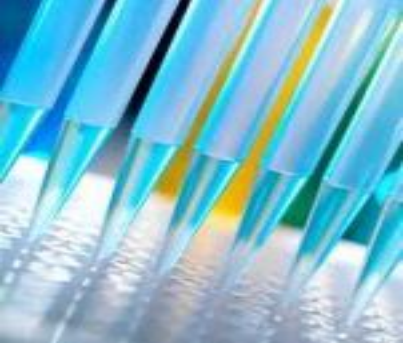
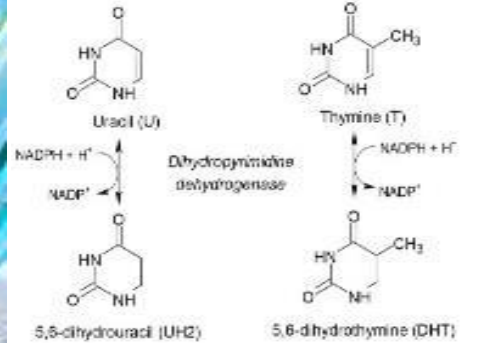





CORATA Belgique
30/06/2023

Amélioration de la sécurité du traitement au Fluoro-Pyrimidines basée sur l'évaluation de l'activité Dihydropyrimidine Déshydrogénase

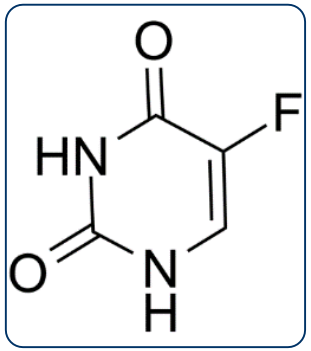
François BOEMER

CHU de Liège

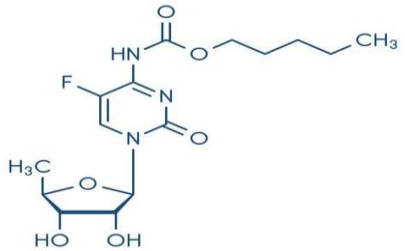
Unilab Lg.

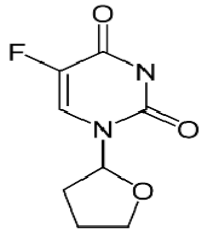
Fluoro-pyrimidines

- Fluoro-pyrimidines are fluorinated-pyrimidine antimetabolite drugs used in oncology.



- 5-Fluorouracil (5-FU) is commonly used in combination with other chemotherapy in patients with breast, colorectal, head and neck,... cancers.
  Capecitabine and Tegafur are prodrugs of 5-FU





13.1. Chimiothérapie

13.1.1. Agents alkylants

13.1.2. Antimétabolites

Les antimétabolites interfèrent avec la synthèse des acides nucléiques et des protéines.

13.1.2.1. Méthotrexate (à fortes doses)

13.1.2.2. Analogues des purines

13.1.2.3. Analogues des pyrimidines

13.1.2.4. Autres antimétabolites

13.1.3. Antibiotiques antitumoraux

13.1.4. Inhibiteurs de la topo-isomérase

13.1.5. Inhibiteurs des microtubules

13.2. Thérapie ciblée

13.3. Immunothérapie

13.4. Antitumoraux divers

13.5. Médicaments antihormonaux utilisés en oncologie

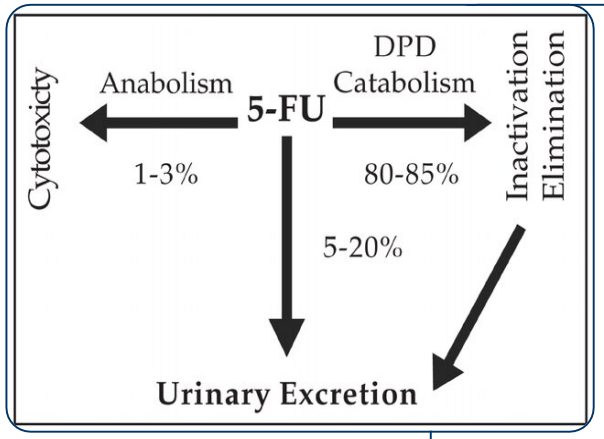
Table 1: Regimens that include 5-FU or capecitabine and their indications[A]

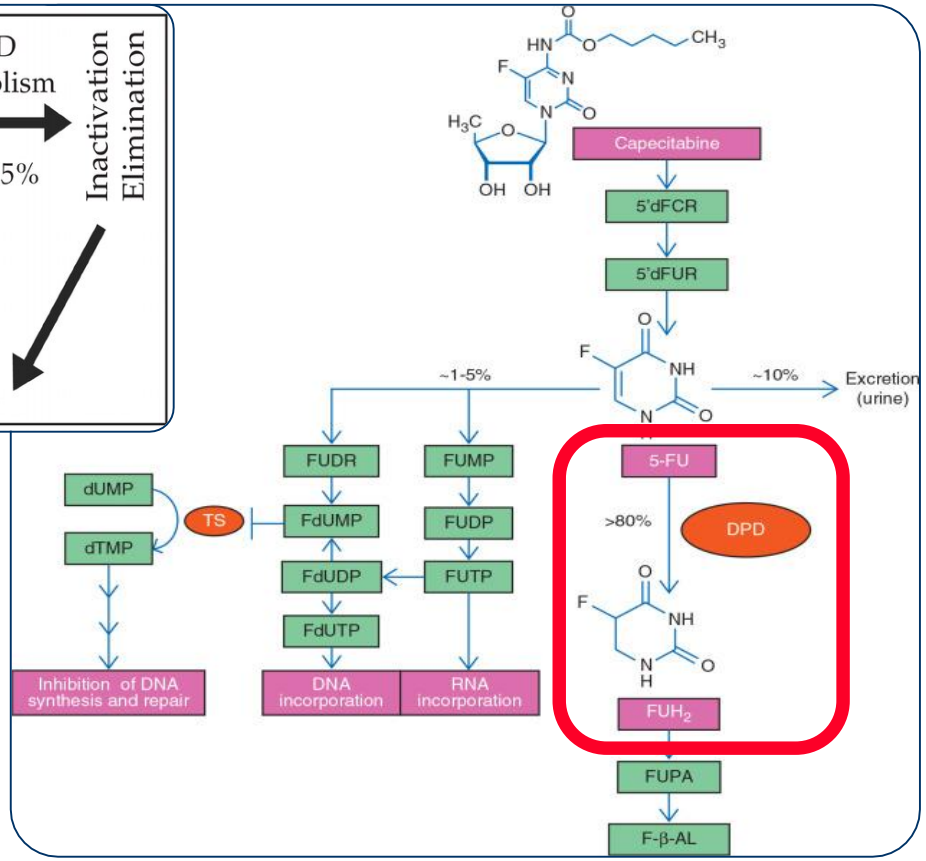
Anal cancer	Locoregional	Mitomycin + **5-fluorouracil** + RT
		5-fluorouracil + cisplatin + external beam RT
	Advanced	Cisplatin + **5-fluorouracil** by CIV
Gallbladder cancer and Cholangiocarcinoma	Advanced	Gemcitabine + **capecitabine**
		Capecitabine + oxaliplatin
		Mitomycin + **capecitabine**
Breast cancer	Adjuvant	Cyclophosphamide + epirubicin + **5-fluorouracil** (FEC) → docetaxel
		Cyclophosphamide + epirubicin + **5-fluorouracil** (FEC) → weekly paclitaxel
		Docetaxel + trastuzumab followed by cyclophosphamide + epirubicin + **5-fluorouracil** (FEC)
	Adjuvant / metastatic	Cyclophosphamide + epirubicin + **5-fluorouracil** (FEC 100)
		Cyclophosphamide + methotrexate + **5-fluorouracil** (CMF)
	Metasatic	**Capecitabine**
		Docetaxel + **capecitabine**
		Ixabepilone + **capecitabine**
		Capecitabine + trastuzumab
Carcinoma of unknown primary	Refractory or recurrent	Oxaliplatin + **capecitabine**
Cervical cancer	Initial	RT + cisplatin + **5-fluorouracil**
Colorectal cancer	Locally advanced	RT + **capecitabine**
	Adjuvant	**Capecitabine** + oxaliplatin (XELOX)
	Adjuvant / Advanced	**Bolus fluorouracil** + leucovorin (Roswell Park regimen)
		Bolus **5-fluorouracil**
		Capecitabine
	Metastatic / Adjuvant	Leucovorin + infusional **5-fluorouracil** + oxaliplatin (FOLFOX)
	Metastatic	Infusional **5-fluorouracil**
		Irinotecan + bolus **5-fluorouracil** + leucovorin (IFL)
		Leucovorin + infusional **5-fluorouracil** + irinotecan (FOLFIRI)
		Cetuximab + FOLFOX-4
		Cetuximab + FOLFIRI
		Panitumumab + FOLFOX-4
		Panitumumab + FOLFIRI
		Ziv-aflibercept + FOLFIRI
		Bevacizumab + FOLFIRI
		Bevacizumab + FOLFOX
Esophageal cancer	Locally advanced	**5-fluorouracil** + cisplatin + RT
		Oxaliplatin + protracted infusion **5-fluorouracil** + RT prior to surgery
		Cisplatin + **capecitabine**
	Recurrent / Metastatic	Epirubicin + cisplatin + **5-fluorouracil** (ECF)
		5-fluorouracil + cisplatin
		Docetaxel + cisplatin + **5-fluorouracil** (DCF)
		Oxaliplatin + **5-fluorouracil** + leucovorin (FOLFOX)
		Epirubicin + oxaliplatin + **capecitabine** (EOC, EOX)
		Irinotecan + **5-fluorouracil** + leucovorin (FOLFIRI)
		Cisplatin + **capecitabine** + trastuzumab
Gastric cancer	Adjuvant	**5-fluouracil** + leucovorin + RT
		Epirubicin + cisplatin + **5-fluorouracil** (ECF)
		Capecitabine + oxaliplatin after D2 gastrectomy
	Advanced disease	Epirubicin + cisplatin + **5-fluorouracil** (ECF)
		Docetaxel + cisplatin + **5-fluorouracil** (DCF)
		Epirubicin + cisplatin + **5-fluorouracil** (ECF)
		Epirubicin + cisplatin + **capecitabine** (ECX)
		Epirubicin + oxaliplatin + **5-fluorouracil** (EOF)
		Epirubicin + oxaliplatin + **capecitabine** (EOX)
		Cisplatin + **5-fluorouracil** (FUP)
		Cisplatin + **5-fluorouracil** (CF)
		Irinotecan + **5-fluorouracil** (IF)
Head and neck cancer	Chemoradiation	Carboplatin + **5-fluorouracil** + RT
		Cisplatin + RT followed by cisplatin + **5-fluorouracil**
	Advanced disease	Docetaxel + cisplatin + **5-fluorouracil** (TPF)
		Cisplatin + **5-fluorouracil** (PF)
	High risk	Postoperative RT + cisplatin + **5-fluorouracil**
	Metastatic / Recurrent	Cisplatin + **5-fluorouracil**
		Carboplatin + **5-fluorouracil**
		Cisplatin or carboplatin + **5-fluorouracil** + cetuximab
PNETS	Advanced / Metastatic	Streptozocin + **5-fluorouracil**
Pancreatic cancer	Advanced / Metastatic	Oxaliplatin + irinotecan + **5-fluorouracil** + leucovorin (FOLFIRINOX)
		Oxaliplatin + folinic acid (leucovorin) + **5-fluorouracil** (OFF + BSC (best supportive care)
Vaginal cancer	Advanced	Cisplatin + **5-fluorouracil** + RT

