1° CONGRESSO NAZIONALE
SOCIETA' SCIENTIFICA COMLAS

SOCIETÀ SCIENTIFICA dei MEDICI LEGALI delle AZIENDE SANITARIE del SERVIZIO SANITARIO NAZIONALE
COMLAS

SIENA, 9-10-11 Ottobre 2014

Curare ed insegnare a curare: la medicina personalizzata

Prof. Maurizio Simmaco MD
Azienda Ospedaliera Sant'Andrea – Università Sapienza di Roma
www.simep.it/dima

AZIENDA OSPEDALIERA SANT' ANDREA
FACOLTÀ DI MEDICINA E PSICOLOGIA

http://www.espt-summerschool2014.it

ESPT
European Society of Pharmacogenomics and Theranostics

"Pharmacogenomics and Other Omics Leading to Personalized Medicine: Established and Emerging Scientific, Clinical and Ethical Aspects"

ESPT 2nd Summer School, Rome, 9th-14th June, 2014

Ateneo Pontificio Regina Apostolorum, Via degli Aldobrandeschi, 190

The 2nd ESPT Summer School is a unique opportunity for young clinical and biomedical professionals to become acquainted with the fields of Pharmacogenomics and Personalized Medicine, in accordance with the educational goals of ESPT, the leading European Society in Pharmacogenomics and Therapeutic Diagnostics.
The course aims to provide students with in-depth understanding of the concepts, as well as state-of-the-art knowledge, in Pharmacogenomics and other omics approaches as they are applied towards realization of Personalized Medicine.
It also aims to provide attendees with ready-to-use tools for applying these concepts and knowledge in their working practice.

Become a full player of the Personalized Medicine European Team!

Check out now the website www.espt-summerschool2014.it and find the detailed School Program, application & registration details and all other practical information about this exciting Summer School.

Participants will be limited to 100, so book early to secure your place!

The deadline for application is *April 30th 2014*

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www.espt-summerschool2014.it/registration.htm

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Helmut Brand, Department of International Health Maastricht University
Hiltrud Brauch, Margarete Fischer-Bosch-Institute of Clinical Pharmacology
Manfred Caeser, Life Science Consulting Network Heidelberg
Ingolf Cascorbi, University Hospital Schleswig-Holstein
Bruno Cazetta, Consultant embedded in Pediatric Meyer Hospital Firenze
Antonio Costanzo, Universita La Sapienza Roma
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Adrian LLerena, Faculty of Medicine, University of Extremadura
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Janja Marc, Clinical Biochemistry at University of Ljubljana
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AB ANALITICA

Integrazione di Genomica e Medicina

Outline

Esigenze Mediche

Natura e cultura (genotipo e fenotipo)

La diversità dei genomi umani

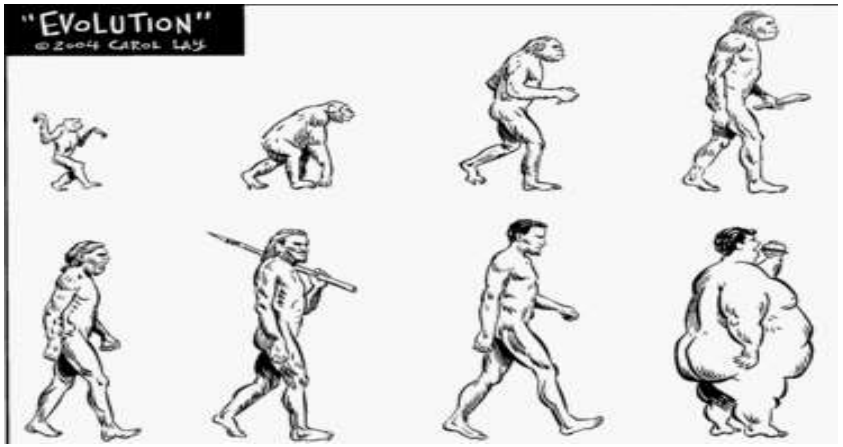
Medicina genomica

Farmacogenomica

Al di là di genomica

Problematiche della salute

1000 morti nel 2008/159 nei paesi ad alto reddito



Fattori di rischio comportamentale

Tabagismo
Dieta non salutare
Sovrapeso
Inattività fisica
Uso di alcool

Esigenze mediche insoddisfatte

Molte comuni malattie (*caancro, demenza, SM, artrite reumatoide, enfisema, etc*.) non esistono terapie realmente efficaci

Anche con terapie farmacologiche consolidate, ci sono molti pazienti che non rispondono

Tutte le terapie farmacologiche portano a effetti indesiderati o nocivi in alcuni pazienti

Esigenze mediche insoddisfatte

Perché non abbiamo efficaci trattamenti per queste malattie?

Perché la risposta ai farmaci così variabile?

Come possiamo migliorare?

Problemi con le terapie

- Carenza di nuovi farmaci (FDA ~ 25 approvazioni / anno)
- Trattamenti esistenti inadeguati (90% dei farmaci funzionano solo nel 30 al 60% dei pazienti)
- Troppi farmaci vengono sospesi a causa di effetti avversi
- Molte nuove terapie (mirate) sono efficaci solo in una (piccola) sottopopolazione di pazienti

→ **Il sistema attuale non produce abbastanza terapie nuove ed efficaci**

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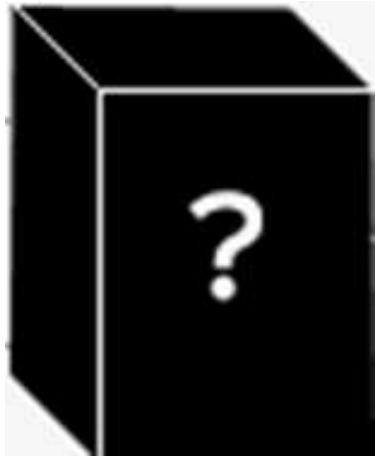
Al di là di genomica

Ogni individuo: Unico corredo di geni (GENOTIPO)
Ogni individuo : Caratteristiche uniche (FENOTIPO)

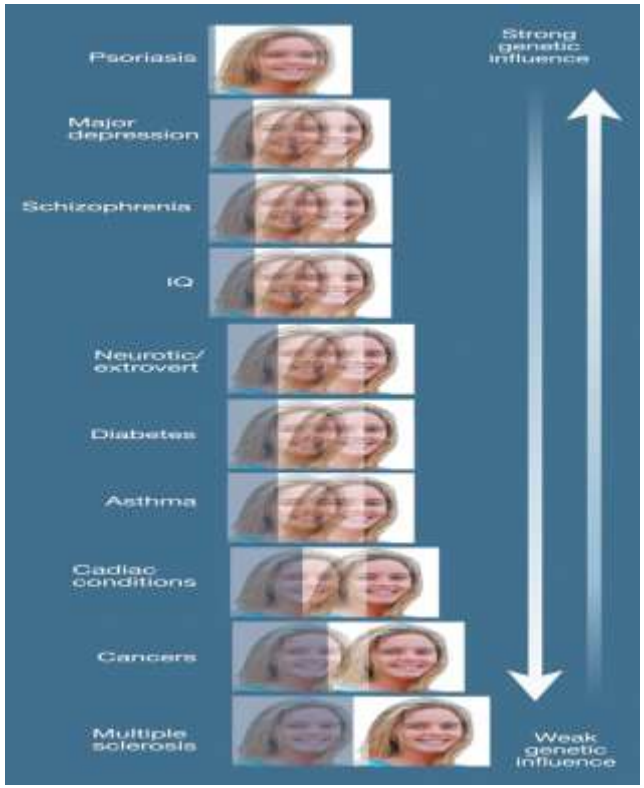
Quale relazione tra genotipo e fenotipo?

Genotipo →  → **Fenotipo**

Stile di vita
Influenza ambientale

Genotipo & Fenotipo o Natura & Cultura

Contributo genetico alla malattia, come rivelato in studi sui gemelli (concordanza, ereditabilità)

