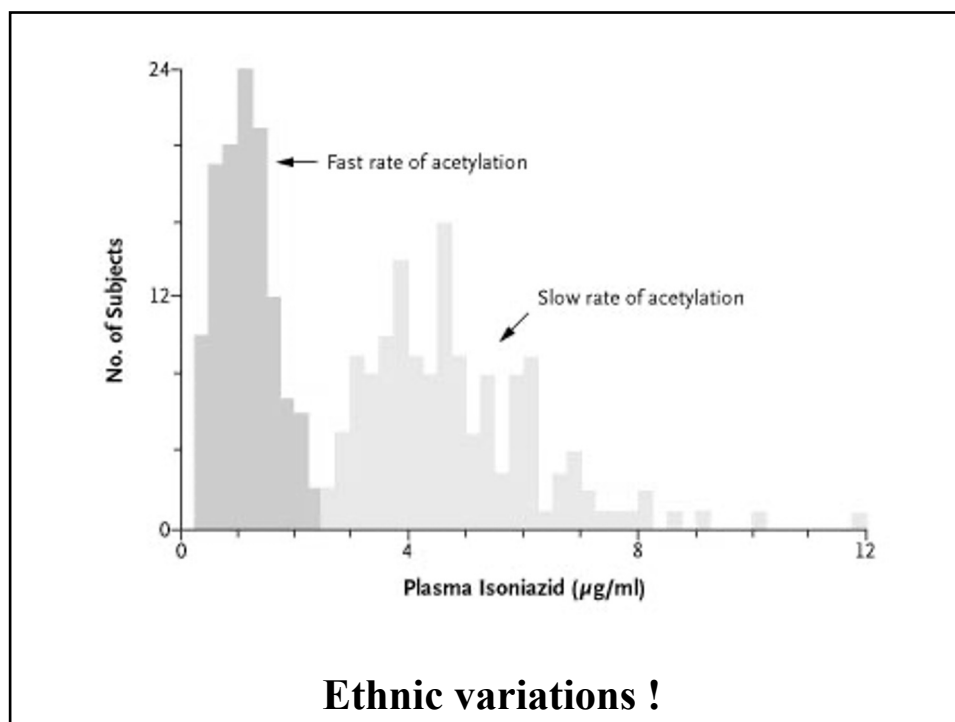
Response to succinylcholine

- Pseudocholinesterase
- 1/3500 white subjects
- Missense mutation

Pharmacokinetics of isoniazid

- N-acetyltransferase

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PERSPECTIVES

Pharmacokinetics

Isoniazid treatment of children: can genetics help guide treatment?

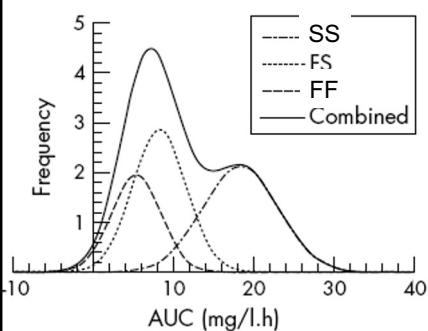
N Cranswick, K Mulholland

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ORIGINAL ARTICLE

Isoniazid pharmacokinetics in children treated for respiratory tuberculosis

H S Schaaf, D P Parkin, H I Seifart, C J Werely, P B Hesselning, P D van Helden, J S Maritz, P R Donald



10 mg/kg

Important proportion of FF patients are under recommended concentrations

Recommendation for FF detection and dose adaptation.

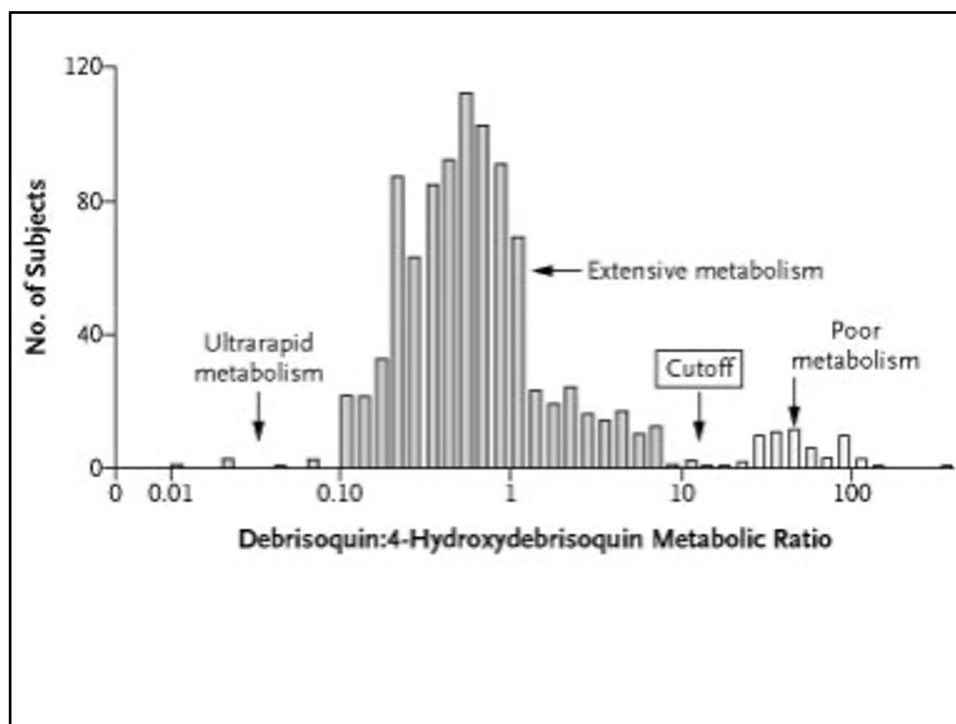
Emerging countries?

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Cytochrome P450 2D6 (CYP2D6)

Codeine, nortryptiline, ...

