PROGRAMMA SCIENTIFICO

SOCIETÀ MEDICA DI SANTA MARIA NUOVA

L'Ospedale dei Fiorentini

Giornate Mediche di Santa Maria Nuova 2015

VII EDIZIONE

L'ECCELLENZA DELLE CURE IN OSPEDALE:
Santa Maria Nuova si confronta con la sua storia e con l'innovazione

2 - 3 Ottobre 2015

Sala Verde - Palazzo Incontri - Banca CR Firenze
Via de' Pucci, 1 - Firenze

"FINESTRA SUL CORTILE DI SANTA MARIA NUOVA"

Genetica Medica

Elisabetta Pelo

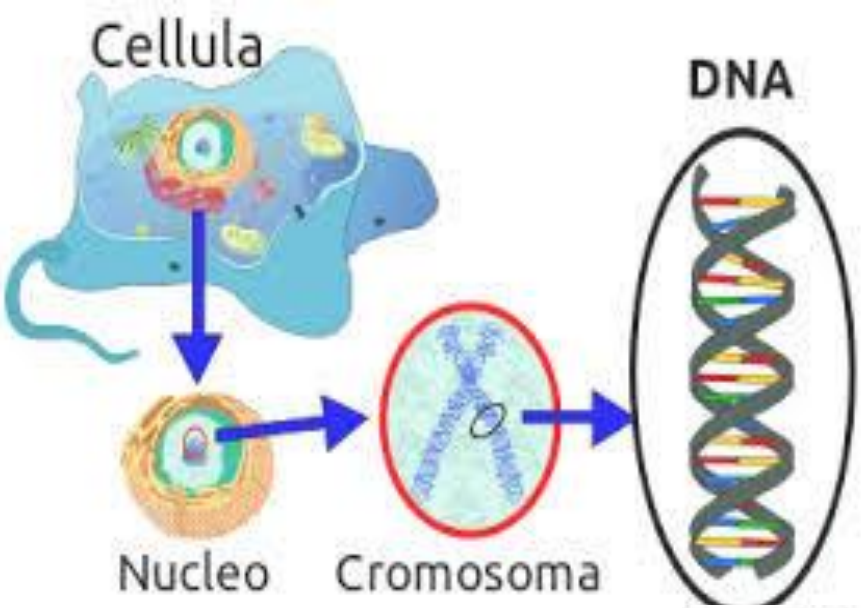
SOS Genetica Medica
P.O. Santa Maria Nuova

II SESSIONE

Approccio diagnostico terapeutico multimarker

Moderatori: A. Lagi; F. Veneziani


TIME
What scientists have uncovered about HOW MEMORY WORKS and how to improve it
THE I.Q. GENE?
LIFE
WERE YOU BORN THAT WAY?
Personality, temperament, even life choices. New studies show it's mostly in your genes.
TSUNAMI SCIENCE: ONE YEAR AFTER THE WAVE THAT ROCKED THE WORLD
SCIENTIFIC AMERICAN
Alternatives to Toxic Tests on Animals
Know Your DNA
Inexpensive gene readers will soon unlock the secrets in your personal double helix
The Hazy Origin of Brown Dwarf Stars
TIME
SPECIAL REPORT
SOLVING THE MYSTERIES OF DNA
The 50th Anniversary: Reliving Watson and Crick's historic discovery
How gene science has changed our lives
Visions of the future
TIME
THE FUTURE OF MEDICINE
LIFE
JACKIE ROBINSON SCOUTS THE SERIES
The Secret of Life
2NeatBooks.com

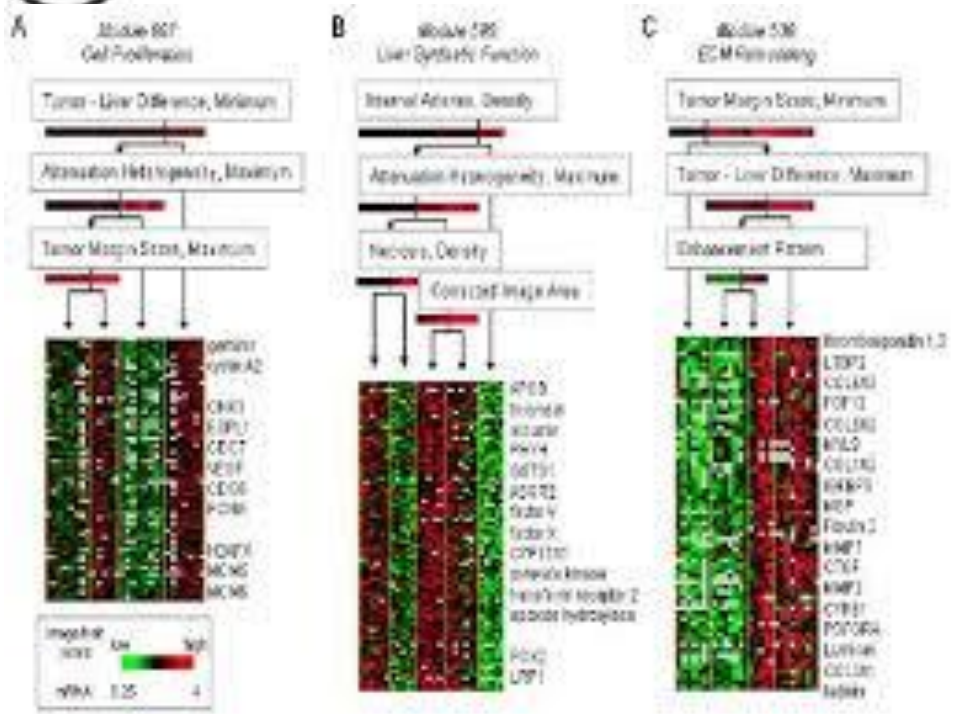


Genetica classica:

un gene = una malattia

Genomica :

Sistemi di geni = vie metaboliche

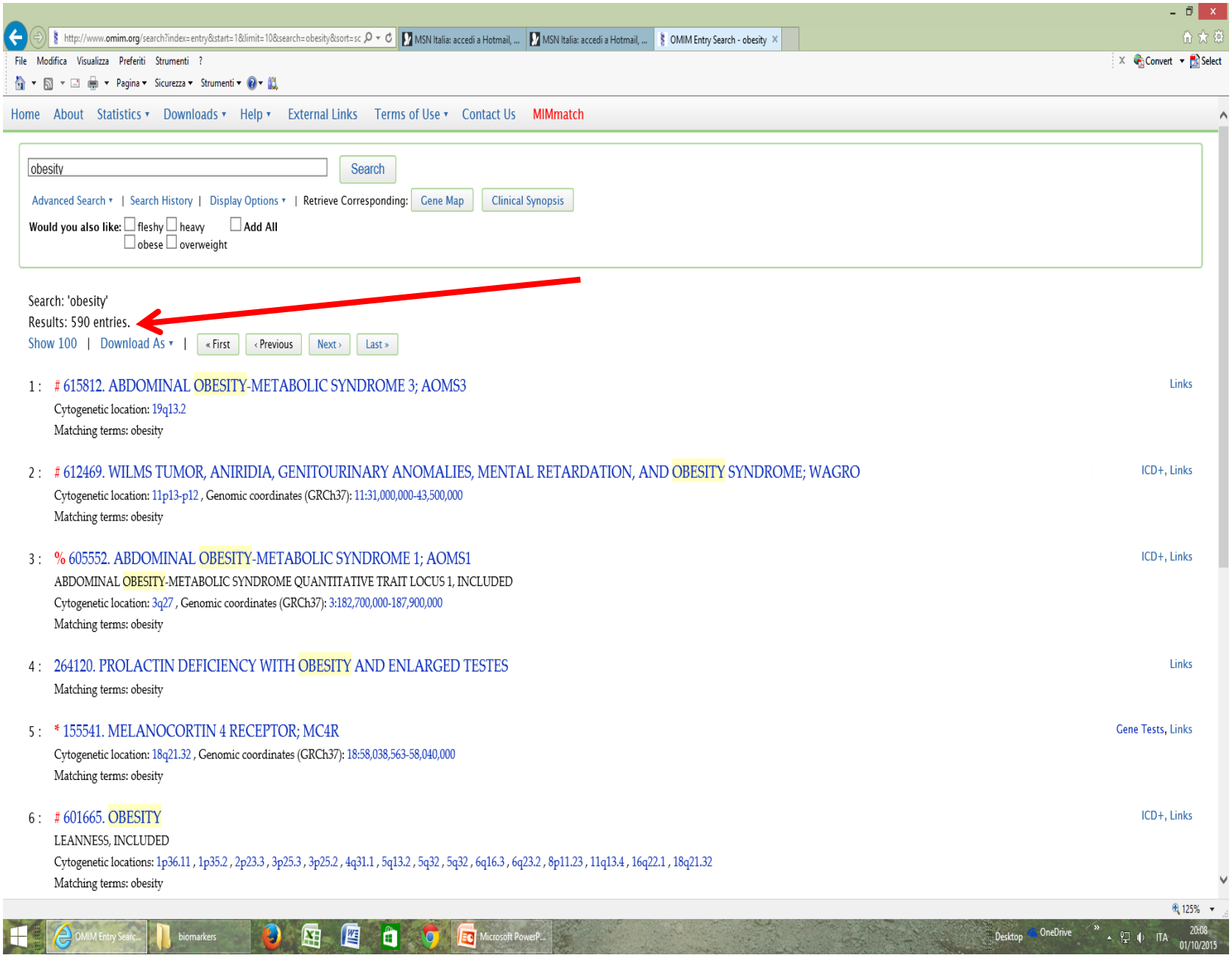


OMIM Entry Statistics

Number of Entries in OMIM (Updated September 30th, 2015) :

Prefix	Autosomal	X Linked	Y Linked	Mitochondrial	Totals
* Gene description	14,253	702	48	35	15,038
+ Gene and phenotype, combined	82	2	0	2	86
# Phenotype description, molecular basis known	4,227	298	4	29	4,558
% Phenotype description or locus, molecular basis unknown	1,509	129	5	0	1,643
Other, mainly phenotypes with suspected mendelian basis	1,706	112	2	0	1,820
Totals	21,777	1,243	59	66	23,145