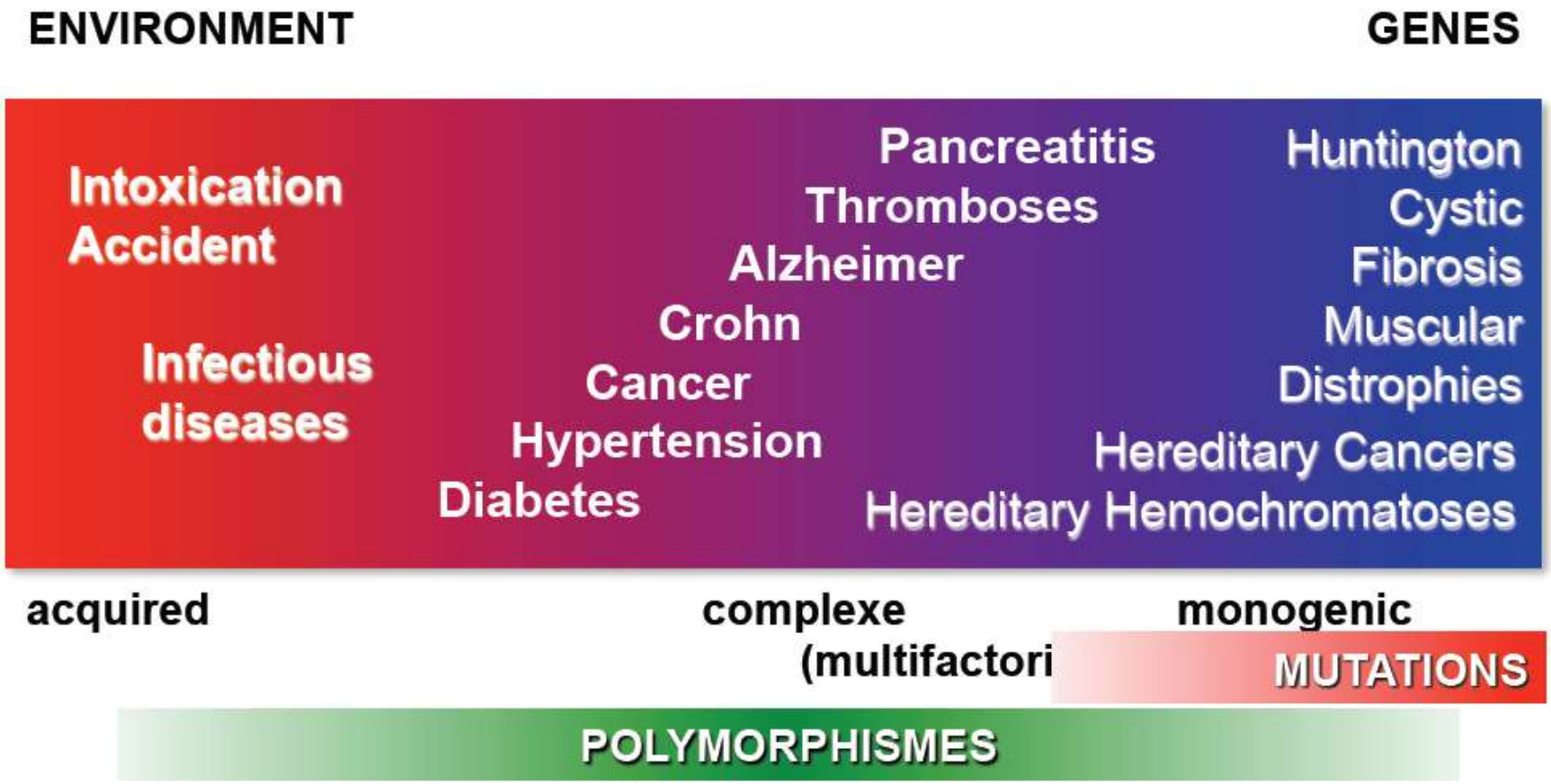


NATURE REVIEWS/ GENETICS 13: 640-653 (September) 2012

Table 3 | **MZ and DZ twin concordance for complex disease**

	Probandwise concordance* (%)	
	MZ twins	DZ twins
Type 1 diabetes	42.9	7.4
Type 2 diabetes	34	16
Multiple sclerosis	25.3	5.4
Crohn's disease	38	2
Ulcerative colitis	15	8
Alzheimer's disease	32.2	8.7
Parkinson's disease	15.5	11.1
Schizophrenia	40.8	5.3
Major depression	31.1‡ or 47.6§	25.1‡ or 42.6§
Attention-deficit hyperactivity disorder	82.4	37.9
Autism spectrum disorders	93.7	46.7
Colorectal cancer	11	5
Breast cancer	13§	9§
Prostate cancer	18	3

Genotipo & Fenotipo o Natura & Cultura



Modified from Stylianos Antonarakis

VARIABILI CHE INFLUENZANO IL RISCHIO DI MALATTIA E LA RISPOSTA AI FARMACI

Fattori clinici

Età
Genere
Storia familiare
BMI
Malattie
Effetto placebo
Compliance

Personal omics

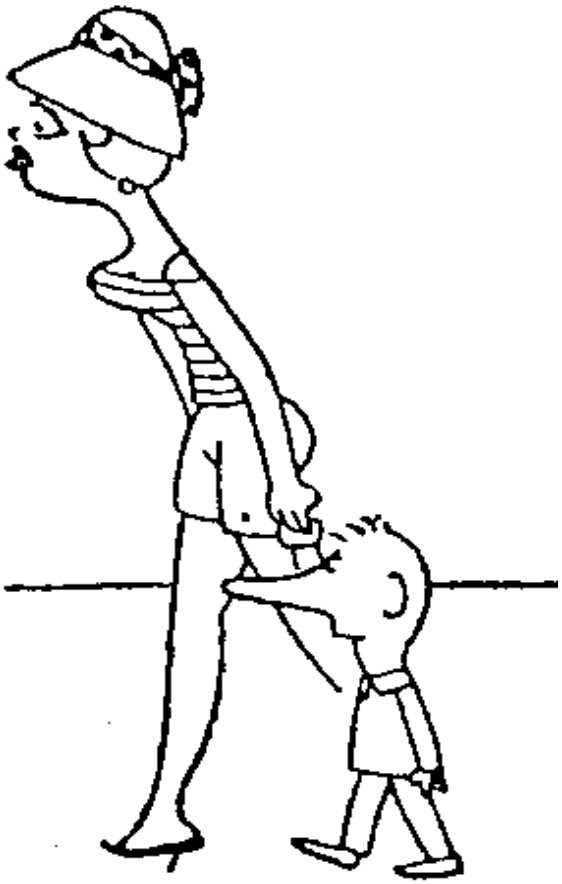
Genome
Transcriptome
Proteome
Metabolome
Epigenome

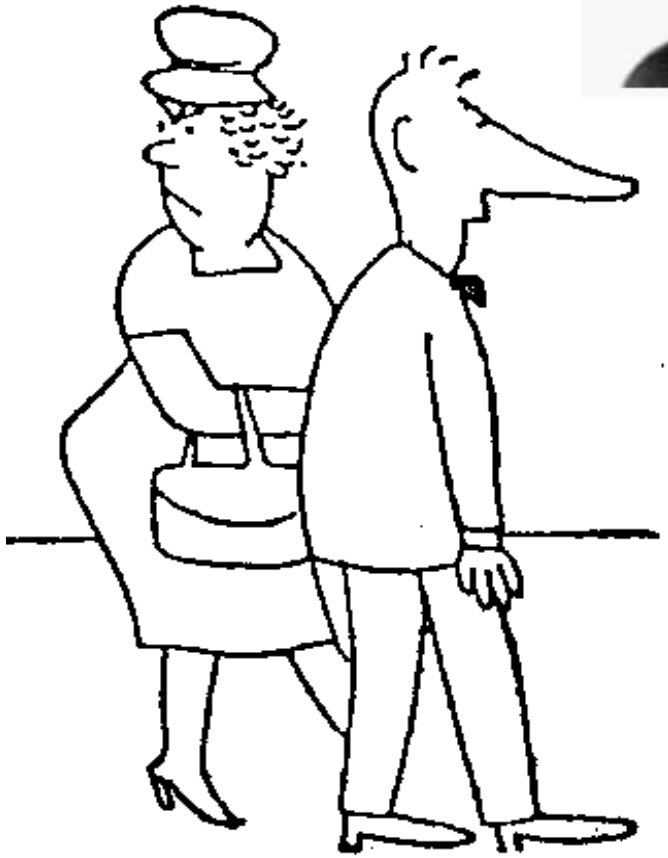
Ambiente

Background etnico
Nutrizione
Farmaci (DDIs)
Esposizione chimica
Stile di vita
Eventi
Microbioma

tori clinici + *Personal omics* + Ambiente = **Fenotipo**

Maledizione di Gregor Mendel





Quanto è genetica, quanto ambiente?

Strategia

Nuovi & più efficaci approcci per andare dall'innovazione scientifica all'utilità clinica

- **Medicina genomica (uso di informazioni del genoma)**
- **Medicina Personalizzata / Individualizzata**
- **Medicina di precisione (nuova tassonomia)**
- **Medicina stratificata (gruppi con risultati condivisi)**
- **Medicina traslazionale (dal lab al letto del Paziente)**

Strumenti: Biomarkers – Diagnostica molecolare

Medicina personalizzata

La promessa

- Diagnosi precoce e più precisa
- Trattamento più efficace, con minori eventi avversi
- Effetto positivo sullo sviluppo dei farmaci

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Human Genome

Recenti sviluppi per spiegare la diversità Nel rischio di malattia e di risposta ai farmaci

2001 **2004**

Sequencing (NGS, più veloce, più economico, più accurato)

Studi di associazione genome-wide (GWAS con SNP)

Mappe aplotipo (HapMap)

Sviluppo parallelo di altre tecnologie «omiche»

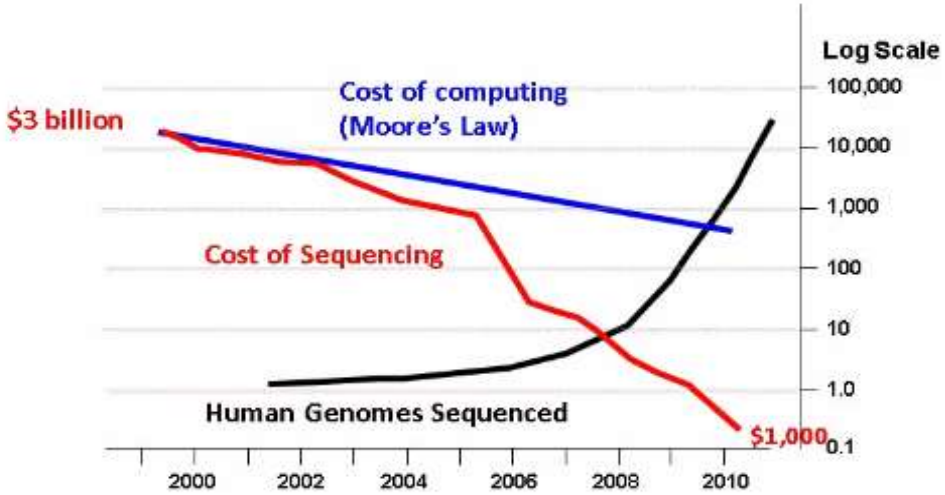
Sequenziamento intero del genoma: più semplice, più veloce, più economico

Pocket Money Sequencing

While Roche and Applied Biosystems launch price cutting sequencing systems, former 454 protagonist Jonathan Rothberg is announcing his own solution.

Adapted from The Economist

The Sequencing Explosion



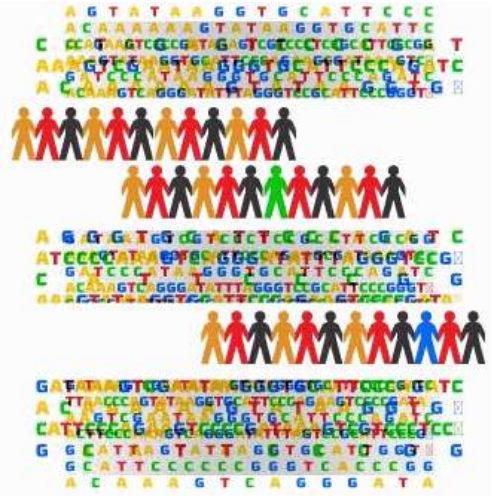
illumina

SAN DIEGO--(BUSINESS WIRE)--Jan. 14, 2014-

Illumina announces landmark $1,000 human genome sequencing

'Next-next generation'

Fluoresence			Electronic			Atomic
Labelled polymerase Life Technologies	**Tethered polymerase** Pacific Biosciences	**Reversible termination** Helicos	**pH** IonTorrent/Life Technologies	**Biological nanopores** Oxford Nanopore	**Solid-state nanopores** IMB/Roche, NABSys	**Microscopy** Halcyon Molecular, ZS Genetics



