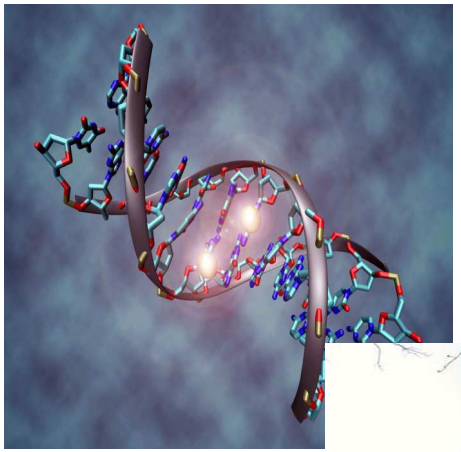
U-PGx | Ubiquitous Pharmacogenomics

The GoldenHelix FOUNDATION

3rd UPGx Personalized Medicine Day

Pharmacogenomics to increase anti-cancer drugs safety, from research to clinical implementation



Erika Cecchin, PharmD, PhD

Experimental and Clinical Pharmacology Unit
Centro di Riferimento Oncologico- Aviano- Italy

Adverse Drug Reactions in pharmacological treatment

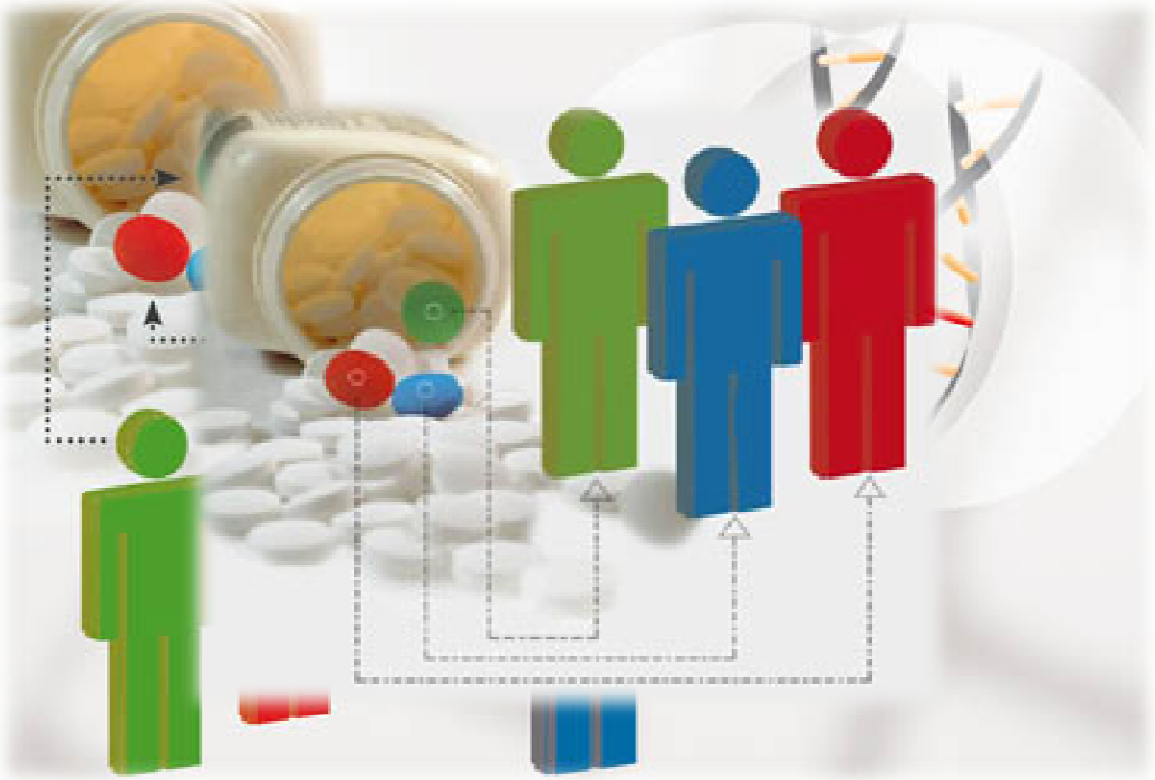
- Over 2 millions ADRs yearly in US, 100,000 resulting in death (*Inst Med, Nat Acad Press, 2000*)

- They are estimated to cost £1 billion in UK (Pirmohamed, Br Med J, 2004), and $4 billion annually in the US (*Lazarou J et al, JAMA, 1998)*

- A revision of more than 4,000 patients treated for mCRC in the US in 2014 demonstrated that about 90% developed at least one ADR with a sginificant economic burden (*Latremouille et al, J Med Economics, 2016*)

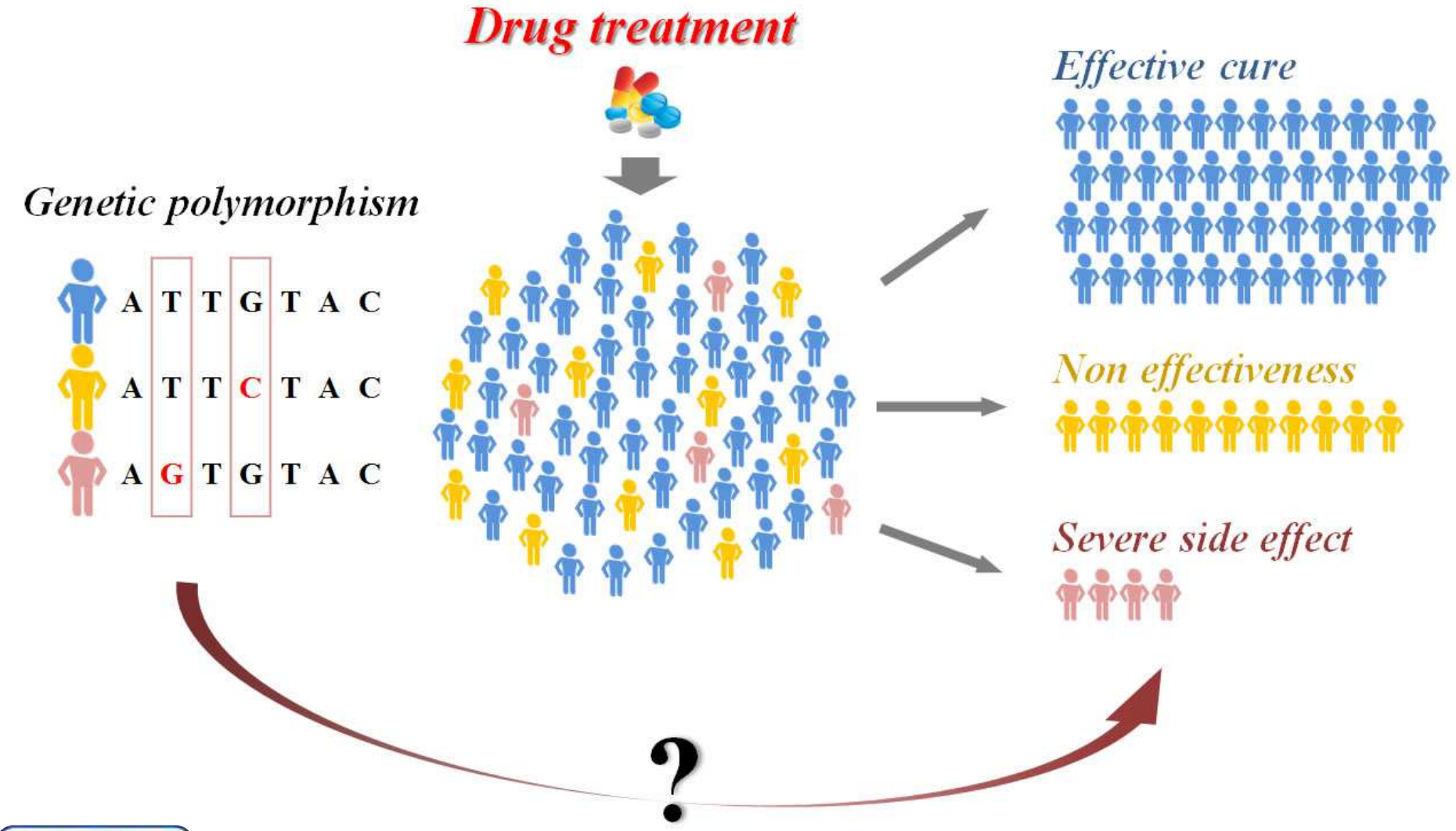
"If it were not for the great variability among individuals, medicine might as well be a science and not an art"

Sir William Osler, 1892



CRO AVIANO

Pgx approach to increase drug safety



Retrieved from http://xyc.ideaco.org/wp-content/uploads/2014/07/pharmacogenomics1.jpg

Implementation of pre-emptive genotyping of the HOST for increasing treatment safety