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Cytochrome P450 2D6 (CYP2D6)

Codeine, nortriptyline, ...

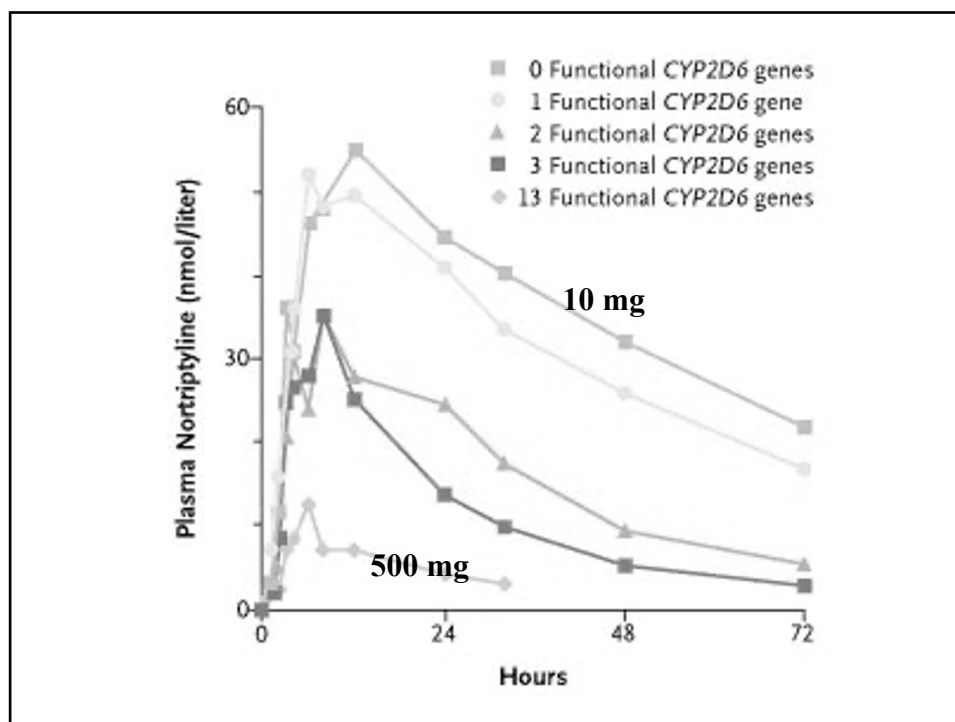
**5-10% of caucasians:
deficit of Cyt P450 2D6**

> 75 alleles

**Slow metabolisers: nortriptyline side effects, no
response to codeine**

**Very-fast metabolisers
Multiples gene copies (0-13)
East Africa: 29%**

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**Cytochrome P450 2D6 (CYP2D6)
Codeine**

Activated in morphine

**Slow metabolisers: no response
Fast metabolisers: morphine overdose**

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FDA: No Codeine After Tonsillectomy for Children.

A review of cases reported to the FDA's Adverse Event Reporting System between 1969 and May 2012 identified 10 deaths and 3 overdoses in children who had been treated with codeine; 7 of the cases were also reported in the medical literature. Of the 13 cases, 8 occurred in children after adenotonsillectomy

Some of the affected children may have been rapid metabolizers of codeine, according to the FDA's warning. All humans convert codeine into morphine, but individuals who have certain genetic variants encoding the enzyme cytochrome P450 2D6 do so more rapidly

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FDA Warns of Rare Morphine Overdose in Breastfed Babies

Nursing mothers with a genetic predisposition for rapidly metabolizing codeine in pain medication can seriously overdose their babies with morphine.

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Safety of codeine during breastfeeding

Fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine

Parvaz Madadi, Gideon Koren, MD, FRCPC, [...], and Katarina Aleksa,

Abstract

QUESTION Recently a newborn died from morphine poisoning when his mother used codeine while breastfeeding. Many patients receive codeine for postlabour pain. Is it safe to prescribe codeine for nursing mothers?

ANSWER When a mother is an ultrarapid metabolizer of cytochrome P450 2D6, she produces much more morphine when taking codeine than most people do. In this situation, newborns might be exposed to toxic levels of morphine when breastfeeding.

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Other Cytochrome P450 isoforms

2C9

2C19

3A5

...

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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*

**Génotyping of the cyt P450 2C9 (3 alleles) and the
VKORC1 gene (1 SNP) allow a good prediction of the
appropriate warfarin dose (>4000 pts)**

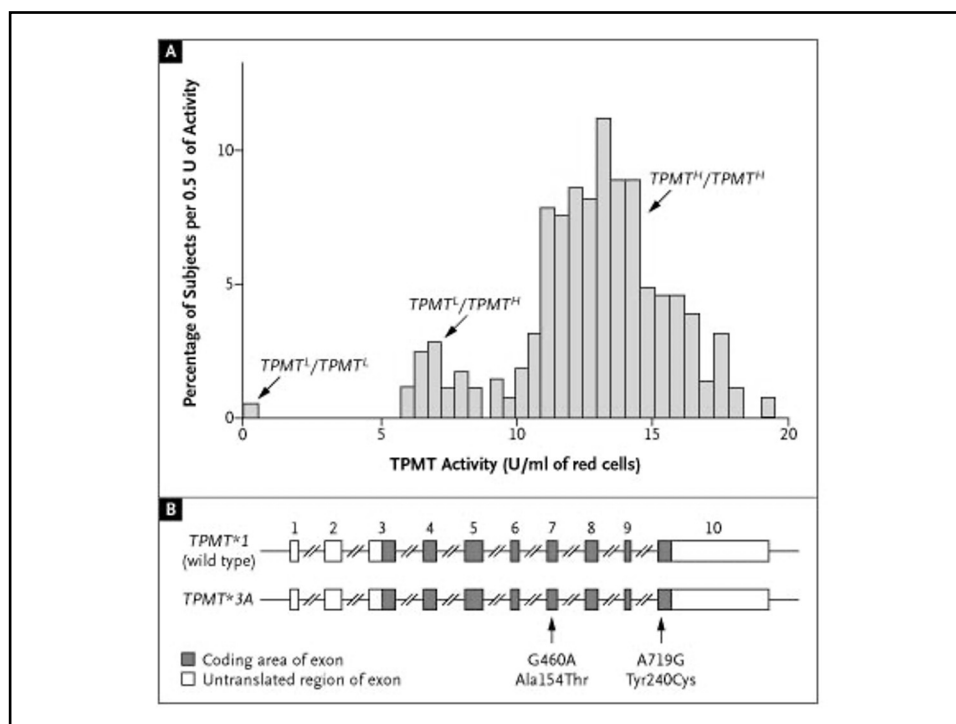
**The FDA recommended (2007) to include information on
pharmacogenetics in the drug sheet and encouraged to use
pharmacogenetics to define the treatment**