http://www.omim.org/


http://www.omim.org/search?index=entry&start=1&limit=10&search=obesity&sort=sc
MSN Italia: accedi a Hotmail, ...
MSN Italia: accedi a Hotmail, ...
OMIM Entry Search - obesity
File Modifica Visualizza Preferiti Strumenti ?
Convert
Select
Pagina
Sicurezza
Strumenti
Home About Statistics Downloads Help External Links Terms of Use Contact Us MIMmatch
obesity
Search
Advanced Search | Search History | Display Options | Retrieve Corresponding: Gene Map Clinical Synopsis
Would you also like: fleshy heavy Add All
obese overweight
Search: 'obesity'
Results: 590 entries.
Show 100 | Download As | « First ‹ Previous Next › Last »
1 : # 615812. ABDOMINAL OBESITY-METABOLIC SYNDROME 3; AOMS3
Links
Cytogenetic location: 19q13.2
Matching terms: obesity
2 : # 612469. WILMS TUMOR, ANIRIDIA, GENITOURINARY ANOMALIES, MENTAL RETARDATION, AND OBESITY SYNDROME; WAGRO
ICD+, Links
Cytogenetic location: 11p13-p12 , Genomic coordinates (GRCh37): 11:31,000,000-43,500,000
Matching terms: obesity
3 : % 605552. ABDOMINAL OBESITY-METABOLIC SYNDROME 1; AOMS1
ICD+, Links
ABDOMINAL OBESITY-METABOLIC SYNDROME QUANTITATIVE TRAIT LOCUS 1, INCLUDED
Cytogenetic location: 3q27 , Genomic coordinates (GRCh37): 3:182,700,000-187,900,000
Matching terms: obesity
4 : 264120. PROLACTIN DEFICIENCY WITH OBESITY AND ENLARGED TESTES
Links
Matching terms: obesity
5 : * 155541. MELANOCORTIN 4 RECEPTOR; MC4R
Gene Tests, Links
Cytogenetic location: 18q21.32 , Genomic coordinates (GRCh37): 18:58,038,563-58,040,000
Matching terms: obesity
6 : # 601665. OBESITY
ICD+, Links
LEANNESS, INCLUDED
Cytogenetic locations: 1p36.11 , 1p35.2 , 2p23.3 , 3p25.3 , 3p25.2 , 4q31.1 , 5q13.2 , 5q32 , 5q32 , 6q16.3 , 6q23.2 , 8p11.23 , 11q13.4 , 16q22.1 , 18q21.32
Matching terms: obesity
125%
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biomarkers
Microsoft PowerP...
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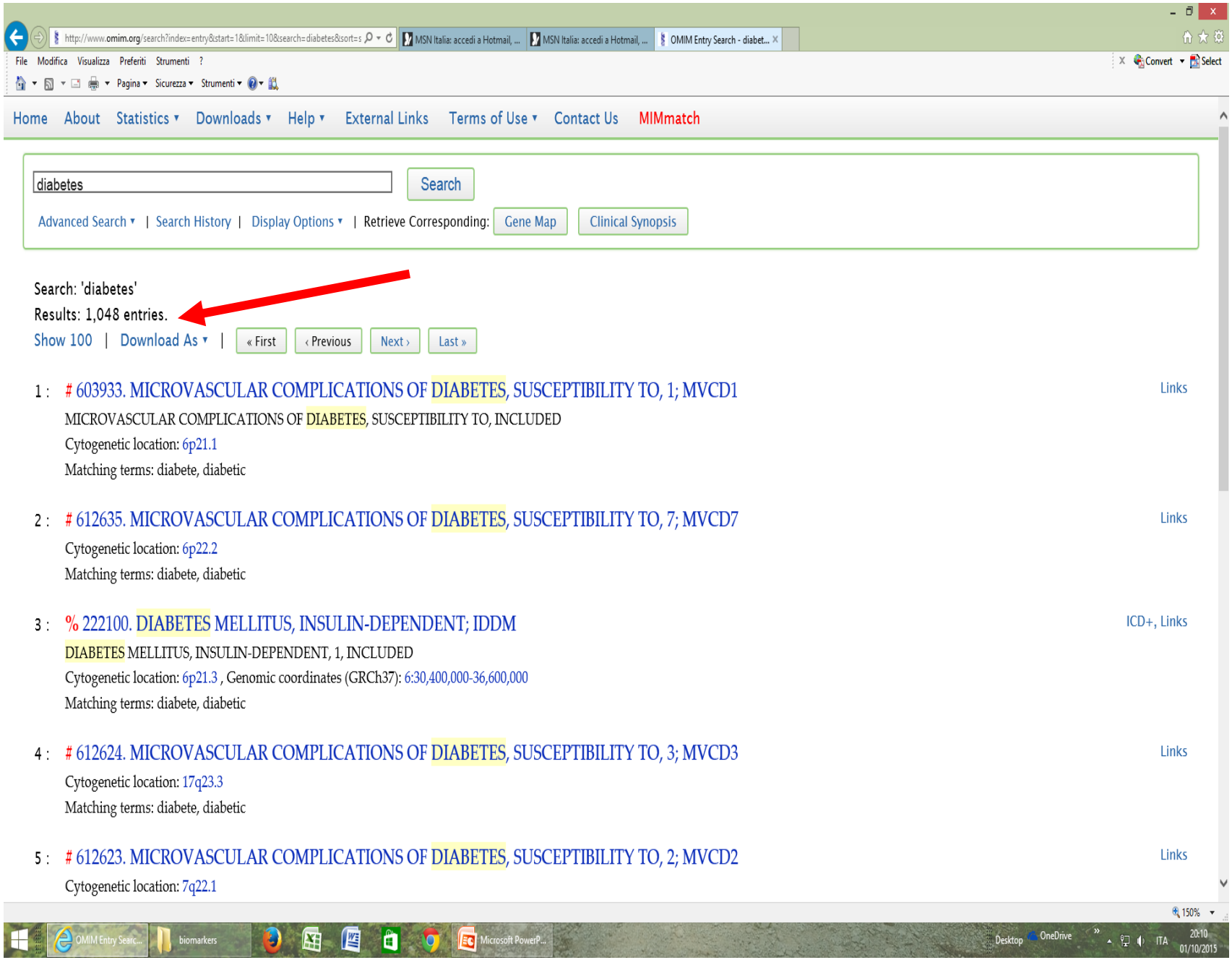
http://www.omim.org/search?index=entry&start=1&limit=10&search=diabetes&sort=s
MSN Italia: accedi a Hotmail, ...
MSN Italia: accedi a Hotmail, ...
OMIM Entry Search - diabet...
File Modifica Visualizza Preferiti Strumenti ?
Pagina Sicurezza Strumenti
Convert
Select
Home About Statistics Downloads Help External Links Terms of Use Contact Us MIMmatch
diabetes
Search
Advanced Search | Search History | Display Options | Retrieve Corresponding: Gene Map Clinical Synopsis
Search: 'diabetes'
Results: 1,048 entries.
Show 100 | Download As | « First ‹ Previous Next › Last »
1 : # 603933. MICROVASCULAR COMPLICATIONS OF DIABETES, SUSCEPTIBILITY TO, 1; MVCD1
Links
MICROVASCULAR COMPLICATIONS OF DIABETES, SUSCEPTIBILITY TO, INCLUDED
Cytogenetic location: 6p21.1
Matching terms: diabete, diabetic
2 : # 612635. MICROVASCULAR COMPLICATIONS OF DIABETES, SUSCEPTIBILITY TO, 7; MVCD7
Links
Cytogenetic location: 6p22.2
Matching terms: diabete, diabetic
3 : % 222100. DIABETES MELLITUS, INSULIN-DEPENDENT; IDDM
ICD+, Links
DIABETES MELLITUS, INSULIN-DEPENDENT, 1, INCLUDED
Cytogenetic location: 6p21.3 , Genomic coordinates (GRCh37): 6:30,400,000-36,600,000
Matching terms: diabete, diabetic
4 : # 612624. MICROVASCULAR COMPLICATIONS OF DIABETES, SUSCEPTIBILITY TO, 3; MVCD3
Links
Cytogenetic location: 17q23.3
Matching terms: diabete, diabetic
5 : # 612623. MICROVASCULAR COMPLICATIONS OF DIABETES, SUSCEPTIBILITY TO, 2; MVCD2
Links
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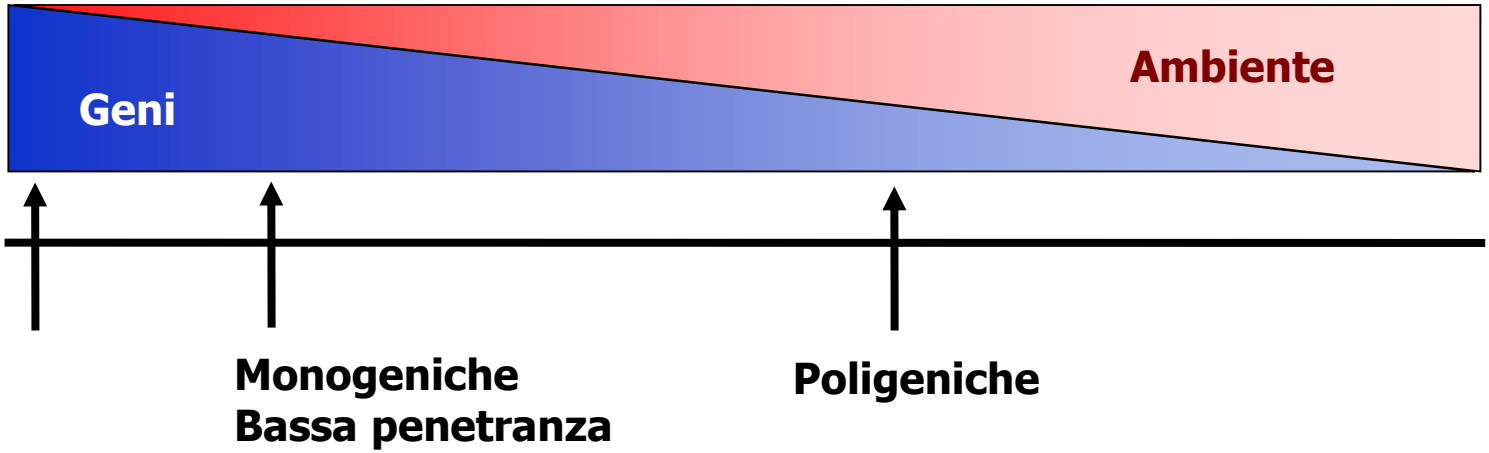


- Forme rare
- Sindromi

- Studi di popolazione
- Genetica epidemiologica

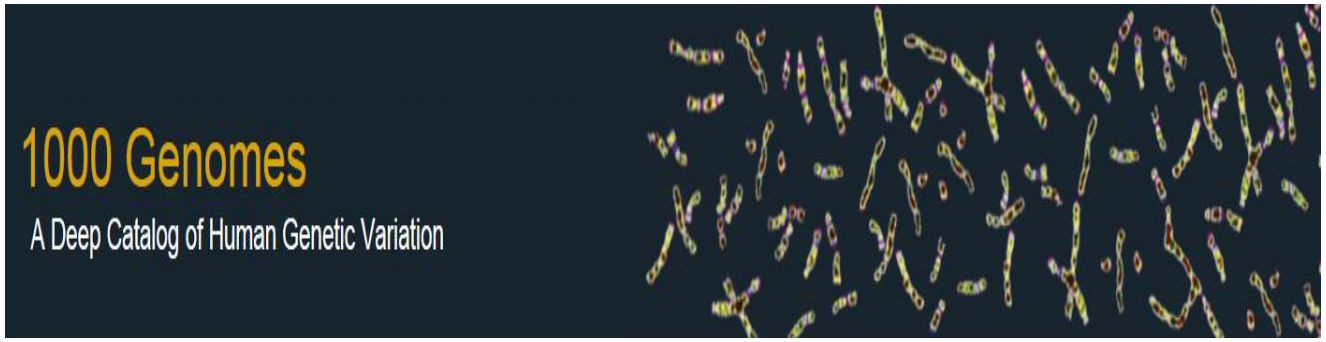
- Studi di associazioni

Table I - Classification of genetic tests according to their purpose*.

Population screening	Conducted to identify asymptomatic individuals from within a particular community or a subsection of that community who have an increased chance of having a specific genetic disorder, of carrying a specific genetic predisposition to disease or of being a carrier of a recessive genetic variant. For example, women may be tested for BRCA1&2 - genes associated with breast cancer, so that preventative measures and early intervention can be considered.
Diagnostic testing	These tests are conducted to confirm or rule out a known or suspected genetic disorder in a symptomatic individual. For example, genetic testing is often used to confirm the clinical diagnosis of cystic fibrosis (CF).
Predictive testing	These tests are conducted to determine the probability of asymptomatic individuals who are suspected of having an inherited disorder developing the clinical manifestations.
Carrier testing	Conducted to determine if an individual is a "carrier" of a gene for an autosomal recessive or X-linked genetic disorder. For example, couples undergo carrier testing for disorders such as Tay-Sachs disease, to assist in their reproductive decisions.
Prenatal testing	Conducted during pregnancy to determine whether there is an increased risk of having a child with a genetic disorder. Down's Syndrome is the most common genetic disease screened by this method.
Newborn screening	These tests focus on the identification of metabolic disorders in newborns. Early detection and treatment may be crucial to reduce the progression of such diseases. One example is the newborn screening for phenylketonuria (PKU).
Pre-symptomatic testing	These tests are conducted on healthy individuals to determine whether or not they carry a genetic mutation that increases their likelihood of developing late-onset diseases and disorders. Examples include Huntington's disease and Alzheimer's disease.
Susceptibility (or predisposition) testing	These tests are conducted to determine the risk or probability that individuals with the genetic variant will develop a particular disease.
Pharmacogenetic testing	Conducted to determine individual genetic variability impact on drug efficacy and toxicity.
Forensic/Identity testing	These tests are conducted to discover genetic linkages in criminal investigations between suspects and evidence or between children and their biological parents.

* Modified from OECD (DSTI/STP/BIO 2006)17.

Un evento che ha segnato in maniera significativa questo passaggio epocale, è sicuramente l'annuncio nel 1990 del Progetto Genoma Umano che prevedeva 15 anni di ricerca e 3 miliardi di dollari di finanziamento



La quantità di informazione genetica già disponibile è impressionante e cresce a ritmo vertiginoso..

La disponibilita di questa massa di informazioni sta cambiando la ricerca biologica

Genomes | Genome Browser | Tools | Mirrors | Downloads | My Data | Help | About Us

Human (*Homo sapiens*) Genome Browser Gateway

The UCSC Genome Browser was created by the Genome Bioinformatics Group of UC Santa Cruz.
Software Copyright (c) The Regents of the University of California. All rights reserved.

group	genome	assembly	position	search term
Mammal	Human	Dec. 2013 (GRCh38/hg38)	chr9:133,252,000-133,280,861	enter position, gene symbol or search terms — submit

Click here to reset the browser user interface settings to their defaults.

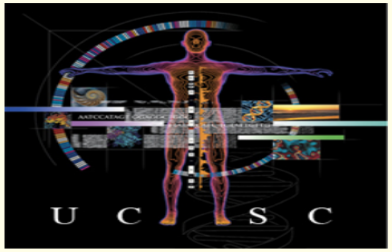
track search | add custom tracks | track hubs | configure tracks and display

Human Genome Browser – hg38 assembly (sequences)

UCSC Genome Browser assembly ID: hg38
Sequencing/Assembly provider ID: GRCh38 Genome Reference Consortium Human Reference 38 (GCA_000001405.15)
Assembly date: Dec. 2013
GenBank accession ID: GCA_000001305.2
NCBI Genome information: NCBI genome/51 (Homo sapiens)
NCBI Assembly information: NCBI assembly/883148 (GRCh38/GCA_000001405.15)
BioProject information: NCBI Bioproject: 31257

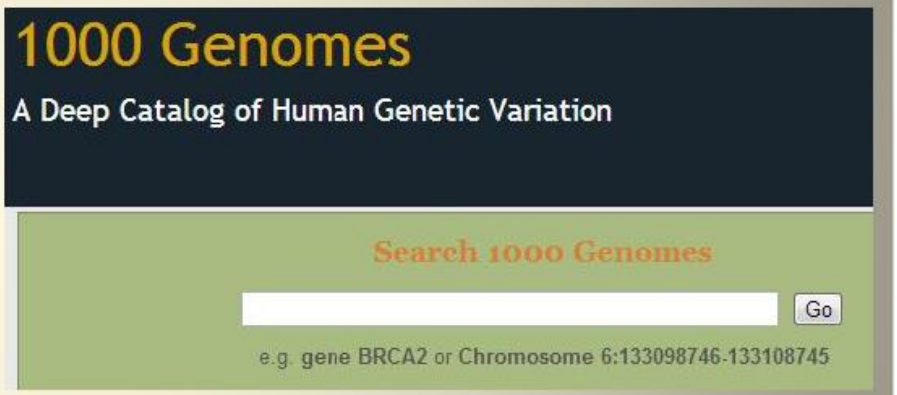
Search the assembly:

- **By position or search term:** Use the "position or search term" box to find areas of the genome associated with many different attributes, such as a specific chromosomal

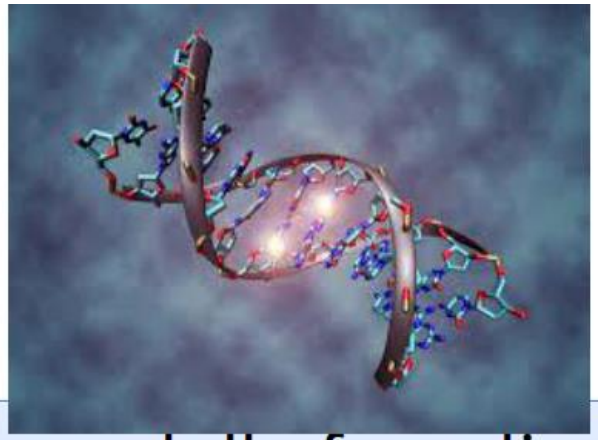


Homo sapiens

COME INTERPRETARE LA VARIABILITA' INDIVIDUALE?