Two gene-drug interactions from the oncological practice: *DPYD* and *UGT1A1*

CRO AVIANO

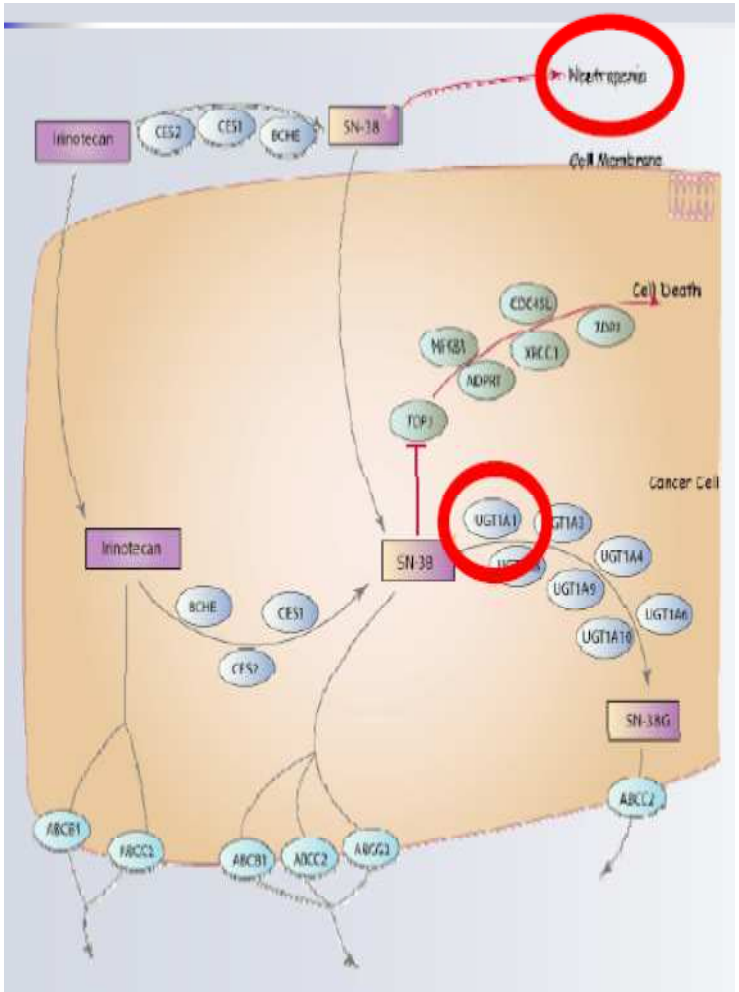
UGT1A1-Irinotecan

•Irinotecan is approved for the first line treatment of metastatic colorectal cancer and other solid tumors

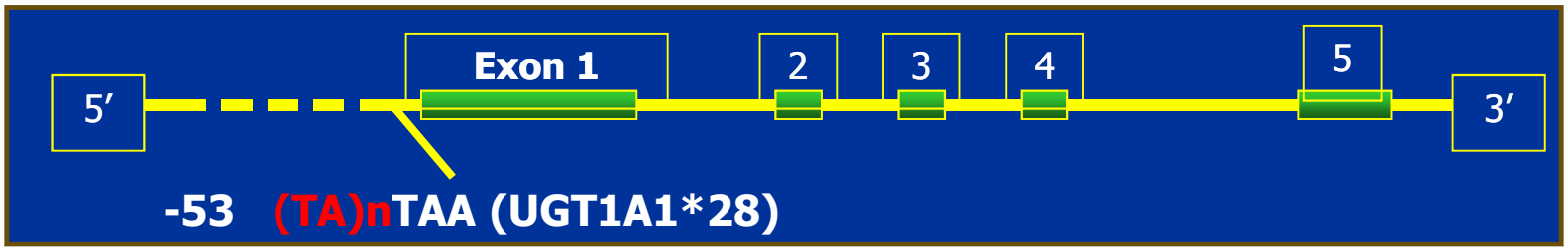
•Exposure to the active irinotecan metabolite SN-38 is the major cause of adverse events

•Severe neutropenia and delayed diarrhea are the dose-limiting toxicities, with the sporadic occurrence of severe and occasionally life-threatening complications possibly causing the failure of the treatment

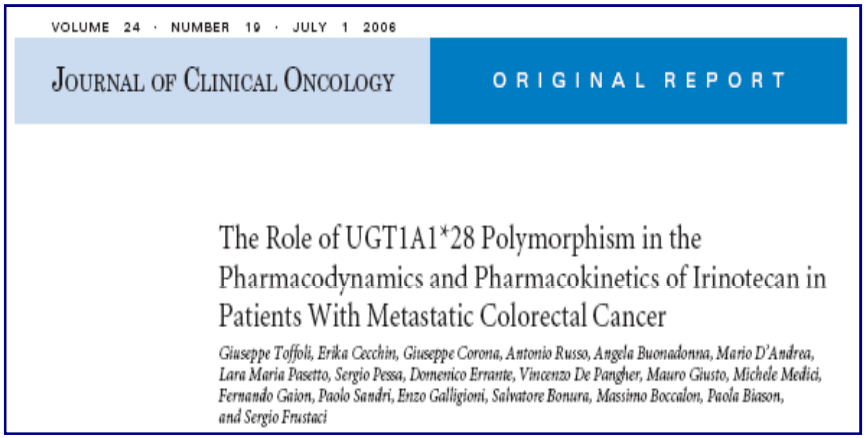
•UGT1A1 has a major role in SN-38 detoxification



UGT1A1-Irinotecan



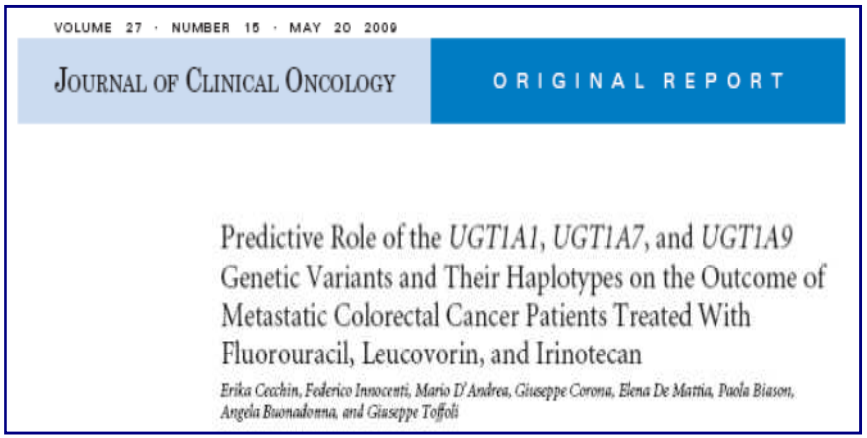
- *UGT1A1* encoding gene is polymorphic
- *UGT1A1*28* polymorphism is common in Caucasian population (10% is homozygous)
- *UGT1A1*28* polymorphism is related to lower UGT1A1 enzyme expression, therefore SN-38 glucuronidation could be less efficient


VOLUME 24 · NUMBER 19 · JULY 1 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

The Role of UGT1A1*28 Polymorphism in the Pharmacodynamics and Pharmacokinetics of Irinotecan in Patients With Metastatic Colorectal Cancer

Giuseppe Toffoli, Erika Cecchin, Giuseppe Corona, Antonio Russo, Angela Buonadonna, Mario D'Andrea, Lara Maria Pasetto, Sergio Pessa, Domenico Errante, Vincenzo De Pangher, Mauro Giusto, Michele Medici, Fernando Gaion, Paolo Sandri, Enzo Galligioni, Salvatore Bonura, Massimo Boccalon, Paola Biason, and Sergio Frustaci


VOLUME 27 · NUMBER 15 · MAY 20 2009

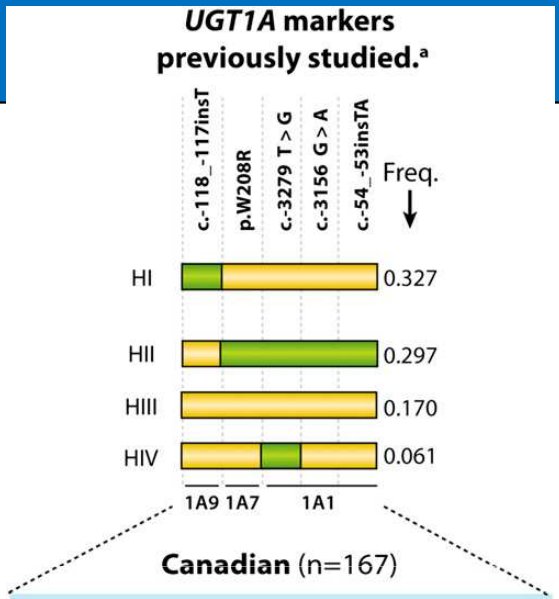
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Predictive Role of the *UGT1A1*, *UGT1A7*, and *UGT1A9* Genetic Variants and Their Haplotypes on the Outcome of Metastatic Colorectal Cancer Patients Treated With Fluorouracil, Leucovorin, and Irinotecan