Clinical utility ? Reduction of side effects?

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Thiopurine S-methyltransferase (TPMT) Mercaptopurine, Azathioprine

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Thiopurine S-methyltransferase (TPMT)

Mercaptopurine, Azathioprine

**Weak metabolisers: myelosuppression after
regular doses**

Clinically relevant test

Ethnic differences

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Table 1. Pharmacogenetics of Phase I Drug Metabolism.*			
Drug-Metabolizing Enzyme	Frequency of Variant Poor-Metabolism Phenotype	Representative Drugs Metabolized	Effect of Polymorphism
Cytochrome P-450 2D6 (CYP2D6)	6.8% in Sweden 1% in China ¹⁷	Debrisoquin ¹⁵ Sparteine ¹⁶ Nortriptyline ²³ Codeine ^{27,28}	Enhanced drug effect Enhanced drug effect Enhanced drug effect Decreased drug effect
Cytochrome P-450 2C9 (CYP2C9)	Approximately 3% in England ²⁹ (those homozygous for the *2 and *3 alleles)	Warfarin ^{29,30} Phenytoin ^{31,32}	Enhanced drug effect ²⁹⁻³²
Cytochrome P-450 2C19 (CYP2C19)	2.7% among white Americans ³³ 3.3% in Sweden 14.6% in China ¹⁷ 18% in Japan ³³	Omeprazole ^{34,35}	Enhanced drug effect ^{36,37}
Dihydropyrimidine dehydrogenase	Approximately 1% of population is heterozygous ³⁸	Fluorouracil ^{39,40}	Enhanced drug effect ^{39,40}
Butyrylcholinesterase (pseudocholinesterase)	Approximately 1 in 3500 Europeans ⁴¹	Succinylcholine ^{9,41}	Enhanced drug effect ^{9,41}

* Examples of genetically polymorphic phase I enzymes are listed that catalyze drug metabolism, including selected examples of drugs that have clinically relevant variations in their effects.

Phase 1 reactions: oxidation, reduction, hydrolysis ...

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Table 2. Pharmacogenetics of Phase II Drug Metabolism.*			
Drug-Metabolizing Enzyme	Frequency of Variant Poor-Metabolism Phenotype	Representative Drugs Metabolized	Effect of Polymorphism
N-Acetyltransferase 2	52% among white Americans ¹⁰ 17% of Japanese ⁵⁸	Isoniazid ¹⁰ Hydralazine ¹¹ Procainamide ¹²	Enhanced drug effect ¹³
Uridine diphosphate-glucuronosyltransferase 1A1 (TATA-box polymorphism)	10.9% among whites ⁵⁹ 4% of Chinese ⁶⁰ 1% of Japanese ⁶⁰	Irinotecan ⁶¹ Bilirubin ⁶²	Enhanced drug effect ⁶³ Gilbert's syndrome ⁶²
Thiopurine S-methyltransferase	Approximately 1 in 300 whites ^{50,57} Approximately 1 in 2500 Asians ⁵⁷	Mercaptopurine ⁵¹ Azathioprine	Enhanced drug effect (toxicity) ⁵¹⁻⁵³
Catechol O-methyltransferase	Approximately 25% of whites ^{51,64}	Levodopa ^{51,65}	Enhanced drug effect ^{51,65}

* Examples of genetically polymorphic phase II (conjugating) enzymes are listed that catalyze drug metabolism, including selected examples of drugs that have clinically relevant variations in their effects.

Phase 2 reactions: conjugation (acetylation, methylation, glucuronidation, ...)

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<h1>Pharmacogenetics</h1> <h2>1. Drug metabolism</h2> <ul style="list-style-type: none"> - Phase I: CYP, ... - Phase II: TPMT, NAT2, GST, ... <h2>2. Transport</h2> <ul style="list-style-type: none"> - MDR (ABC)

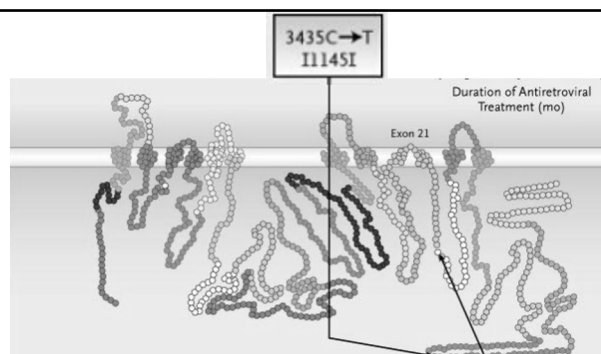
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Drug Transporters