IN HOUSE DATABASE!



Attualmente siamo nel pieno della fase di applicazione alla clinica delle conoscenze derivate dal Progetto Genoma Umano:

il DNA è il biomarcatore più sensibile presente in natura.

In due genomi umani “normali” ci sono milioni di differenze:

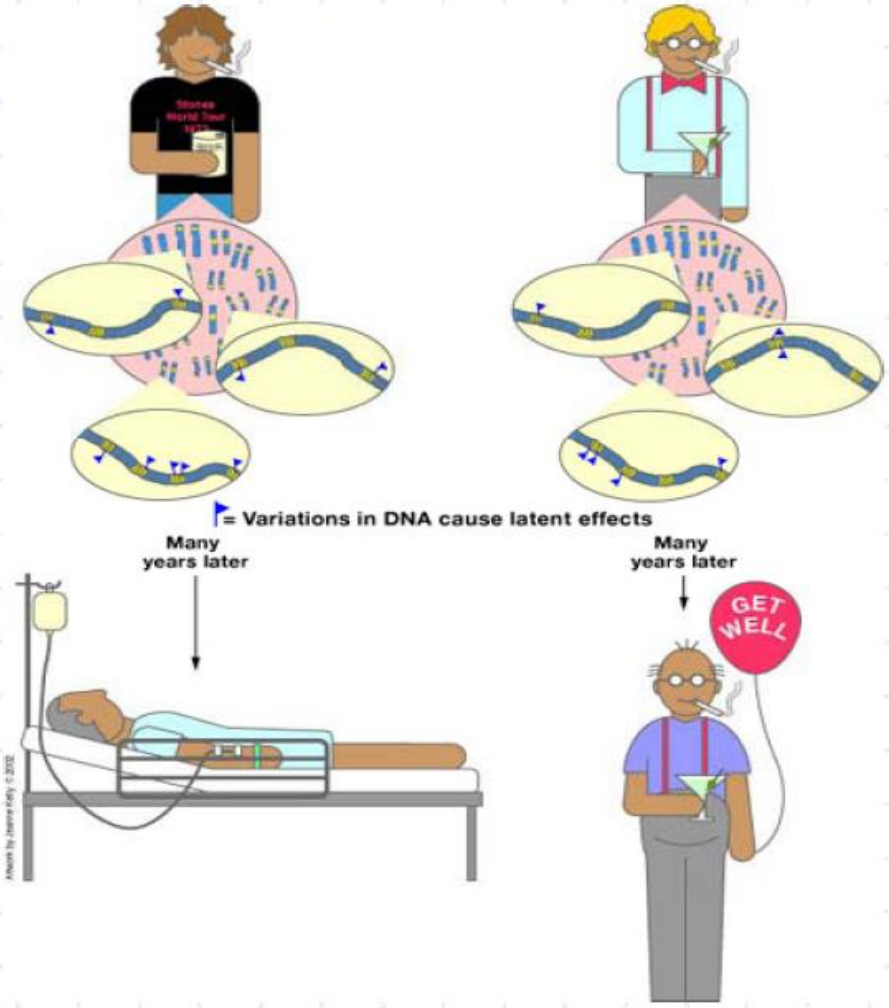
- alcune riguardano singoli nucleotidi presenti anche in zone codificanti, che possono variare da un individuo all’altro;
- altre, possono addirittura coinvolgere delezioni o duplicazioni di zone più estese del genoma e variazioni nel numero di copie.

Alcune di queste variabili possono conferire agli individui che le possiedono resistenze o suscettibilità a malattie

“Il genoma con cui siamo concepiti non è lo stesso di quello con cui moriamo, almeno non in tutte le cellule del nostro corpo" Bruder.

“In media una coppia di gemelli porta 359 varianti genetiche diverse che si sono stabilite precocemente nel corso dello sviluppo”

BIOMARCATORI DI SUSCETTIBILITÀ INDIVIDUALE



Direct-to-consumer genetic test

"Direct-to-consumer genetic testing refers to genetic tests that are **marketed directly to consumers** via television, print advertisements, or the Internet. This form of testing, which is also known as at-home genetic testing, provides access to a person's genetic information **without necessarily involving a doctor** or insurance company in the process."

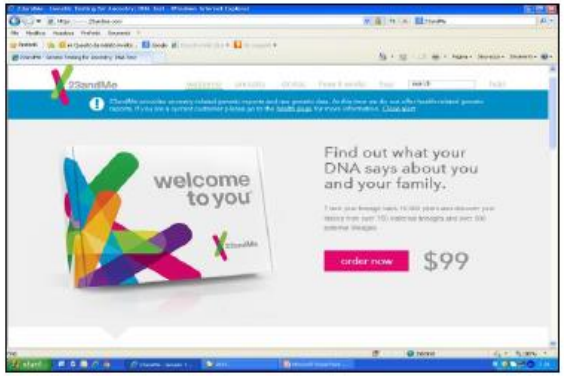
Available on: http://ghr.nlm.nih.gov/handbook/testing/directtoconsumer

In vista dell'**aumento dell'offerta di test genomici predittivi di suscettibilità alle malattie complesse**, tutte le autorità competenti hanno riconosciuto l'importanza di governare questa materia:

- rendere facilmente accessibili le informazioni sui test agli utenti/pazienti, ai clinici, ai ricercatori e agli Enti paganti;

- rendere edotti i medici prescrittori in merito alle potenzialità e ai limiti degli stessi.

I test genetici diretti ai consumatori



suscettibilità a centinaia di malattie

crema di bellezza personalizzata

medicina personalizzata

possibilità di eccellere nello sport

dieta personalizzata

scelta del partner

MEDICINA GENOMICA

Diagnosi e prevenzione

Terapia «su misura»

MEDICINA GENOMICA :

- suscettibilità ⇨ prevenzione
- Mutazione ⇨ diagnosi
- causa specifica ⇨ terapia mirata
- risposta individuale ai farmaci

⇩

Scelta e dosaggio personalizzati

Risk Management and Healthcare Policy

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

The Human Genome Project, and recent advances in personalized genomics

This article was published in the following Dove Press journal:
Risk Management and Healthcare Policy
16 February 2015

Pharmacogenomics and Personalized Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Personalized antiplatelet and anticoagulation therapy: applications and significance of pharmacogenomics

This article was published in the following Dove Press journal:
Pharmacogenomics and Personalized Medicine
9 February 2015
Number of times this article has been viewed

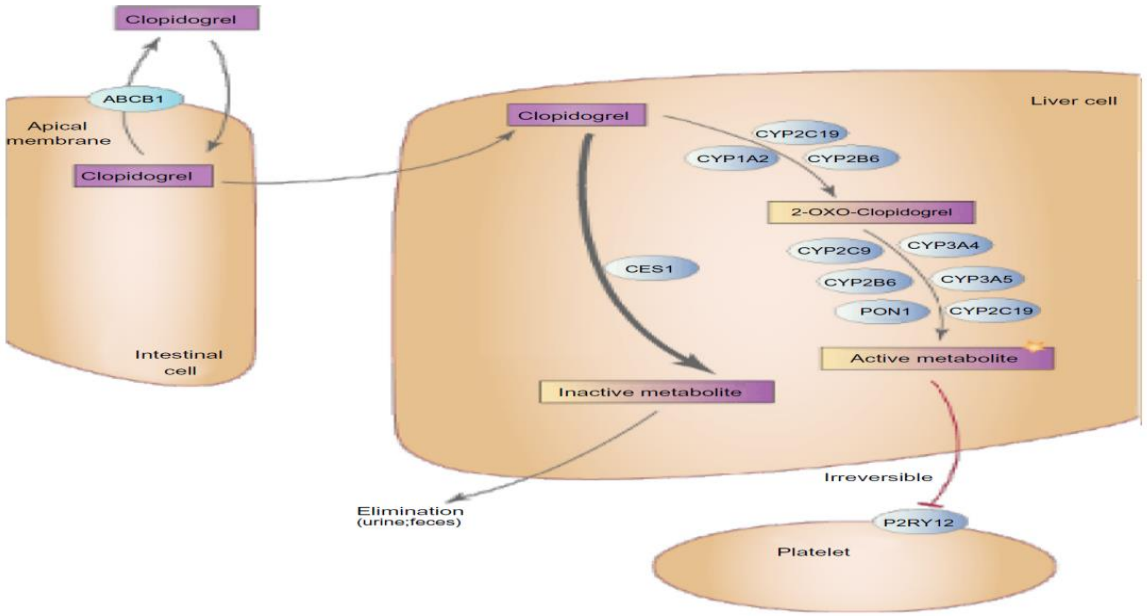


Figure 1 Major proteins involved in clopidogrel transport and metabolism.

ELSEVIER

DRUG DISCOVERY TODAY TECHNOLOGIES

Drug Discovery Today: Technologies

Vol. 11, 2014

Editors-in-Chief
Kelvin Lam – Simplex Pharma Advisors, Inc., Arlington, MA, USA
Henk Timmerman – Vrije Universiteit, The Netherlands

Drug resistance

Personalized HIV therapy to control drug resistance☆

Thomas Lengauer[1,*], Nico Pfeifer[1], Rolf Kaiser[2]

[1]Department of Computational Biology and Applied Algorithmics, Max Planck Institute for Informatics, Saarbrücken, Germany
[2]Institute of Virology, University of Cologne, Germany

The therapy of HIV patients is characterized by both the high genomic diversity of the virus population harbored by the patient and a substantial volume of therapy options. The virus population is unique for each patient and time point. The large number of therapy options makes it difficult to select an optimal or near optimal therapy, especially with therapy-experienced patients. In the past decade, computer-based support for therapy selection, which assesses the level of viral resistance against drugs has become a mainstay for HIV patients. We discuss the properties of available systems and the perspectives of the field.

Section editors:
Jürgen Moll – Boehringer-Ingelheim, Vienna, Austria.
Gemma Texidó – Nerviano Medical Sciences S.r.l, Nerviano, Italy.

profile manifested by the virus population presently in the patient. This is a difficult task to accomplish, but suitable software can help to select efficient therapy options for these patients. This review summarizes the history and state-of-the-art of bioinformatics-based resistance analysis and outlines perspectives into the future. For a previous review of the field see [1].

History of analysis of HIV drug resistance

Published OnlineFirst April 7, 2015; DOI: 10.1158/1535-7163.MCT-14-1061

Companion Diagnostics and Cancer Biomarkers

Molecular Cancer Therapeutics

On the Road to Precision Cancer Medicine: Analysis of Genomic Biomarker Actionability in 439 Patients

Maria Schwaederle, Gregory A. Daniels, David E. Piccioni, Paul T. Fanta, Richard B. Schwab, Kelly A. Shimabukuro, Barbara A. Parker, and Razelle Kurzrock

Abstract

Despite the increased use of molecular diagnostics, the extent to which patients who have these tests harbor potentially actionable aberrations is unclear. We retrospectively reviewed 439 patients with diverse cancers, for whom next-generation sequencing (mostly 236-gene panel) had been performed. Data pertaining to the molecular alterations identified, as well as associated treatment suggestions (on- or off-label, or experimental), were extracted from molecular diagnostic reports. Most patients (420/439; 96%) had at least one molecular alteration: 1,813 alterations (in 207 distinct genes) were identified [the majority being mutations (62%) or amplifications (29%)]. The three most common gene abnormalities were *TP53* (44%), *KRAS* (16%), and *PIK3CA* (12%). The median number of alterations per patient was 3 (range, 0–16). Nineteen patients (4%) had no alterations; 48 patients (11%) had only one alteration; and 372 patients had two or more abnormalities (85%). The median number of potentially actionable anomalies per patient was 2 (range, 0–8). Most patients (393/439; 90%) had at least one potentially actionable alteration, and in all these cases the aberration could at least be targeted by an experimental drug in a clinical trial. A total of 307 patients (70%) had an alteration that was actionable with an approved drug, but in only 89 patients (20%) was the drug approved for their disease (on-label). Next-generation sequencing identified theoretically actionable aberrations in 90% of our patients. Many of the drugs are, however, experimental or would require off-label use. Strategies to address drug access for patients harboring potentially actionable mutations are needed. *Mol Cancer Ther; 14(6); 1488–94. ©2015 AACR.*

PROFILO INDIVIDUALE DEI POLIMORFISMI GENICI

MARKER BIOLOGICO

Un marker biologico valido può essere definito come un parametro misurato mediante test analitici specifici.

Tale parametro permette di valutare un processo biologico stabilendo il significato fisiologico, tossicologico, farmacologico o clinico del risultato dei test.