Erika Cecchin, Federico Innocenti, Mario D'Andrea, Giuseppe Corona, Elena De Mattia, Paola Biason, Angela Buonadonna, and Giuseppe Toffoli

CRO AVIANO

External validation in collaboration with Università Laval-Quebec



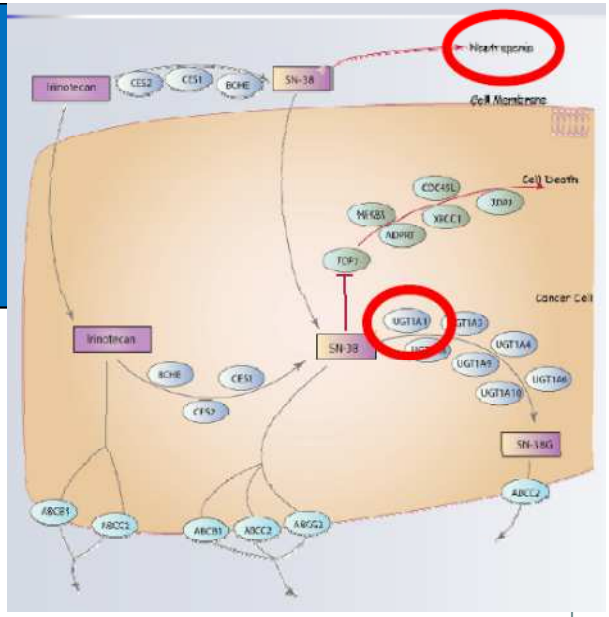
Canadian (n=167)

Allele	Neutropenia Freq (%) 3-4/0-2	*P*	*OR (CI95%)*
I	0.27/0.34	0.350	0.71 (0.38-1.35)
II	**0.46/0.26**	**0.004**	**2.43 (1.35-4.39)**
III	0.18/0.17	0.846	1.08 (0.51-2.29)
IV	0/0.07	0.032	-

OUR RESULTS ON HAPLOTYPE II (as reported by us, all "defective" UGT1A alleles; Cecchin 2009) PREDICTIVE VALUE ON NEUTROPENIA (UNPUBLISHED DATA) WERE REPLICATED IN AN INDEPENDENT COHORT OF 167 CANADIAN mCRC PATIENTS TREATED WITH FOLFIRI-BASED REGIMENS.

Lévesque E, Bélanger AS, Harvey M, Couture F, Jonker D,Innocenti F, Cecchin E, Toffoli G, and Guillemette C J Pharmacol and Exp Ther, 2013

Phase 1b studies based on the patient genotype for re-definition of MTD: the study design



Eligible mCRC patients

↓

Genotyping for UGT1A1 *28

↓

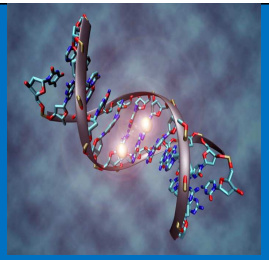
Stratification into two groups

GROUP 1:
UGT1A1 *1/*1
WILD TYPE PTS
IRI dose escalation

GROUP 2:
UGT1A1 *1/*28
HETEROZYGOUS PTS
IRI dose escalation

Patients with *28/*28 genotype excluded.
Clinical and pharmacokinetic monitoring

Phase 1b studies based on the patient genotype for re-definition of MTD: the results



Therapy	*1/*1 genotype, Dose (mg/m²)	1/*28 genotype, Dose (mg/m²)	
FOLFIRI, standard dose	**180**	**180**	*Ducreux et al, J Clin Oncol, 1999*
FOLFIRI	**370**	**310**	*Toffoli et al, J Clin Oncol , 2010*
FOLFIRI plus BEVACIZUMAB	**310**	**260**	*Toffoli et al, Clin Cancer Res, 2016*
FOLFIRI plus CETUXIMAB	**ongoing**	**ongoing**	*ongoing*

The stratification of patients in FOLFIRI or FOLFIRI plus bevacizumab regimens according to *UGT1A1*28* genotype led to a higher MTD both in *UGT1A1*1/*28* and *UGT1A1*1/*1* patients.

Clinical Pharmacology & Therapeutics

ASCPT

ARTICLES

Cost Evaluation of Irinotecan-Related Toxicities Associated With the *UGT1A1*28* Patient Genotype

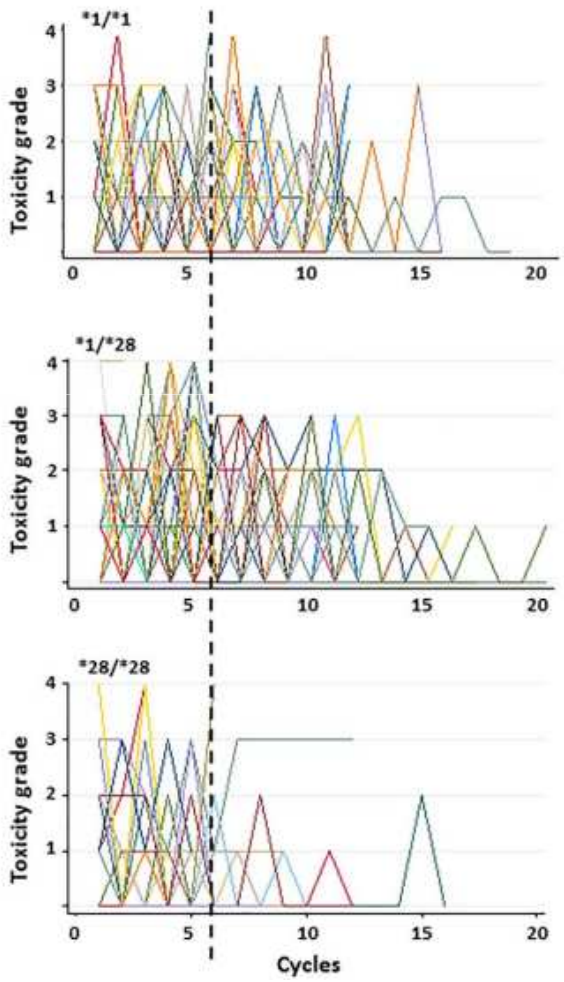
R Roncato[1], E Cecchin[1], M Montico[1], E De Mattia[1], L Giodini[1], A Buonadonna[2], V Solfrini[3], F Innocenti[4] and G Toffoli[1]

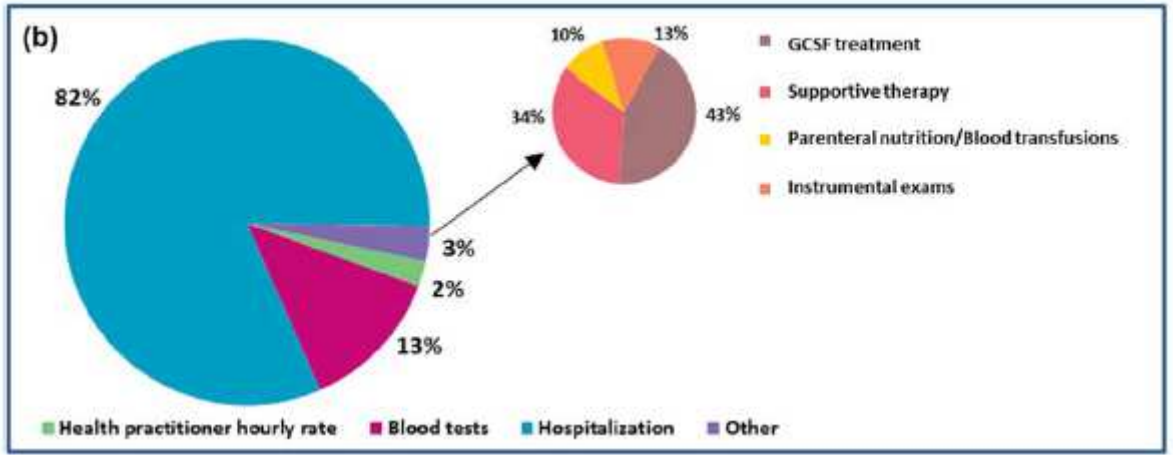
Spreading of *UGT1A1*28* pre-emptive genotyping to increase irinotecan safety is still limited. The definition of the cost consequences of patients genotype is one of the pending issues. A survey of the toxicity associated costs in 243 FOLFIRI treated mCRC

UGT1A1 genotype	Number of patients	Mean predicted cost per patient[a] (95% CI) (Euro)		Regression coefficient	95% CI	*P*-value	Regression coefficient	95% CI	*P*-value
*1/*1	109	812	(653–970)	Ref[b]					
*1/*28	112	1,119	(885–1,353)	0.32	0.04–0.60	0.024	Ref[b]		
*28/*28	22	4,886	(2,611–7,160)	1.79	1.31–2.28	<0.001	1.47	0.99–1.95	<0.001

CI, Confidence Interval; Ref, Reference Category.
[a]By generalized linear model, adjusted by age, sex, adjuvant chemotherapy, and total number of chemotherapy cycles. [b]Reference category for regression coefficients calculation.