ATP-binding cassette
P-glycoprotéine MDR1 ABCB1

Drug efflux, blood-brain barrier, urine
or bile excretion of xenobiotics

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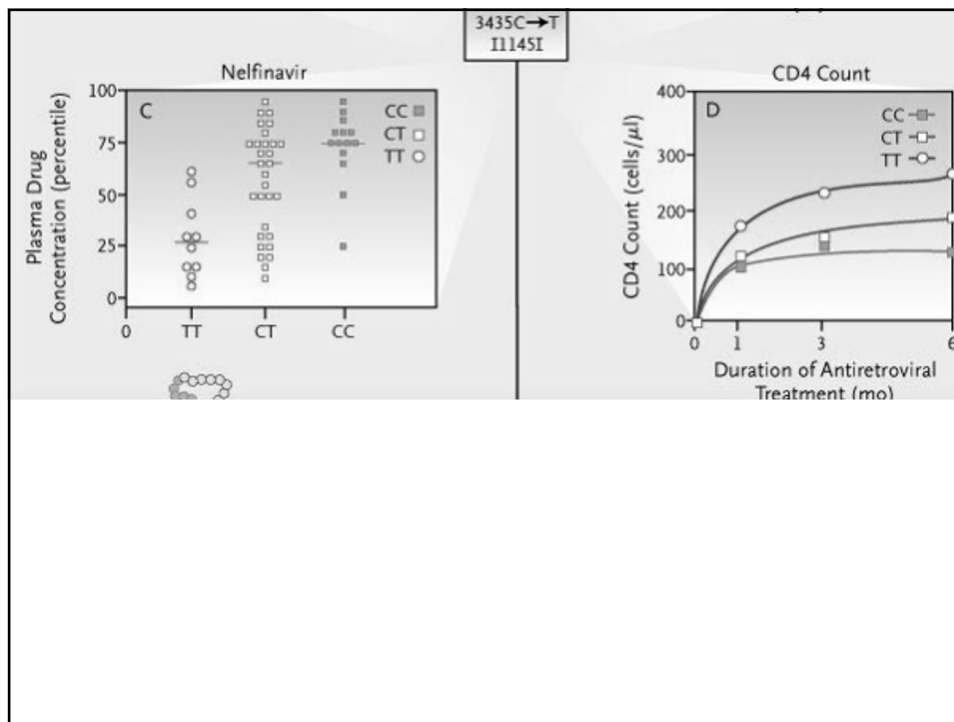
Variable expression of P-glycoprotein

TT lower expression

CC higher expression, lower cell drug retention

Linked with another polymorphism (missense)

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Pharmacogenetics

1. Drug metabolism

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- Phase II: TPMT, NAT2, GST, ...

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3. Targets

- Beta-adrenergic receptor

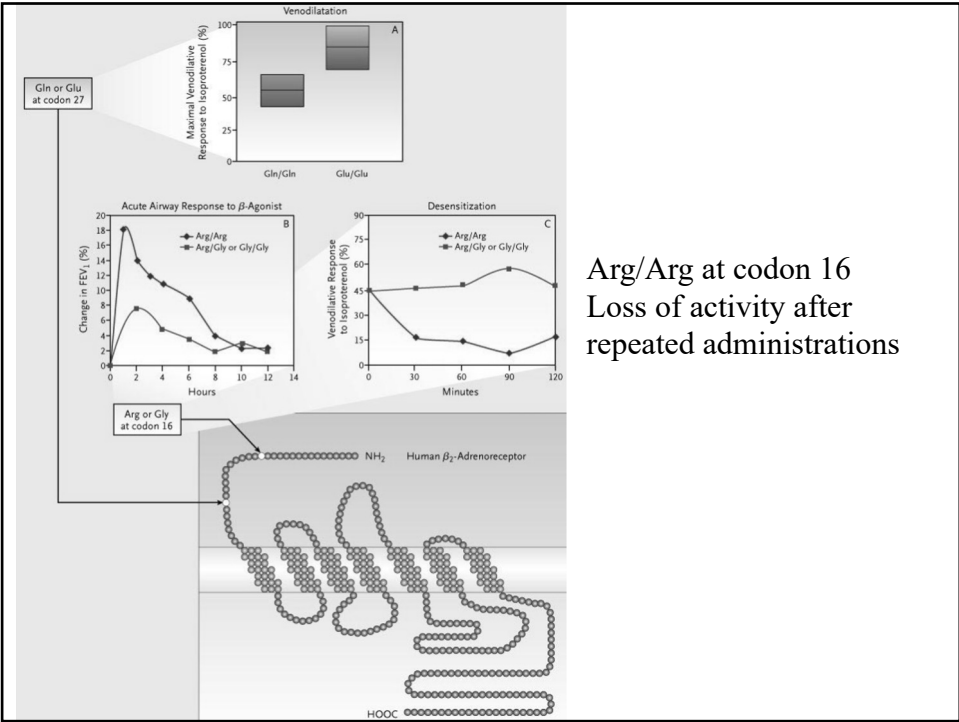
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Récepteurs

Récepteur β_2 -Adrénurgique

Frequent SNPs affecting signal transduction

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β 2-Adrenergic Receptor

At least 13 SNPs
12 haplotypes

Correlation clinical response/haplotype

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Table 1. Genetic Polymorphisms in Drug Target Genes That Can Influence Drug Response.*

Gene or Gene Product	Medication	Drug Effect Associated with Polymorphism
ACE	ACE inhibitors (e.g., enalapril) Fluvastatin	Renoprotective effects, blood-pressure reduction, reduction in left ventricular mass, endothelial function ³²⁻⁴⁰ Lipid changes (e.g., reductions in low-density lipoprotein cholesterol and apolipoprotein B); progression or regression of coronary atherosclerosis ⁴¹
Arachidonate 5-lipoxygenase	Leukotriene inhibitors	Improvement in FEV ₁ ⁴²
β 2-Adrenergic receptor	β 2-Agonists (e.g., albuterol)	Bronchodilatation, susceptibility to agonist-induced desensitization, cardiovascular effects ⁴³⁻⁵⁰
Bradykinin B2 receptor	ACE inhibitors	ACE-inhibitor-induced cough ⁵¹
Dopamine receptors (D2, D3, D4)	Antipsychotics (e.g., haloperidol, clozapine)	Antipsychotic response (D2, D3, D4), antipsychotic-induced tardive dyskinesia (D3), antipsychotic-induced acute akathisia (D3) ⁵²⁻⁵⁶
Estrogen receptor- α	Conjugated estrogens Hormone-replacement therapy	Increase in bone mineral density ⁵⁷ Increase in high-density lipoprotein cholesterol ⁵⁸
Glycoprotein IIIa subunit of glycoprotein IIb/IIIa	Aspirin or glycoprotein IIb/IIIa inhibitors	Antiplatelet effect ⁵⁹
Serotonin (5-hydroxytryptamine) transporter	Antidepressants (e.g., clomipramine, fluoxetine, paroxetine)	5-Hydroxytryptamine neurotransmission, antidepressant response ⁶⁰⁻⁶²

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Pharmacogenetics

1. Drug metabolism

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4. Unexpected side effects

- Long QT
- Deafness and aminoglycosids, ...