Genomes by the Thousands

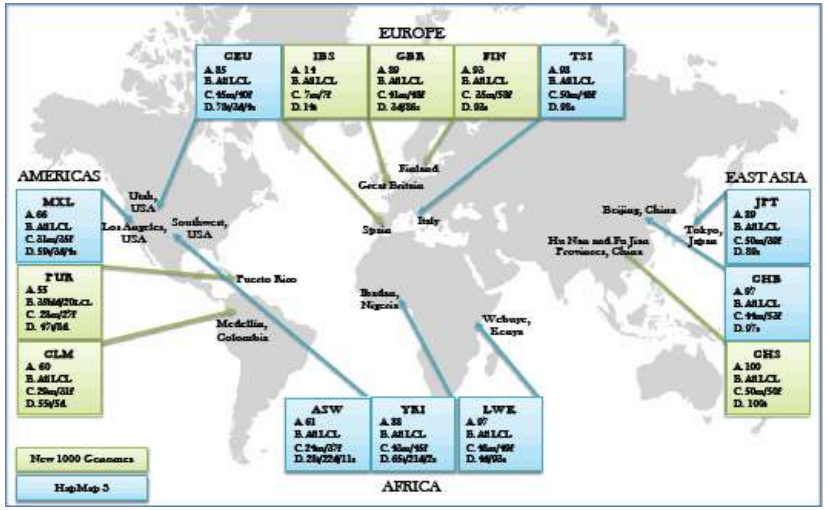
ARTICLE

doi:10.1038/nature11632

An integrated map of genetic variation from 1,092 human genomes

The 1000 Genomes Project Consortium*

Nature 491: 56 - 65, 2012



- Informazioni sulla sequenza del genoma di 1.000 persone provenienti da 14 popolazioni
- Haplotype mappa di 38 milioni di SNPs 1,4 milioni di brevi inserzioni e delezioni
- > 14.000 grandi delezioni

www.1000genomes.org

VARIABILITÀ INTERINDIVIDUALE DELLA SEQUENZA DEL GENOMA UMANO

Ogni individuo è diverso dal gruppo di riferimento del genoma aploide da:

~ 3.6 million basepairs difference (SNPs, SNVs)

~ 24’000 SNPs in coding regions

~ 350’000 small indels (insertions, deletions)

~ 700 large deletions

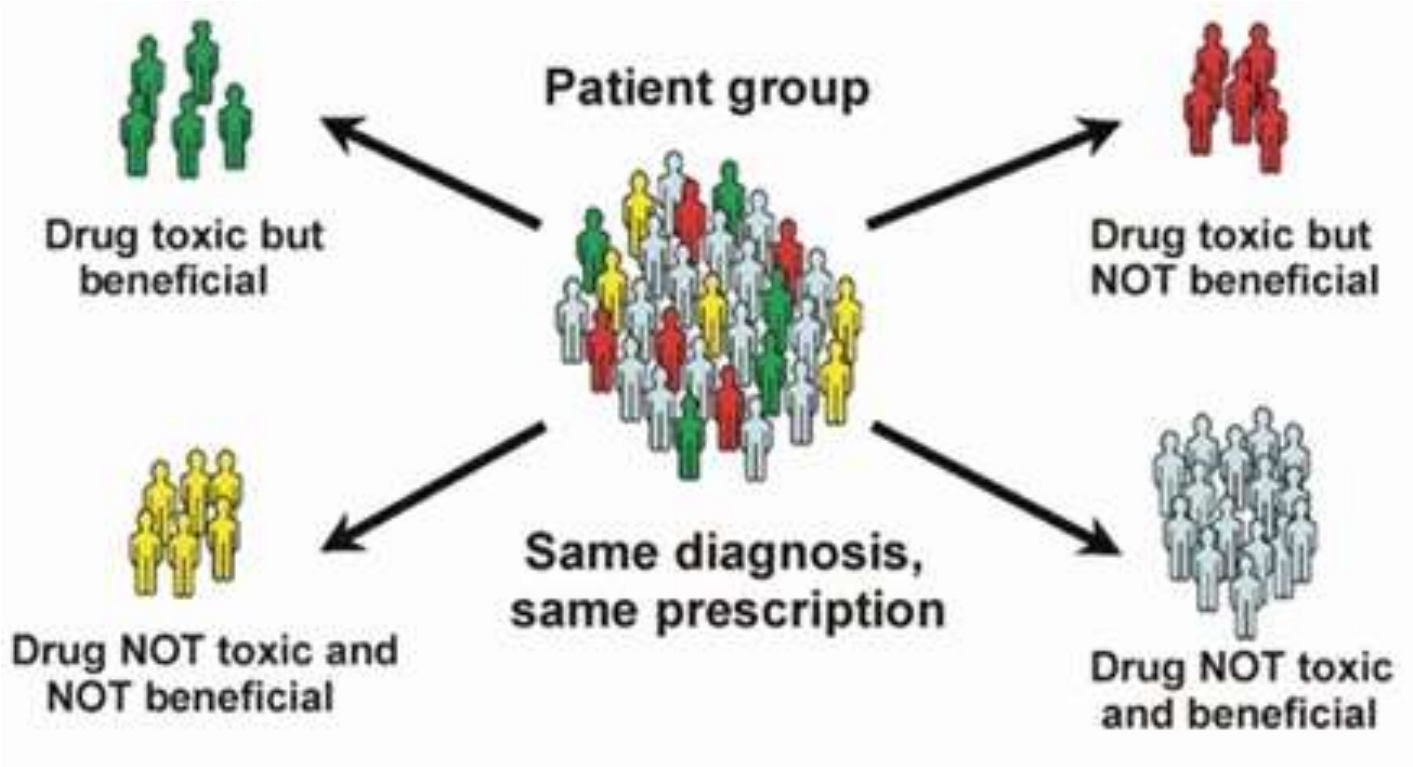
~ 400’000 to 600’000 new or private SNVs

~ 1000 copy number variants (CNVs) exceeding 500bp & other structural changes

~ 100 loss of function (LoF) variants of «disease» genes

Totale variazione di sequenza ~ 1 %

Variabilità interindividuale nella risposta ai farmaci



- Identificare responders alla terapia farmacologica
- Identificare i pazienti a rischio di ADR *

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Human Genome Sequence
Benefici per la medicina

My genome. So what?

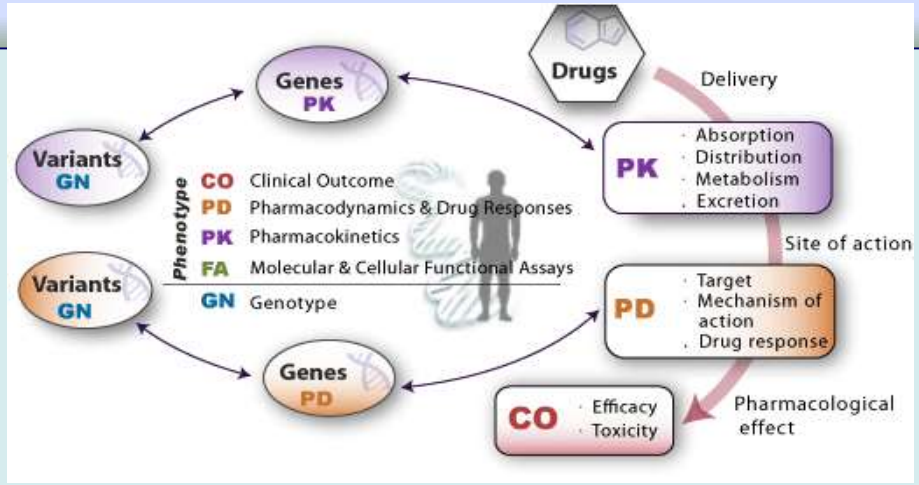
Research is needed into the way individuals use their genomic information, and into protection from its abuse by others.

Comprensione delle malattie monogeniche (2048 nel 2007, 3834 nel 2013)
Comprensione patologie complesse poligeniche
Comprensione diversi tipi di cancro
Fornire una diagnosi più precisa
Stimare predisposizioni ai disturbi
Opportunità per nuovi trattamenti
Opportunità per medicina personalizzata / individualizzata

Basic science – clinical science integration: how to reach the goal?

2001

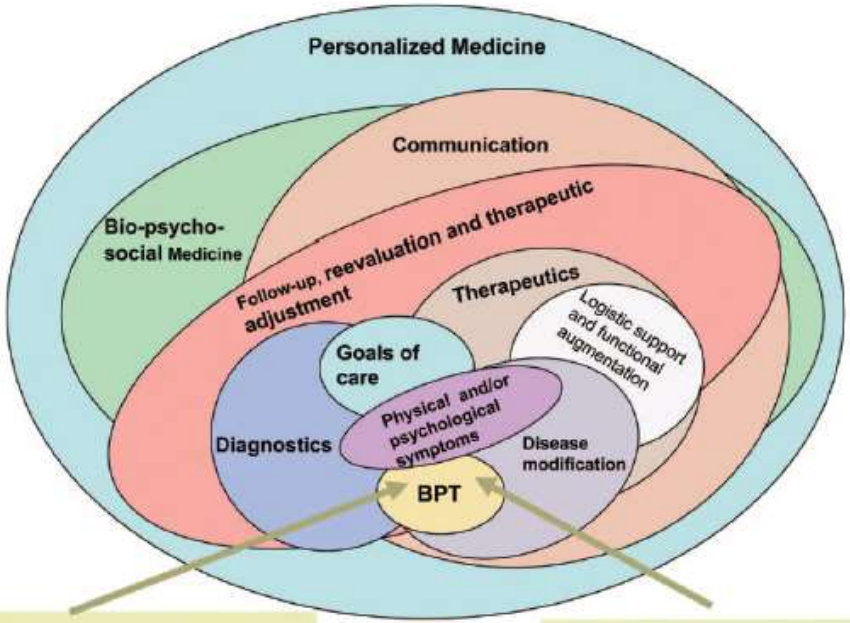
- ✓ sharing language
- ✓ sharing resources
- ✓ promoting partnerships



- Genomics
- TDM
- Metabolomics

2014

Medicina Personalizzata e Terapia Personalizzata Biologicamente (BTP)



Disease Specific

target specific identifiable molecular targets or receptors

genomic analysis for positive or negative predictive indicators for specific therapeutic options

individualized drug selection based on sophisticated in-vivo drug testing on individual patient's tumor clones

identification of rare altered molecules in bodily fluids to monitor disease burden and response to treatment

others

Host Specific

germline polymorphisms and pharmacogenomics to better select drugs and avoid toxicity