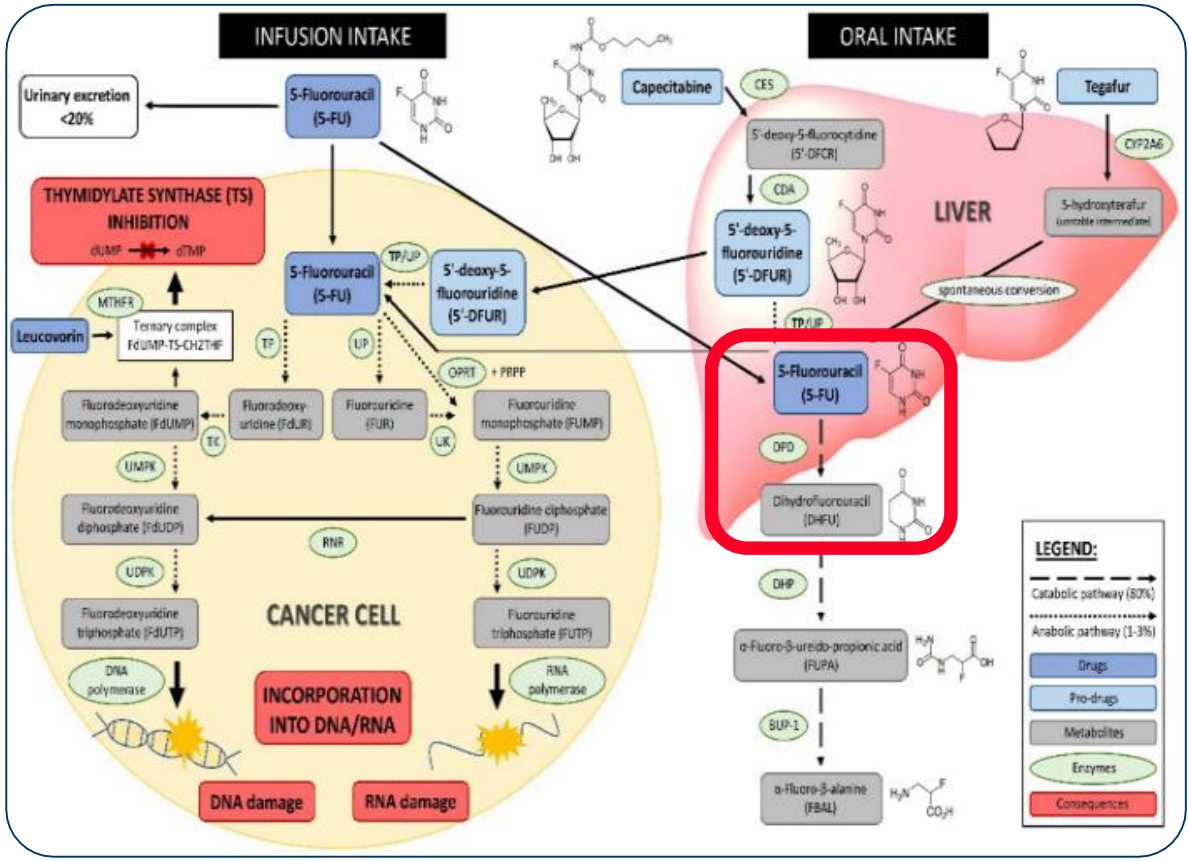
[A]Source: Hematology Oncology Therapy. Boyladzis. Kohler, Frame, Fojo 2nd Edition 2014[54]
Abbreviations: RT, radiation therapy; CIV, continuous intravenous infusion

Fluoro-pyrimidines metabolism

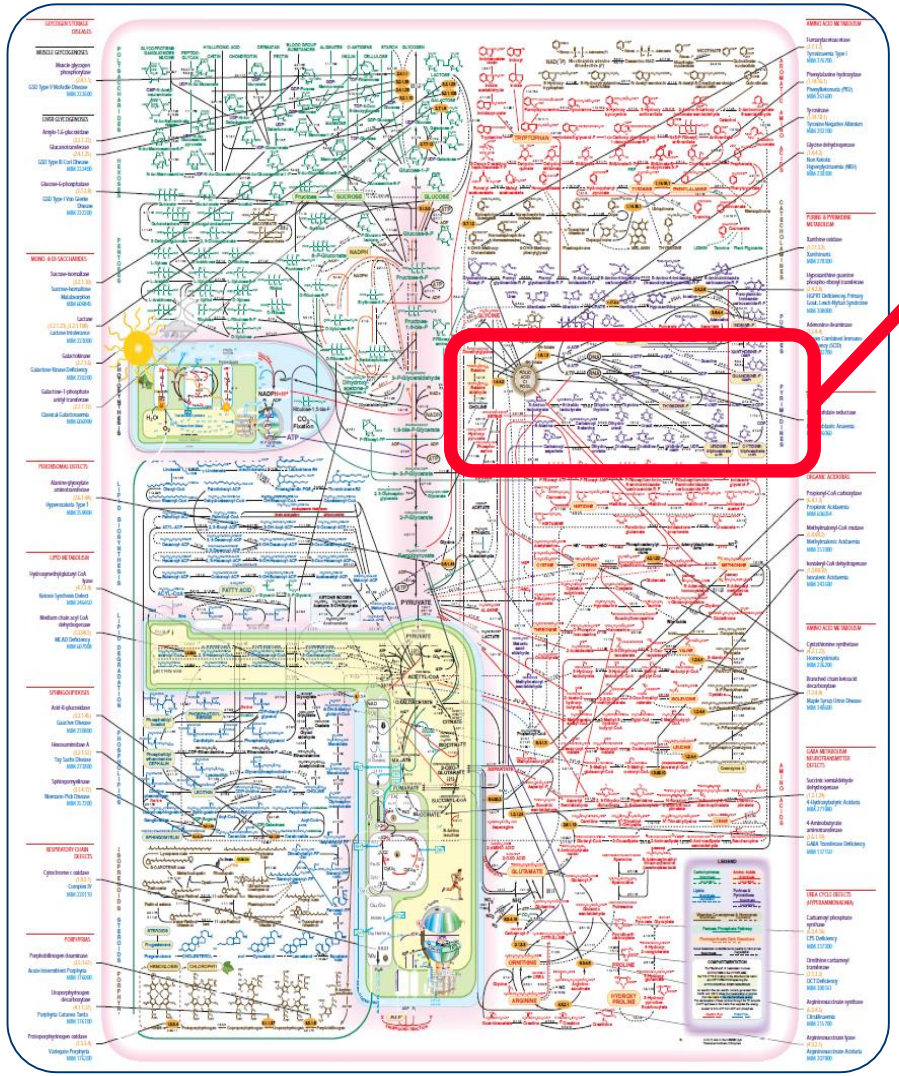
- Metabolism of 5-FU is mainly mediated by Dihydropyrimidine Dehydrogenase (DPD), an enzyme encoded by the DPYD gene with a limiting function in the degradation of pyrimidine bases. DPD is responsible for the degradation of more than 80% of standard doses of 5-fluorouracil.

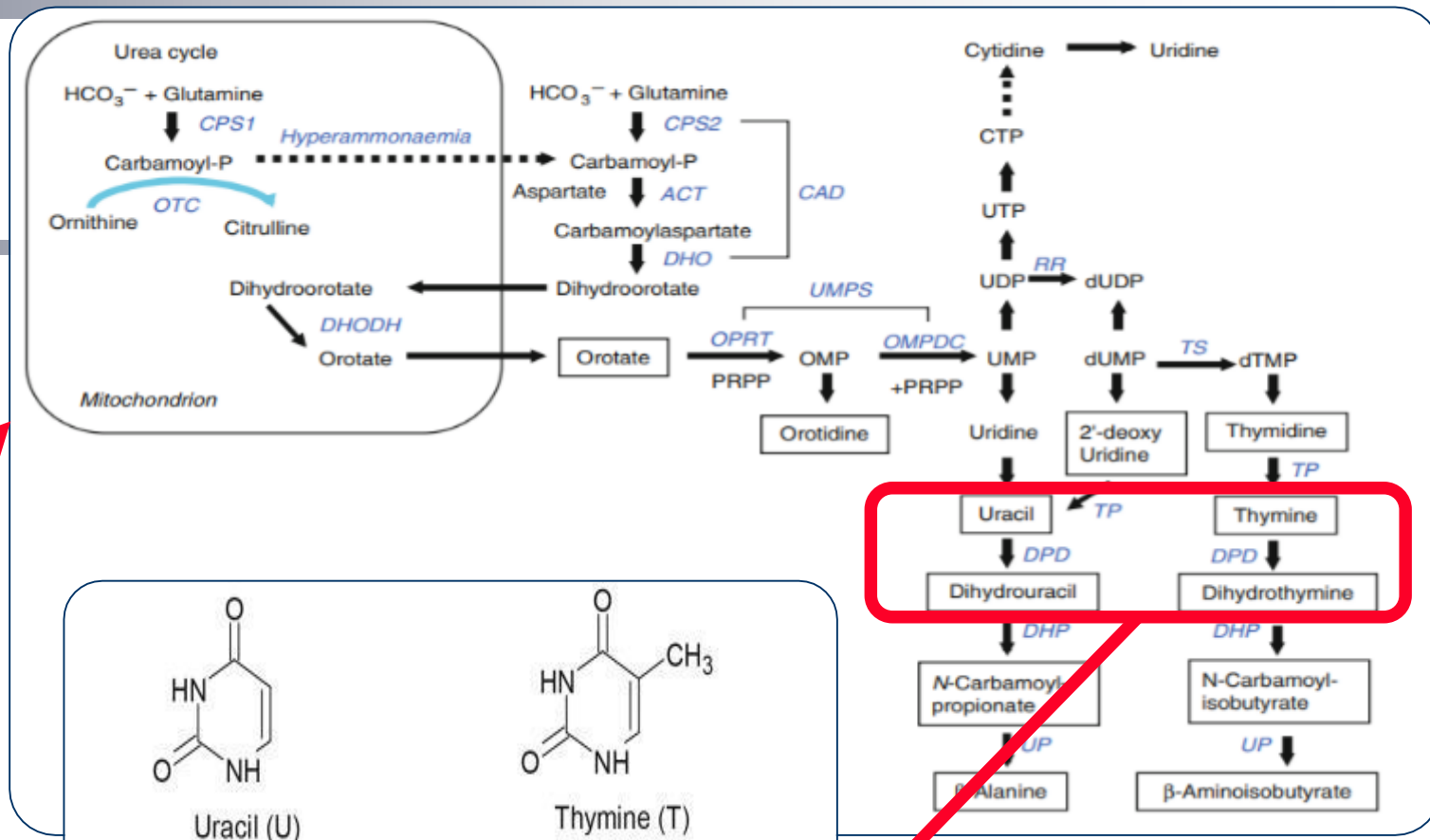


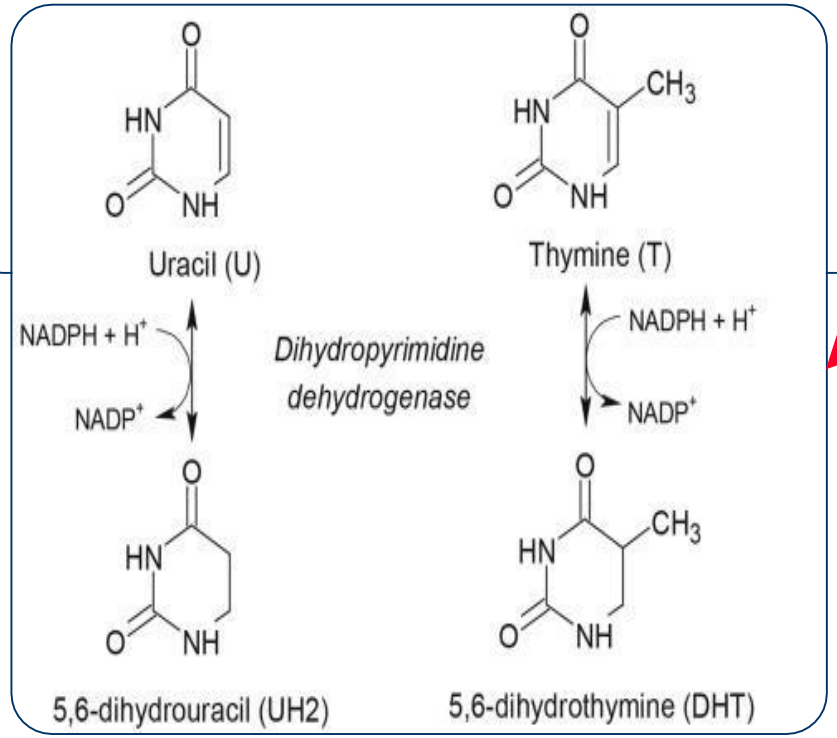




DPD & Pyrimidine metabolism







Fluoro-pyrimidines toxicity

- **A 30-years old story**

Familial Pyrimidinemia and Pyrimidinuria Associated with Severe Fluorouracil Toxicity

Mendel Tuchman, M.D., Joel S. Stoeckeler, M.D., David T. Kiang, M.D., Ph.D., Robert F. O'Dea, M.D., Ph.D., et al.