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Deafness induced by aminoglycosids

Polymorphisms in the mitochondrial 12S rRNA

Targeted by the antibiotics

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Hypersensitivity reactions

Carbamazepin:

- HLA B*15:02: Asia, standard practice in Taiwan before carbamazepin prescription

-HLA A*31:01: Europe

Abacavir: HLA-B*5701

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Table 2. Genetic Polymorphisms in Disease-Modifying or Treatment-Modifying Genes That Can Influence Drug Response.*			
Gene or Gene Product	Disease or Response Association	Medication	Influence of Polymorphism on Drug Effect or Toxicity
Adducin	Hypertension	Diuretics	Myocardial infarction or strokes ⁶⁹
Apolipoprotein E (APOE)	Progression of atherosclerosis, ischemic cardiovascular events	Statins (e.g., simvastatin)	Enhanced survival ^{70,71}
Apolipoprotein E (APOE)	Alzheimer's disease	Tacrine	Clinical improvement ⁷²
HLA	Toxicity	Abacavir	Hypersensitivity reaction ^{73,74}
Cholesterol ester transfer protein (CETP)	Progression of atherosclerosis	Statins (e.g., pravastatin)	Slowing of progression of atherosclerosis by pravastatin ⁷⁵
Ion channels (HERG, KvLQT1, Mink, MIRP1)	Congenital long-QT syndrome	Erythromycin, terfenadine, cispripide, clarithromycin, quinidine	Increased risk of drug-induced torsade de pointes ⁷⁶⁻⁷⁸
Methylguanine methyltransferase (MGMT)	Glioma	Carmustine	Response of glioma to carmustine ⁶³
<i>Parkin</i>	Parkinson's disease	Levodopa	Clinical improvement and levodopa-induced dyskinesias ⁷⁹
Prothrombin and factor V	Deep-vein thrombosis and cerebral-vein thrombosis	Oral contraceptives	Increased risk of deep-vein and cerebral-vein thrombosis with oral contraceptives ⁸⁰
Stromelysin-1	Atherosclerosis progression	Statins (e.g., pravastatin)	Reduction in cardiovascular events by pravastatin (death, myocardial infarction, stroke, angina, and others); reduction in risk of repeated angioplasty ⁸¹

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<p>Recommended tests</p> <p>DPYD (5-Fu)</p> <p>TPMT</p> <p>UGT1A1 (irinotecan)</p> <p>HLA-B*57:01 (abacavir)</p> <p>...</p>
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Website Stanford University

<http://www.pharmgkb.org>

Reviews the clinical utility of pharmacogenetic tests

<http://www.pharmgkb.org/search/clinicalAnnotationList.action?levelOfEvidence=top>

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CPIC

**Clinical pharmacogenetics
Implementation Consortium**

<https://cpicpgx.org>

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Recommended tests

DPYD (5-Fu)

TPMT

UGT1A1 (irinotecan)

HLA-B*57:01 (abacavir)

...

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DPYD (5-Fu)

French recommendations (2018)

Based on the levels of evidence from the literature data and considering current French practices, the Group of Clinical Pharmacology in Oncology (GPCO)-UNICANCER and the French Network of Pharmacogenetics (RNPGx) recommend the following: (1) to screen DPD deficiency before initiating any chemotherapy containing 5-FU or capecitabine; (2) to perform DPD phenotyping by measuring plasma uracil (U) concentrations (possibly associated with dihydrouracil/U ratio), and DPYD genotyping (variants *2A, *13, p.D949V, HapB3); (3) to reduce the initial FU dose (first cycle) according to DPD status, if needed, and further, to consider increasing the dose at subsequent cycles according to treatment tolerance.

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DPYD (5-Fu)

Common mutations with enzyme low activity

Do not identify all patients with DPYD deficiency

Dosage of the ratio dihydrouracil/uracil in the plasma : better sensitivity

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DPYD (5-Fu)

EMA recommendations (March 2020)

<https://www.esmo.org/oncology-news/ema-provides-new-testing-and-treatment-recommendations-for-fluorouracil-capecitabine-and-tegafur>

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DPYD (5-Fu)

EMA recommendations (March 2020)

EMA PROVIDES NEW TESTING AND TREATMENT RECOMMENDATIONS FOR FLUOROURACIL CAPECITABINE AND TEGAFUR

Patients should be tested for DPD deficiency before starting treatment

Date: 20 Mar 2020

Topics: Anticancer agents & Biologic therapy

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DPYD (5-Fu)

Joint Belgian Recommendation on Screening for DPD-deficiency in patients treated with 5-FU, capecitabine (and tegafur)

we recommend phenotype or targeted genotype testing for DPD deficiency before starting 5-FU, capecitabine or tegafur. We strongly suggest a stepwise approach using phenotype testing upfront because of the higher sensitivity and the lower cost for the society.