*Severe toxicity related to hospitalization costs (grade 4) are significantly more prevalent in patients that are carriers of *28 allele.*





Most of the costs are related to hospitalization (grade 4 toxicity). The risk of grade 4 toxicity is *28 allele dependent

Table 4 Occurrence of any kind of grade 4 toxicities based on *UGT1A1*28* polymorph

UGT1A1 genotype	Number of patients	Toxicity before the sixth cycle		OR (95% CI)	*P*-value
		G0-G3	G4 (%)		
*1/*1	109	108	1 (0.9)	Ref	
*1/*28	112	103	9 (8.0)	9.4 (1.2–75.8)	0.019
*28/*28	22	20	2 (9.1)	10.8 (0.9–124.9)	0.073
*1/*28/ and *28/*28	134	123	11 (8.2)	9.7 (1.2–76.1)	0.014

G, Grade; CI, Confidence Interval; Ref, Reference Category.

RONCATO R ET AL, CLIN PHARMACOL THER , 2017

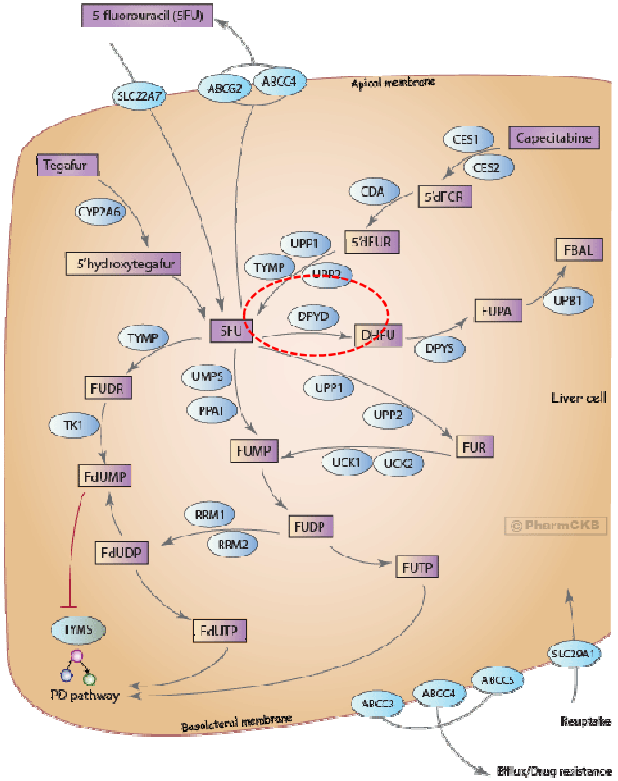
DPYD-Fluoropyrimidines

5-FU for 40 Yrs

- 5-FU bolus
- 5-FU infusion
  - 24 hrs
  - 48 hrs
  - 46 hrs
  - 120 hrs
  - ∞ hrs
- LV + 5-FU
- 5-FU + LV
- 5-FU + Lev
- 5-FU + everything
- ……

•FL are the mainstay of many chemotherapeutic schemes in different combination for different pathologies and settings

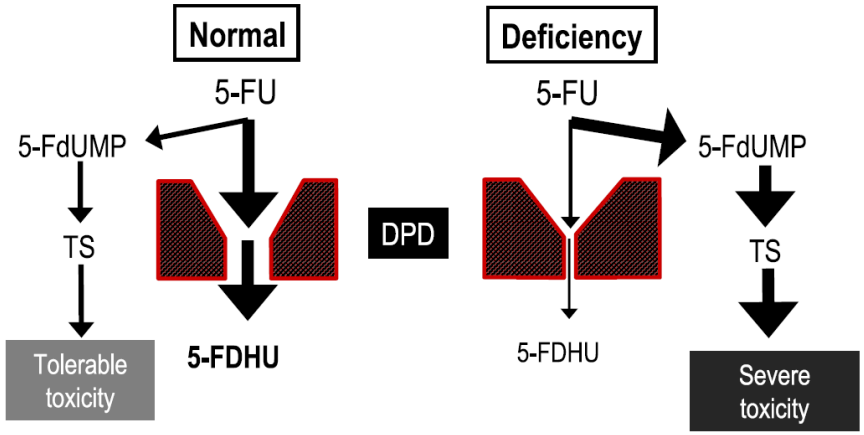
•10 to 26% of patients experiencing acute severe or life-threatening toxicity even in monotherapy regimens

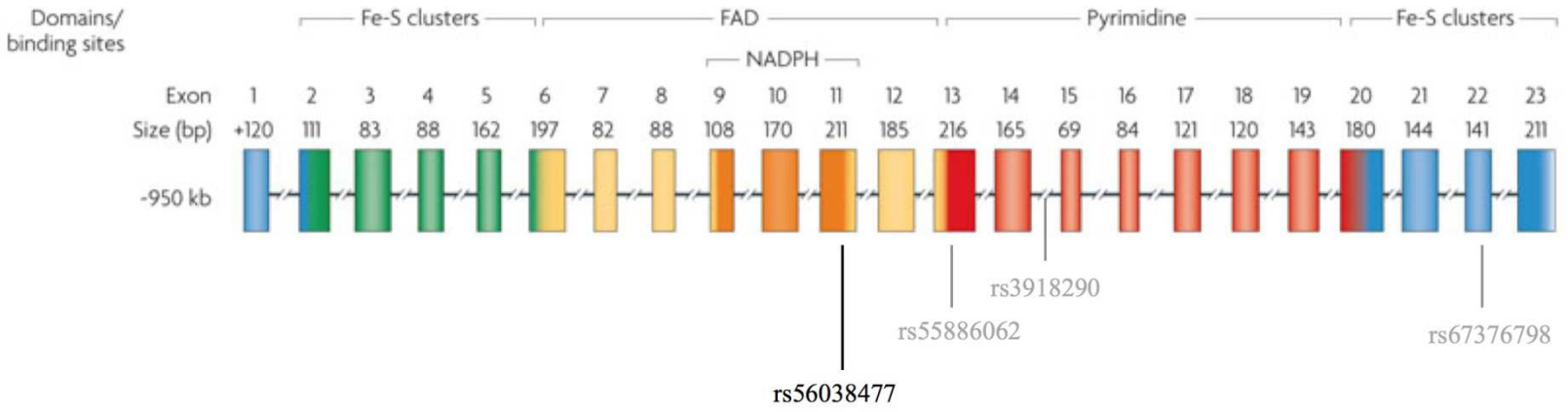


DPYD IS A KEY ENZYME REPRESENTING A BOTTLENECK IN FL CELL DETOXIFICATION

CRO AVIANO

DPYD-Fluoropyrimidines





Retreived from Goodsaid, F. M. et al. Nat Rev Drug Discov ***2010****, 9, 435–445*

IJC International Journal of Cancer

uicc

IJC
International Journal of Cancer

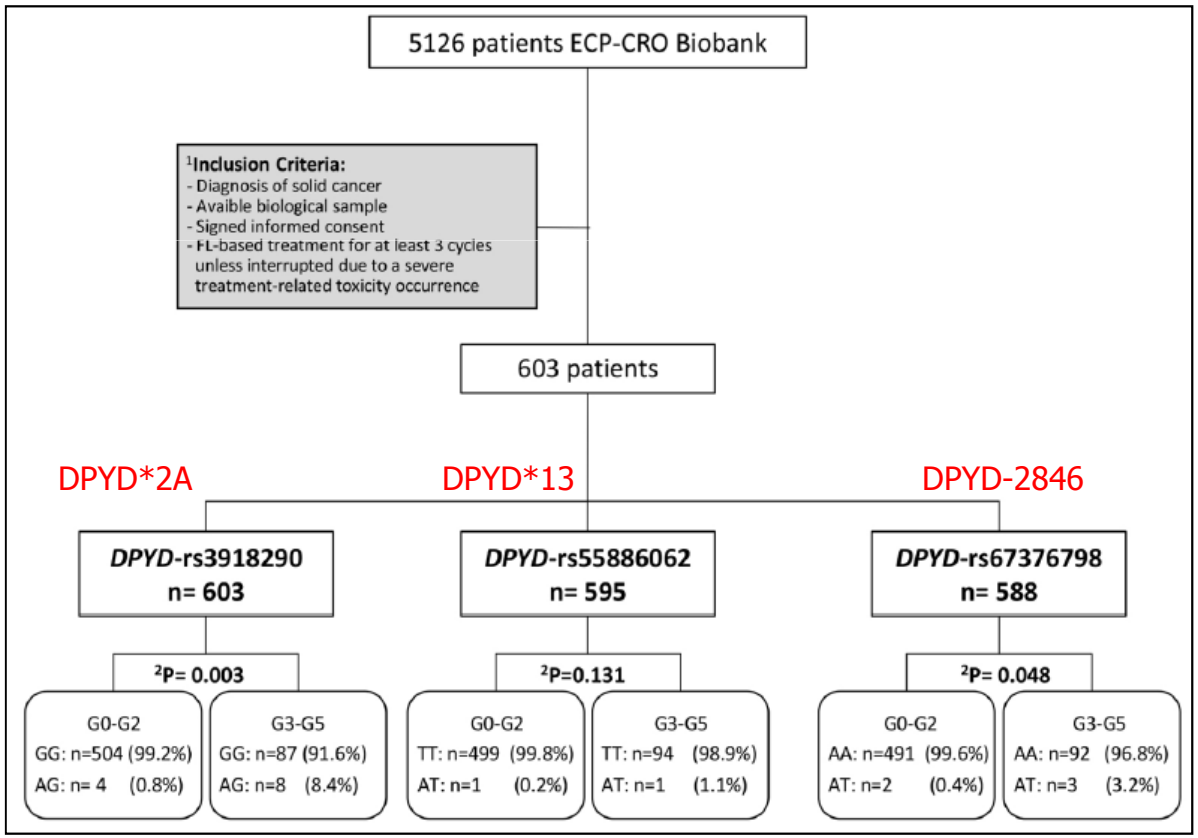
Clinical validity of a *DPYD*-based pharmacogenetic test to predict severe toxicity to fluoropyrimidines