The NEW ENGLAND JOURNAL of MEDICINE
1985; 313:245-249

Dehydropyrimidine Dehydrogenase Deficiency in a Cancer Patient Undergoing 5-Fluorouracil Chemotherapy

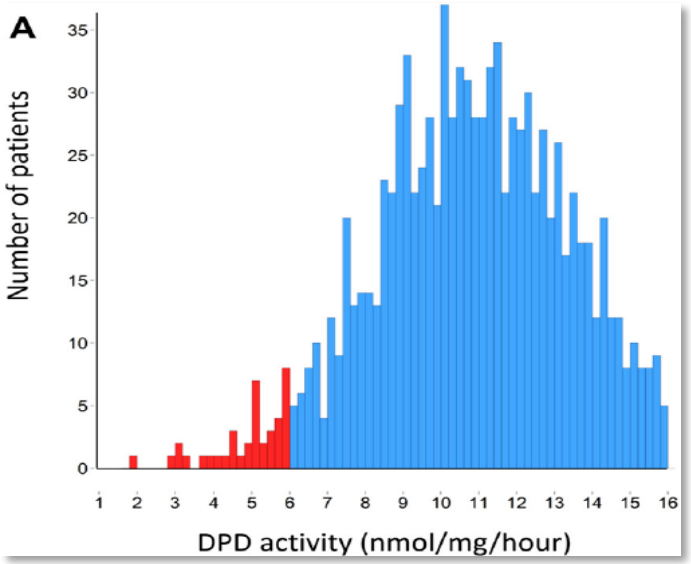
H.B. SCHNEIDER and H. BECKER ANTICANCER RESEARCH *24*: 1091-1092 (2004)

Dihydropyrimidine Dehydrogenase (DPD) deficiency

- AR disorder, characterized by a wide range of severity with neurological problems (including seizures, intellectual disability, microcephaly, autistic behavior) in some individuals and no symptoms in others

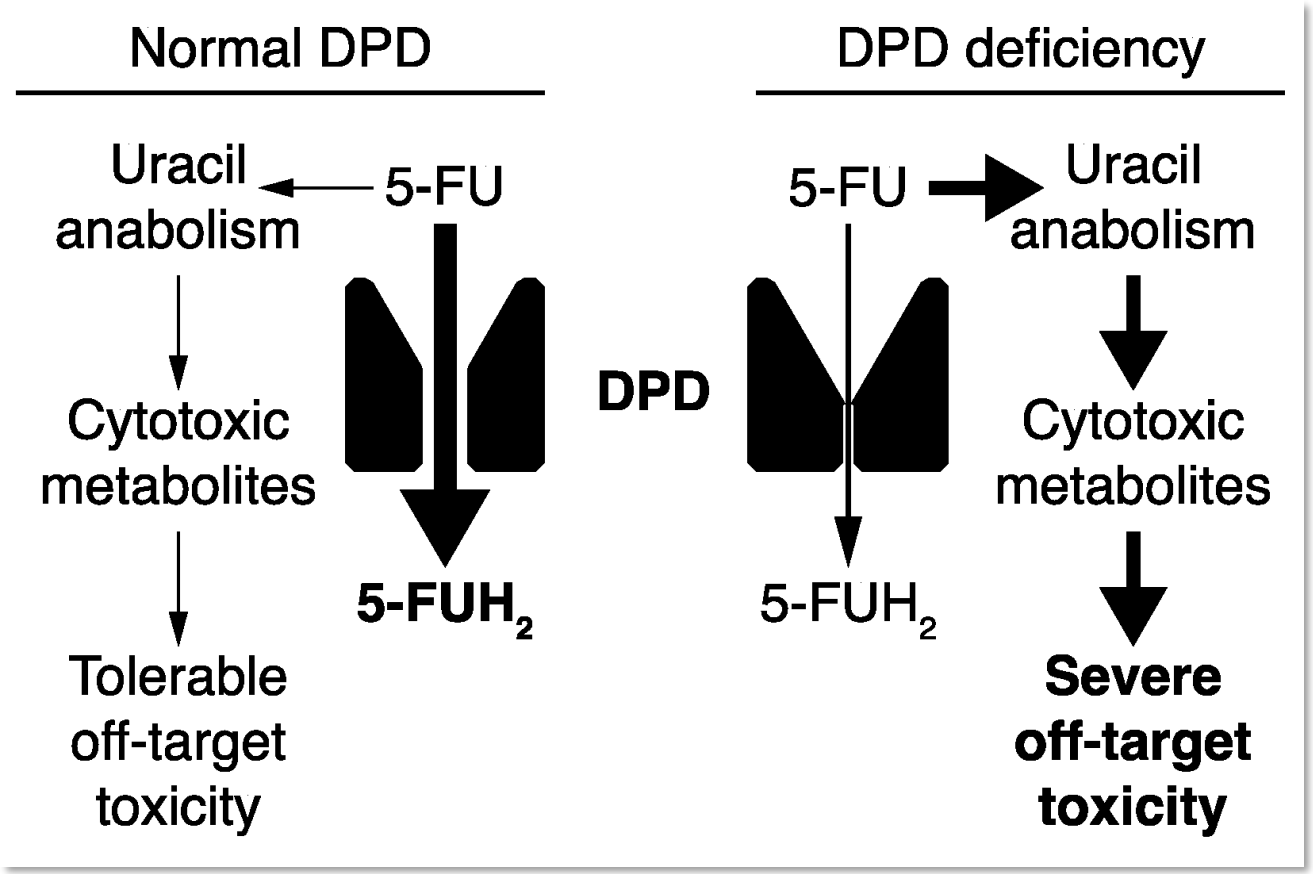
- Approximately 5-8% of the Caucasian population has a partial DPD deficiency, which can cause fatal toxicity when using Fluoro-pyrimidines.
  Up to 0.5% of the population is fully DPD deficient.

  - 17000 new patients potentially exposed yearly to Fluoro-pyrimidines in Belgium
    - 1300 present partial DPD deficiency
    - 85 have non-functional DPD



Fluoro-pyrimidines toxicity

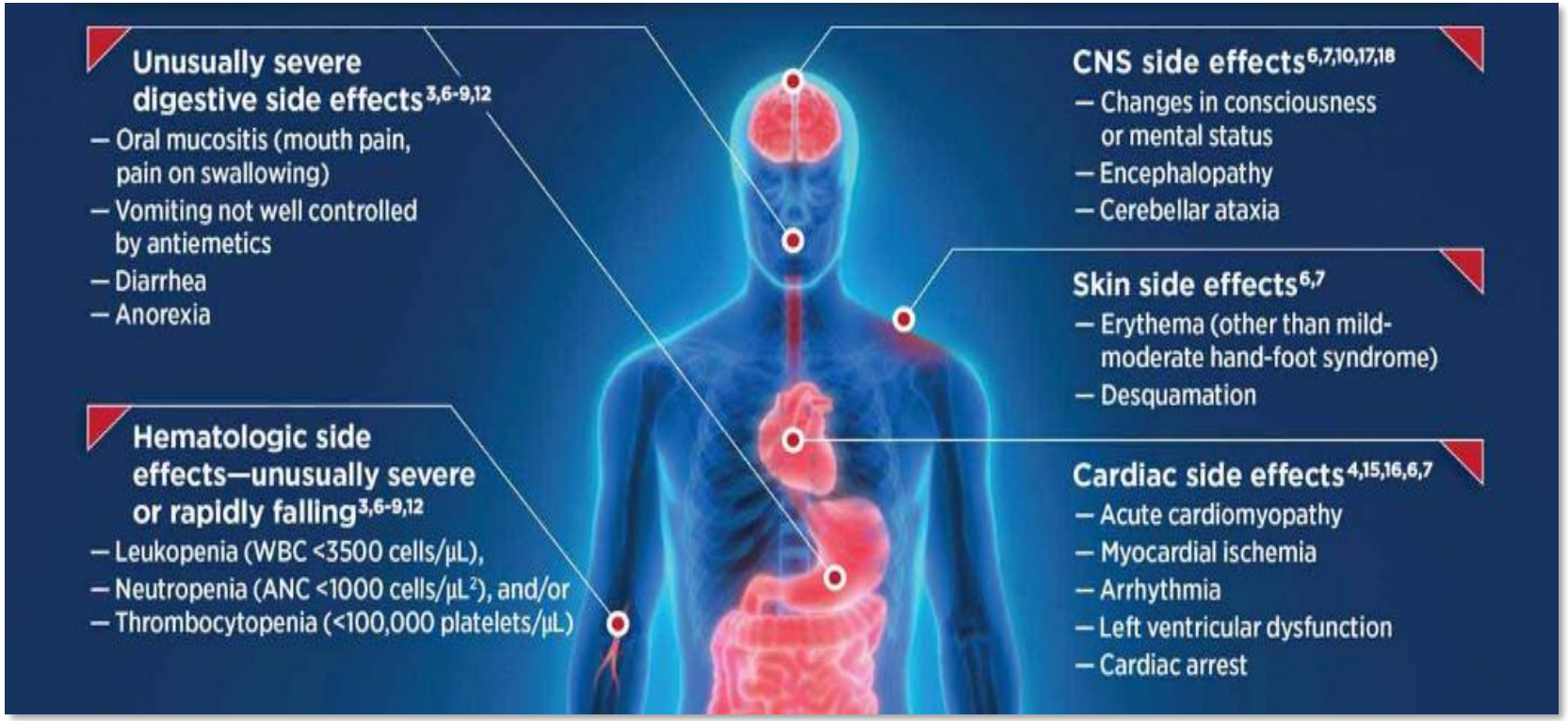
- For patients with total DPD deficiency, loss of this enzyme activity increases the half-life of 5-FU, leading to toxic accumulation.

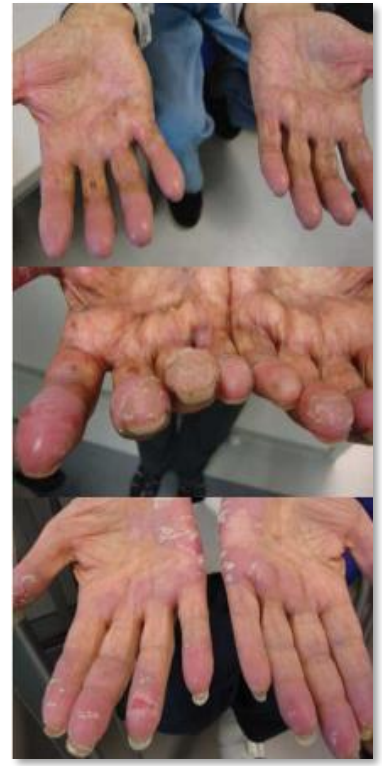


Fluoro-pyrimidines toxicity

- Acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions (ie. fever, mucositis, vomiting, diarrhea, neutropenia, skin effects, neurotoxicity, cardiotoxicity).

  Complete deficiency may lead to patient's death due to MOF.