Casneuf et al., Acta Clin Belg, 2022

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Gene panels

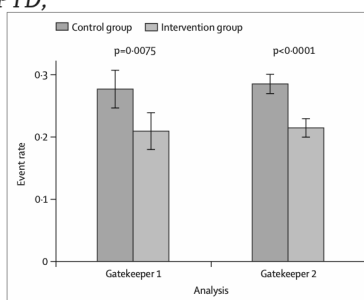
TEST WITH GENE PANELS EVERY PATIENT THAT RECEIVES ONE « RELEVANT » DRUG.

A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study

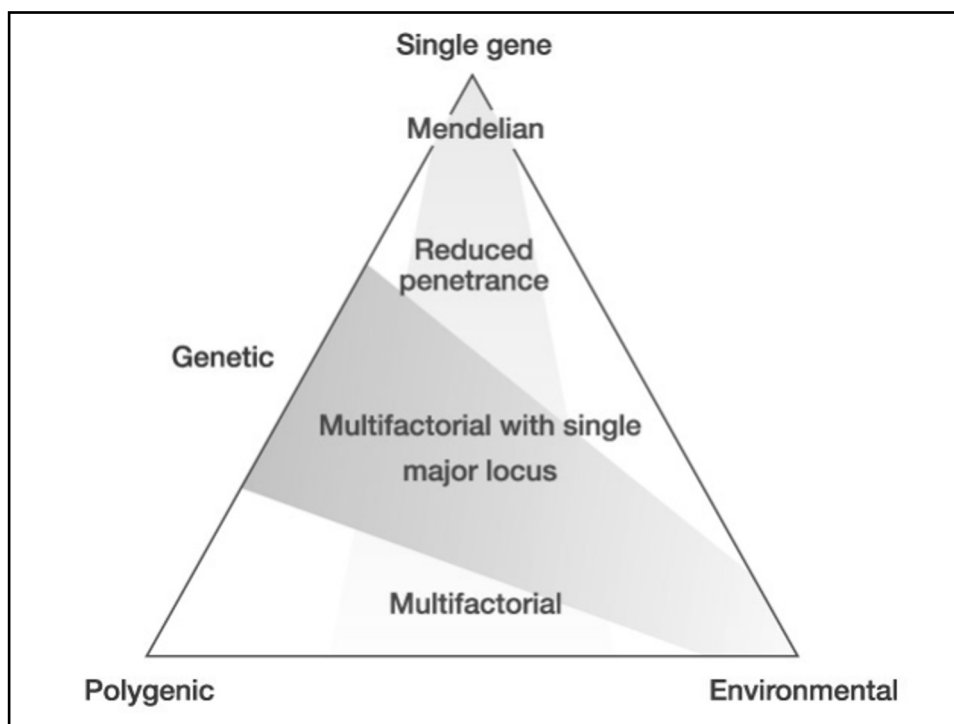
Lancet 2023

(CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-B, SLCO1B1, TPMT, UGT1A1, VKORC1), and

(CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-B, SLCO1B1, TPMT, UGT1A1, VKORC1),



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CANCER

1. « Host » pharmacogenetics

- TPMT and mercaptopurine.
- Dihydropyrimidine dehydrogenase and 5-fluoruracile
- UGT1A1

2. « Tumour » pharmacogenetics / theranostics

- HER2 amplification and Herceptin
- Ras mutation and resistance to anti-EGFR antibodies
- Bcr-Abl fusion gene and response to glivec
- MGMT methylation and response to alkylating agents ,

= target identification or acquired resistance

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CANCER

1. « Host » pharmacogenetics

+

2. « Tumour » pharmacogenetics

**BRCA mutations linked with clinical
response to platine agents and PARP
inhibitors**

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Clinical relevance

**Goal: to predict a clinical response, to prevent side effects, to adapt the doses.
Tailored treatment.**

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Political/economic relevance

Goal: to save money (avoiding useless treatments or important side effects).

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Companies

Goal: to save money

Defining the target population
Reducing the size of clinical trials
Reducing and predicting side effects

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Current research and future directions

**Include
pharmacogenetic/pharmacogenomic tests
in clinical trials.**

Consider ethnical differences.

**Perspectives for a large screening of PG
variants in every individual ??**

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Pharmacogenetics in emerging countries

Impact of pharmacogenomics on neglected diseases in the developing world

T Pang, Am J Pharmacogenomics, 2003

Important impact on treatment of tuberculosis, malaria and HIV

Response rates different than in Occident

Development of therapeutics more adapted to African patients??

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Pharmacogenetics in emerging countries

**Pharmacogenetics and rational drug use around the world.
Pharmacogenetics and rational drug use around the world.**

Roederer et al., Pharmacogenomics, 2011

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Pharmacogenetics in emerging countries

http://apps.who.int/iris/bitstream/handle/10665/43669/9789241595469_eng.pdf?sequence=1&isAllowed=y

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Pharmacogenetics: new developments

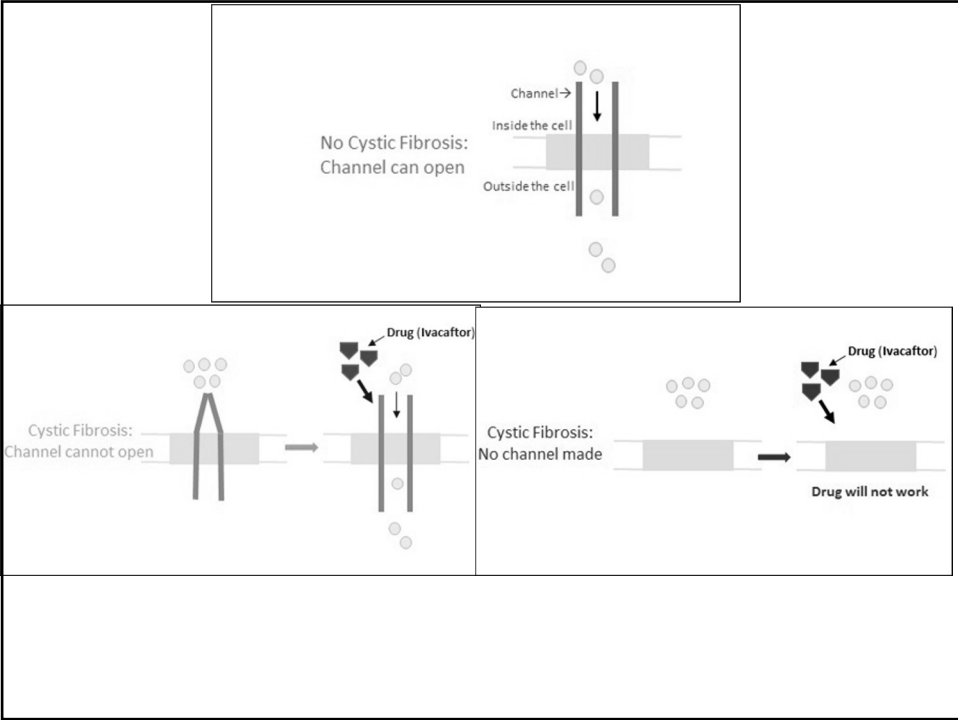
Genotype-based treatment of genetic diseases