Giuseppe Toffoli[1*], Luciana Giodini[1*], Angela Buonadonna[2], Massimiliano Berretta[3], Antonino De Paoli[4], Simona Scalone[2], Gianmaria Miolo[2], Enrico Mini[5], Stefania Nobili[6], Sara Lonardi[7], Nicoletta Pella[8], Giovanni Lo Re[9], Marcella Montico[1], Rossana Roncato[1], Eva Dreussi[1], Sara Gagno[1] and Erika Cecchin[1]

- **603** solid cancer patients treated with FL-based regimen
- **Clinical End-Point**: Severe (≥G3) or lethal toxicity related to FL administration

- Characterizing prospectively these SNPs would have possibly spared 10 severe toxic events and 1 toxic death (**11.6% of severe toxic events**)

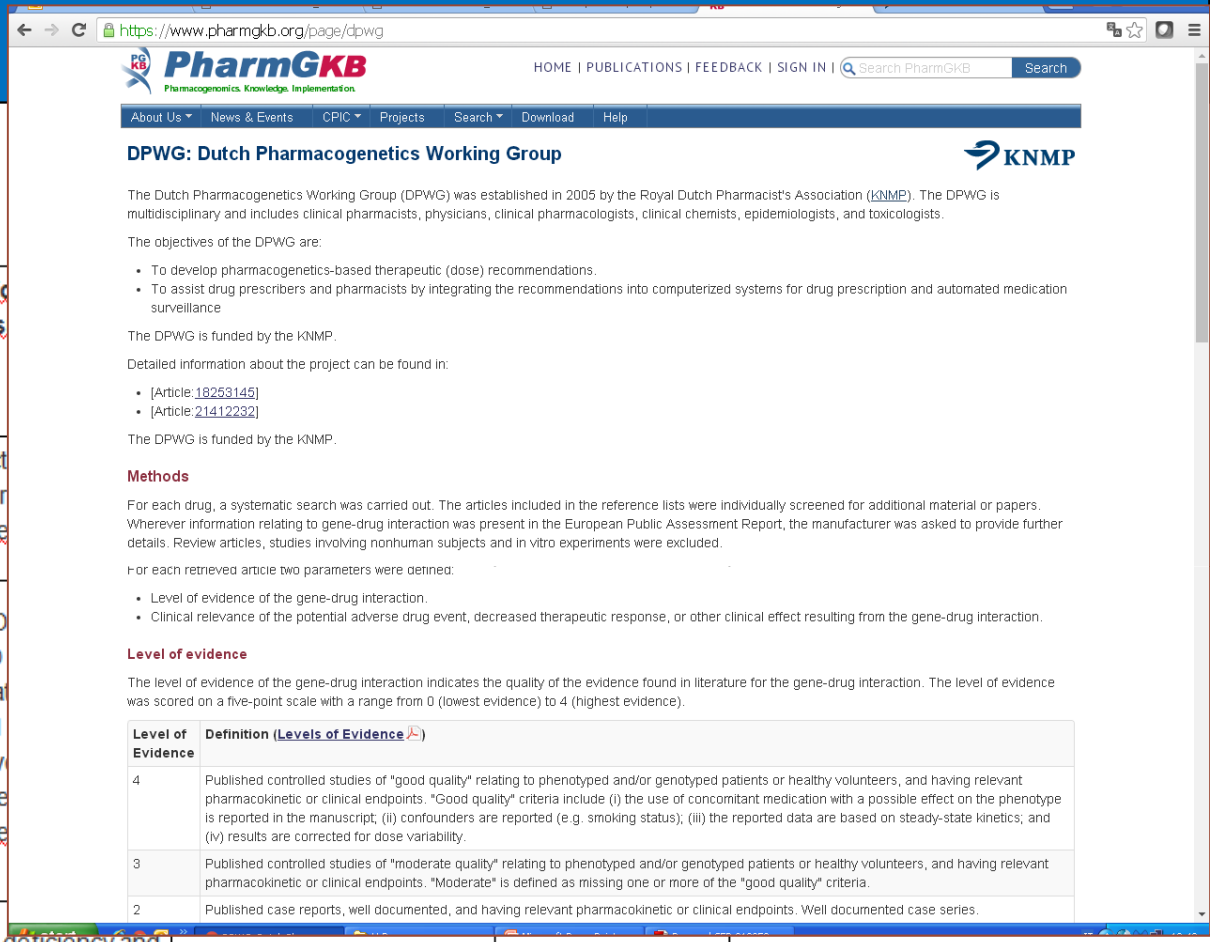
- The patient with toxic death was compound heterozygous for *DPYD*2A*, and *DPYD*13* and was treated in an adjuvant regimen for gastric cancer



CRO AVIANO

*UGT1A1*28* and *DPYD*2A*, **13*, and *2846A>T* still not at the bedside.. further proofs of clinical validity and utility requested?

Pharmacogenomics guidelines are available up to date



Phenotype (genotype)	Examples of diplotypes	Implications fo meas		
Homozygous wild-type or normal, high DPD activity (two or more functional *1 alleles)	*1/*1	Normal DPD act "normal" risk for fluoropyrimidine		
Heterozygous or intermediate activity (~3-5% of patients), may have partial DPD deficiency, at risk for toxicity with drug exposure (one functional allele *1, plus one nonfunctional allele - *2A, *13 or rs67376798)	*1/*2A; *1/*13; *1/ rs67376798)	Decreased DPD (leukocyte DPD 30% to 70% tha population) and for severe or ev toxicity when tre fluoropyrimidine		
Homozygous variant, DPD deficiency (~0.2% of patients), at risk for toxicity with drug exposure (2 nonfunctional alleles - *2A, *13 or rs67376798)	*2A/*2A; *13/*13; rs67376798 / rs67376798	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs	Select alternate drug	Strong