Fluoro-pyrimidines toxicity

5FU a toxic drug

► In France with an estimated : ~ 80 000-100 000 pts /year treated with 5FU

Patients receiving a systemic CT (Sources INCa 2012)	Fluoropyrimidines estimate (FUSAFE)
- 65 000 GI cancers	83%
- 56 000 breast cancer	50%
- 13 000 head and neck	66%

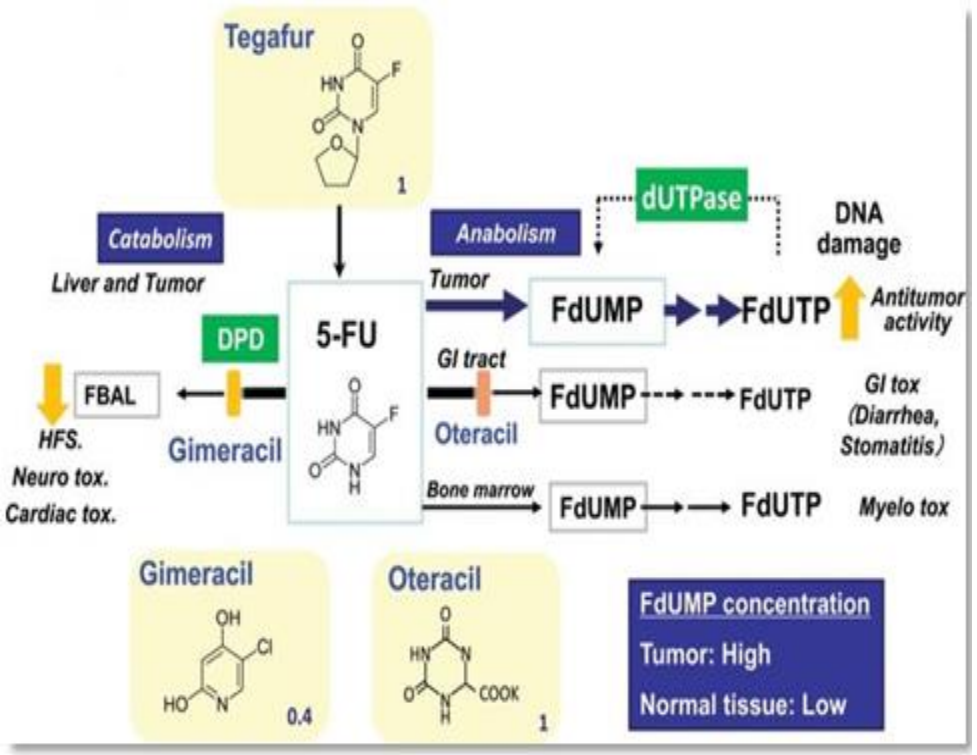
► **500 deaths/ year**

► **5000 major toxicities/ year**

Management of Fluoro-pyrimidines toxicity

- Dose adaptation / Treatment discontinuation
- Hemodialysis
- Oteracil: inhibitor of OPRT enzyme, used to reduce undesirable effect on GI mucosa
  Gimeracil: inhibitor of DPD enzyme, used to increase half-life of 5-FU, resulting in higher systemic concentrations

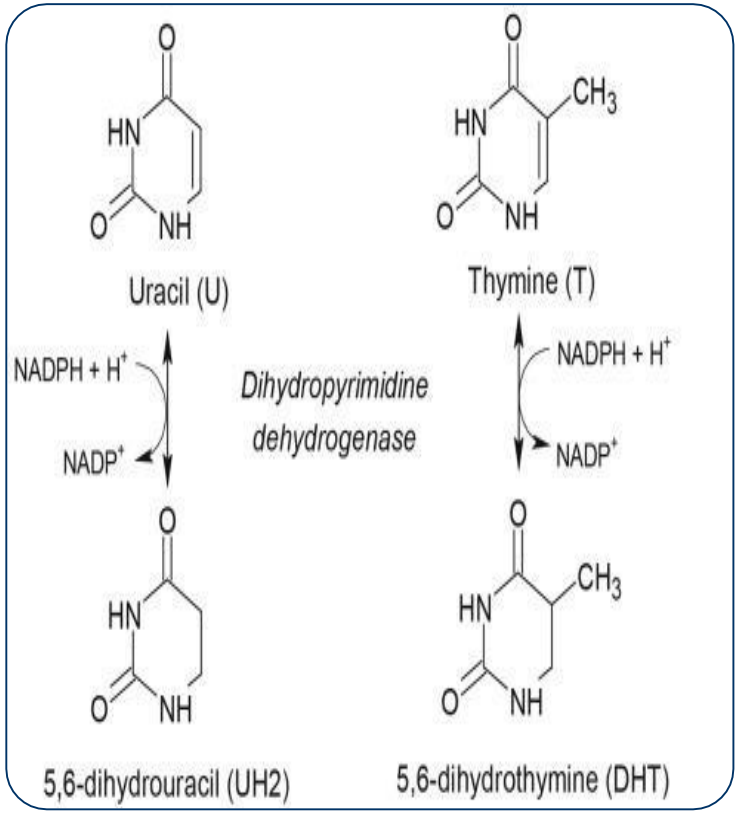
  > Association Tegafur/Oteracil/Gimeracil: Teysuno®



- Antidote: Uridine triacetate (Vistogard®), orally active prodrug of the naturally occurring nucleoside uridine which competitively inhibits cell damages caused by 5-FU
  Low availability, should be administered within 96h after 5-FU administration

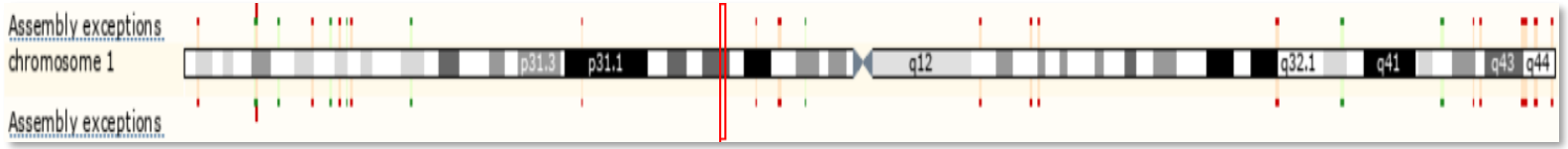
Assessment of DPD Activity

- Assessment of DPD activity rely on:
  - (Targeted) Genotyping of DPYD gene
  - Phenotyping
    - Uracile / Dihydrouracile (Thymine / Dihydrothymine) on plasma
    - DPD activity on leukocytes (PBMC)
- 5-FU monitoring



DPYD gene

- Chromosome 1p21.3
  23 exons



- > 1000 variants described

Exons/ Introns: Translated sequence | Flanking sequence | Intron sequence | UTR

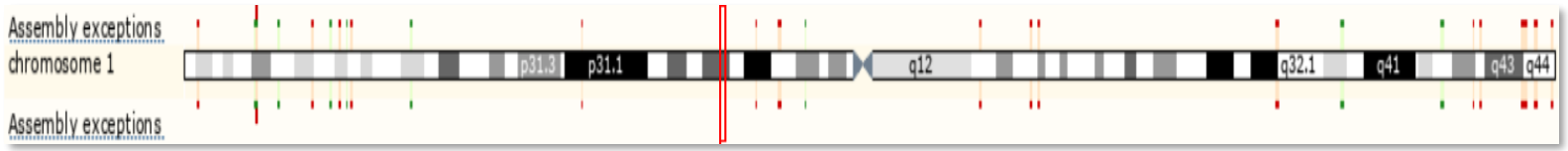
Variants: 3 prime UTR | 5 prime UTR | Coding sequence | Frameshift | Inframe deletion | Inframe insertion | Missense | Protein altering variant | Splice acceptor | Splice donor | Splice region | Start lost | Stop gained | Synonymous

Markup: loaded

No.	Exon / Intron	Start	End	Start Phase	End Phase	Length	Sequence
12	ENSE00001416589	97,549,744	97,549,560	1	0	185	TAAAAGAAGCCTTGAGCCCTATAAAATTTAACAGATGGGGTCTCCCAGAAGTAGATCCAG AAACTATGCAAACTAGTGAAGCATGGGTATTTGCAGGTGGTGATGTCGTTGGTTTGGCTA ACACTACAGTGGAATCGGTGAATGATGGAAAGCAAGCTTCTTGGTACATTCACAAATACG TACAG
	Intron 12-13	97,549,559	97,515,942			33,618	gtaggcatttgccatcatttccact.....ccaagtattggtttgtattttgcag
13	ENSE00001175948	97,515,941	97,515,726	0	0	216	TCACAATATGGAGCTTCCGTTTCTGCCAAGCCTGAACTACCCCTCTTTTACACTCCTATT GATCTGGTGGACATTAGTGTAGAATGGCCGGATTGAAGTTTATAAATCCTTTTGGTCTT GCTAGCGCAACTCCAGCCACCAGCACCATCAATGATTCGAAGAGCTTTTGAAGCTGGATGG GGTTTTGCCCTCACCAAAACTTTCTCTCTTGATAAG

DPYD gene

- Chromosome 1p21.3
  23 exons

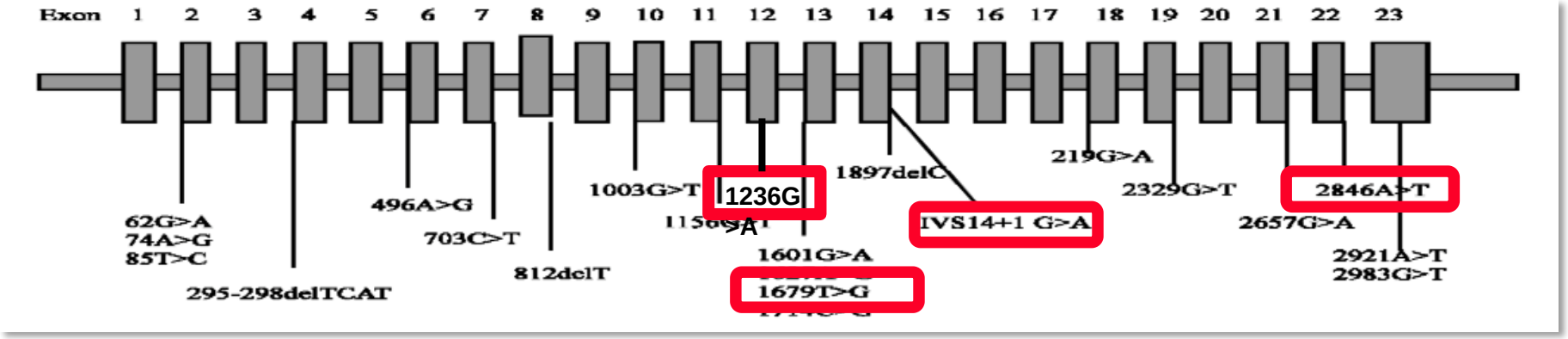


- > 1000 variants described

- 'Hotspots'
  - c.1679T>G, p.I560S (DPYD*13), rs55886062
  - c.1905+1G>A (IVS14+1G>A, DPYD*2A), rs3918290
  - c.2846A>T, p.D949V, rs67376798
  - c.1236G>A, p.E412E (Hap3B), rs56038477

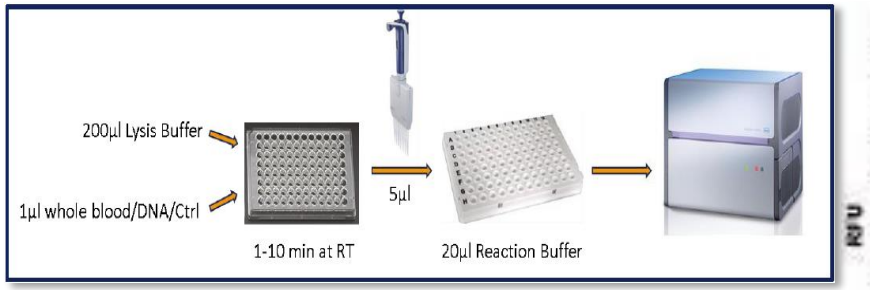
Tableau 3. Principaux variants *DPYD* recherchés et fréquences estimées/calculées dans les populations d'origine caucasienne[14]

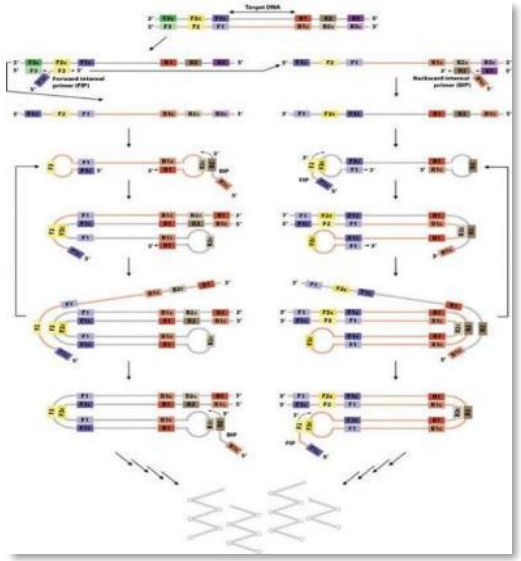
Variants *DPYD*	Fréquence en population (sources bibliographiques)	Taux de porteurs		Nombre de porteurs / 100 000 patients	
		hétérozygotes	homozygotes	hétérozygotes	homozygotes
***DPYD**2A** (IVS14+1G>A, c.1905G>A)	**0,8 %** (11, 13, 24, 29)	1,5 %	0,01 %	1 500	10
***DPYD**13** (c.1679T>G / p.I560S)	**0,1 %** (8, 11, 23, 24, 29)	0,2 %	0,0001 %	200	0,1
c.2846A>T (p.D949V)	**0,6 %** (11, 23, 24, 28, 29)	1 %	0,004 %	1 000	4
HapB3[15]	**2,4 %** (24, 29)	4,6 %	0,06 %	4 600	60