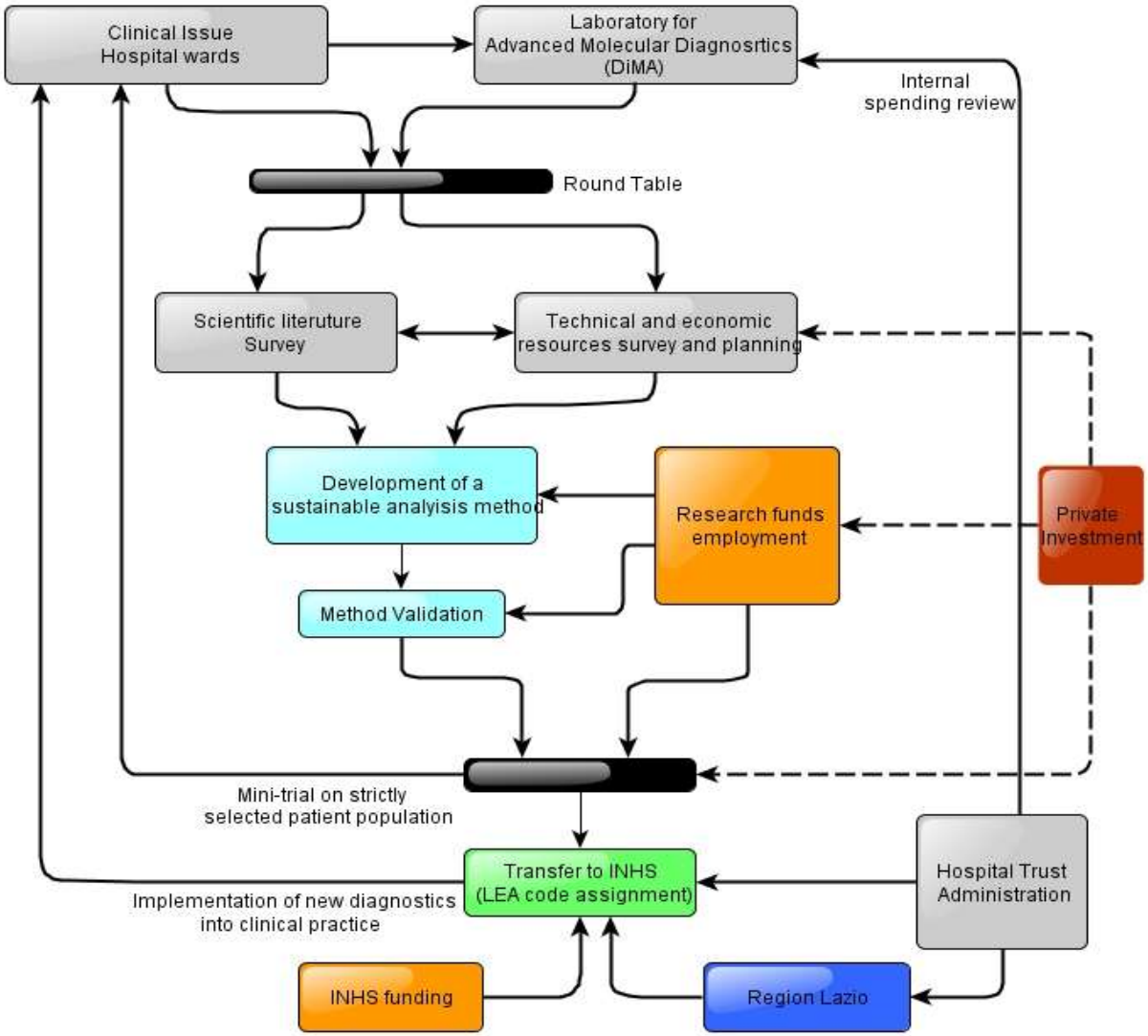
others

Words Matter: Distinguishing "Personalized Medicine" and "Biologically Personalized Therapeutics"

Nathan I. Cherny, Elisabeth G. E. de Vries, Linda Emanuel, Lesley Fallowfield, Prudence A. Francis, Alberto Gabizon, Martine J. Piccart, David Sidransky, Lior Soussan-Gutman, Chariklia Tziraki

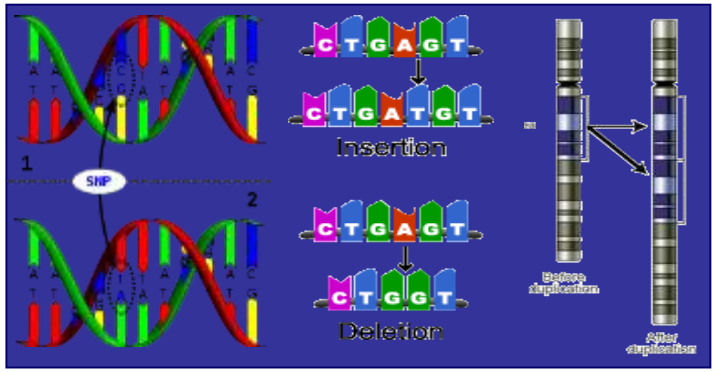
Manuscript received April 10, 2014; revised June 30, 2014; accepted August 28, 2014.

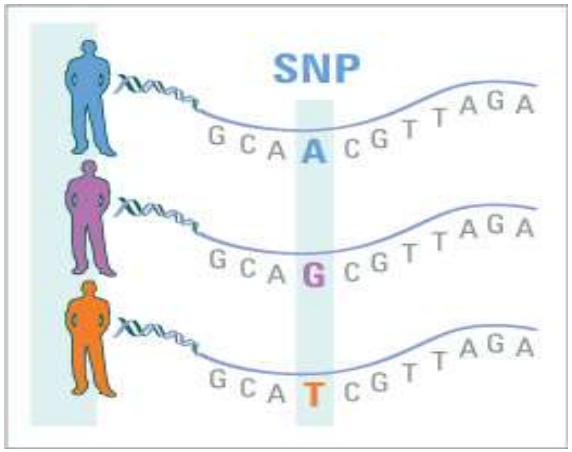
Sant'Andrea work-flow



PERSONAL GENOMICS

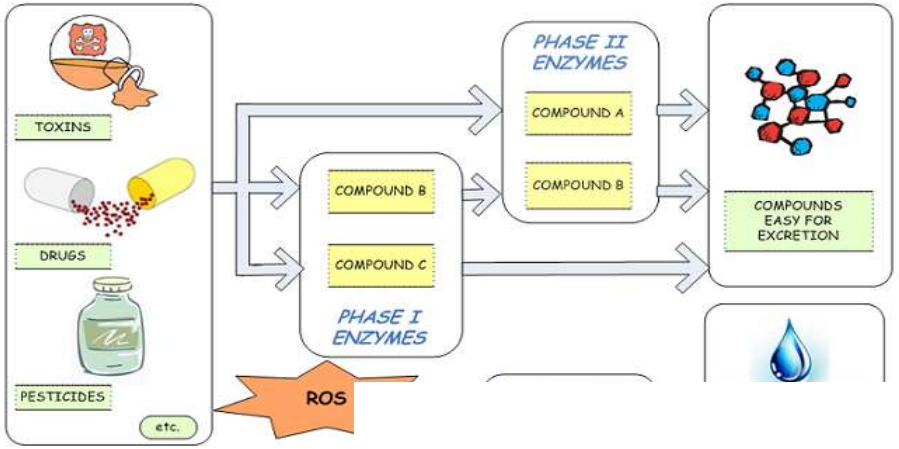
Genomic variation:
- single nucleotide polymorphisms (SNPs)
- nucleotide insertion/deletion (I/d)
- copy number variation (CNV)