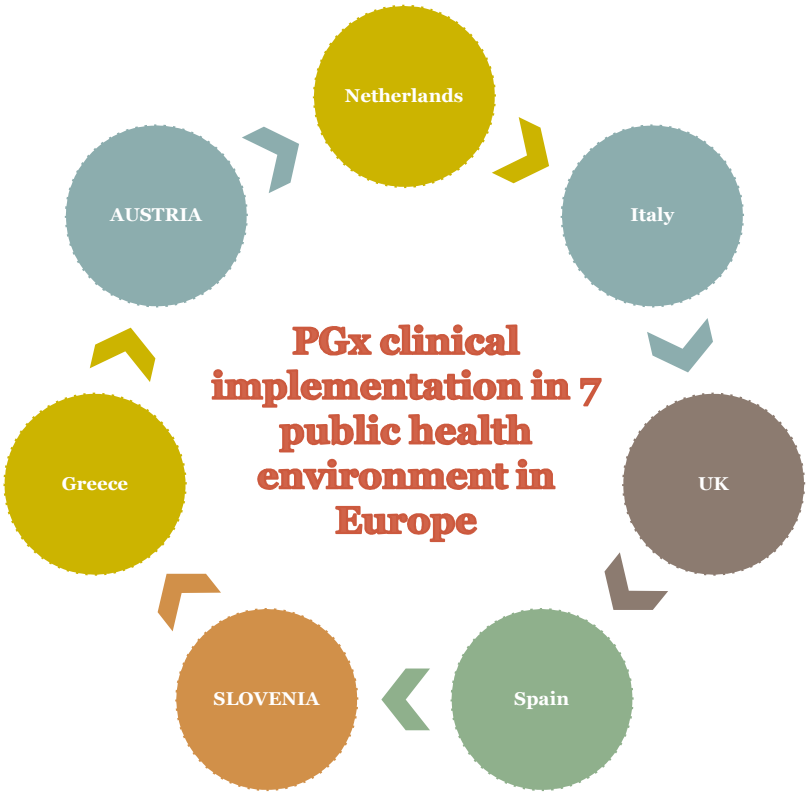
U-PGx | Ubiquitous Pharmacogenomics

Coordinated by Leiden University-Prof HJ Guchelaar

http://upgx.eu/

10 EU countries
15 research organizations
1 SME

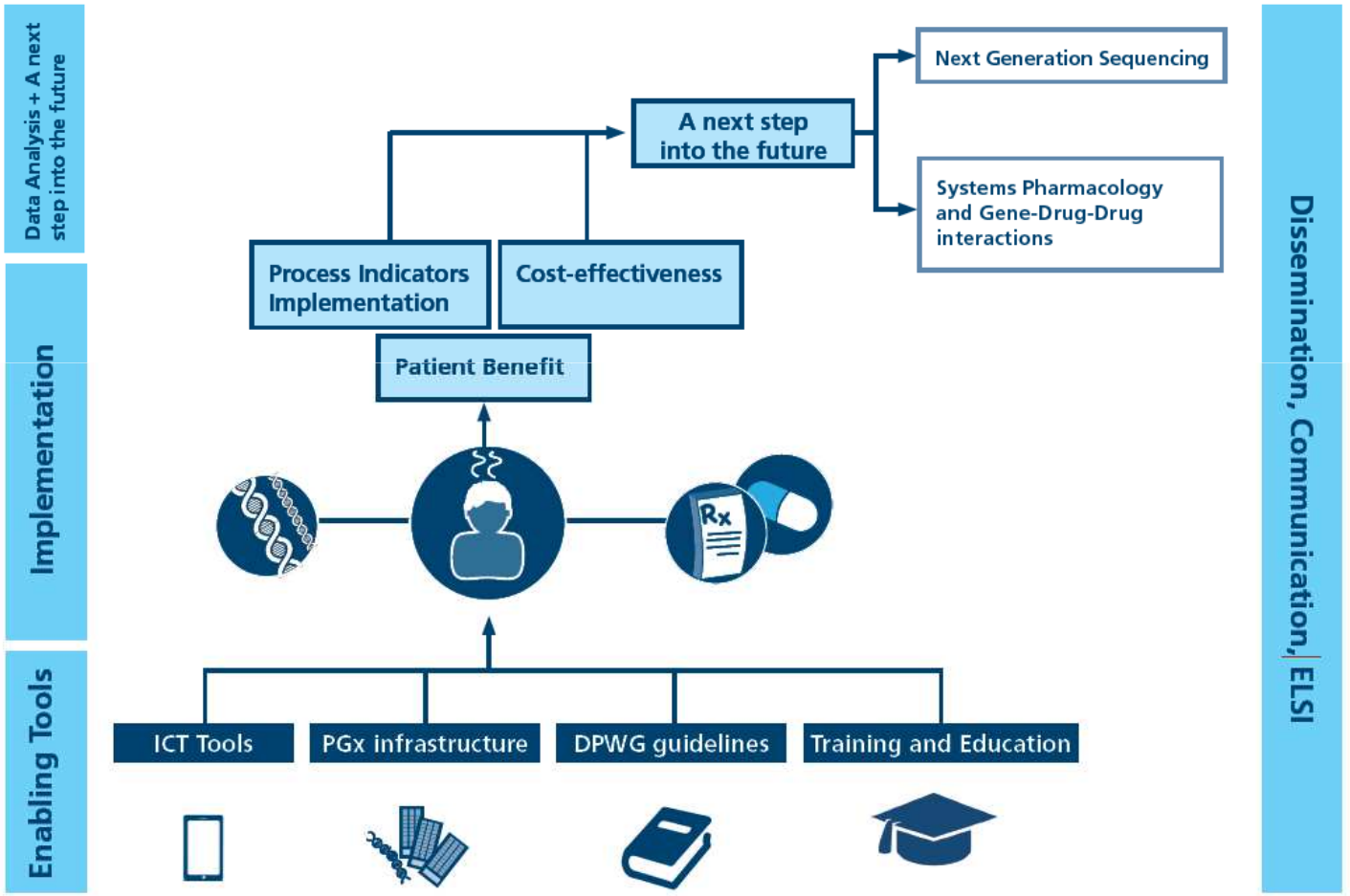
Ubiquitous Pharmacogenomics (U-PGx): **Making actionable pharmacogenomic data and effective treatment optimization accessible to every European citizen**
www.upgx.eu



List of participants

Participant Name	Acronym	Participant organisation name	Country
1 H-J Guchelaar, coordinator JJ Swen M Kriek	LUMC	Dept. Clinical Pharmacy & Toxicology, Leiden University Medical Center, University of Leiden Dept. of Clinical Genetics, Dept. of Human Genetics, Leiden University Medical Center, University of Leiden	Netherlands
2 M Pirmohamed R Turner	PHUL	Dept. of Molecular & Clinical Pharmacology, Royal Liverpool University Hospital, University of Liverpool	UK
3 J Stingl	FDMD	The Federal Institute for Drugs and Medical Devices, Bonn	Germany
4 M Ingelman-Sundberg	PPKI	Dept. of Physiology & Pharmacology, Karolinska Institute, Stockholm	Sweden
5 C Mitropoulou	GHXF	The Golden Helix Foundation, London	UK
6 M. Van Rhenen K-C Cheung	KNMP	Royal Dutch Pharmacists Association (KNMP), The Hague	Netherlands
7 D Steinberger (SME)	BIOL	bio.logis, Center for Human Genetics and bio.logis Genetic Information Management GmbH, Frankfurt Innovation Center for Biotechnology, Frankfurt	Germany
8 VHM Deneer	STZN	Dept. Clinical Pharmacy, St. Antonius Hospital, Nieuwegein/Utrecht	Netherlands
9 CL Davila Fajardo	SASG	Dept. of Pharmacy, Servicio Andaluz de Salud, San Cecilio University Hospital Granada, Granada	Spain
10 G Sunder-Plassmann M Samwald	MUWV	Div. of Nephrology & Dialysis, Medical University of Vienna, Vienna Center for Med. Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna	Austria
11 GP Patrinos	UPAT	Dept. of Pharmacy, University of Patras, Patras	Greece
12 V Dolžan	ULMF	Pharmacogenetics Lab., Faculty of Medicine, University of Ljubljana, Ljubljana	Slovenia
13 A Cambon-Thomsen	UPS	University Toulouse III Paul Sabatier, Toulouse	France
14 G Toffoli E Cecchin	CROA	Experimental and Clinical Pharmacology Unit, Centro di Riferimento Oncologico, National Cancer Institute, Aviano	Italy
15 M Karlsson S Jönsson	PBUU	Dept. Pharmaceutical Biosciences, Uppsala University, Uppsala	Sweden
16 M Schwab E Schaeffeler	IKP	Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Robert Bosch Hospital Stuttgart	Germany

Project Flow-chart



C.H.van Der Wouden et al, Clin Pharmacol Ther, VOLUME 101 NUMBER 3 | MARCH 2017

U-PGx | Ubiquitous Pharmacogenomics

STUDY DESIGN

Randomization of the 7 Clinical centers to start with

Study Arm:

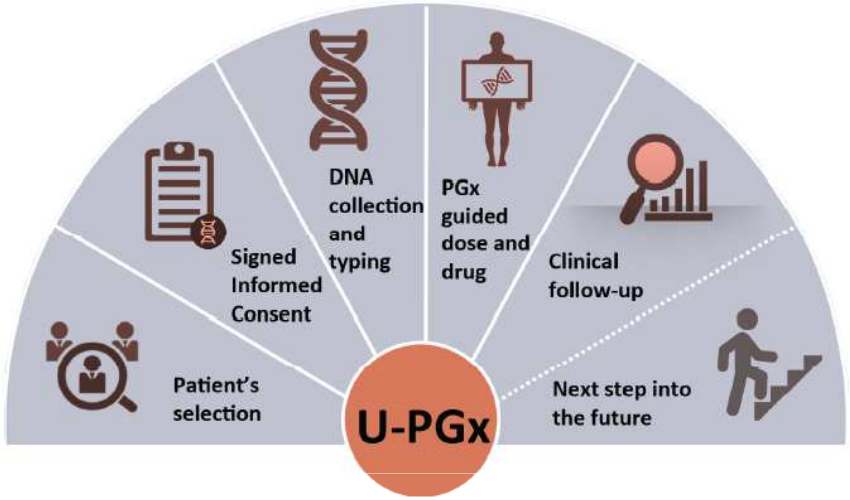
Pgx guided drug prescription for 42 drugs according to 50 genetic variants in ADME genes

Control Arm:

Current clinical practice with a patients surveillance program

Center	Starting Arm
LUMC (Netherlands)	Standard of care
SASG (Spain)	PGx Guided Prescription
MUWV (Austria)	Standard of care
UPAT (Greece)	PGx Guided Prescription
ULMF (Slovenia)	PGx Guided Prescription
PHUL (UK)	Standard of care
CROA (Italy)	Standard of care