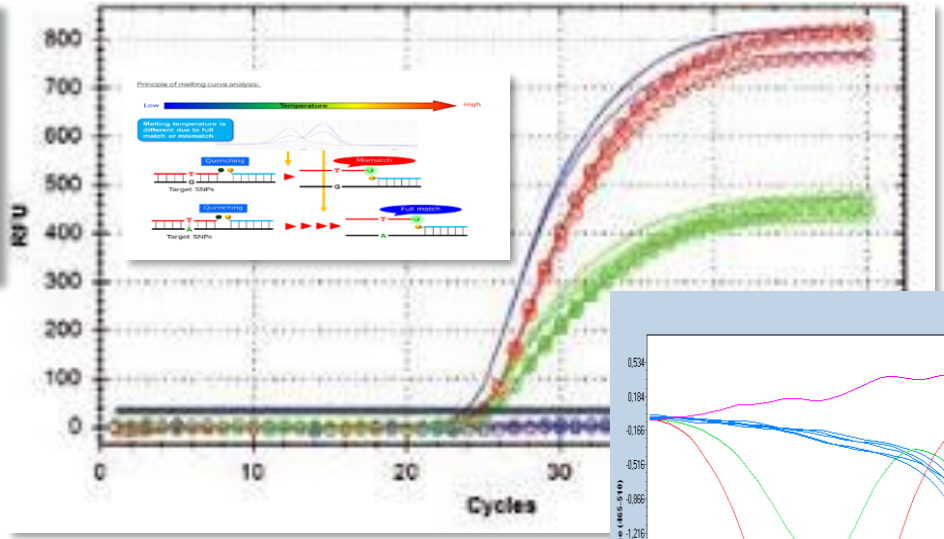


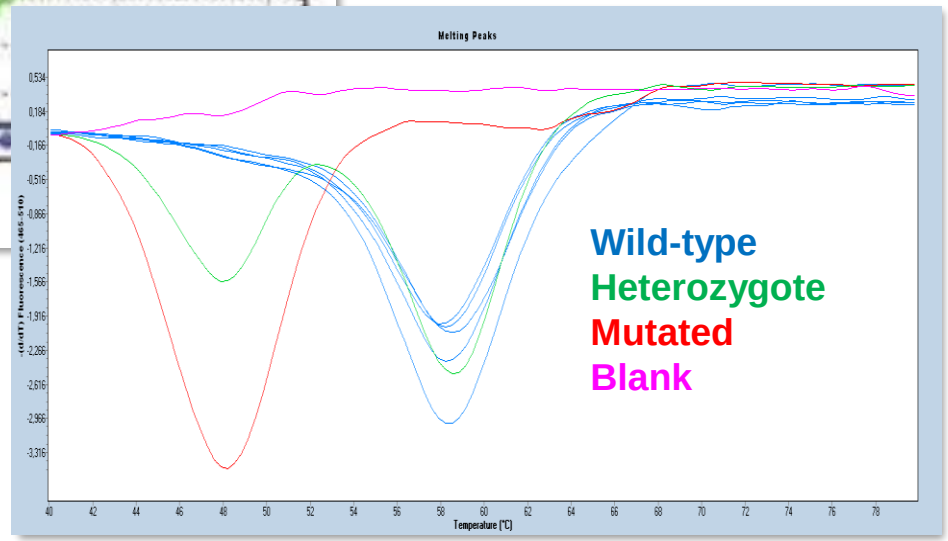
Genotyping assay

- LAMP (Loop-mediated isothermal amplification) or qPCR assay





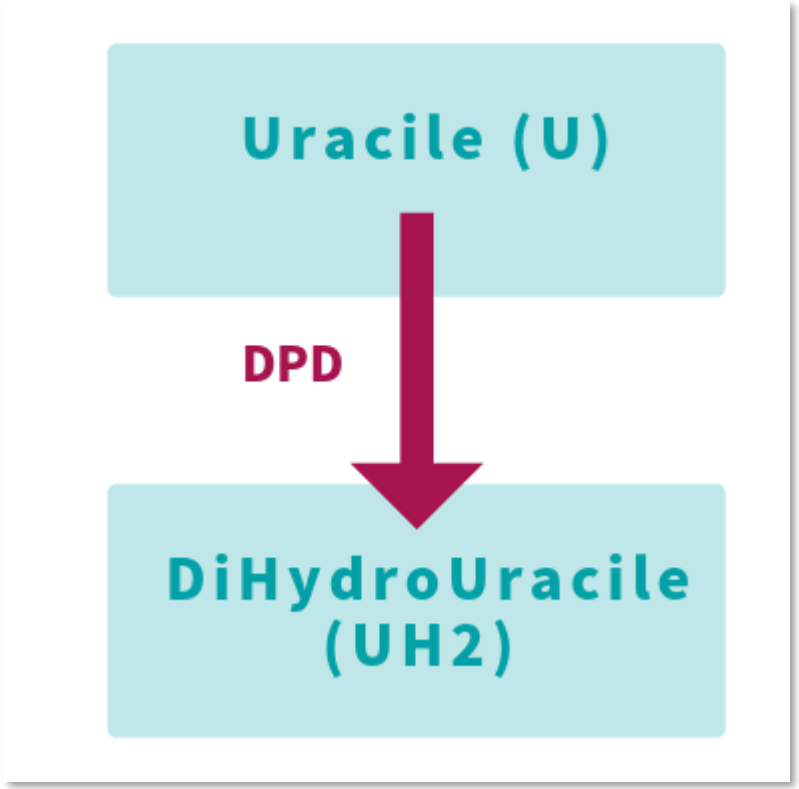




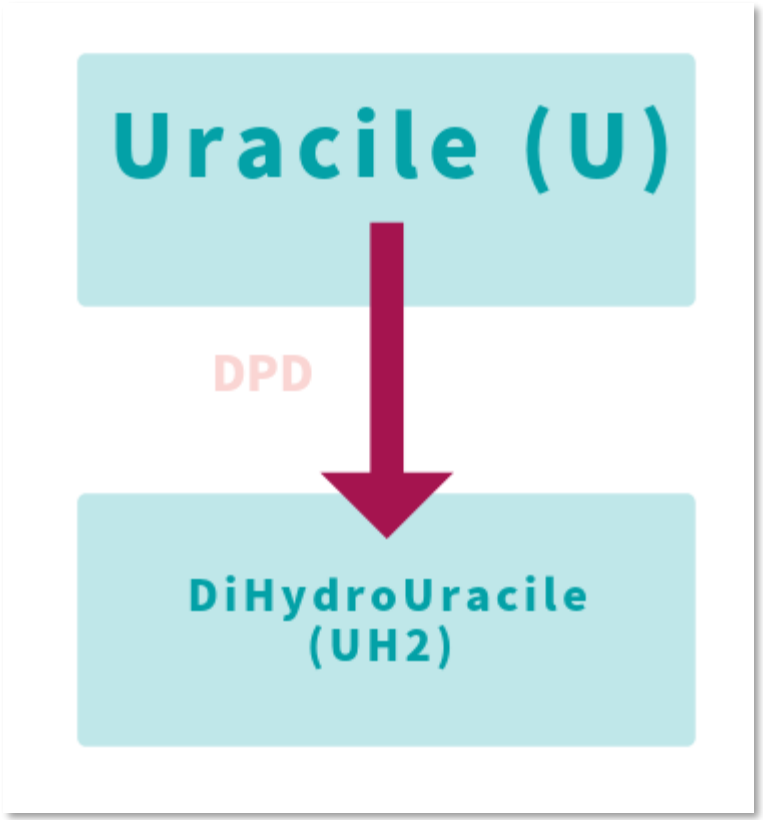
- Gene sequencing

Phenotyping assay

Functional DPD

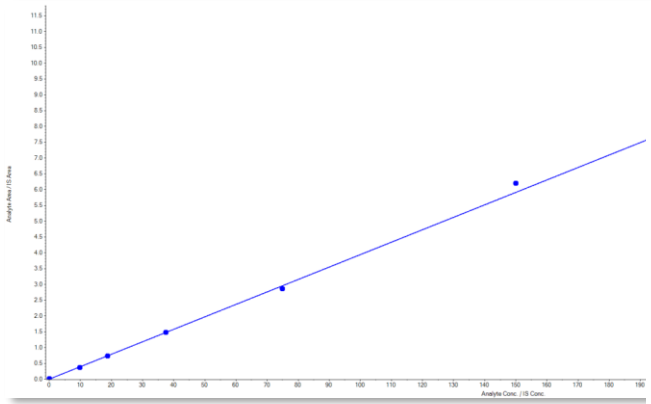


Deficient DPD

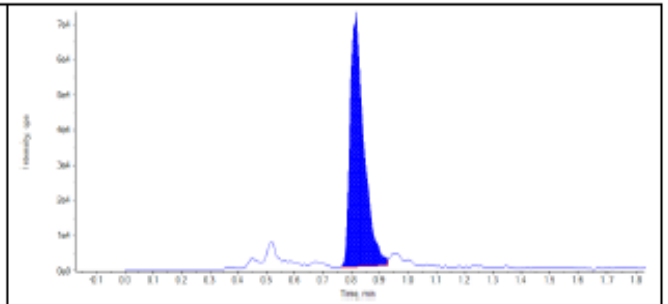


Phenotyping assay

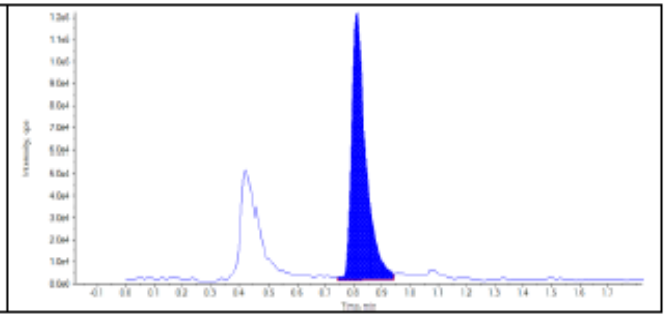
- LC-MS-MS (or HPLC-UV)
  - Measurement of Uracil (U) and Di-Hydrouracil (UH2) in plasma
  - Ratio UH2 / U



Sample Name:	14-210105-010101
Analyte:	U (113.100/70.000 Da)
RT (Exp. RT):	0.816 (0.826) min
Calculated Conc:	14.6 ng/mL
Area:	2.40e+005
Sample Type:	(Unknown)



Sample Name:	14-210105-010101
IS :	U_IS (116.100/71.000 Da)
RT (Exp. RT):	0.811 (0.822) min
Area:	4.27e+005
Sample Type:	(Unknown)



DPD testing & Dose adaptation

- Targeted genotyping

Table 1. Most frequent alleles found, based on a presentation of V haufroid, BGDO april 2019.

Haplotype	rsID	Nucleotide change	Protein change	Allele Functional Status	Activity Score	Ref
*2A	rs3918290[a]	c.1905 + 1 G > A	N/A	No function	0	14
*5	rs1801159	c.1627A>G	p.I543V	Normal	1	14
*9A	rs1801265	c.85 T > C	p.C29R	Normal	1	15
*13	rs55886062	c.1679 T > G	p.I560S	No function	0	14
	rs67376798	c.2846A>T	p.D949V	Decreased	0,5	16
HapB3	rs75017182, rs56038477, rs56276561	c.1129–5923 C > G, c.1236 G > A, c.483 + 18 G > A	N/A, p.E412E, N/A	Decreased	0,5	17

- Pros / cons of targeted genotyping

Sensitivity: 25 %
Specificity: 95 %

  - Simplicity of implementation
  - Prospectively validated genotype-based dosing guidelines

  - Quite low sensitivity to detect total (and partial) DPD deficiency
  - Only validated in Caucasian population

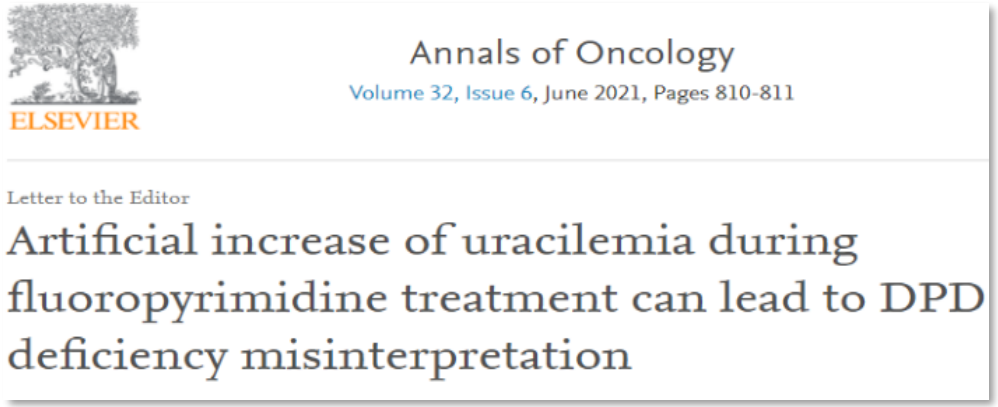
DPD testing & Dose adaptation

- Targeted genotyping : scoring system
  - *DPYD**2A and *DPYD**13 alleles
    - Non-functional enzyme (Activity score 0)
    - Homozygous patients: contra-indication for administration of 5-FU and capecitabine.
  - *DPYD* c.2846A>T and HapB3
    - Reduced DPD activity of 50% (Activity score 0.5),
    - Recent insights suggest an even lower activity and score (Activity score 0?).
  - Normal alleles (absence of any of the 4 variants)
    - Normal DPD activity (Activity score 1).
  - Activity should be counted for each allele and summed
    - Score 2: Normal dose
    - Score 1,5 or 1: 50% of the dose
    - Score 0,5 or 0: Contraindication