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Cystic fibrosis

CFTR modulators

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CF: genotype – treatment correlation

Mutation class	Defect	Phenotype	Example	Treatment strategy
I	Reduced CFTR protein expression	No protein	Gly542X Trp1282X	Production correctors (ataluren)
II	Misfolded CFTR protein not transported to the cell surface	No traffic	Phe508del ($\Delta F508$) Asn1303Lys Ala561Glu	Corrector + potentiator (lumacaftor + ivacaftor, VX-661+ ivacaftor)
III	Reduced/lack of CFTR channel opening	Impaired gating	Gly551Asp Ser549Arg Gly1349Asp	Potentiator (ivacaftor)
IV	Misshaped CFTR pore restricts Cl ⁻ movement	Decreased conductance	Arg117His Arg334Trp Ala455Glu	Potentiator (ivacaftor)
V	Reduced CFTR protein production	Less protein	3849+10 kb C→T Ala455Glu 3272-26A → G	No data available
VI	High CFTR protein turnover at the cell surface	Less stable	120del23 rPhe508del	No data available
VII	No transcription due to large deletions on CFTR gene	No mRNA	dele2,3 (21kb) 1717-1G → A	Unrescuable (By pass therapies?)

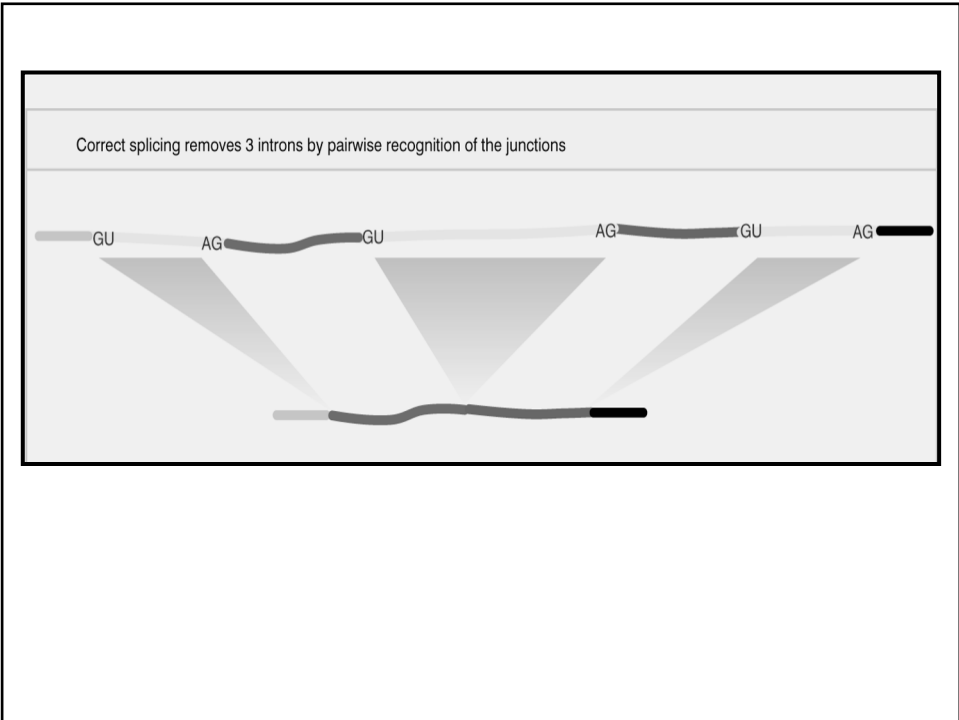
Kb: Kilobases, CFTR: Cystic fibrosis transmembrane conductance regulator

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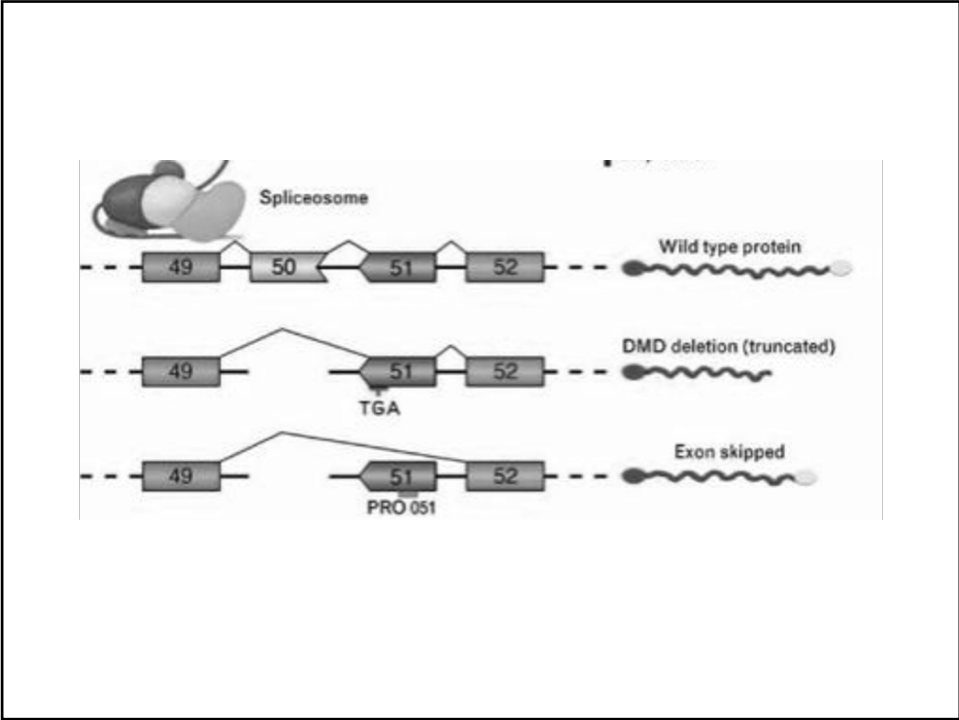
Duchenne muscular dystrophy