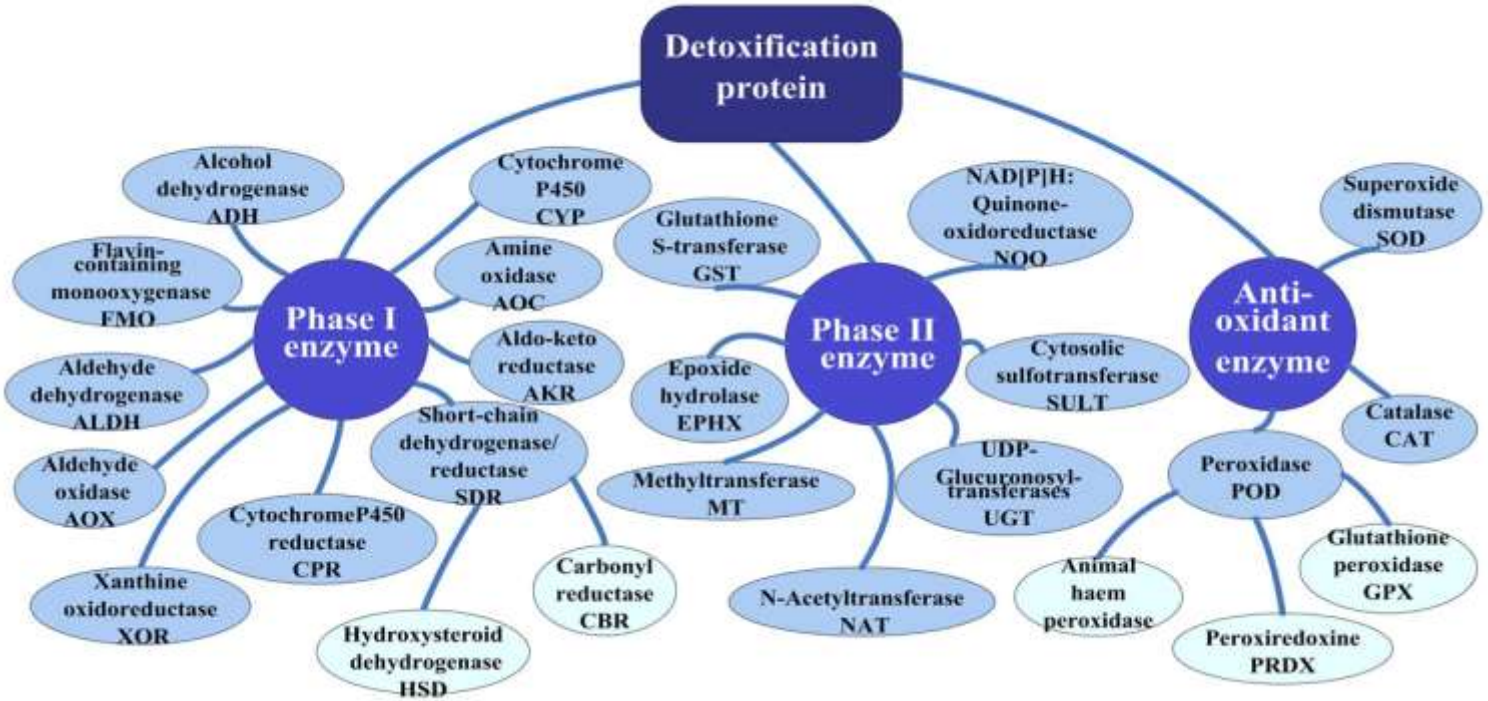




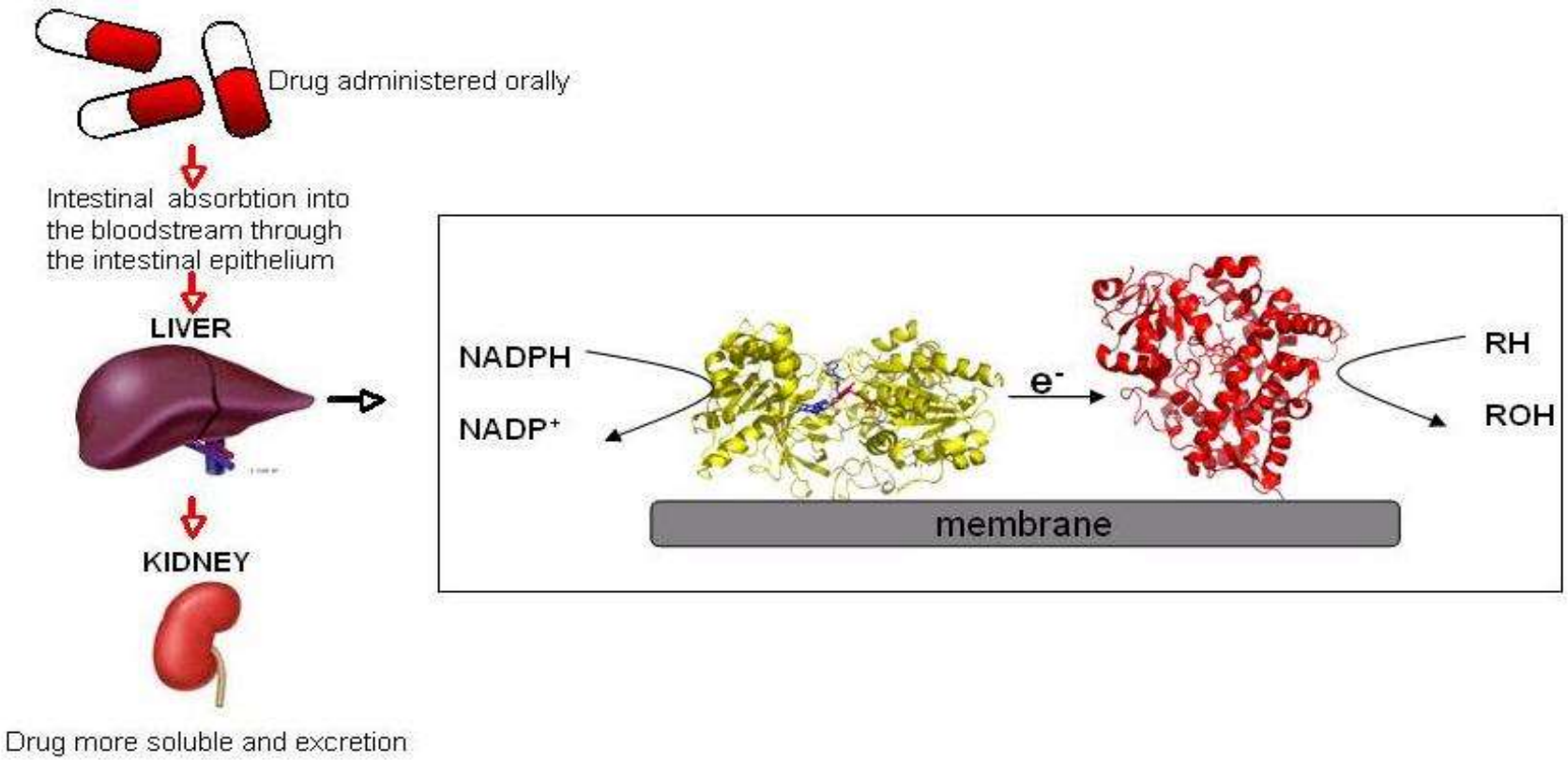
Genomic variations affecting diseases development/progression and individual response to pharmacological treatment (efficacy and safety) are known

Drug metabolism: Phase I and Phase II enzymes

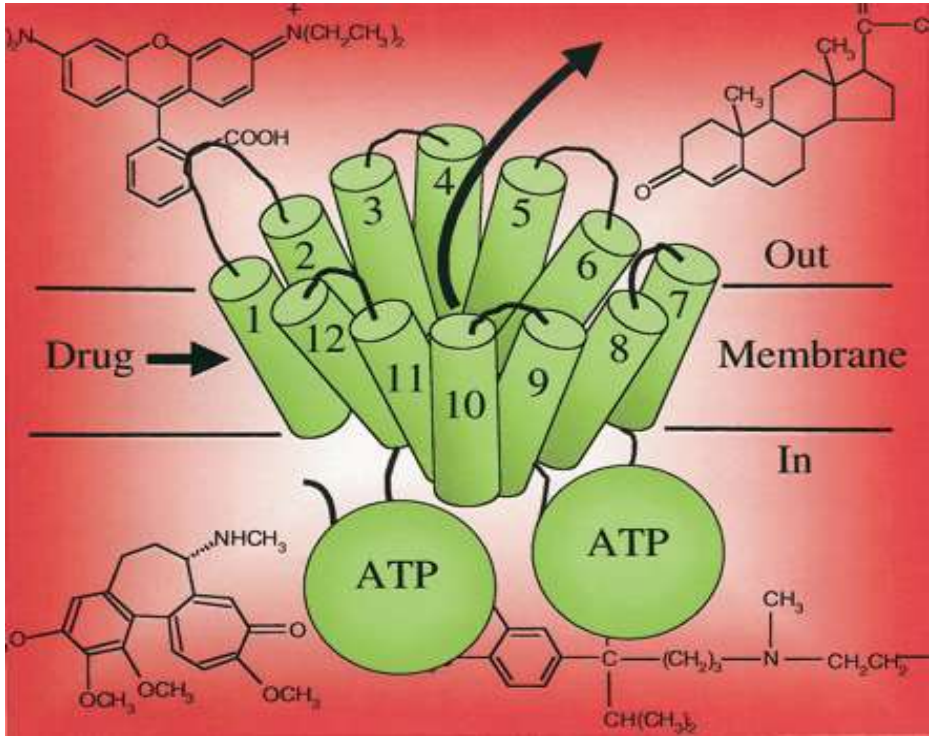




Cytochrome P450 aids in the metabolism of xenobiotics by adding OH to increase the water solubility of the compound



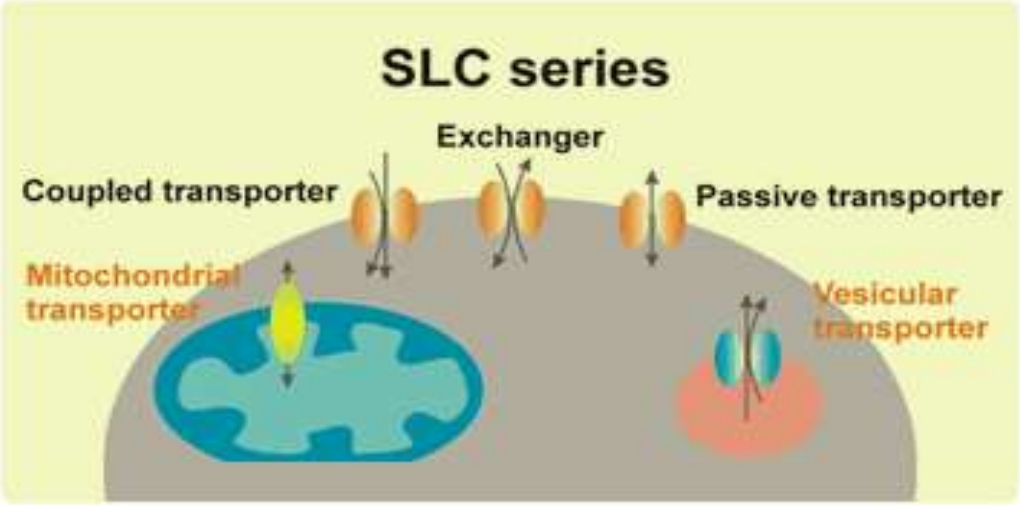
ATP-binding cassette transporter



- Drive the transport of various molecules across all cell membranes

- 48 known members
- 7 subfamilies are designated ABCA → ABCG

Solute Carrier Family of Transporters



- Family of transporters includes over 300 proteins functionally groped into 47 families

The SLC family of transporters includes facilitative transporters, primary and secondary active transporters, ion channels, and the aquaporins.

PHARMACOGENETICS
PHARMACOGENOMICS

La questione non può più essere l'opportunità di ordinare un test di farmacogenomica,

ma come utilizzare al meglio i risultati dei test genomici già esistenti !!

“The right drug for the right patient”

DRUGBANK

Open Data Drug & Drug Target Database

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Identification | Taxonomy | Pharmacology | Pharmacoeconomics | Properties | References | Interactions | 0 Comments

targets (25) | enzym

Identification	
Name	A
Accession Number	D
Type	s
Groups	a
Description	A p n D a a
Structure	

SuperCYP

- > Home
- Drug
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Results

In this table you can see all cyps that are involved in the metabolism of your drug-cocktail. If two or more drugs are metabolized by the same CYP, the column is coloured yellow (2 drugs), orange (3 drugs) or red (4 and more drugs). The table gives alternatives for all chosen drugs and their metabolism based on their ATC-groups.

Legend	s = substrate, inh = inhibitor, ind = inducer By clicking on the the drug you get information about it. By clicking on the cyp you get information about it. By clicking on a relation (s, inh or ind) you get the source.

Name	1A1	1A2	2B6	2C19	2D6	3A4	3A5	3A7	nocyp
Aripiprazole					S Ind Inh	S	S	S	
alternative drugs for Aripiprazole	1A1	1A2	2B6	2C19	2D6	3A4	3A5	3A7	nocyp
Reserpin							Ind		
Risperidone					S Inh	S Inh	S	S	
Clotiapine								S	
Zotepine	S	S	S	S	S	S	S		
Prothipendyl									X

Substrate-Substrate Interaction	If more than one drug is metabolized by the same CYP, it is possible that its metabolism is inhibited because of the competition between the drugs. That means, it can be useful to lower the dosage of the drugs in the drug-cocktail because they remain longer in the organism than in monotherapy.
Inhibitor-Substrate Interaction	Combining drugs that have inhibitory effect and are substrates of one particular CYP, should be compensated by lowering the dosage. They rest longer in the organism than in monotherapy. Not adapting the dosage bears the risk of even more side effects.
Inducer-Substrate Interaction	Combining drugs that are inducers and substrates of one CYP should be compensated by increasing the dosage because metabolism is stimulated and faster than in monotherapy. Therefore, the drugs are even earlier eliminated.
Inducer-Inducer Interaction	Combining two or more inducers of one CYP, should be compensated by increasing the dosage to reach the normal therapeutic effect because their metabolism is stimulated. Therefore, the drugs are even earlier eliminated.
Inhibitor-Inhibitor Interaction	Combining two or more inhibitors of one CYP, should be compensated by lowering the dosage of these drugs because the metabolism is reduced and the drugs remain longer in the organism than in monotherapy. Not adapting the dosage bears the risk of even more side effects.