	Allelic frequency	heterozygous	homozygous	score
*DPYD*2A*	*0.5%*	Activity 50%	0%	0
*DPYD*13*	*0.1%*	Activity 25%		0
C.2846 A>T	*0.6%*	Activity 75%		0.5
Hap B3	*2%*	Activity 65%	50%	0.5

DPD testing & Dose adaptation

- Phenotyping
  - Uracil ≤16 ng/mL
    - Compatible with a normal DPD activity.
  - 16 ng/mL < Uracil < 150 ng/mL
    - Compatible with partial DPD deficiency.
    - Associated with increased risk of toxicity. Reduction of 50% is recommended.
  - Uracil ≥ 150 ng/mL
    - Compatible with total DPD deficiency.
    - Administration of 5-FU or capecitabine is contra-indicated, risk of severe toxicity is very high.
  - UH2 / U ratio and Uracil should be reported, potentially useful information.
  - Existence of interaction between 5-FU and U occurring when sampling is performed during fluoropyrimidine exposure => subsequent risk of misinterpreting U values with false positive results



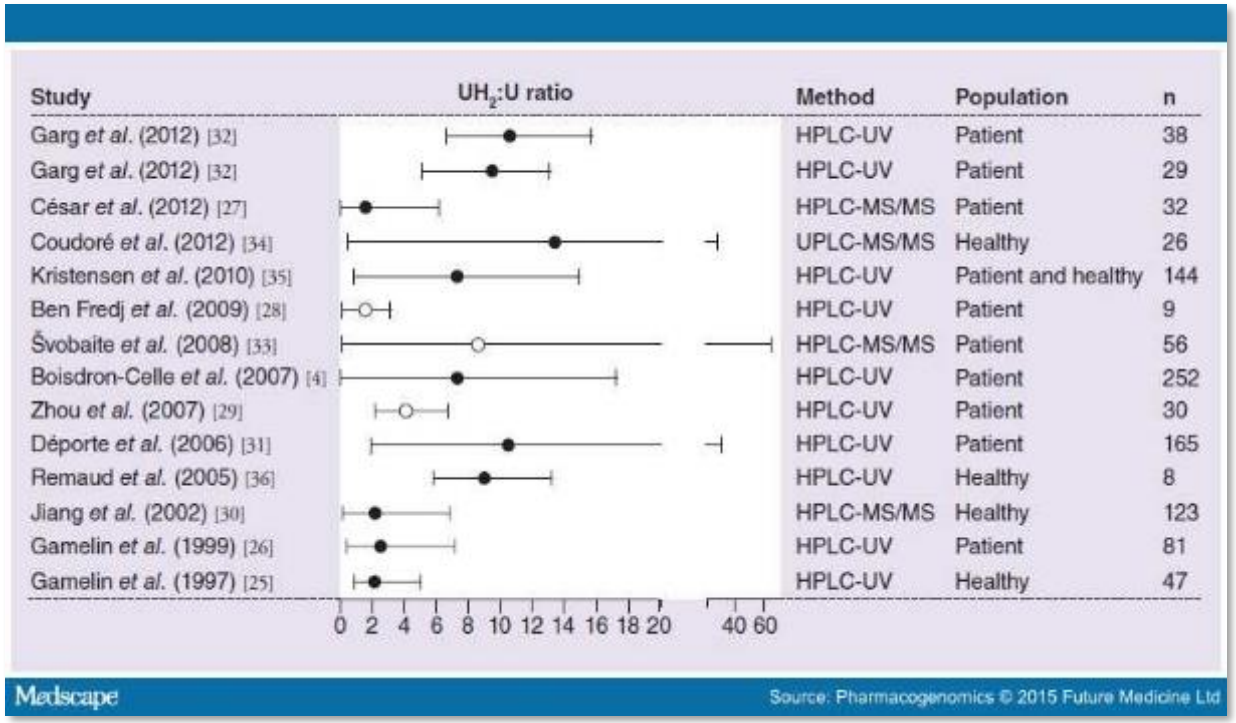
DPD testing & Dose adaptation

- Pros / cons of phenotyping

Sensitivity: 82 %
Specificity: 80 %

  - Better sensitivity, compared with the genotyping approach, to detect total and partial DPD deficiency
  - Interpretation not dependent of ethnic origin of the patient

  - Strict pre-analytical requirements (risk of false positive)
  - Phenotype-based dosing recommendations still need to be validated in prospective trials

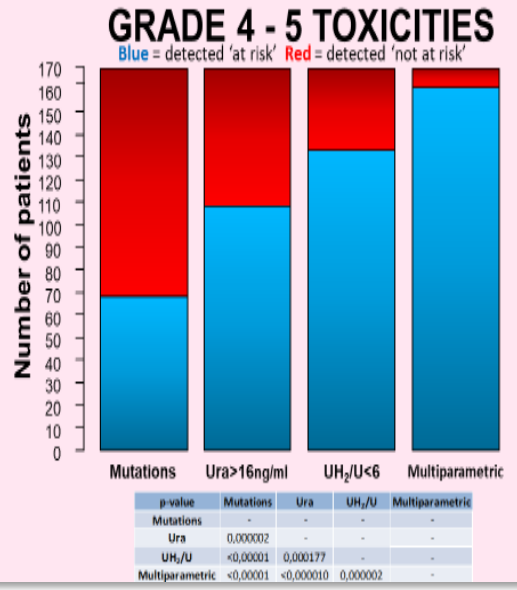


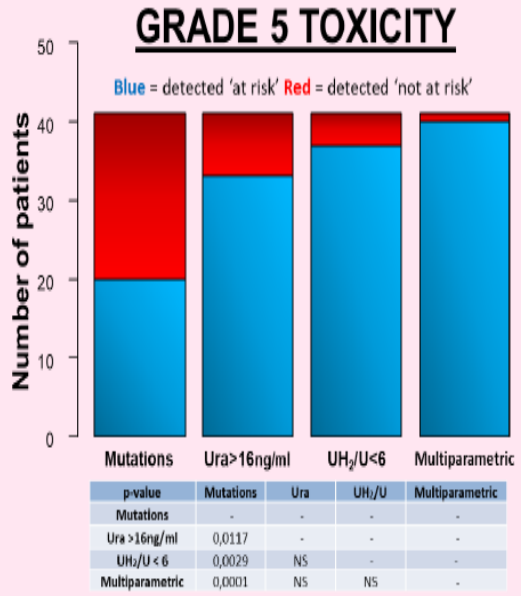
DPD testing & Dose adaptation

Toxicity grade	CTCAE v. 4.0	RTOG
Grade 1	Mild pain	Intestine: mild diarrhea, cramping, bowel movements five times daily, slight rectal discharge, or bleeding Subcutaneous/mucous membrane: slight induration, loss of subcutaneous fat, slight atrophy, and dryness
Grade 2	Moderate pain	Subcutaneous/mucous membrane: moderate fibrosis and moderate atrophy
Grade 3	Severe pain	Bone: severe pain, tenderness, complete arrest of bone growth, and dense bone sclerosis Subcutaneous/mucous membrane: severe induration, loss of subcutaneous tissue, marked atrophy, and complete dryness
Grade 4	Life threatening	Intestine: necrosis, perforation, and fistula
Grade 5	Death	Death

- Multiparametric approach:
  - Genotyping
  - Uracile
  - UH2 / U
  - Co-variables (age, sex, …)

The multiparametric approach is statistically (p<0.0001) the most efficient in terms of preventing grade 4 and 5 toxicity (death) following treatment with FPs. Around 290,000 patients are treated with FPs per year in the USA. Assuming a 0.2% mortality rate due to toxicity, **around 580 lives could be saved per year using the multiparametric pre-treatment test.**

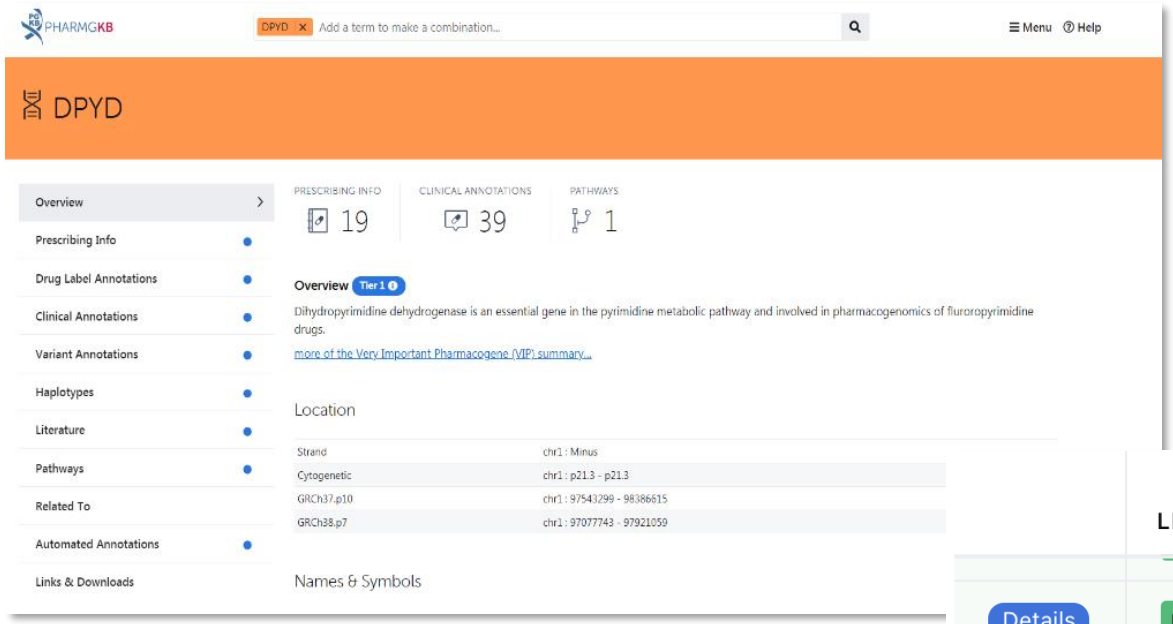


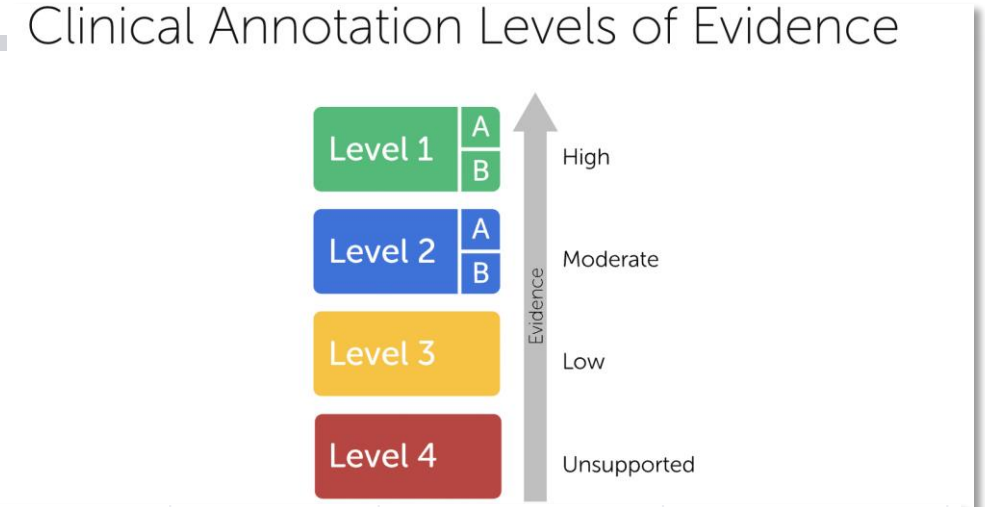


References

[1] Morel et al., Mol Cancer Ther. 2006; Morel et al. Clin Biochem 2007,
[2] Boisdron Celle M et al. Cancer Lett 2007,
[3] Henricks LM et al. Lancet Oncol 2018,
[4] HAS-INCa December 2018
[5] Boisdron-Celle M. et al. Seminars in Oncology 2017;
Patents : 0503616, 06290592.2