"Guidance for Industry
Pharmacogenomic Data Submissions"
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
November 2003

Biomarcatore genomico

"Una caratteristica misurabile del DNA o dell'RNA che indica un processo biologico normale o un processo patologico o una risposta a un intervento terapeutico o di altro tipo"

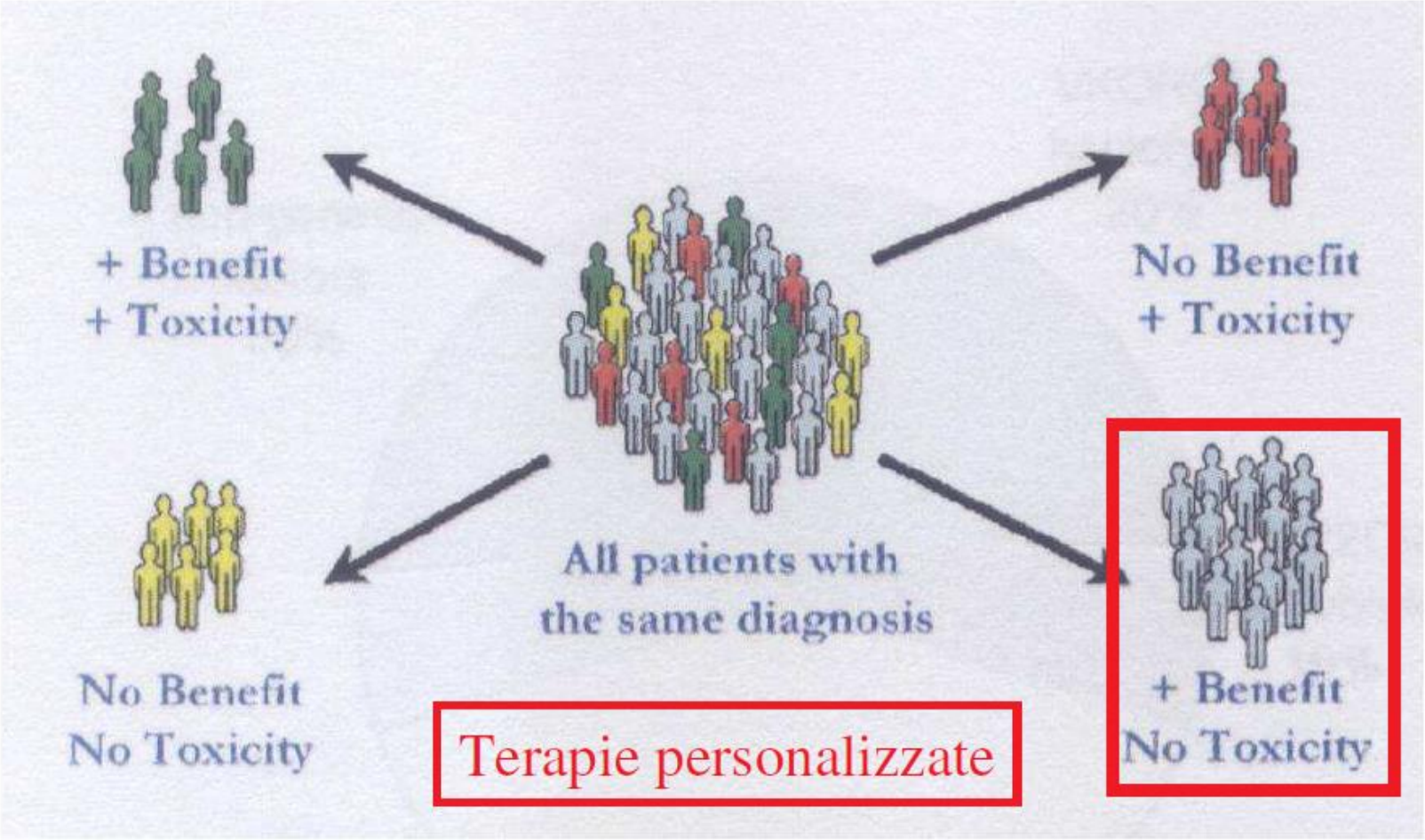
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002880.pdf

TEST di FARMACOGENETICA

finalizzati a determinare un'associazione tra una caratteristica genetica (polimorfismo) e la risposta individuale a una determinata molecola (farmaco) in termini di *efficacia* e di *effetti collaterali*

- GENI COINVOLTI NEL METABOLISMO DI UN FARMACO
- GENI CHE CODIFICANO PER RECETTORI DEI FARMACI
- GENI CHE CODIFICANO PER PROTEINE-BERSAGLIO DEI FARMACI

TEST FARMACOGENETICI



S Marsh S, McLeod HL 2006

Table 2. Examples of Drugs with Genetic Information in Their Labels.*

Drug	Sponsor	Indication	Gene or Genotype	Effect of Genotype	Clinical Directive on Label
Abacavir (Ziagen)	GlaxoSmithKline	HIV-1	*HLA-B*5701*	Hypersensitivity	Black-box warning: "Prior to initiating therapy with abacavir, screening for the *HLA-B*5701* allele is recommended." "Your doctor can determine with a blood test if you have this gene variation."
Azathioprine (Imuran)	Prometheus	Renal allograft transplantation, rheumatoid arthritis	*TPMT*2*, *TPMT*3A*, and *TPMT*3C*	Severe myelotoxicity	"*TPMT* genotyping or phenotyping can help identify patients who are at an increased risk for developing Imuran toxicity." "Phenotyping and genotyping methods are commercially available."
Carbamazepine (Tegretol)	Novartis	Epilepsy, trigeminal neuralgia	*HLA-B*1502*	Stevens–Johnson syndrome or toxic epidermal necrolysis	Black-box warning: "Patients with ancestry in genetically at-risk populations should be screened for the presence of *HLA-B*1502* prior to initiating treatment with Tegretol. Patients testing positive for the allele should not be treated with Tegretol." "For genetically at-risk patients, high-resolution *HLA-B*1502* typing is recommended."
Cetuximab (Erbitux)	Imclone	Metastatic colorectal cancer	*KRAS* mutations	Efficacy	"Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for Erbitux in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Erbitux is not recommended for the treatment of colorectal cancer with these mutations."
Clopidogrel (Plavix)	Bristol-Myers Squibb	Anticoagulation	*CYP2C19*2*3*	Efficacy	"Tests are available to identify a patient's *CYP2C19* genotype; these tests can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers."
Irinotecan (Camptosar)	Pfizer	Metastatic colorectal cancer	*UGT1A1*28*	Diarrhea, neutropenia	"A reduction in the starting dose by at least one level of Camptosar should be considered for patients known to be homozygous for the *UGT1A1*28* allele." "A laboratory test is available to determine the *UGT1A1* status of patients."
Panitumumab (Vectibix)	Amgen	Metastatic colorectal cancer	*KRAS* mutations	Efficacy	"Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for Vectibix in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Vectibix is not recommended for the treatment of colorectal cancer with these mutations."
Trastuzumab (Herceptin)	Genentech	HER2-positive breast cancer	HER2 expression	Efficacy	"Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied and for whom benefit has been shown." "Several FDA-approved commercial assays are available to aid in the selection of breast cancer and metastatic gastric cancer patients for Herceptin therapy."
Warfarin (Coumadin)	Bristol-Myers Squibb	Venous thrombosis	*CYP2C9*2*3* and *VKORC1* variants	Bleeding complications	Includes the following table: Range of Expected Therapeutic Warfarin Doses Based on *CYP2C9* and *VKORC1* Genotypes.

* All drug labels were accessed through Drugs@FDA at www.accessdata.fda.gov/scripts/cder/drugsatfda. HIV-1 denotes human immunodeficiency virus type 1, *TPMT* thiopurine methyltransferase, *UGT1A1* UDP glucuronosyltransferase 1 family polypeptide A1, and *VKORC1* vitamin K epoxide reductase complex subunit 1.

Dosing Recommendations with Consideration of Genotype

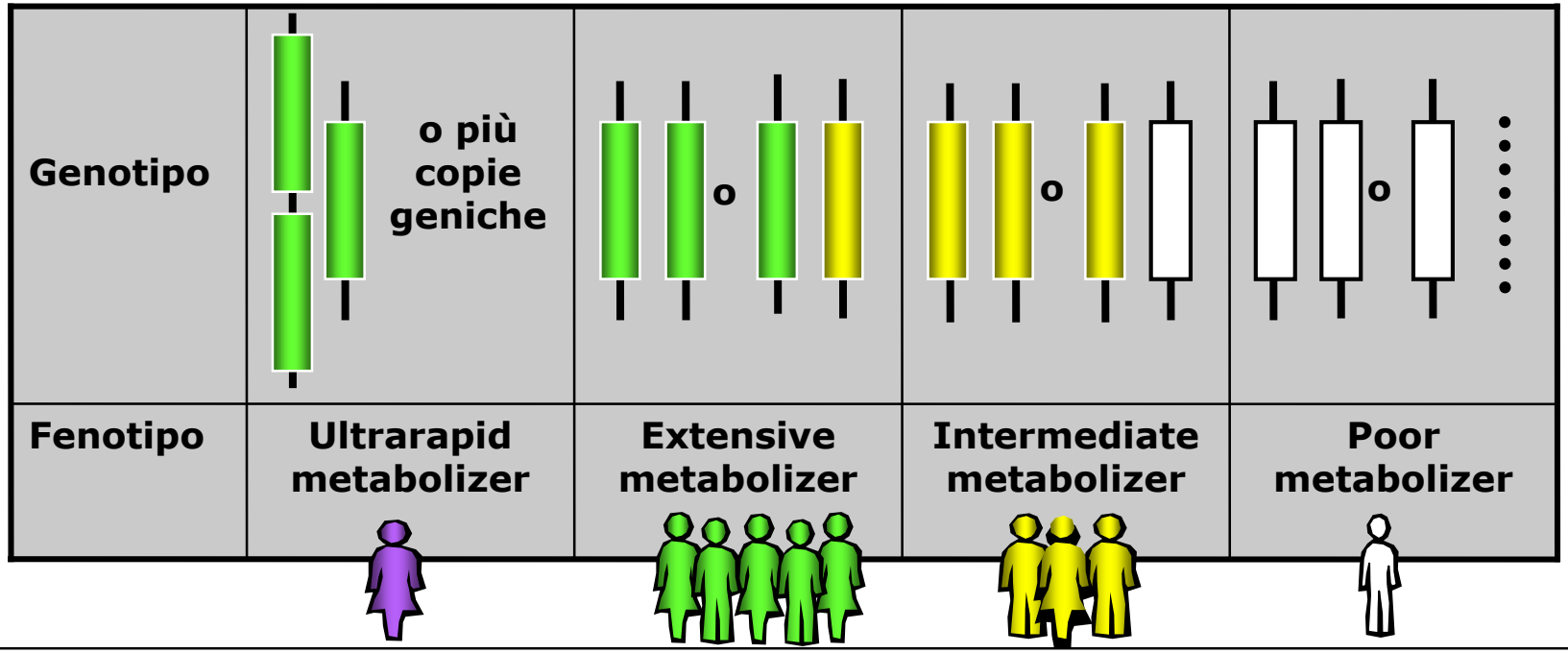
Table 1 displays three ranges of expected maintenance COUMADIN doses observed in subgroups of patients having different combinations of CYP2C9 and VKORC1 gene variants [see *Clinical Pharmacology (12.5)*]. If the patient's CYP2C9 and/or VKORC1 genotype are known, consider these ranges in choosing the initial dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen than patients without these CYP variants.

Table 1: Three Ranges of Expected Maintenance COUMADIN Daily Doses Based on CYP2C9 and VKORC1 Genotypes†

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

†Ranges are derived from multiple published clinical studies. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.

Dal genotipo al fenotipo



Esempio farmaco X: dosaggi giornalieri richiesti per raggiungere lo stesso livello di farmaco

500 mg **100 mg** **10 mg**

Alleli completamente funzionali

Alleli funzionali ma alterati

Alleli non funzionali

Delezione del gene completo

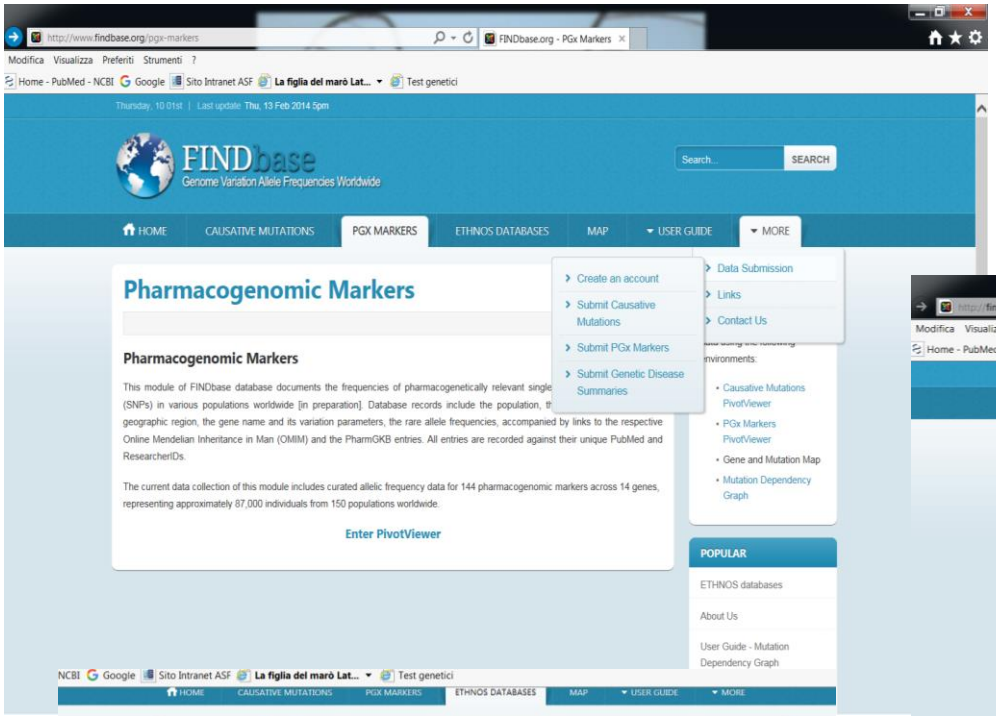
Modificato da H-G Xie & F.W. Frueh (2005) Personalized Medicine 2(4), 325-337