CHARITÉ Charité Berlin Structural Bioinformatics Group

The genomic road map

- Patient's genomic profile as new tool for clinicians
  - Side effects prevention
  - Drug Metabolism optimization
    - SNPs realted to Diagnosis-specific chemotherapics
    - SNPs realted to Complementary therapy
    - SNPs realted to Pain control drugs
      - **Metabolic drug interactions integration/evaluation**

SNPs for Diagnosis-specific chemotherapics drugs

Breast Cancer	5FU, capecitabine Paclitaxel Docetaxel Anastrozole, letrozole, exemestane Doxorubicin, farmorubicin Cisplatin, carboplatin Cyclophosphamide Methotrexate, gemcitabine Vinorelbine Eribulin mesylate Fulvestant Tamoxifen Trastuzumab, pertuzumab, bevacizumab Lapatinib Everolimus	-MTHFR C677T -MTHFR A1298C -DPYD IVS14 -DPYD A166G -DPYD A949T -TSER VNTR -UGT1A1*28 -ABCB1 C3435T -ABCB1 C1236T -CYP3A4*1B -CYP3A5*32C9 C430T -CYP2C9*3 A1075C -CYBA C242T -NCF4 A212G -RAC2 T7508A -MRP1 G671V -MRP2 V1188E -MRP2 C1515T -CBR3 V244M -GSTP1 A313G -XRCC1 G28152A -ERCC1 C8092A -ERCC1 T19007C -CYP1A2*1C -CYP1A2*1F -CYP2D6 (14 Polimorfismi) -CYP2C19 (10 Polimorfismi)

Similar panels available for:

NSCLC (NON-SMALL CELLS LUNG CANCER)
SCLC (SMALL CELLS LUNG CANCER)
CRC (COLORECTAL CANCER)
BREAST CANCER
OVARIAN CANCER
STOMACH CANCER
PROSTATE CANCER
PANCREATIC & BILIARY TRACT CANCER
HEPATOCELLULAR CARCINOMA
ENDOMETRIAL CANCER
CERVICAL CANCER
BLADDER & UROTELIAL CANCER
TESTICULAR CANCER
ANAL CANCER
RENAL CANCER
MELANOMA
SARCOMA

SNPs related to Complementary therapy

CYP2C19: *2 19154G/A *3 17948G/A *4 1AG *5 90033C/T *6 12748G/A *7 19294T/A *8 12711T/C *9 12884G/A *10 19153C/T **Trasportatori**: -ABCC2 C24T -ABCB1 C3435T -ABCB1 C1236T -MRP1 G671V -MRP2 V1188E -MRP2 C1515T	**Valutazione CYP2D6**: *2 2850C/T *3 2549 delA *4 1846G/A *5 Delezione *6 1707delT *7 2935A/C *8 1785G/T *9 2613_2615 del AGA *10 100C/T *12 124G/A *14 1785G/A *17 1023C/T *29 1659G/A *41 2988G/A *XN (ripetizioni geniche)	**Capacità metabolica per Tiopurine**: -TPMT G460A -TPMT A719G **Capacità metabolica per Warfarin**: -CYP2C9 C430T -CYP2C9 A1075C -VKORKC1 G1639A **Valutazione Citocromi:** -CYP3A4*1B -CYP3A5*3
Derive information for: Perfalgan, metocloparmide, ondasetron, ranitidin, pantoprazol, esomeprazol, desametasone, betametasone, rocuronium, remifentanil, sufentanil, tramadol, ketoralac, droperidol, succinylcholine, naropin, lidocaine		

SNPs related to Pain control drugs

Drugs	SNPs investigated
Morphine Hydromorphone Oxycodone Naloxone Codeine Fentanyl Tapentadol Buprenorphine	OPRM1 CYP2C9 CYP2D6 CYP3A4 CYP3A5 CYP2C19 1A2 UGT1A9 ABCB1 ABCC2

Opioid-derivates and anti-pain drugs are largely used in pain-therapy but they often show large inter-individual variability in therapeutic dosage and side effects.

Characterization of SNPs in genes involved in opioid metabolism, transport and target could help clinicians in the management of pain-therapy.

Psychiatric drugs: genomic metabolism profile

Metabolita attivo	**Stazioni enzimatiche di metabolizzazione**
Acamprosato	Non coinvolti (non metabolizzati)
Agomelatina	**CYP1A2**, CYP2C19
Amantadina	Coinvolgimento marginale (il 90% viene escreto senza essere metabolizzato)
Alprazolam	**CYP3A4/5**
Amisulpride	Coinvolgimento marginale (oltre il 90% viene escreto dai reni senza essere metabolizzato)
Amitriptilina e ossido di amitriptilina (amitriptilina, nortriptilina)	CYP1A2, CYP2C9, **CYP2C19**, **CYP2D6**, CYP3A4
Aripiprazolo (deidroaripiprazolo)	**CYP2D6, CYP3A4,**
Asenapina	Glucuroniltransferasi e CYP1A2
Atomoxetina	**CYP2D6**
Benperidolo	**Incerti**
Benserazide	**Idrossilazione,** COMT
Biperidene	**Idrossilazione**
Bromocriptina	**CYP3A4**
Bromperidolo	**CYP3A4**
Brotizolam	**CYP3A4**
Buprenorfina (Norbuprenorfina)	CYP2C8, **CYP3A4**
Bupropione (Idrossibupropione)	**CYP2B6**
Buspirone	**CYP3A4**
Cabergolina	**Idrolisi,** CYP3A4

Carbidopa	Vie metaboliche sconosciute 1/3 non metabolizzato
Carbamazepina, CBZ (CBZ-10,11-eposside)*	CYP1A2, CYP2B6, CYP2C8, **CYP3A4/5**
Clorpromazina	**CYP1A2, CYP2D6**
Citalopram	**CYP2C19**, CYP2D6, CYP3A4
Clomipramina (Norclomipramina)	CYP1A2, **CYP2C19, CYP2D6,** CYP3A4
Clometiazolo	CYP2A6, CYP2B6, CYP3A4
Clozapina	**CYP1A2**, **CYP2C19,** CYP3A4

MassArray

• • • • • •

Sertralina	**CYP2B6, CYP2C19**, CYP2C9, CYP2D6
Tioridazina	**CYP1A2**, CYP2C19, **CYP2D6**, CYP3A4
Tiapride	**Principalmente non metabolizzato**
Tolcapone	**Glucuroniltransferasi**
Trimipramina (nortrimipramina)	**CYP2C19, CYP2D6,** CYP2C9
Tranilcipromina	Monoaminossidasi, incerti
Trazodone	**CYP3A4,** CYP2D6
Acido valproico	**Glucuronosiltransferasi**, CYP2A6, CYP2B6, CYP2C9, **beta-ossidazione**
Venlafaxina (O-desmetil-venlafaxina)	CYP2C19, **CYP2D6**, CYP3A4
Zaleplon	Aldeide ossidasi, CYP3A4
Ziprasidone	CYP3A4, aldeide ossidasi
Zolpidem	CYP1A2, CYP2C9, **CYP3A4**
Zopiclone	CYP2C8, **CYP3A4**
Zotepina	**CYP1A2**, CYP2D6, **CYP3A4**
Zuclopentixolo	**CYP2D6**

Development of methods for determination of metabolites and xenobiotics

QTrap LC/MS/MS API 2000 - Applied Biosystems

- urinary metabolites
- urinary and plasma amino acids
- antiepileptics
- antipsychotic drugs
- antiarrhythmic drugs
- test for intestinal permeability
- dosage of the chemotherapy drug 5-fluorouracil

-endocrinology
-pediatrics
-psychiatry
-oncology
-cardiology
-neurology
-infectious diseases
-diabetology
-gastroenterology
-Occupational Medicine

AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry: Update 2011

Hiemke C et al. AGNP Consensus Guidelines for… Pharmacopsychiatry 2011; 44: 195–235

Table 6 Typical indications for measuring plasma concentrations of medications in psychiatry.

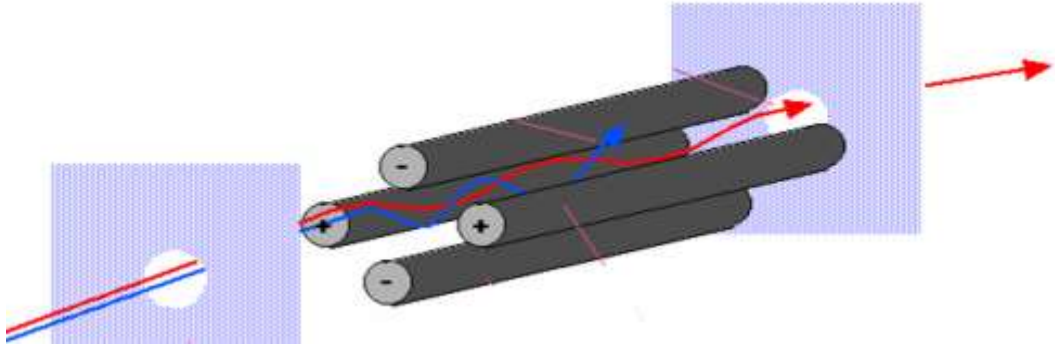
– Dose optimization after initial prescription or after dose change
– Drugs, for which TDM is mandatory for safety reasons (e.g., lithium)
– Suspected complete or partial non-adherence (non-compliance) to medication
– Lack of clinical improvement under recommended doses
– Adverse effects and clinical improvement under recommended doses
– Combination treatment with a drug known for its interaction potential or suspected drug interaction
– TDM in pharmacovigilance programs
– Relapse prevention under maintenance treatment
– Recurrence under adequate doses
– Presence of a genetic particularity concerning drug metabolism (genetic deficiency, gene multiplication)
– Pregnant or breast feeding patient
– Children and adolescent patient
– Elderly patient (>65 y)
– Individuals with intellectual disabilities
– Patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease)
– Forensic patient
– Problems occurring after switching from an original preparation to a generic form (and vice versa)