Exon skipping

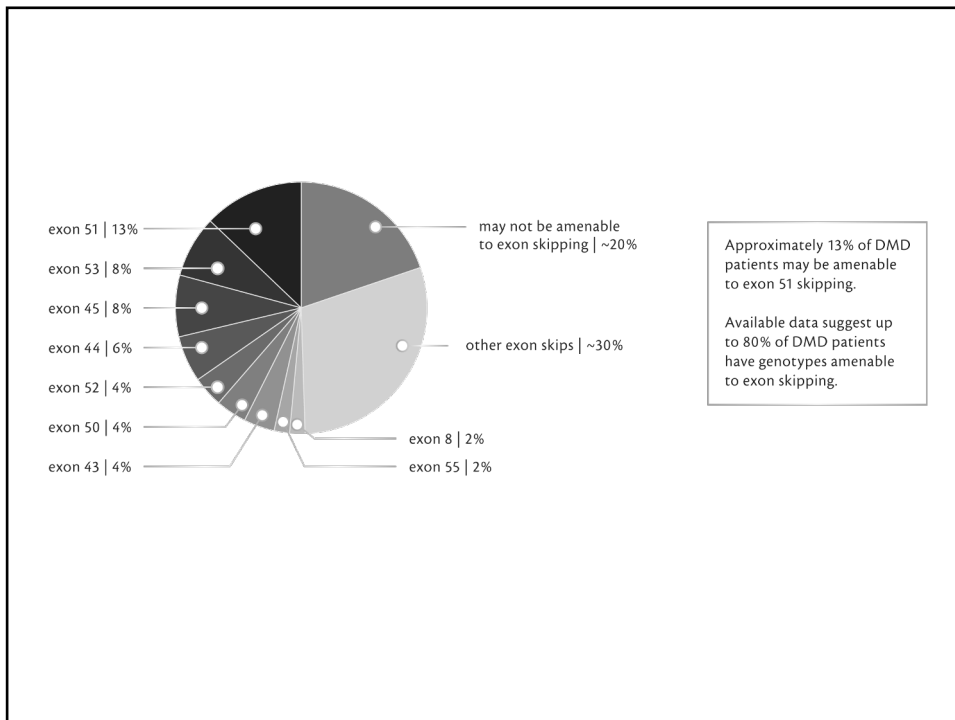
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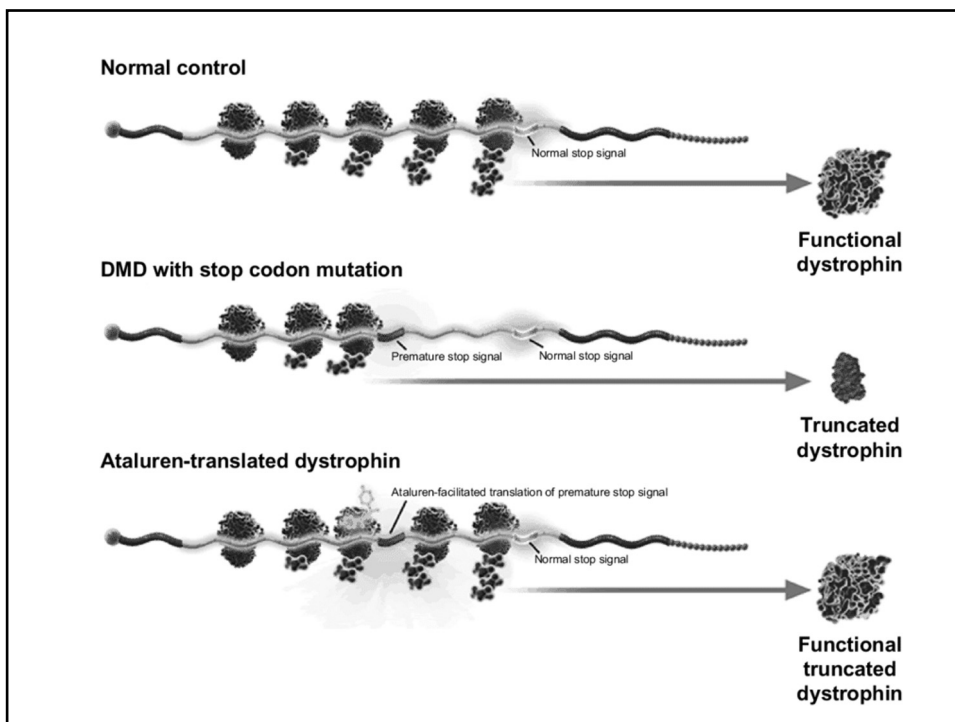
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Pharmacogenetics

A few clinically actionable tests

To be done « on demand » or »prospectively »?

Ethnic variations in allele frequencies

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Pharmacogenetics

Novel mutation-specific treatments for genetic diseases

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