Differenze di popolazione per CYP2D6

Allele	Attività enzimatica prevista	Giappone	Cina	Caucasici EU	Caucasici US	Neri Americani	Neri Africani
*1	Normale	42-43%	23%	33-37%	37-40%	29-34%	28-56%
*2	Normale	9-13%	20%	22-33%	26-34%	20-27%	11-45%
*4	Nessuna	<1%	0-1%	12-23%	18-23%	7-9%	1-7%
*5	Nessuna	5-6%	6%	2-7%	2-4%	6-7%	1-6%
*10	Ridotta	39-41%	50-70%	1-2%	4-8%	3-8%	3-9%
*17	Ridotta	*	*	<1%	*	15-26%	9-34%
*41	Ridotta	*	*	20%	*	*	*

Le percentuali rappresentano i range delle frequenze alleliche riportate negli studi pubblicati

AmpliChip CYP450 Test package insert; from Bradford, L.D. 2002. Pharmacogenomics. 3:229-243


FINDbase.org - PGx Markers
Modifica Visualizza Preferiti Strumenti ?
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Thursday, 10 01st | Last update: Thu, 13 Feb 2014 5pm
FINDbase
Genome Variation Allele Frequencies Worldwide
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Pharmacogenomic Markers
This module of FINDbase database documents the frequencies of pharmacogenetically relevant single
(SNPs) in various populations worldwide [in preparation]. Database records include the population, t
geographic region, the gene name and its variation parameters, the rare allele frequencies, accompanied by links to the respective
Online Mendelian Inheritance in Man (OMIM) and the PharmGKB entries. All entries are recorded against their unique PubMed and
ResearcherIDs.
The current data collection of this module includes curated allelic frequency data for 144 pharmacogenomic markers across 14 genes,
representing approximately 87,000 individuals from 150 populations worldwide.
Enter PivotViewer
nvironments.
Causative Mutations PivotViewer
PGx Markers PivotViewer
Gene and Mutation Map
Mutation Dependency Graph
POPULAR
ETHNOS databases
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User Guide - Mutation Dependency Graph


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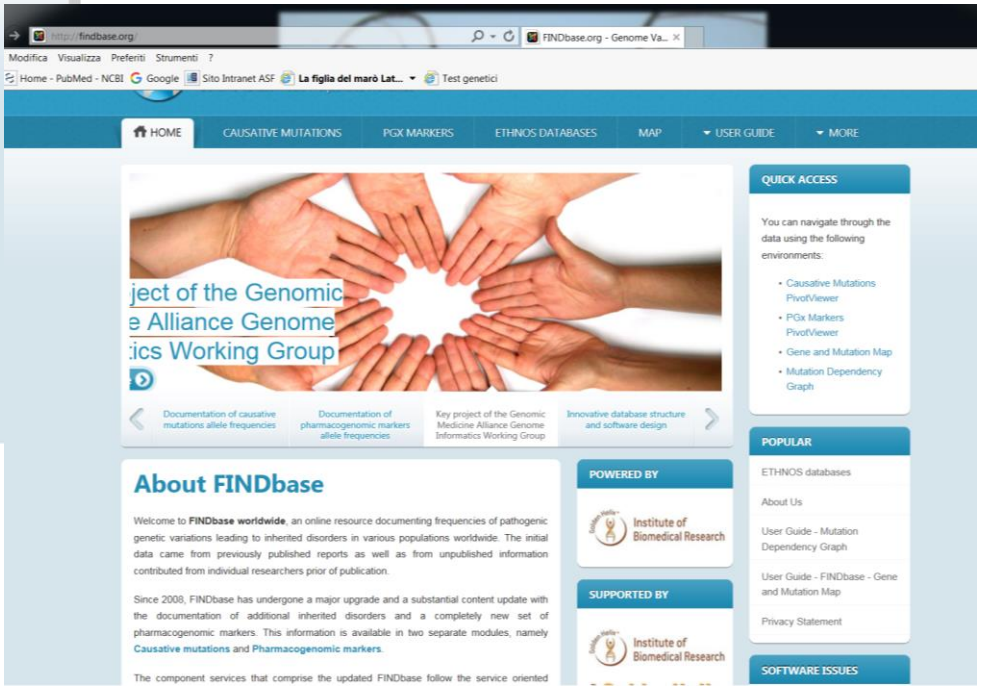
ETHNOS databases
The National/Ethnic Genetic Databases are mutation depositories, recording extensive information over the described genetic heterogeneity of an ethnic group or population. Until now, there are several National/Ethnic Genetic databases, many of which are developed using the ETHNOS software, an off-the-shelf bioinformatics suite developed in 2003 by the Golden Helix Institute of Biomedical Research to facilitate development and curation of National/Ethnic Genetic and Mutation frequency databases. These databases can be exploited as a central repository for the genetic services in any given country. Since 2012, the ETHNOS software has been upgraded with new functionalities and currently several National/Ethnic Mutation Databases are either being migrated to the new software or being developed.
Please click on the following links to access the content of the National/Ethnic Genetic databases currently available in the ETHNOS Database:
Africa
Algeria Botswana Egyptian Gambia Guinea Mali Mauritius Moroccan
Mozambique Namibia Nigeria Republic of Congo Somalia South Africa Tunisia
America
Asia
Europe
Oceania


FINDbase.org - Genome Va...
Modifica Visualizza Preferiti Strumenti ?
Home - PubMed - NCBI Google Sito Intranet ASF La figlia del marò Lat... Test genetici
HOME CAUSATIVE MUTATIONS PGX MARKERS ETHNOS DATABASES MAP USER GUIDE MORE
ject of the Genomic
e Alliance Genome
ics Working Group
Documentation of causative mutations allele frequencies
Documentation of pharmacogenomic markers allele frequencies
Key project of the Genomic Medicine Alliance Genome Informatics Working Group
Innovative database structure and software design
About FINDbase
Welcome to FINDbase worldwide, an online resource documenting frequencies of pathogenic genetic variations leading to inherited disorders in various populations worldwide. The initial data came from previously published reports as well as from unpublished information contributed from individual researchers prior of publication.
Since 2008, FINDbase has undergone a major upgrade and a substantial content update with the documentation of additional inherited disorders and a completely new set of pharmacogenomic markers. This information is available in two separate modules, namely Causative mutations and Pharmacogenomic markers.
The component services that comprise the updated FINDbase follow the service oriented
POWERED BY
Institute of Biomedical Research
SUPPORTED BY
Institute of Biomedical Research
QUICK ACCESS
You can navigate through the data using the following environments:
Causative Mutations PivotViewer
PGx Markers PivotViewer
Gene and Mutation Map
Mutation Dependency Graph
POPULAR
ETHNOS databases
About Us
User Guide - Mutation Dependency Graph
User Guide - FINDbase - Gene and Mutation Map
Privacy Statement
SOFTWARE ISSUES

Genomics

Overview of the Genomics and Targeted Therapy Group

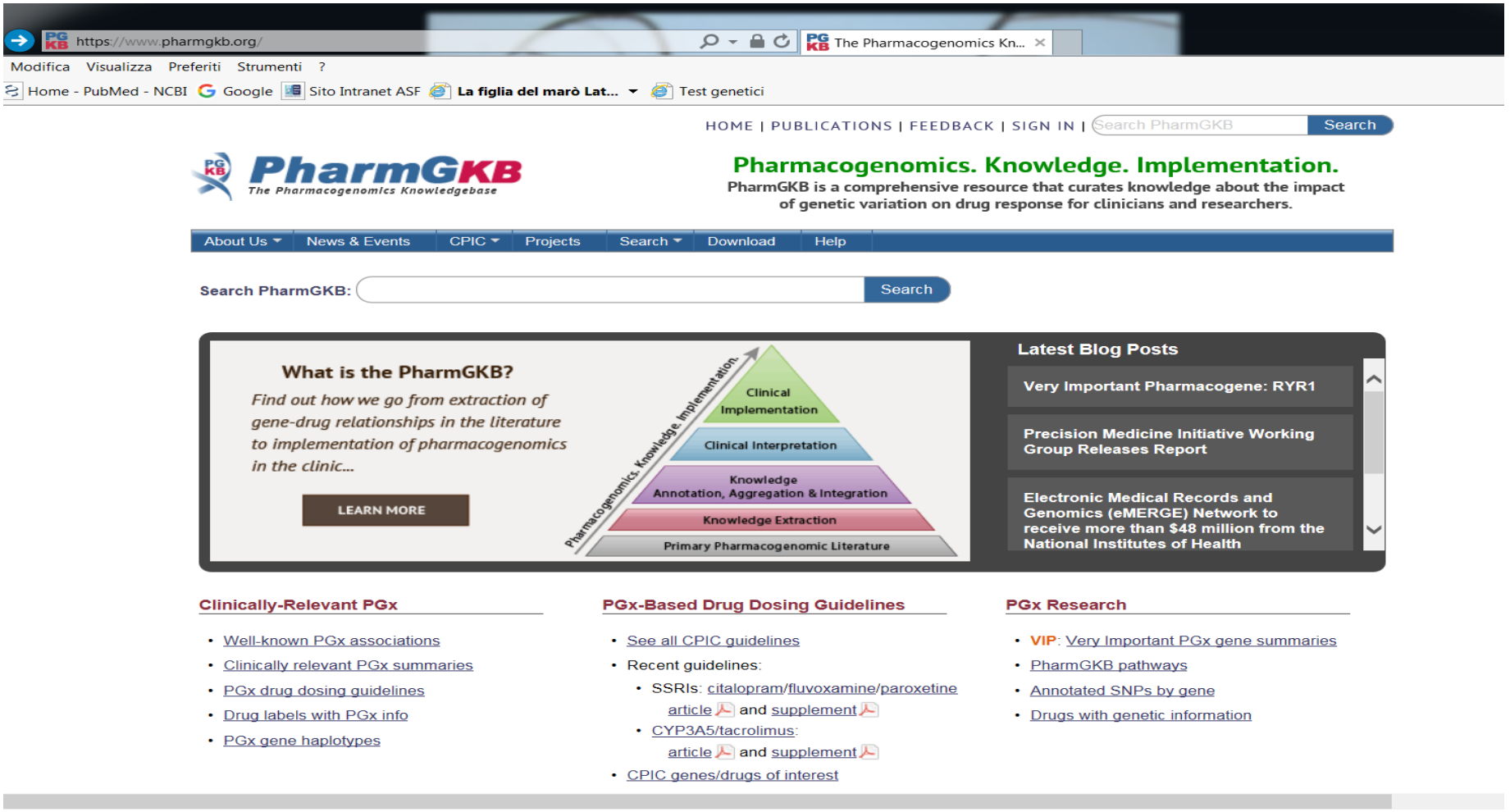
Publications on Genomics

Table of Pharmacogenomic Biomarkers in Drug Labeling

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labeling may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

The table below lists FDA-approved drugs with pharmacogenomic information in their labeling. The labeling for some, but not all, of the products includes specific actions to be taken based on the biomarker information. Pharmacogenomic information can appear in different sections of the labeling depending on the actions. For more information, please refer to the appropriate labeling guidance.



https://www.pharmgkb.org/

Impatto della Genomica in Sanità Pubblica: il punto di vista degli economisti sanitari

The NEW ENGLAND JOURNAL of MEDICINE

GETTING READY FOR GENE-BASED MEDICINE

'Quanto l'incrementato utilizzo delle informazioni genetiche incrementerà ulteriormente il costo della sanità e chi pagherà per questo?'

Varmus, 2002

'Aspettative troppo entusiastiche rispetto ai benefici della ricerca genetica per la prevenzione delle malattie sono potenzialmente in grado di falsare le priorità di ricerca e della spesa per la salute.'

Willett W, 2002

'...in questa epoca di crescente preoccupazione per i costi sanitari, non sarà possibile prendere in considerazione le implicazioni della medicina genomica senza considerare le implicazioni economiche.'