Therapeutic Drug Monitoring in Psichiatry

Farmaco	Metabolita	Informazioni per il clinico (Rapporti delle concentrazioni metabolita:composto progenitore (Media-DS - Media+DS))
Amitriptilina	Nortriptilina*	0.2-1.8 (n=83)
Aripiprazolo	Deidroaripirazolo(*)	0.3-0.5 PM di CYP2D6: 0.2
Bromperidolo	Bromperidolo ridotto	0.11-0.51 (n=31)
Buprenorfina	Norbuprenorfina	0.8-2.0 (n=5)
Bupropione	Idrossibupropione	5-47 (24 h, n=9) 6-30 (12 h, n=9)
Buspirone	6-Idrossibuspirone	25-53 (n=20)
Carbamazepina	Carbamazepina-10,11-epossidе	0.07-0.25 (n=14)
Citalopram	N-desmetilcitalopram	0.31-0.60 (n=2330)
Clomipramina	Norclomipramina*	0.8-2.6 (n=115)
Clozapina	Norclozapina	Non fumatori (n=98) 0.5-0.6 Fumatori (n=198) 0.4-0.7
Dotiepina	Nordotiepina	0-1.4 (n=50)
Doxepina	Nordoxepina	0.6-1.6 (n=12) PM CYP2C19: 1.8 (n=4) PM CYP2D6: 0.8 (n=6)
Escitalopram	N-Desmetilescitalopram	0.3-1.0 (n=243)
Fluoxetina	Norfluoxetina*	0.7-1.9 (n=334)
Fluvoxamina	Acido di fluvoxamina	0-1.2 (n= 49)
Aloperidolo	Aloperidolo ridotto	Media 0.6
Imipramina	Desipramina	0.6-3.2 (n=14) PM CYP2D6 4.1 (n=2)
Maprotilina	Desmetilmaprotilina	1.1-3.7 (n=76) PM CYP2D6 4.9
Mianserina	N-Desmetilmianserina	0.5-0.8 (n=182)
Mirtazapina	N-Desmetilmirtazapina	0.2-1.2 (n=100)
Moclobemide	Moclobemide N-ossido	0.8-2.5 (n= 6)
Olanzapina	N-Desmetilolanzapina	Non fumatori: 0.1-0.3 (n=76) Fumatori: 0.2-0.4 (n=69)
Perazina	Desmetilperazina	1.1-3.3 (n= 27)
Perfenazina	N-Dealchilperfenazina	0.6-2.8 (n = 54)
Quetiapina	Norquetiapina	0.1-3.8 (n=25) (Calcolato per 400 mg)
Reboxetina	O-Desetil-reboxetina	<0.1
Risperidone	9-Idrossirisperidone*	2D6: 1.5-10.0 PM CYP2D6: ≤ 1
Risperidone depot	9-Idrossirisperidone*	EM: 1.2-4.3
Sertindolo	Diidrosertindolo	1.1-2.7 (n=6) 1.0 nei PM di CYP2D6
Sertralina	Norsertralina	1.7-3.4 (n=348)
Trazodone	m-clorofenil-piperazina (mCPP)	0.04-0.22 (range totale)
Trimipramina	Nortrimipramina*	0-12.0 (n=17)
Venlafaxina	O-Desmetil-venlafaxina* N-Desmetilvenlafaxina	26: 0.3-5.2 PM CYP2D6: ≤ 0.3 UM CYP2D6: > 5.2 0.46-1.48

Potential Cost-effectiveness of Therapeutic Drug Monitoring for Depressed Patients Treated With Citalopram.

Ostad Haji E, Mann K, Dragicevic A, Müller MJ, Boland K, Rao ML, Fric M, Laux G, **Hiemke C**. Ther Drug Monit. 2013 Jun;35(3):396-401.



Drug metabolism assay

Pharmacogenomics and Drug monitoring synergism:

Evaluation of 5-fluorouracil response

5-FU Pharmacogenomics

DPYD IVS14+1G>A
DPYD A166G
DPYD A949T

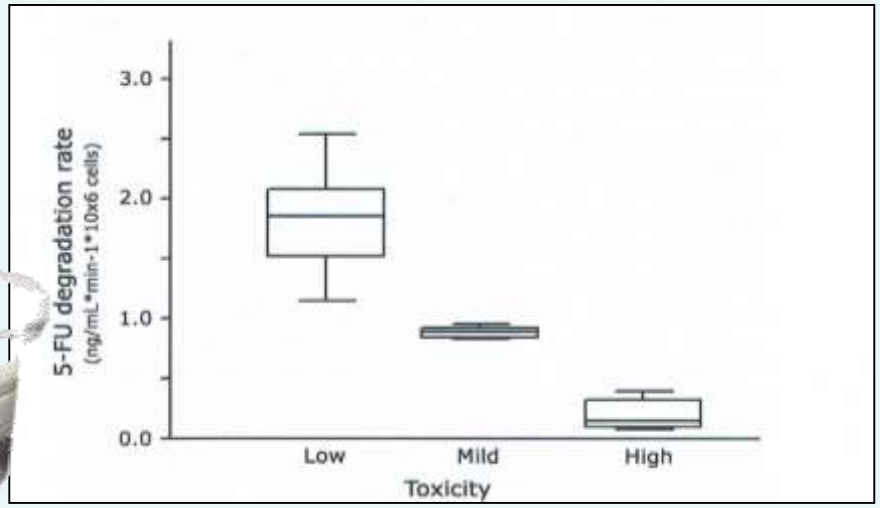
1% frequency

5-FU side effects
6-7 % treated
Patients

5

5-FU degradation rate in intact PBMC

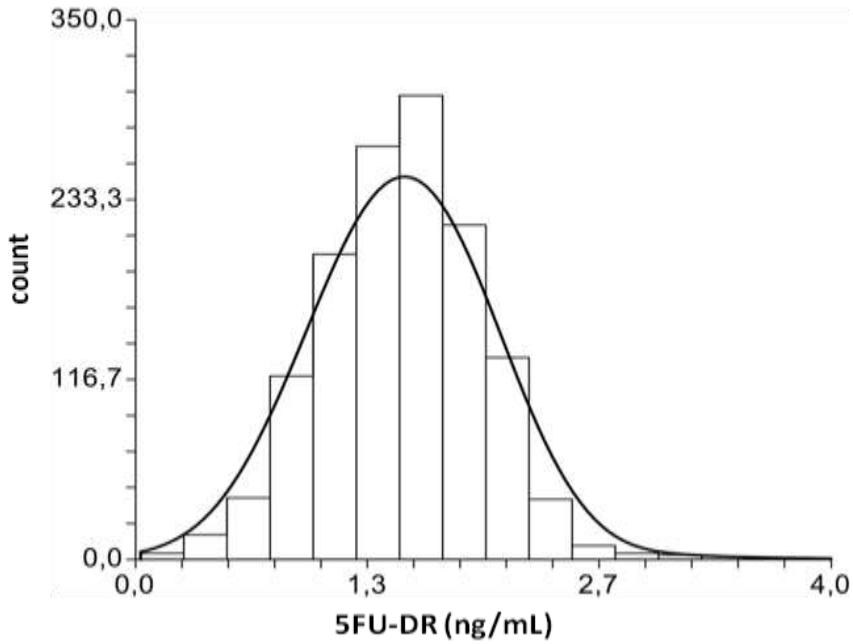
$(5\text{-FU } t_0 - 5\text{-FU}t_{2h})\text{ng} \times \text{min}^{-1} \times 10^{6} \text{ cell.}^{-1}$

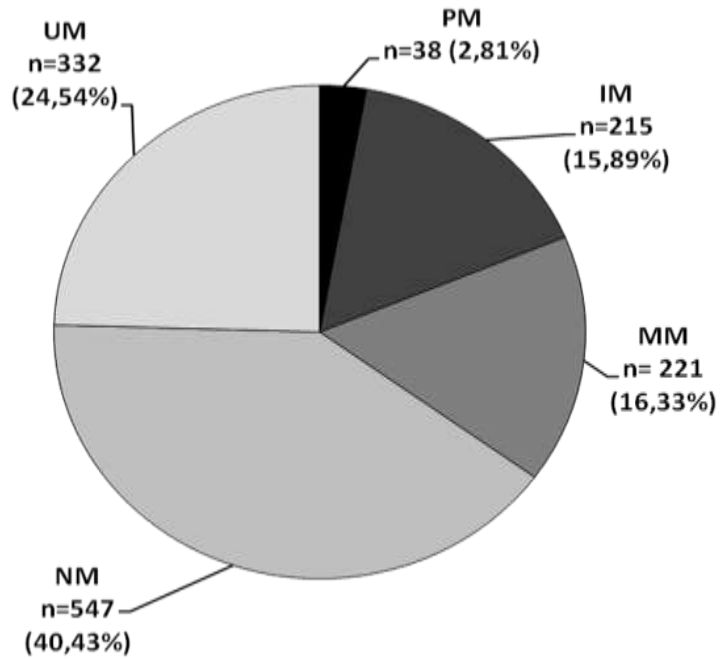


Lostia 2009 Ther Drug Monit.

Evaluation of 5-fluorouracil response

Distribution of degradation rate (N=1353)





Metabolic groups distribution(N=1353)

Ther Drug Monit. submitted

DPD deficiency: Medicoeconomic evaluation of pretreatment screening of 5-FU toxicity.
Sory Traoré
2012 Gastrointestinal Cancers Symposium
Cancers of the Colon and Rectum
Abstract No: 410
J Clin Oncol 30, 2012 (suppl 4; abstr 410)

Retrospective study:

1700 Patients treated with 5-FU for colon-rect cancer

886 standard treated: toxicity 5,80% - 6,90%

856 treated with PM strategy: toxicity 0,5 – 0,9%

(saved from 313€ up to 2780 €)