DPYD ressources - PHARMGKB





DPYD

- 661 variants reported
- 57 with clinical annotation

	LEVEL	VARIANT	GENE	MOLECULES	PHENOTYPE CATEGORIES
Details	Level 1A	rs72549303	DPYD	fluorouracil	Other
Details	Level 1A	rs67376798	DPYD	capecitabine	Toxicity
Details	Level 1A	rs3918290	DPYD	fluorouracil	Toxicity
Details	Level 3	rs748620513	DPYD	fluorouracil	Other
Details	Level 3	rs1184321568	DPYD	fluorouracil	Other
Details	Level 3	rs12022243	DPYD	capecitabine	Toxicity

DPD testing recommendations in Belgium


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 April 2020
EMA/229267/2020

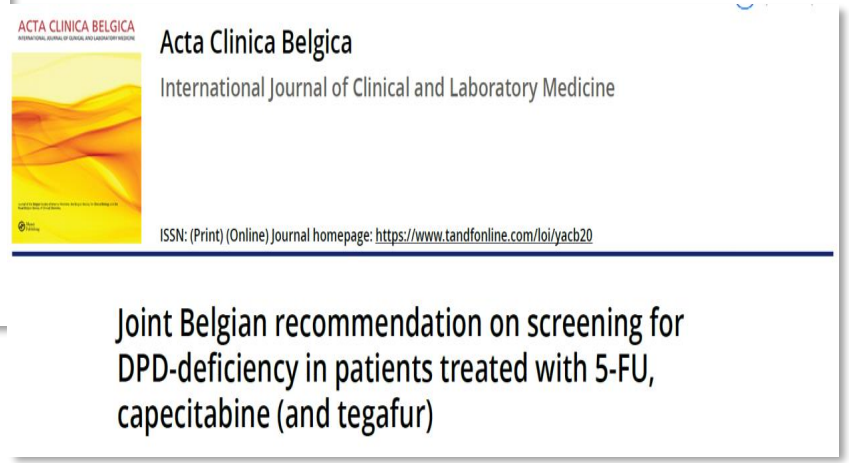
EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine


afmps fagg
agence fédérale des médicaments et des produits de santé
federaal agentschap voor geneesmiddelen en gezondheidsproducten

Bruxelles, le 02/06/2020

Information transmise sous l'autorité de l'AFMPS et de la Direction de la Santé, Division Pharmacie et Médicaments, au Luxembourg
Communication directe aux professionnels de la santé

Médicaments contenant du 5-fluorouracile (i.v.), de la capécitabine et du tégafur * : Tests de prétraitement pour identifier les patients déficients en DPD à risque accru de toxicité sévère



- DPD testing is recommended **before** any use of Fluoro-pyrimidines
- Stepwise Phenotype > Genotype approach is suggested
  - Higher sensitivity
  - Lower societal cost
- Collection of 2 blood samples in any cases (to reduce delays)

Foreign experiences & Perspectives

HAS
HAUTE AUTORITÉ DE SANTÉ

In France, pharmacists are not allowed anymore to deliver 5-FU or capecitabine without any DPD activity assessment

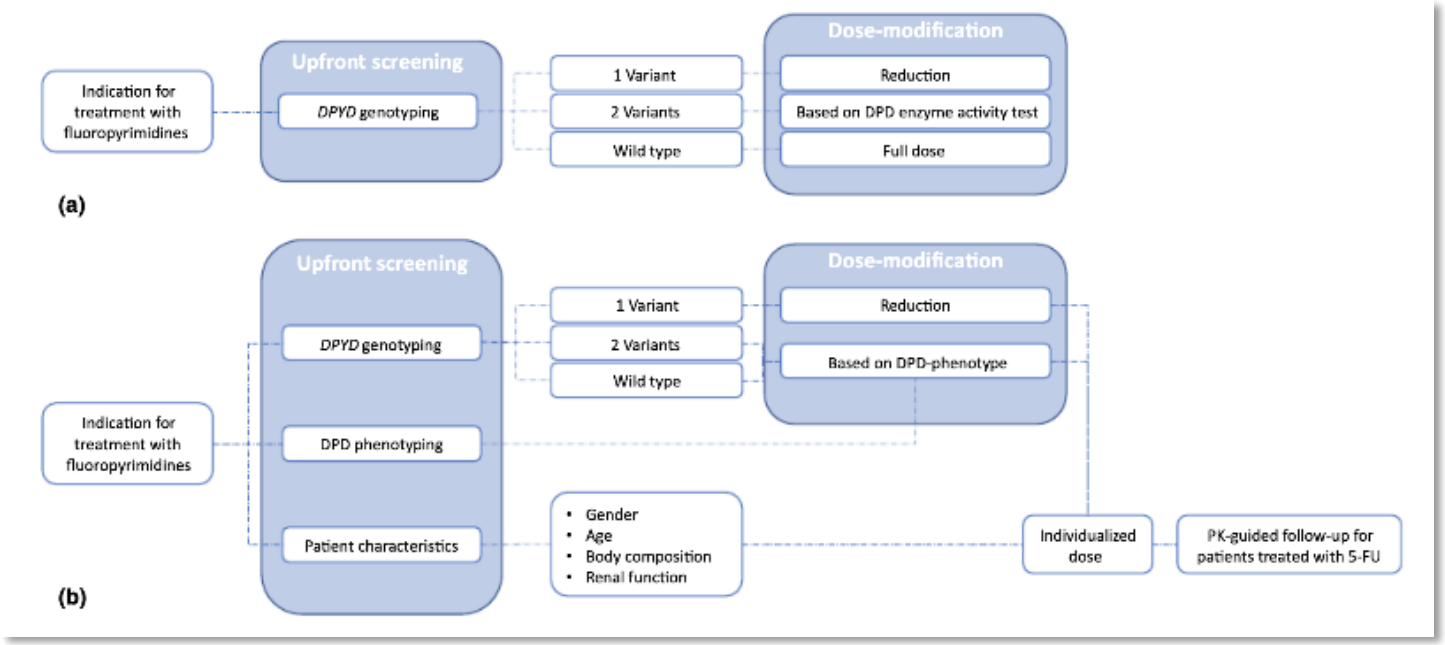
Oncology Research and Treatment

Review Article

Oncol Res Treat 2020;43:628–636
DOI: 10.1159/000510258

Received: July 11, 2020
Accepted: July 17, 2020
Published online: October 23, 2020

Dihydropyrimidine Dehydrogenase Testing prior to Treatment with 5-Fluorouracil, Capecitabine, and Tegafur: A Consensus Paper



Very slow awareness

JOURNAL OF CLINICAL ONCOLOGY EDITORIAL

Journal of Clinical Oncology

The Official Journal of the American Society of Clinical Oncology

Vol 12, No 11 November 1994

EDITORIAL

Dihydropyrimidine Dehydrogenase Activity and Fluorouracil Chemotherapy

1994

Predicting Fluorouracil Toxicity: Can We Finally Do It?

Hany H. Ezzeldin and Robert B. Diasio, *Mayo Clinic Cancer Center, Rochester, MN*

2008

Is It Finally Time for a Personalized Medicine Approach for Fluorouracil-Based Therapies?

Steven M. Offer and Robert B. Diasio, *Mayo Clinic, Rochester, MN*

2016

Cost-effectiveness of DPD testing

ELSEVIER

European Journal of Cancer
Volume 107, January 2019, Pages 60-67

Original Research

A cost analysis of upfront *DPYD* genotype–guided dose individualisation in fluoropyrimidine-based anticancer therapy

Results

Expected total costs of the screening strategy were €2599 per patient compared with €2650 for non-screening, resulting in a net cost saving of €51 per patient. Results of the probabilistic sensitivity and one-way sensitivity analysis demonstrated that the screening strategy was very likely to be cost saving or worst case cost-neutral.

Conclusions

Upfront *DPYD*-guided dose individualisation, improving patient safety, is cost saving or cost-neutral but is not expected to yield additional costs. These results endorse implementing *DPYD* screening before start of fluoropyrimidine treatment as standard of care.

DPD testing request forms

CHU de Liège — GENETIQUE HUMAINE

Etude du phénotype et/ou génotype de la DihydroPyrimidine Dehydrogenase (DPYD)

IDENTIFICATION DU PATIENT — N°

Nom | Prénom | Date de prélèvement / Date de réception

Date de naissance

Adresse complète: Rue, Code Postal, Ville

N° Mutuelle, N° Matricule, Titulaire

ETIQUETTE PATIENT (espace réservé au laboratoire)

ETIQUETTE DEMANDE (espace réservé au laboratoire)

MEDECIN PRESCRIPTEUR

Nom, N° INAMI, Adresse, Date et signature | Copie à

BIOCHIMIE GENETIQUE

☐ Uracile / Dihydrouracile

Prélèvement EDTA 10 mL
Transport urgent au laboratoire
Centrifugation et décantation endéans 1h30 après prélèvement
Conservation et transport à -20°C
Contacter immédiatement le laboratoire après prélèvement (04/3667701)

Contact : Dr F. Boemer 04/3667701 Tour 2, +6 CHU - Liège

BIOLOGIE MOLECULAIRE

☐ Gène DPYD (Variants *2A, *13, p.D949V et HapB3)

Prélèvement EDTA 10 ml – Conservation : +4°C

Contact : Dr V. Dideberg 04/3662478 Tour 3, +3, p20, CHU - Liège

CHU de Liège — **GENETIQUE HUMAINE - CONSTITUTIONNEL -** — Unilab Lg — Version 2020

IDENTIFICATION DU PATIENT

Nom : | Prénom :
Date de naissance : | Sexe : ☐ M ☐ F
Adresse complète — Rue : — Code postal :
N° Mutuelle :
N° Matricule :
Titulaire :

ETIQUETTE PATIENT (espace réservé au laboratoire)

ETIQUETTE PATIENT (espace réservé au laboratoire)

MEDECIN PRESCRIPTEUR

Nom : | Copie à :
N° INAMI :
Adresse :
Téléphone : | Date et signature :

PRELEVEMENT (indiquer clairement le nom, prénom et date de naissance du patient sur tous les tubes)

Date et heure de prélèvement :..... | Date et heure de réception :.....

Type de prélèvement	Conservation	Délai de transmission
☐ Sang (5ml (nné:2ml)) sur EDTA E	4°C	48h
☐ Sang (5ml (nné:2ml)) sur Héparié H	Température ambiante	48h
☐ Tissu (sur milieu de culture ou LP stérile). Type :	Température ambiante	Le jour même
☐ Autre : ..... (Contacter le laboratoire)		

RENSEIGNEMENTS CLINIQUES OBLIGATOIRES

A compléter par le patient lorsque les analyses sont demandées en dehors des règles diagnostiques :
"Je déclare avoir reçu des informations claires sur l'utilité de réaliser les analyses demandées. Ces analyses n'étant pas remboursées par l'assurance maladie, je marque mon accord pour en supporter le coût qui me sera facturé par le laboratoire (montants variant entre 78 € et 1350 €)"

Date : ... / ... /..... Signature : .....