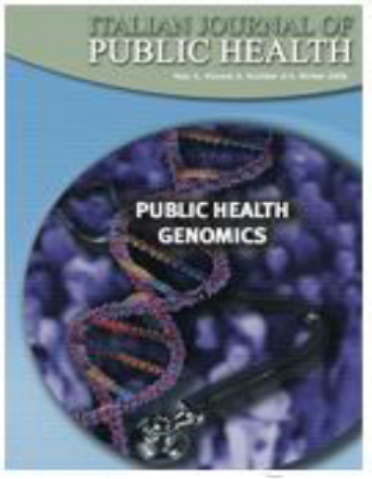
Phillips KA, 2004

THE AMERICAN JOURNAL OF MANAGED CARE

Network Italiano per la Genomica in Sanità Pubblica (GENISAP)

IJPH - YEAR 4, VOLUME 3, NUMBER 3-4, 2006

ITALIAN JOURNAL OF PUBLIC HEALTH



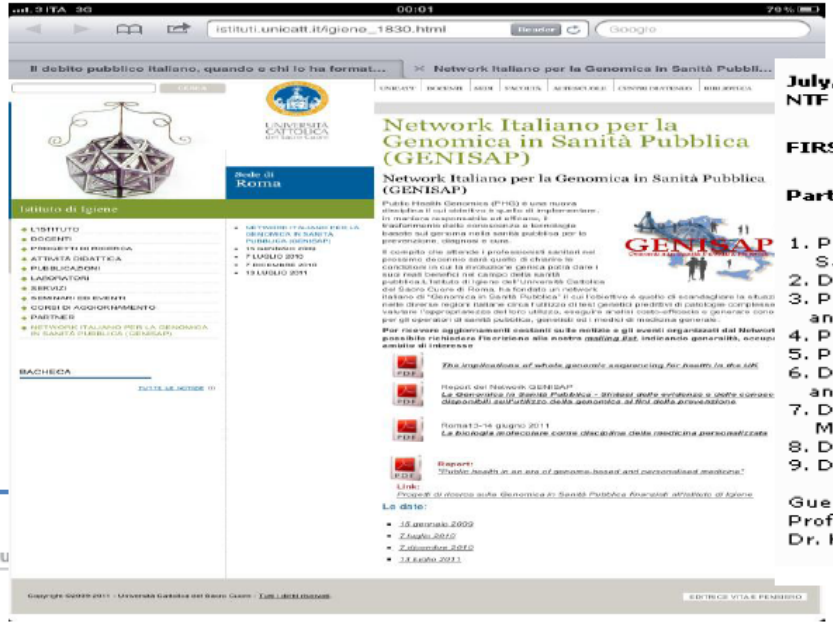
Challenges for the Italian Public Health Genomics Task Force

Stefania Boccia[1], Walter Ricciardi[1,2]

[1,2]*Italian Task Force on PHG,* [2]*Director of the Institute of Hygiene of the Catholic University of Sacred Heart; Member of the Steering Committee of Public Health Genomics European Network (PHGEN)*

Correspondence to: Stefania Boccia, Istituto di Igiene, Universita Cattolica del Sacro Cuore, L.go F. Vito, 1, ROMA. E-mail: sboccia@rm.unicatt.it

Key words: Italian Task Force, PHG, HTA



July, 10th 2006
NTF Italy has met in Rome for the first time. Here is the report:

FIRST MEETING of the ITALIAN PHGEN NATIONAL TASK FORCE (NTF)

Participants:

1. Prof. W. Ricciardi (Head of the Institute of Hygiene, Catholic University of Sacred Heart-UCSC)
2. Dr. Stefania Boccia (Institute of Hygiene, UCSC)
3. Prof. Paolo Villari (Hygiene Section- Department of Experimental Medicine and Pathology, University "La Sapienza")
4. Prof. Alberto Izzotti (Hygiene Section, University of Genoa)
5. Prof. Elisa Calzolai (Head of the Genetics Institute, University of Ferrara)
6. Dr. Franca Dagna Bricarelli (President of Italian Society of Human Genetics and Head of Laboratory of Medical Genetics, Hospital Galliera, Genoa)
7. Dr. Domenico Coviello (Head of Laboratory of Medical Genetics, Hospital Maggiore Policlinico, Mangiagalli e Regina Elena- IRCCS, Milan)
8. Dr. Anna Baroncini (Head of Medical Genetics Service, AUSL Imola)
9. Dr. Laura Murianni (Institute of Hygiene-UCSC)

Guests:
Prof. Angela Brand (Public Health Genomics European Network, Bielefeld)
Dr. Helmut Brand (Public Health Genomics European Network, Bielefeld)

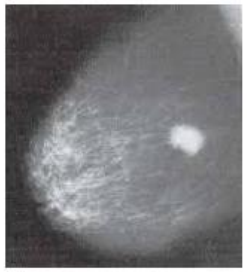
PIANO NAZIONALE DI PREVENZIONE per la Genomica in Sanità Pubblica

- Costituisce una delle **Azioni centrali a supporto del Piano Nazionale della Prevenzione 2010-12**, definite dall'Intesa del 29/4/2010 e poste sotto le responsabilità del Ministero della Salute – Direzione Generale della Prevenzione.
- Viene pensato per **suggerire strategie di intervento\azioni alle Regioni**, al fine di sviluppare e\o promuovere la comprensione delle applicazioni genomiche predittive e di definirne l'uso sulla base del principio della *Evidence Based Medicine*
- Una bozza preliminare è stata elaborata dalla Unità di epidemiologia genetica e genomica di sanità pubblica dell'Istituto di Igiene, a seguito di due focus-meeting del GENISAP

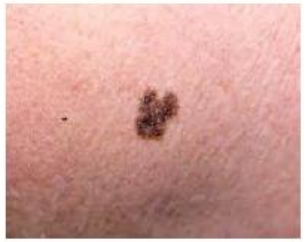
Primo esempio in EU

Celiachia

Carcinoma mammella

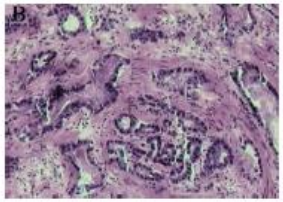


Melanoma



Diabete Mellito 1

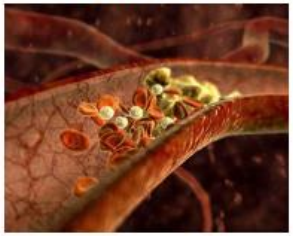
Carcinoma prostata



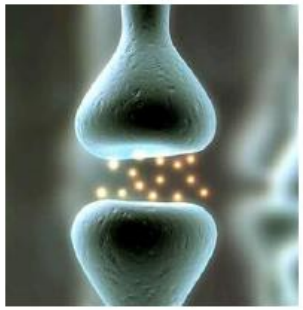
pimaco.it
portale italiano malattie complesse

Carcinoma colon retto

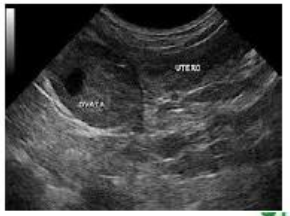
Tromboembolismo venoso



Morbo di Parkinson



Carcinoma ovaio



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portale italiano malattie complesse

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portale italiano malattie complesse

Ministero della Salute

Home | Malattie complesse | Laboratori | Notizie | Contatti

- Cosa sono le Malattie Complesse?
- Quali sono le principali Malattie Complesse?
- Che cosa è un Test Genetico?
- Quando eseguire un Test Genetico?
- Quanti tipi di test genetici esistono?
- Quale è la differenza tra i Test per Geni-Malattia e quelli per Geni di Suscettibilità?

Sei qui: Home

Accedi

Come utilizzare questo sito

Questo portale vuole essere una guida per orientarsi nel complesso mondo dei test genetici e delle malattie complesse. Non sostituisce in alcun modo il colloquio e la visita con il proprio medico di fiducia né la consulenza del genetista. Il sito è rivolto in particolare a:

- Cittadini interessati per motivi personali o familiari a capire potenzialità e limiti dei test genetici
- Medici, soprattutto non specialisti in Genetica o discipline affini, che possono trovare uno strumento utile per aiutare ad orientare i propri pazienti

Come questo sito può essere utile per i cittadini: leggi >>>

Come questo sito può essere utile per i medici: leggi >>>

Laboratori in Italia

Il portale è stato realizzato nel contesto del progetto CCM finanziato dal Ministero della Salute dal titolo "Test genomici predittivi: censimento in alcune regioni italiane per l'istituzione di un registro dell'offerta, e promozione di interventi formativi per i medici prescrittori" anno 2012-2014.

Laboratori

- Obesità
- Diabete mellito
- Cardiomiopatie
- Cancro della mammella e dell'ovaio
- Cancro della prostata
- Feocromocitoma-paraganglioma ereditario
- Malattia di Alzheimer
- Melanoma
- Sclerosi Laterale Amiotrofica
- Malattia di Parkinson
- Trombofilia
- Cancro ereditario del colon-retto
- Ipercolesterolemia familiare
- Celiachia

Link utili

- CCM - Network
- Ministero della Salute
- Orphanet
- Azioni per una vita in salute
- Ebp e lavoro
- Ebp e obesità
- EpiCentro
- Guadagnare Salute
- Guadagnare Salute in adolescenza
- Infezioni correlate all'assistenza
- Okkio alla Salute
- Osservatorio nazionale screening
- Passi
- Passi d'Argento
- Progetto Cuore
- Progetto Igea

Laboratori in Italia

Cosa sono le Malattie Complesse?

Quali sono le principali Malattie Complesse?

Che cosa è un Test Genetico?

Quando eseguire un Test Genetico?

Quanti tipi di test genetici esistono?

Quale è la differenza tra i Test per Geni-Malattia e quelli per Geni di Suscettibilità?

- ASL8 Cagliari - Ospedale "R. Binaghi"
- Azienda Ospedaliera Città della Salute e delle Scienza di Torino – Ospedale Regina Margherita
- Azienda Ospedaliera di Bologna – Policlinico S. Orsola-Malpighi
- Azienda Ospedaliera Niguarda Ca' Granda
- Azienda Ospedaliera-Universitaria di Ferrara
- Azienda Ospedaliero-Universitaria di Careggi
- Azienda Ospedaliero-Universitaria Pisana Ospedale S. Chiara
- Azienda Ospedaliero-Universitaria Policlinico di Tor Vergata
- B.I.R.D. Foundation
- Clinica Neurologica
- Consiglio Nazionale delle Ricerche
- Fondazione e Istituto Neurologico "C. Mondino" – IRCCS
- Fondazione IRCCS Istituto Neurologico "Carlo Besta"
- IRCCS Azienda Ospedaliera-Universitaria San Martino – IST Genova
- IRCCS "E. Medea"
- Laboratorio Genoma
- Università degli Studi di Padova

Grazie per l'attenzione

La Farmacogenomica

La variabilità del genoma è stata recentemente utilizzata anche per studiare la diversa risposta ai farmaci degli individui, creando un settore della biologia molecolare chiamato *Farmacogenomica.*

La farmacogenomica è in condizione di stabilire perché un soggetto è resistente o responsivo a un determinato medicamento, consentendo in alcuni casi un dosaggio personalizzato e diminuendo di conseguenza gli effetti collaterali

I test molecolari nella terapia

La conoscenza della variabilità genetica individuale ci consente di parlare di medicina personalizzata e di adattare le terapie al genoma individuale.

European Medicines Agency

Farmacogenomica

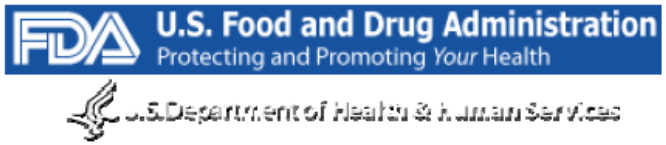
"Farmacogenomica (PGx): lo studio di varianti del DNA e dell'RNA correlate alla risposta ai farmaci"

Farmacogenetica (PGt): lo studio di varianti nella sequenza del DNA correlate alla risposta ai farmaci. La farmacogenetica è intesa come parte della farmacogenomica

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002880.pdf

Pharmacogenomic Biomarkers in Drug Labeling

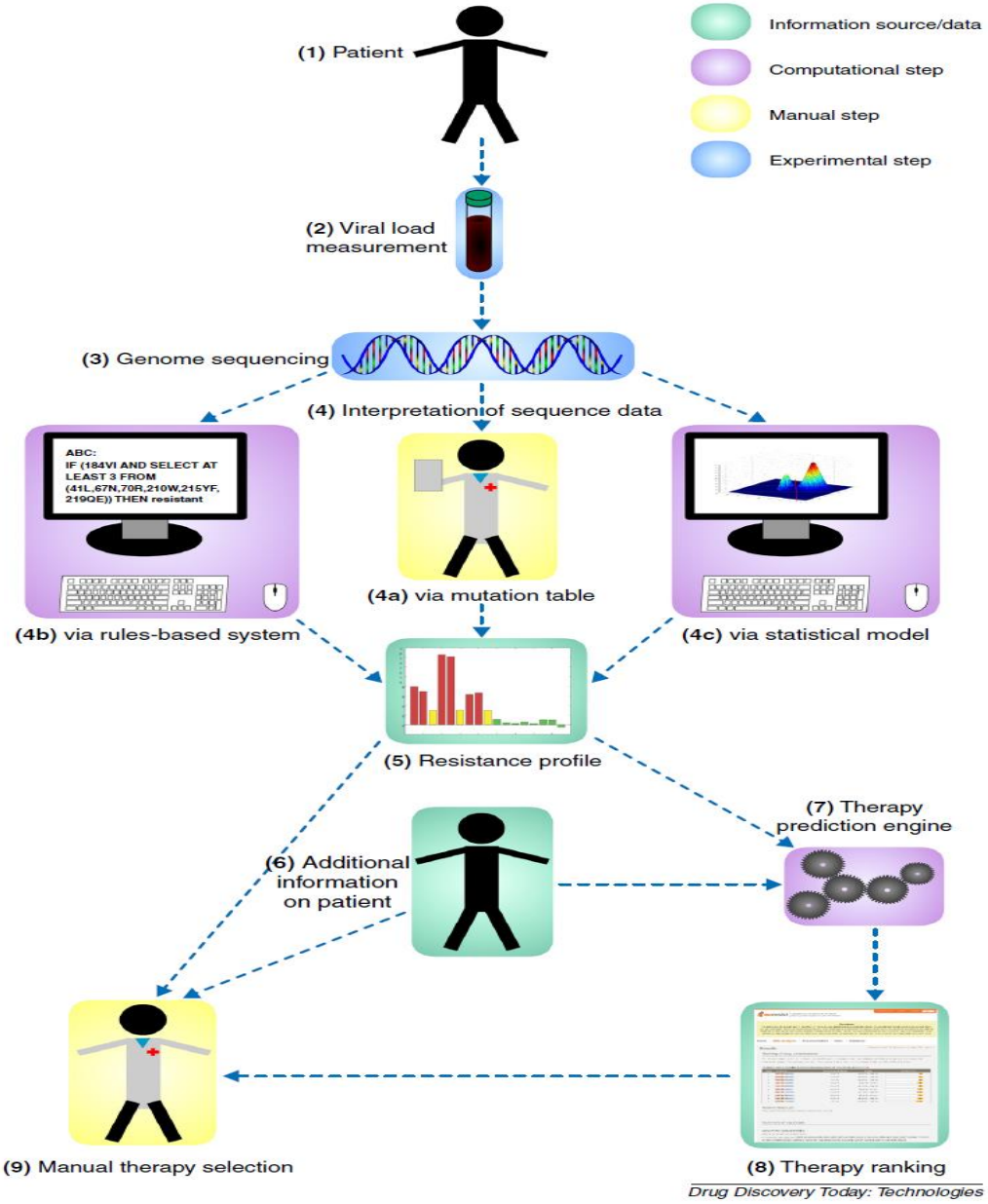
Drug	Therapeutic Area*	Biomarker†	Referenced Subgroup	Labeling Sections
Ceritinib	Oncology	ALK	ALK gene rearrangement positive	Indications and Usage, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Cetuximab (1)	Oncology	EGFR	EGFR protein expression positive	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Cetuximab (2)	Oncology	KRAS	KRAS codon 12 and 13 mutation negative	Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Cevimeline	Dental	CYP2D6	CYP2D6 poor metabolizers	Precautions
Chloroquine	Infectious Diseases	G6PD	G6PD deficient	Precautions
Chlorpropamide	Endocrinology	G6PD	G6PD deficient	Precautions
Cisplatin	Oncology	TPMT	TPMT intermediate or poor metabolizers	Clinical Pharmacology, Warnings, Precautions, Adverse Reactions
Citalopram (1)	Psychiatry	CYP2C19	CYP2C19 poor metabolizers	Clinical Pharmacology, Warnings, Dosage and Administration
Citalopram (2)	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Clinical Pharmacology
Clobazam	Neurology	CYP2C19	CYP2C19 poor metabolizers	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Clomipramine	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Precautions