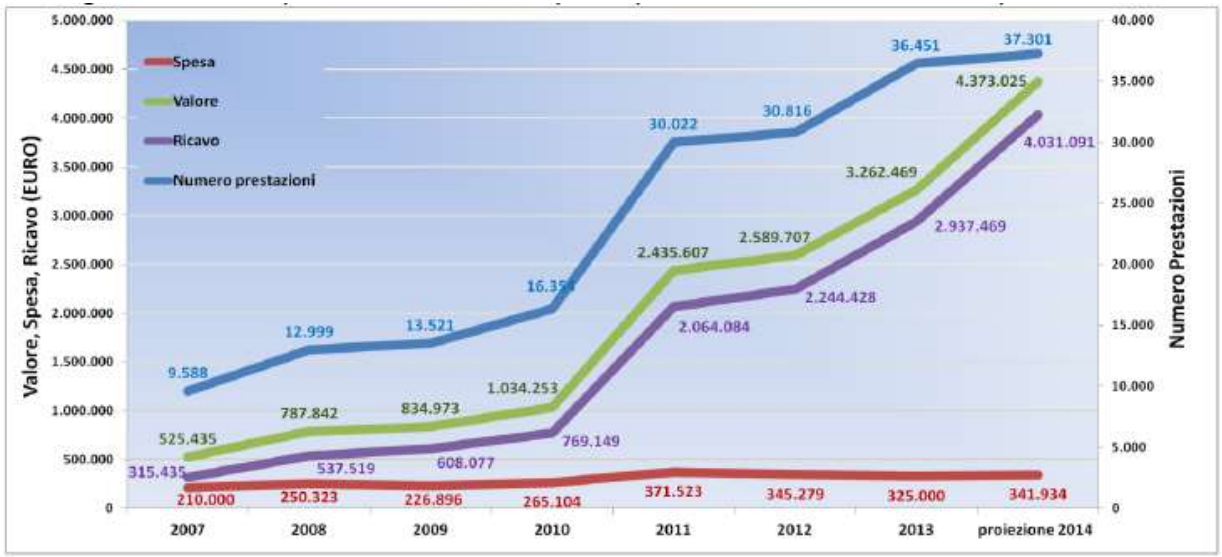
– Average 426€ saved for each Patient

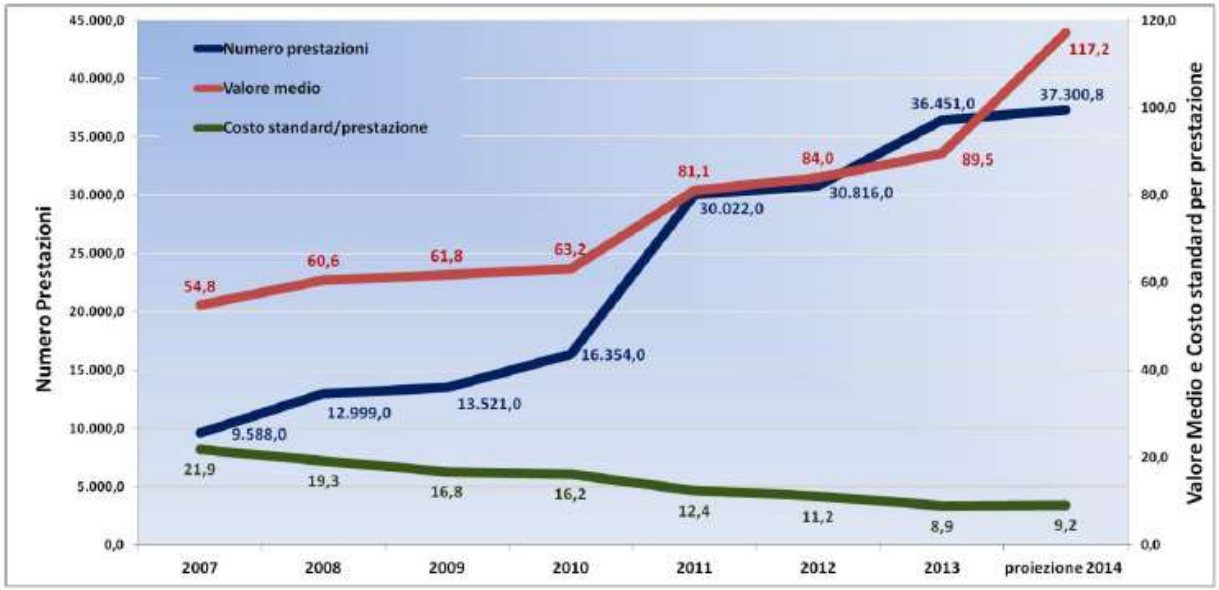
- **Sant'Andrea Hospital Oncology unit:**

  2009 - 2013 1920 Pz all treated in Personalized strategy:

saved about 817.920 €

Quanto ci costa





Dati: UOC Controllo di Gestione Azienda Ospedaliera Sant'Andrea

Integrazione di Genomica e Medicina

Outline

Esigenze Mediche

Natura e cultura (genotipo e fenotipo)

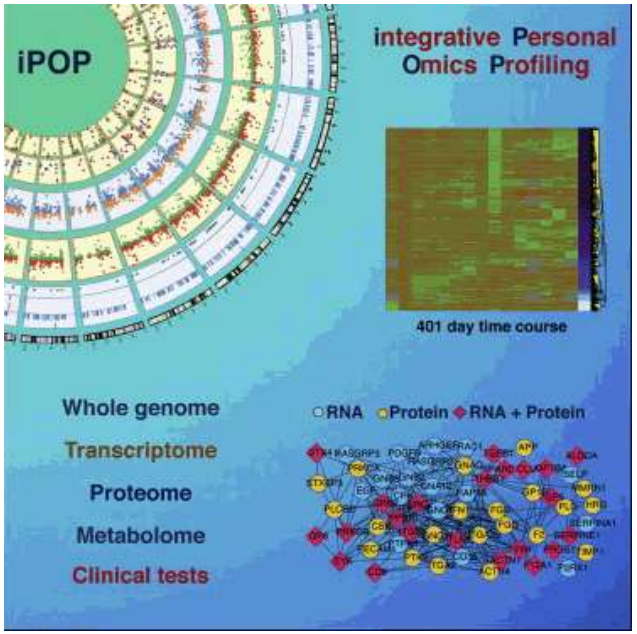
La diversità dei genomi umani

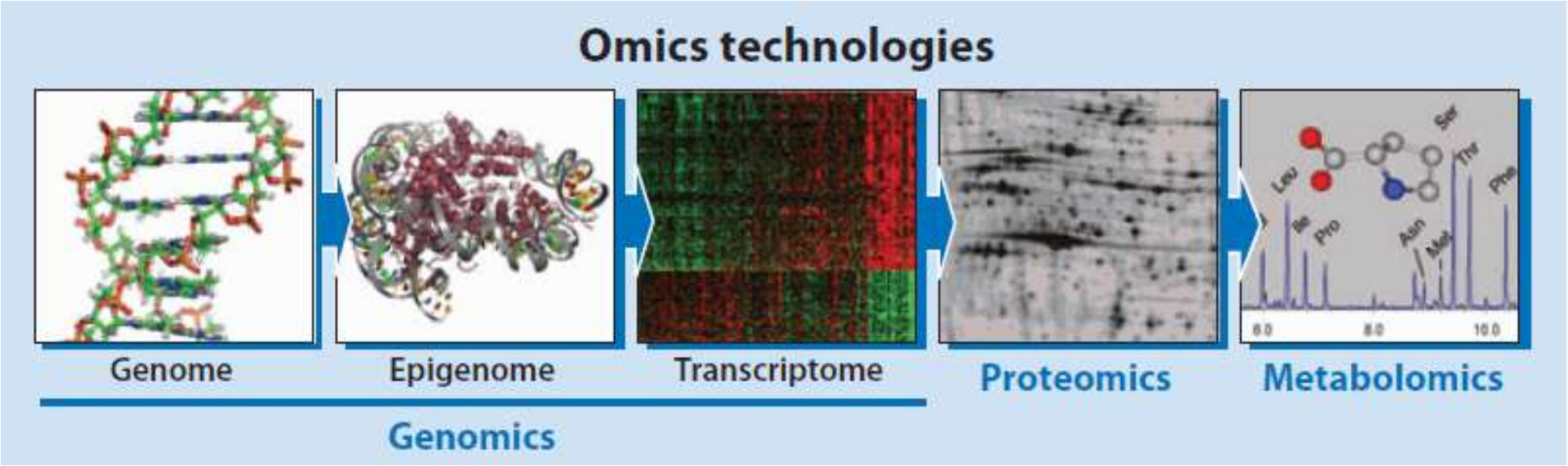
Medicina genomica

Farmacogenomica

Al di là della genomica

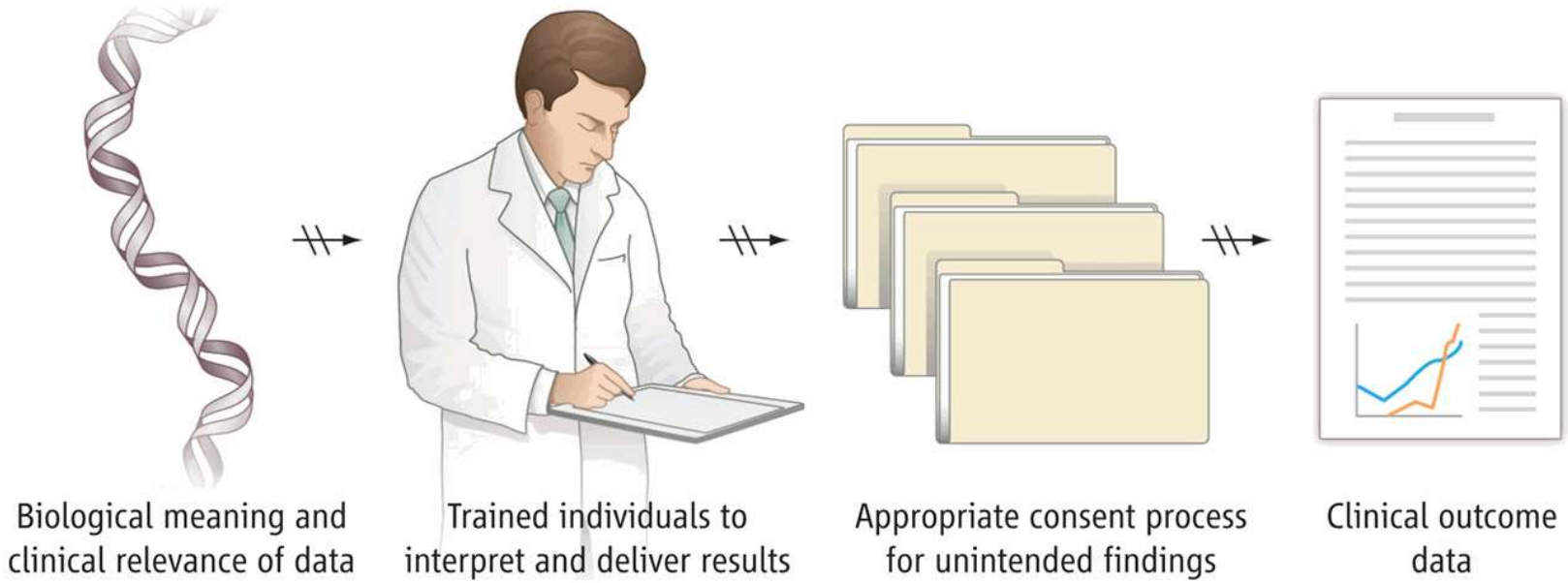
The OMICs World





Il genoma personale
futuro della medicina individualizzata?

La sfida



I medici potrebbero essere impreparati, sovraccarichi di responsabilità di cura del paziente, mal preparati ad integrare tante nuove conoscenze mediche ???

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- Neurologia
- Malattie Infettive
- Pediatria
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- Ginecologia
- Oculistica

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AB SCIEX