Indiquer les informations cliniques relevantes *(ex: greffe moelle osseuse)* et/ou compléter l'arbre généalogique :

Arbre généalogique
● ■ : Atteint
○ □ : Sain
◑ ◨ : Conducteur
↗ : Patient à investiguer

Ethnie : ..... Nom du cas index : .....
Grossesse en cours : ..... semaines

INDICATION DE L'ANALYSE :
☐ Confirmation/ exclusion diagnostique
☐ Etude familiale (Nom et DN du cas index:.....)
☐ Test présymptomatique (2 éch. indépdts obligatoires)
☐ **Urgent (motif :.....)**
☐ BIOBANQUE (En cochant cette case, vous avez informé le patient d'un éventuel stockage du surplus d'ADN au sein de la biobanque des maladies génétiques ainsi que du respect de son anonymat. Cet échantillon pourra être utilisé à des fins de recherche. **Dans ce contexte, le consentement éclairé du patient et le formulaire d'information du patient signés ont été obtenus et sont conservés dans le dossier médical du patient).**

CONTACTS dispa.genetique@chuliege.be

Biochimie Génétique	Génétique Moléculaire Humaine	Oncogénétique Moléculaire	Biologie Moléculaire Hématologique	Cytogénétique
Dr Phar.Biol. F. BOEMER / Dr Sc. M. DEBERG / Secrétariat : 04.366.76.95	Dr V. DIDEBERG / Dr Sc. C. LIBIOULLE / Dr Sc. E. CASTERMANS / Dr Sc. JH.CABERG / Dr Sc. M. HANNON / Secrétariat : 04/366.24.78	Dr Sc. Vet. K. SEGERS Secrétariat : 04/366.24.78	Dr F. LAMBERT / Dr Sc. S FRANKE / Dr Sc. B. KOOPMANSCH / Dr Sc. R. FERNANDEZ CARAZO / Secrétariat : 04.366.25.61	Dr M. JAMAR / Dr W. COURTENS / Dr Sc. JS. GATOT / Dr Sc. C. MENTEN / Dr Sc. C. LETE / Dr Sc. N. LEROI / Dr Sc. M. DEBERG Secrétariat : 04.366.25.61

Fichier téléchargeable à l'adresse : http://www.chuliege.be/unilab/formulaires — MQ.A11.24 – version 17 - Page 1/4

BIOLOGIE MOLECULAIRE E

Règles	Gène	DIVERS (suite)	Règles	Gène
	CFTR	☐ ALPHA-1 ANTITRYPSINE		SERPINA1
	µDel AZF	☐ ACHONDROPLASIE/ ☐ HYPOCHONDROPLASIE/ ☐ CRANIOSTENOSE / ☐ CROUZON/ (2)		FGFR3
	FMR1	☐ APERT		FGFR2
	SRY	☐ SYNDROME CARDIO-FACIO-CUTANE (1)		BRAF MAP2K1 MAP2K2 KRAS
	DLK1 KISS1 KISS1R MKRN3 PROKR2	☐ SYNDROME DE COSTELLO		HRAS
	61 gènes	**HEMATOLOGIE** E Règles		Gène
		☐ ANGIOEDEME HEREDITAIRE DE TYPE 3		F12
		☐ Facteur 5 C ☐ APC résistance (Laboratoire de thrombose-hémostase) ☐ Mutation R506Q (Leiden) *APCR positive (critère obligatoire !) ?* ☐ Oui, valeur : ..... ☐ Non		FV
	WNT4	☐ Autres variants (Liverpool, Cambridge et Hong-Kong)		
	SHOX	☐ PROTHROMBINE *(critère obligatoire !)* ☐ Age < 55 ans CE JOUR ET Accident Thrombotique ☐ ATCD familiaux ☐ CIVD		F2
	MC4R	☐ HEMOCHROMATOSE *(critère obligatoire !)* ☐ Diagnostic ☐ Hyperferritinémie ☐ Coefficient saturation transferrine > 45% ☐ Etude familiale ☐ Apparentés 1er degré porteur de mutation ☐ Partenaire porteur de mutation		HFE
	ATP8B1 ABCB11 ABCB4	☐ FERROPORTINE (1)		SLC40A1
	CDKN1B	☐ HEMOCHROMATOSE JUVENILE Gène HFE testé ? ☐ Oui ☐ Non		HAMP HJUV
	CASR GNA11 AP2S1	☐ HEMOGLOBINOPATHIES BETA ☐ Diagnostic Electrophorèse Hb : Réalisée : Oui/Non Résultat : ..... ☐ Etude familiale : Mutation identifiée :..... ☐ Conjoint porteur : Mutation identifiée :.....		HBB
	HNF1B			
	MEFV			
	E.X2			
	AIP MEN1 RET CDKN1B GNAS SDHD SDHC SDHB VHL	**ONCO - HEMATOLOGIE** Règles		Gène
		☐ SYNDROMES MYELODYSPLASIQUES/ LA (1) ☐ Panel de gènes candidats ou Exome sequencing (WES) B		GATA2, CEBPA...
		☐ SYNDROMES D'INSUFFISANCES MEDULLAIRES (1) ☐ Panel de gènes candidats ou Exome sequencing (WES) B E		TERT, TERC, FANCA,...
		☐ ERYTHROCYTOSE (1) ☐ Taux EPO sérique bas à effondré : *EPOR* ☐ Taux EPO sérique normal à haut : *VHL/EGLN1(PHD2), EPAS1(HIF2A)* E		EPOR VHL,PHD2,HIF3A
		☐ THROMBOCYTOSE (1) ☐ THPO élevé : *EPOR* (THCYT1) ☐ THPO normal ou bas : *MPL, JAK2* (THCYT2 ou 3) E		THPO MPL, JAK2
		☐ NEUTROPENIE (1) ☐ *CSF3R* ☐ *GATA2* ☐ Autre (Sous-traitance) : ..... E		CSF3R GATA2
	CFTR	**PHARMACOGENETIQUE** E Règles		Gène
	CASR, CFTR, CLDN2, CPA1, CTRC, PRSS1, SPINK1	☐ RÉSISTANCE À L'IMURAN		TPMT
		☐ TOXICITÉ DU 5-FU		DPYD
	PANEL	☐ RÉSISTANCE AU PLAVIX		CYP2C19
	LDLR APOB PCSK9 APOE	**AUTRE**		
		☐ AUTRE ANALYSE : (Contacter le laboratoire)		

+ O xanthomes/arc corneen (perso ou fam. 1er-2eme degr.)
Et/ou O ATCD fam (1er-2eme degr.) ou perso de coronaro-pathie
Et/ou O ATCD fam d'hypercholesterolemie (1er-2eme degr.)
Score du Dutch Lipid Clinic Network: .....
☐ Etude familiale: ID du cas index et mutation/gène .....

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BIOCHIMIE GENETIQUE

ANOMALIES PRIMAIRES DU METABOLISME

	Prélèvement
Pristanique*	P
	SS ou S
	C
	SS
	S
	P
	S
	S
	S
	P
	TS
	TS
	TS
	S
	P
	P
	S
	F
	F

Prélèvement	
	H ou E
	H ou E
	H ou E

Prélèvement	
	H ou E
	H ou E
	H ou E
	H ou E
	H ou E
	SS
	SS

URINE ☐ Diurèse : ..... mL/24h — Prélèvement

☐ Acides aminés	U
☐ Acylcarnitines	U
☐ Acides Organiques*	U
☐ Acide Mévalonique*	U
☐ Acide Pipécolique	U
☐ Créatine et Guanidinoacétate*	U
☐ Acide Orotique*	U
☐ Acide Oxalique (Diurèse 24h — Envoyer urine totale)	U

MALADIE DE SURCHARGE

☐ Mucopolysaccharides – Electrophorèse + Dosage*	U
☐ Oligosaccharides – Chromatographie*	U

METABOLISME DES SUCRES

☐ Fructose	U
☐ Galactose	U

LIQUIDE CEPHALORACHIDIEN

☐ Acides Aminés, dont γ-Aminobutyrate (GABA)	Pc

DIVERS — Prélèvement

☐ 6-Thioguanine – 6-Methylmercaptopurine*	E
☐ Uracile - DihydroUracile (Décanter et congeler immédiatement. Conservé et transporté à -20°C.)	E

DEPISTAGE PRENATAL — Prélèvement

RISQUE DE SPINA BIFIDA sur LIQUIDE AMNIOTIQUE (Communiquer l'âge gestationnel.)

☐ Alpha-Foetoproteine	Pc
☐ Acétylcholinestérase Neuronale	Pc

DEPISTAGE NEONATAL — Prélèvement

☐ Voir Fiche de Prélèvement Spécifique (Conservation et transport à t° ambiante.)	SS

Les buvards pour la collecte de Sang Séché (Dépistage Néonatal, Profil des Acylcarnitines) et les tubes spéciaux pour Acides Organiques Sanguins doivent être fournis obligatoirement par le laboratoire (04 / 366 76 95).

H Tube Héparié sans gel (2 mL)
C Tube Citraté
F Tube Fluoré (tube gris – 2 mL)
SS Sang Séché sur Buvard
TS Tube Spécial (Fourni par le laboratoire. Voir procédure de prélèvement spécifique)

Conservation + Transport à 4°C, sauf recommandation spécifique

Fichier téléchargeable à l'adresse : http://www.chuliege.be/unilab/formulaires — MQ.A11.24 – version 17 – Page 4/4

Sampling

- Genotyping

  - Collection: EDTA tube, 2 mL
  - Storage at 4°C, transport to laboratory within three days at 4°C
  - TAT: 1 week

- Phenotyping

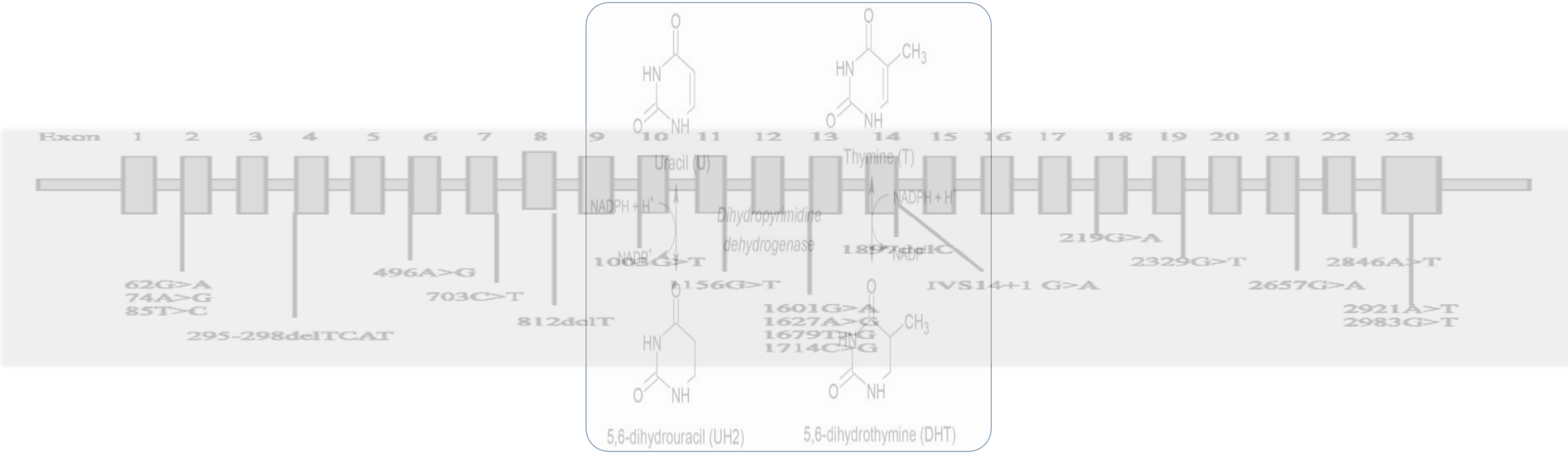
  - Collection: EDTA tube, 5 mL
  - Urgent transport to the laboratory, centrifugation within 1h30 after sampling
  - Storage and transport at -20°C
  - Ideally, contact directly your laboratory after sampling for rapid recovery and centrifugation of the tube.
  - TAT: 1 week

Costs and tests availability

- Cost
  - Genotyping: ~160 €, of which ~9 € are charged to patient
  - Phenotyping: 35-40 € charged to patient, currently not reimbursed by healthcare insurance

- Test availability in Belgium
  - Targeted genotyping
    - CHU Sart-Tilman: Centre de Génétique Humaine
    - KULeuven: Centrum Menselijke Erfelijkheid
    - Cliniques Universitaires St-Luc, UCLouvain: Centre de Génétique Humaine
    - UZ Gent: Centrum Medische Genetica
  - *DPYD* sequencing
    - Cliniques Universitaires St-Luc, UCLouvain: Centre de Génétique Humaine
    - UZ Gent: Centrum Medische Genetica
  - Phenotyping
    - CHU Sart-Tilman: Centre de Génétique Humaine
    - Cliniques Universitaires St-Luc, UCLouvain
    - UZ Gent
    - Labo Klinische Biologie, Onze-Lieve-Vrouwziekenhuis – Aalst

Thank you


Exon 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
62G>A
74A>G
85T>C
295-298delTCAT
496A>G
703C>T
812delT
1003G>T
1156G>T
1601G>A
1627A>G
1679T>G
1714C>G
IVS14+1 G>A
219G>A
2329G>T
2657G>A
2846A>T
2921A>T
2983G>T
Uracil (U)
Thymine (T)
NADPH + H+
NADP+
Dihydropyrimidine dehydrogenase
5,6-dihydrouracil (UH2)
5,6-dihydrothymine (DHT)