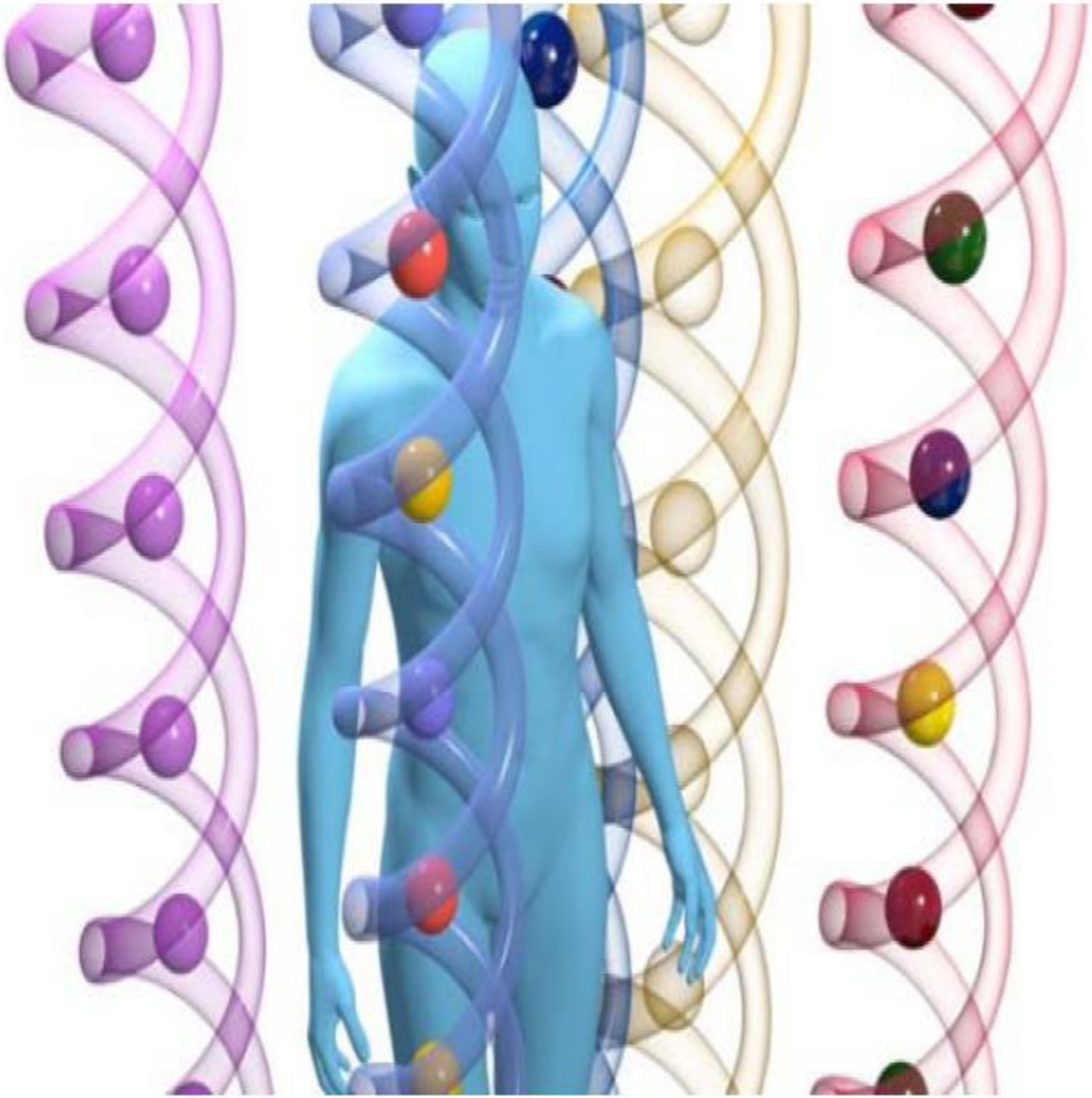


Biomarcatori genomici validi nel contesto dei farmaci approvati

Informazioni farmacogenomiche sono contenute in circa il 10% dei farmaci approvati dall'FDA, cioè più di 200 farmaci in commercio negli USA. Per alcuni di questi farmaci si raccomanda o si prescrive il test genetico

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm


Information source/data
Computational step
Manual step
Experimental step
(1) Patient
(2) Viral load measurement
(3) Genome sequencing
(4) Interpretation of sequence data
ABC:
IF (184VI AND SELECT AT LEAST 3 FROM (41L,67N,70R,210W,215YF, 219QE)) THEN resistant
(4a) via mutation table
(4b) via rules-based system
(4c) via statistical model
(5) Resistance profile
(6) Additional information on patient
(7) Therapy prediction engine
(8) Therapy ranking
(9) Manual therapy selection
Drug Discovery Today: Technologies



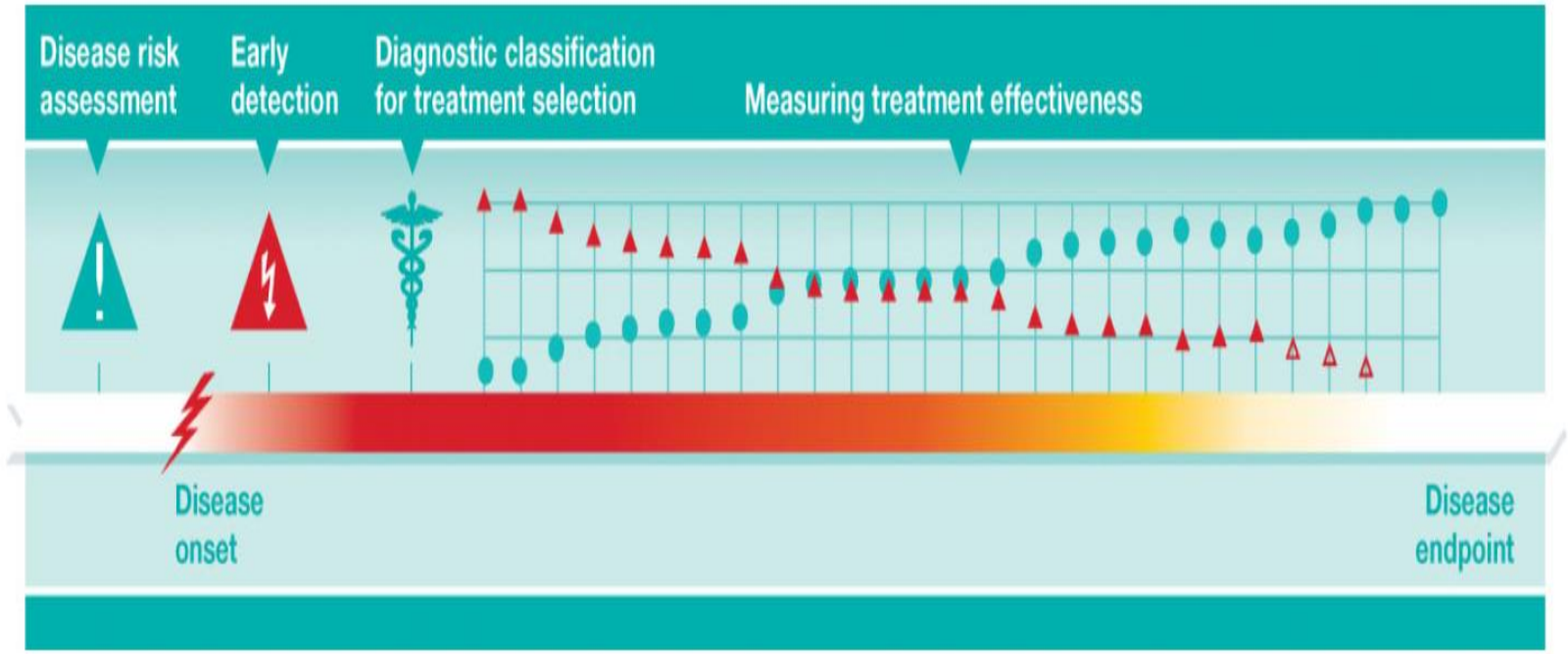


Figure 1. Broad categories of intended use of biomarkers.

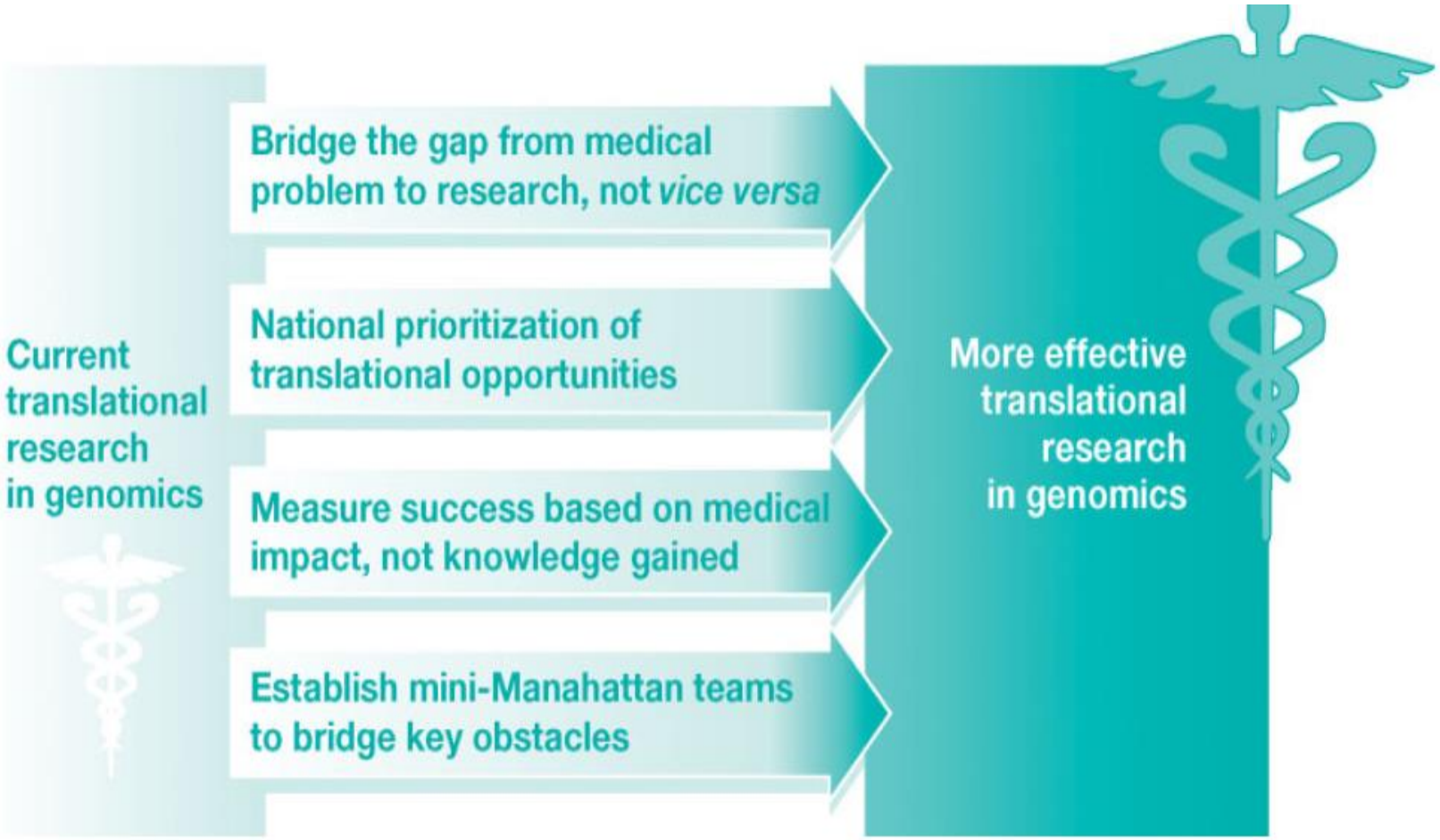


Figure 2. Suggested approaches to improve translational research.