U-PGx | Ubiquitous Pharmacogenomics



ANTIARITMICI	ANALGESICI	ANTICOAGULANTI	ANTIDEPRESSIVI SSRI	ANTIDEPRESSIVI TCA	ANTIBLASTICI
• FLECAINIDE • PROPAFENONE	• CODEINA • TRAMADOLO • OXICODONE	• ACENOCUMAROLO • CLOPIDOGREL • FENPROCUMONE • WARFARINA	• PAROXETINA • SERTRALINA • VENLAFAXINA	• AMITRIPTILINA • CLOMIPRAMINA • DOSULEPINA • IMIPRAMINA • NORTRIPTILINA	• CAPECITABINA • FLUOROURACILE • IRINOTECANO • TAMOXIFENE • TEGAFUR

ANTIEPILETTICI	ANTIPERTENSIVI	ANTI-INFETTIVI	ANTIPSICOTICI	ANTICOLESTEROLEMICI	IMMUNOSOPRESSIVI
• CARBAMAZEPINA • FENITOINA	• CARVEDILOLO • METOPROLOLO	• EFAVIRENZ • FLUCLOXACILLINA • VORICONAZOLO	• ARIPIPRAZOLO • CITALOPRAM • CLOZAPINA • ESCITALOPRAM • ALOPERIDOLO • PIMOZIDE • RISPERIDONE • ZUCLOPENTIXOLO	• ATORVASTATINA • SIMVASTATINA	• AZATIOPRINA • MERCAPTOPURINE • TACROLIMUS • TIOGUANINE

E. Cecchin et al, Curr Pharm Biotech, 2017- VOLUME 18 ISSUE 3 / 204 - 209

Ubiquitous Pharmacogenomics

Patients involvement matters

safety-code
The Medication Safety Code initiative

What is it?

The *Medication Safety Code* on the left represents a patient-specific genetic profile regarding important pharmacogenes.

How does it work?

After scanning the QR code (e.g. with a smartphone), you are led to a website that displays patient-specific drug dosing recommendations.

Laboratory contact
+0123456789
Some lab name
Some street name 123/45
1234 Some city name

www.safety-code.org

U-PGx | Ubiquitous Pharmacogenomics

safety-code
The Medication Safety Code initiative

Name: Jane Doe
Date of birth: 01.02.1934

Gene, status	*Critical drug substances (modification recommended!)*
CYP2C19 Poor metabolizer	Clopidogrel, Sertraline
CYP2D6 Ultrarapid metabolizer	Amitriptyline, Aripiprazole, Clomipramine, Codeine, Doxepin, Haloperidol, Imipramine, Metoprolol, Nortriptyline, Paroxetine, Propafenone, Risperidone, Tamoxifen, Tramadol, Venlafaxine
TPMT Poor metabolizer	Azathioprine, Mercaptopurine, Thioguanine
Other genes Not actionable	ABCB1, ADRB1, BRCA1, COMT, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP3A4, CYP3A5, DPYD, G6PD, HMGCR, P2RY12, SULT1A1, UGT1A1, VKORC1

Date printed: 15.03.2016 Card number: 0000001

Scan QR-Code

SAFETY CODE CARD (http://safety-code.org/)

CRO AVIANO

Developed by Matthias Samwald group (University of Wien)

CRO AVIANO

CRO- Aviano
Oncology Dept

AVIANO/ PORDENONE/ SAN VITO

AZIENDA ULSS 9 TREVISO

Cà Foncello Hospital
Oncology Dept

TREVISO

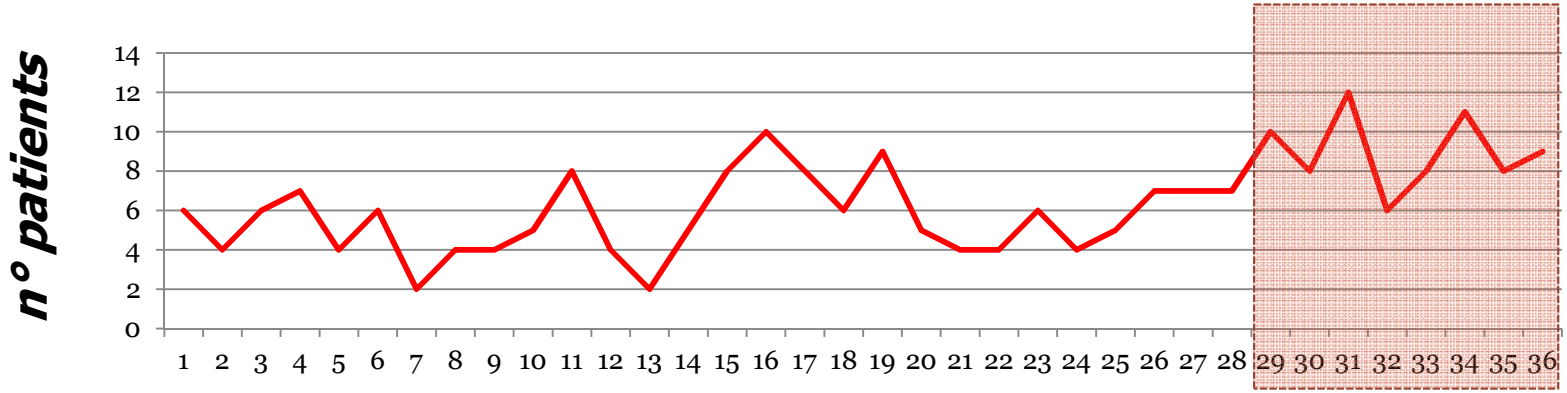
SISTEMA SANITARIO REGIONALE
ASL ROMA 1

San Filippo Neri
Oncology Dept

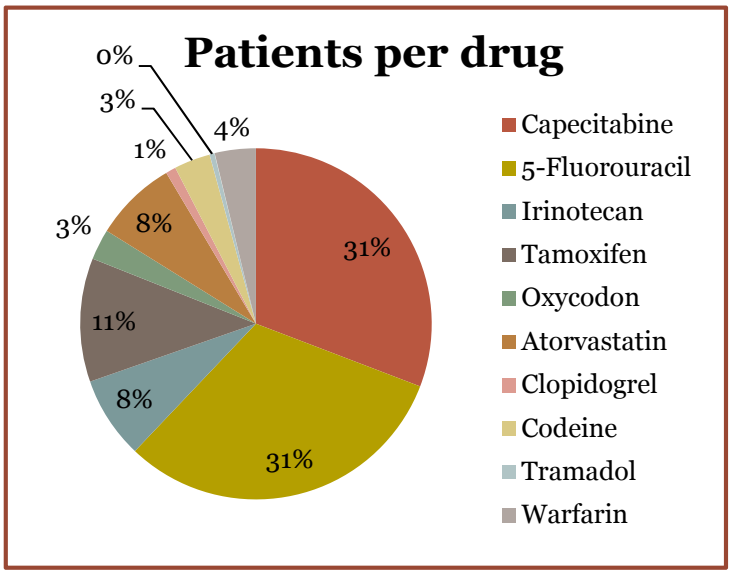
ROME

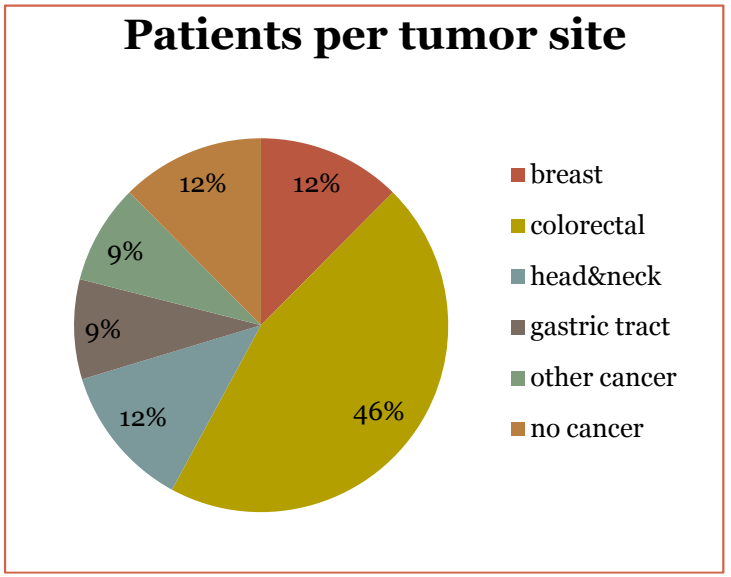
U-PGx | Ubiquitous Pharmacogenomics

Enrollment Rate by time 1,125 patients up-to date/239 at CRO



Mean of 6 patients per week



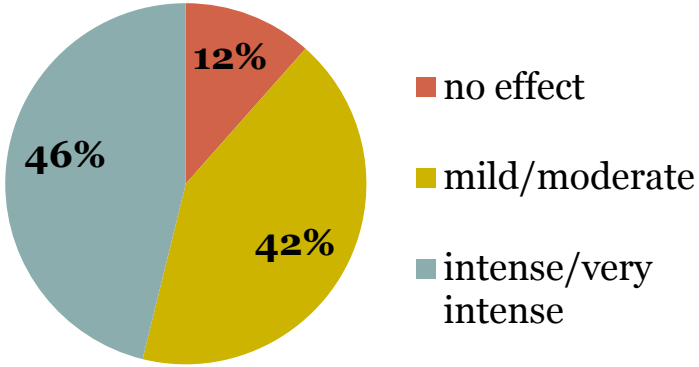


U-PGx | Ubiquitous Pharmacogenomics

Self-reported side effects at 4/12 weeks (calculated on 194 pts)

Center	Index Drug	N° Pts	4 weeks Quest	12 weeks Quest	%
CRO-A	Cape	57	**50**	**29**	51%
	5-FU	27	**21**	**14**	52%
	IRI	12	**8**	**6**	50%
	TAM	19	**15**	**8**	42%
	Other	3	**3**	**2**	67%
SFN-R	Cape	7	**6**	**6**	100%
	5-FU	28	**24**	**18**	64%
	IRI	3	**3**	**2**	67%
	TAM	5	**4**	**4**	80%
	Other	32	**11**	**6**	19%
h-TV	Cape	1	**0**	**0**	0%
Overall		**194**	**145**	**95**	**49%**

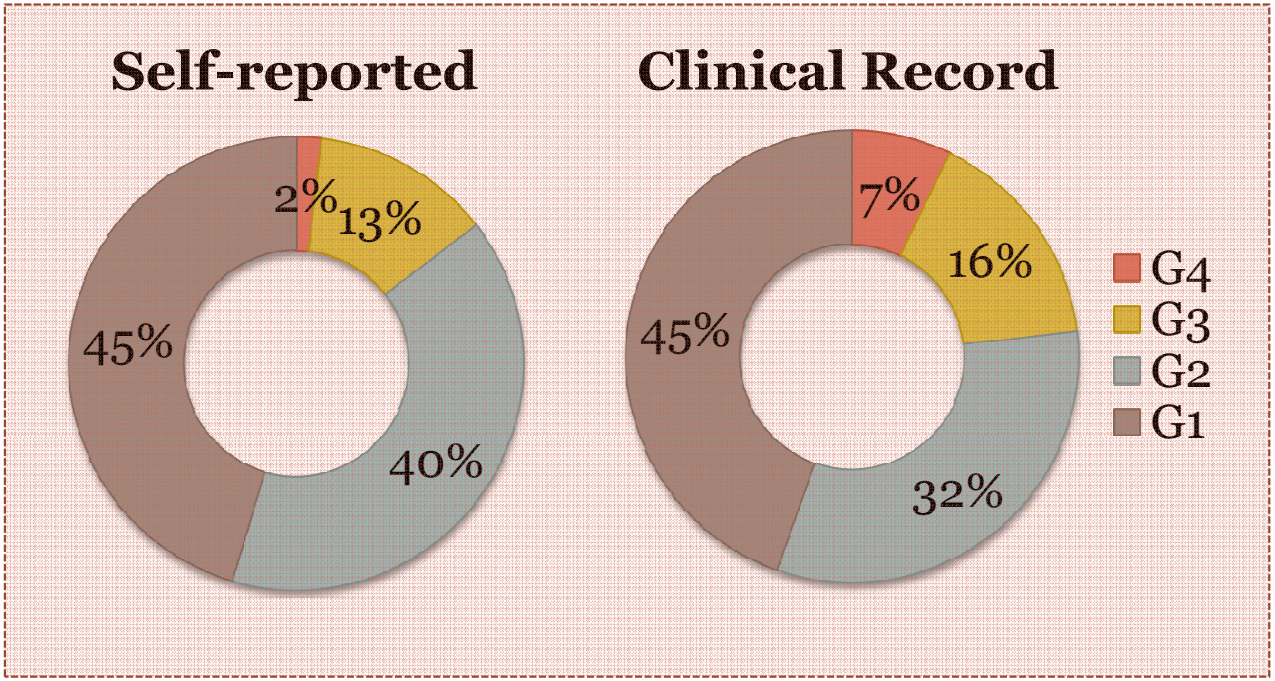
Self-evaluation of side-effects



FOLLOW UP IS ON-GOING

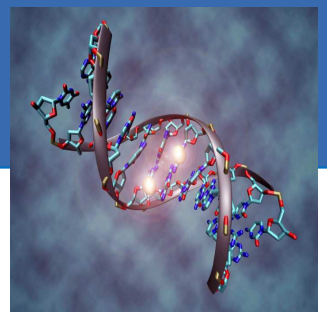
ADRs data collection at 4 weeks and NCI-CTC grading

94 pts



- *Under estimation of ADR severity by the patients*
- *5/94 (5.3%) extreme phenotype patients, hospitalised for toxicity*
- *1 Toxic death*

Conclusion



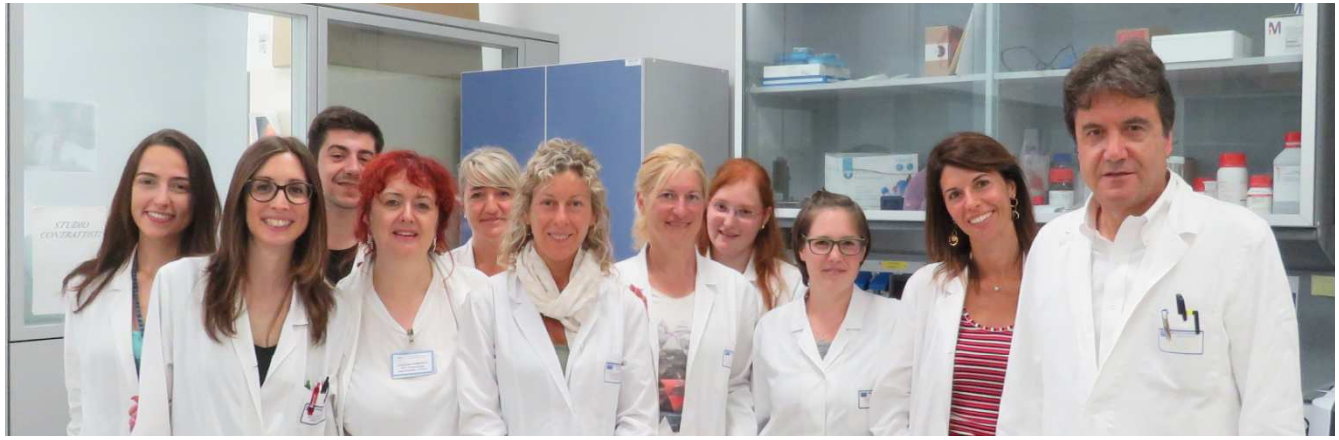
- *UGT1A1* and *DPYD* are two hotspots in the field of cancer pharmacogenomics
- Prospective genotyping of IRI and FL treated patients could spare severe toxicity and save economic resources
- U-PGx is a large and prospective randomized implementation trial conducted in 7 European Health Care Centers with the aim to set the condition for translating PGx in the clinical setting in Europe
- U-PGx will hopefully provide the ultimate proof for the clinical utility of a pharmacogenomic driven treatment

CRO AVIANO

Acknowledgements

POR FESR 2014 2020 Friuli Venezia Giulia
Unione Europea FESR
Repubblica Italiana
AIRC

U-PGx | Ubiquitous Pharmacogenomics



Experimental and Clinical Pharmacology

CRO AVIANO

Director Giuseppe Toffoli

Pgx group: Alessia Bignucolo, Lisa Dal Cin, Chiara Dalle Fratte, Elena De Mattia, Eva Dreussi, Fabrizio Ecca, Marica Garziera, Michela Guardascione , Loredana Romanato, Rossana Roncato, Franca Sartor

U-Pgx European Consortium- Prof HJ Guchelaar

van der Wouden CH, Cambon-Thomsen A, Cecchin E, Cheung K, Dávila-Fajardo CL, Deneer VH, Dolžan V, Ingelman-Sundberg M, Jönsson S, Karlsson MO, Kriek M, Mitropoulou C, Patrinos GP, Pirmohamed M, Samwald M, Schaeffeler E, Schwab M, Steinberger D, Stingl J, Sunder-Plassmann G, Toffoli G, Turner RM, van Rhenen MH, Swen JJ

Quebec University- Prof Chantal Guillemette

University of Chapel Hill- Prof Federico Innocenti

Univ of Padova- Istituto Oncologico Veneto
Univ di Trieste- Burlo Garofolo- Prof G DeCorti, Prof G Stocco
Univ of Florence- Prof E Mini, Dr S Nobili
Hospital San Filippo Neri –Roma- Dr. M D'Andrea, Dr T Diraimo