Table 1 Candidate genes for pharmacogenetic implementation with available practice guidelines and recommendation statements

Gene(s)	Drug	Organization	Practice guidelines/ recommendation statements
CFTR	Ivacaftor	CPIC	Clancy et al; 2014[118]
CYP2C9/VKORC1	Warfarin	ACMG	Flockhart et al; 2008[119]
		CPIC	Johnson et al; 2011[120]
CYP2C19	Clopidogrel	CPIC	Scott et al; 2011,[121] 2013[122]
		ACCF/AHA	Holmes et al; 2010[123]
	TCAs	CPIC	Hicks et al; 2013[124]
CYP2D6	Codeine	CPIC	Crews et al; 2012[125]
	SSRIs	CPIC	In preparation; 2014[a]
		EGAPP	EGAPP Working Group; 2007[70]
	Tamoxifen	ACMG	Lyon et al; 2012[126]
	TCAs	CPIC	Hicks et al; 2013[124]
CYP3A	Tacrolimus	CPIC	In preparation; 2014[a]
DPYD	Fluoropyrimidine	CPIC	Caudle et al; 2013[127]
HLA-B	Abacavir	CPIC	Martin et al; 2012[128]
	Allopurinal	CPIC	Hershfield et al; 2013[129]
	Carbamazepine	CPIC	Leckband et al; 2013[130]
	Phenytoin	CPIC	In preparation; 2014[a]
IFNL3 (IL28B)	Interferon-α	CPIC	Muir et al; 2014[131]
SLCO1B1	Simvastatin	CPIC	Wilke et al; 2012[132]
TPMT	Azathioprine/6-mercaptopurine	CPIC	Relling et al; 2011,[133] 2013[134]
UGT1A1	Irinotecan	EGAPP	EGAPP Working Group; 2009[71]
Multiple (eleven genes)	Multiple (53 drugs)	KNMP-PWG	Swen et al; 2011[72]

Note: [a]Based on information available from Pharmacogenomics Knowledge Base website (http://www.pharmgkb.org/cpic/pairs), and K Caudle, CPIC Coordinator, personal communication.

Abbreviations: TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; ACCF, American College of Cardiology Foundation; ACMG, American College of Medical Genetics and Genomics; AHA, American Heart Association; CPIC, Clinical Pharmacogenetics Implementation Consortium; EGAPP, Evaluation of Genomic Applications in Practice and Prevention; KNMP-PWG, Royal Dutch Association for the Advancement of Pharmacy-Pharmacogenetics Working Group.

Table 2 Pharmacogenetic tests approved by the US FDA for IVD use[a]

Gene(s)	Assay	Alleles interrogated	Company	Date approved
CYP2C9 and VKORC1	Verigene® Warfarin Metabolism Test	*CYP2C9**2, *3, VKORC1* c.174-136C>T (1173C>T)	Nanosphere, Inc.	September 2007
	INFINITI® Warfarin Assay	*CYP2C9**2, *3, VKORC1* c.-1639G>A	AutoGenomics, Inc.	January 2008
	eSensor® Warfarin Sensitivity Test	*CYP2C9**2, *3, VKORC1* c.-1639G>A	GenMark Diagnostics, Inc.	July 2008; December 2011
	eQ-PCR™ LC Warfarin Genotyping Kit	*CYP2C9**2, *3, VKORC1* c.-1639G>A	TrimGen Corporation	February 2009
CYP2C19	AmpliChip® CYP450 Test	*2, *3	Hoffmann-La Roche Ltd	January 2005
	INFINITI® CYP2C19 Assay	*2, *3, *17	AutoGenomics, Inc.	October 2010
	Verigene® *CYP2C19* Test	*2, *3, *17	Nanosphere, Inc.	November 2012
	Spartan RX CYP2C19 Assay	*2, *3, *17	Spartan Bioscience Inc.	August 2013
	xTAG® CYP2C19 Kit v3	*2, *3, *17	Luminex Molecular Diagnostics, Inc.	September 2013
CYP2D6	AmpliChip® CYP450 Test[b]	*2–*11, *15, *17, *19, *20, *29, *35, *36, *40, *41, duplication	Hoffmann-La Roche Ltd	January 2005
	xTAG® CYP2D6 Kit v3	*2–*11, *15, *17, *29, *35, *41, duplication	Luminex Molecular Diagnostics, Inc.	May 2013

Notes: [a]As listed on the US FDA IVD Product Database: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm; [b]the *CYP2D6* star (*) allele nomenclature for the AmpliChip® is based on the available nomenclature at the time of product release. The **41* allele reported by the AmpliChip® is not consistent with the current **41* haplotype nomenclature as it does not interrogate the 2988G>A variant that was discovered after the development of the Amplichip®.[135]
Abbreviations: FDA, Food and Drug Administration; IVD, in vitro diagnostic.

Table 1 Genetic screening interventions

Screening intervention	Target population	Example conditions
Currently available		
Pre-conceptional screening	Individuals planning pregnancy	Recessive conditions, eg, cystic fibrosis
Antenatal screening	Pregnant individuals	Major chromosomal anomalies, eg, Down syndrome
Newborn screening	Neonates	Inborn errors of metabolism, eg, phenylketonuria
Cascade screening	First and second degree relatives of individual with genetic disorder	Recessive conditions, eg, familial hypercholesterolemia
Population carrier screening	Defined population subgroups	Genetic conditions with high prevalence in subgroup, eg, hemoglobinopathies
Direct-to-consumer tests	Individuals willing to purchase	Common disease susceptibility, eg, cardiovascular disease
Potential/in development		
Disease-based case finding	Patients with common serious conditions	Common conditions with genetic subtypes, eg, some cancers
Personalized/ stratified population screening	Target population for standard (non-genetic) screening	Conditions screened for at population level, eg, colorectal cancer
Case finding in whole genome/ exome sequencing	Patients undergoing whole genome/exome sequencing for clinical diagnostic investigation	Rare "actionable" genetic mutations, eg, retinoblastoma

Table 2 Framework for evaluating genetic tests

Components and definitions	Measures
Analytic validity	Analytic sensitivity and specificity
Ability to accurately and reliably measure genotype of interest	Laboratory quality control
	Assay robustness
Clinical validity	Clinical sensitivity and specificity
Ability to detect or predict disorder of interest	Prevalence of disorder
	Test positive and negative predictive value
	Penetrance
	Modifiers
Clinical utility	Natural history of condition
Risks and benefits when used in routine practice	Availability and effectiveness of treatment or preventive interventions
	Education
	Economic evaluation
	Monitoring and evaluation
Ethical, legal, and social issues	Stigmatization, discrimination, privacy/confidentiality, family/social issues
Cross-cutting factors which influence all aspects of test in practice	Consent, ownership of data/samples, licensing, patents
	Safeguards and effectiveness

Note: Data from.[57]

Table 3 Principles of population screening as applied to genetic susceptibility to disease

Public health assessment
The disease or condition should be an important public health burden to the target population in terms of illness, disability, and death.
The prevalence of the genetic trait in the target population and the burden of disease attributable to it should be known.
The natural history of the condition, from susceptibility to latent disease to overt disease, should be adequately understood.
Evaluation of tests and interventions
Data should be available on the positive and negative predictive values of test with respect to a disease or condition in the target population.
The safety and effectiveness of the test and accompanying interventions should be established.
Policy development and screening implementation
Consensus regarding the appropriateness of screening and interventions for people with positive and negative test results should be based on scientific evidence.
Screening should be acceptable to the target population.
Facilities should be available for adequate surveillance, prevention, treatment, education, counseling, and social support.
Screening should be a continual process, including pilot programs, evaluation of laboratory quality and health services, evaluation of the effect of screening, and provisions for changes on the basis of new evidence.
The cost effectiveness of screening should be established.
Screening and interventions should be accessible to the target population.
There should be safeguards to ensure that informed consent is obtained and the privacy of those tested is respected, that there is no coercion or manipulation, and that those tested are protected against stigmatization and discrimination.

Note: From *N Engl J Med*. Khoury MJ, McCabe LL, McCabe ER. Population screening in the age of genomics medicine. 2003;348(1):50–58.

GENI COINVOLTI nel METABOLISMO dei FARMACI

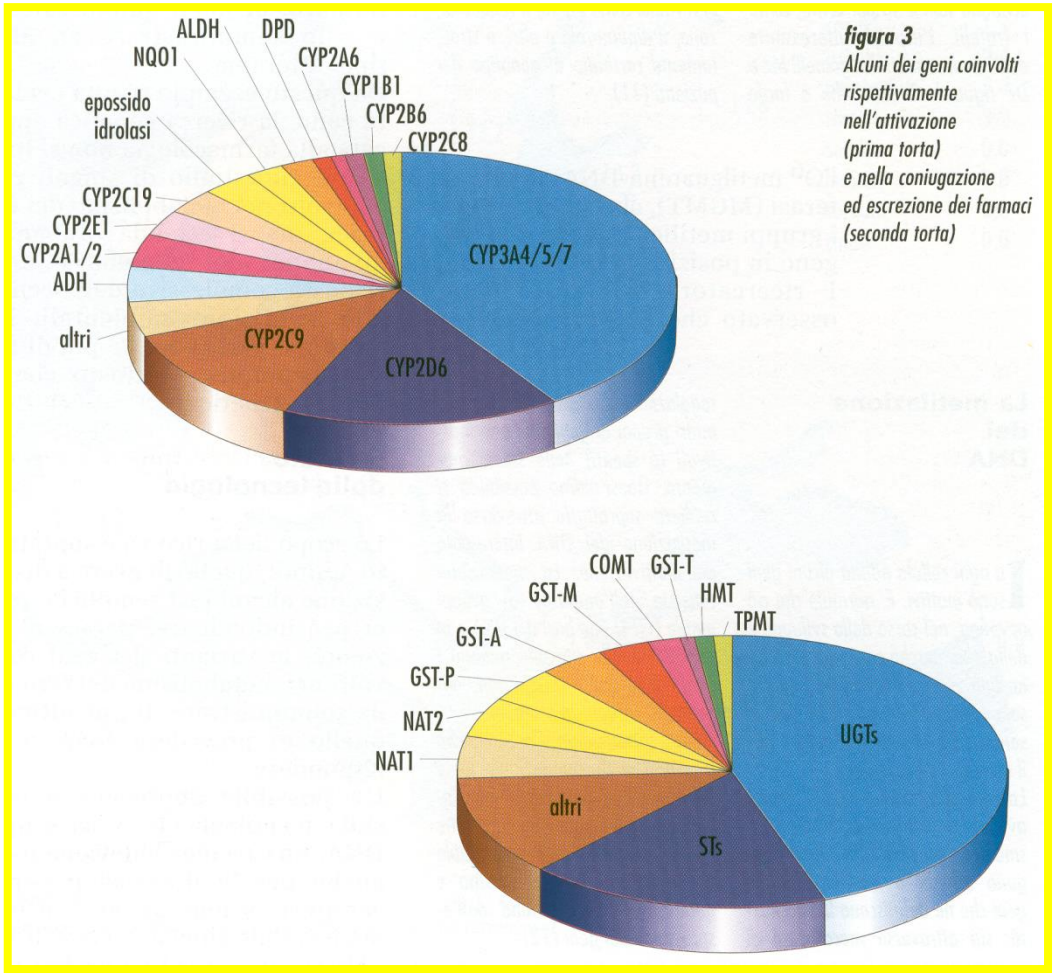


figura 3
Alcuni dei geni coinvolti rispettivamente nell'attivazione (prima torta) e nella coniugazione ed escrezione dei farmaci (seconda torta)

bersagli dei farmaci

I polimorfismi sono in grado di creare differenze interindividuali

enzimi che metabolizzano i farmaci

RISPOSTE FARMACOLOGICHE DIFFERENTI

CITOCROMO P450

Sistema citocromo P450 (CYP450)
famiglia di circa 70 geni
enzimi epatici responsabili del metabolismo di numerosi farmaci

CYP2C9, CYP2C19 , CYP2D6, CYP1A2, CYP3A4 e CYP2E1
geni maggiormente coinvolti nel metabolismo dei farmaci

Famiglia CYP2:
- **COINVOLTA NEL METABOLISMO DI MOLECOLE A LARGA DIFFUSIONE**
- **ESTREMAMENTE POLIMORFICA**

CITOCROMO P450

CYP2C9	CYP2C19	CYP2D6

Varianti con significato clinico noto

Validi biomarker

Oltre 75 diversi alleli descritti

CYP2C9 144Arg>Cys
CYP2C9 359Ile>Leu

CYP2C19 636G>A,
CYP2C19 681G>A

CYP2D6 100C>T
CYP2D6 1023C>T
CYP2D6 1659G>A
CYP2D6 1707 del T
CYP2D6 1846G>A
CYP2D6 2549 del A
CYP2D6 2613-2615 del AGA CYP2D6 2850C>T
CYP2D6 2988G>A
CYP2D6 3183G>A

IMPORTANZA RELATIVA dei diversi geni CYP450 NEL METABOLISMO DEI FARMACI

Citocromo	Substrati		
2E1	Acetaminofene Alotano	Clorzoxazone Enflurano	Etanolo (via minore)
3A4	Acetaminofene Alfentanil Amiodarone Astemizolo Chinidina Ciclosporina Cocaina Cortisolo Dapsone Diazepam Diidroergotamina Diidropiridine Diltiazem Etinil estradiolo	Gestodene Indinavir Lidocaina Lovastatina Macrolidi Midazolam Metadone Miconazolo Mifepristone (RU 486) Paclitaxel Progesterone Rapamicina Ritonavir	Saquinavir Spironolattone Sufentanil Sulfametossazolo Tacrolimo Testosterone Tamoxifene Terfenadina Tetraidrocannabinolo Triazolam Trioleandomicina Verapamile

LE DIVERSE ISOFORME DEL CYP450 METABOLIZZANO IL 40-50% DEI FARMACI

Citocromo	Substrati		
1A2	Acetaminofene Antipirina Caffeina	Clorimipramina Fenacetina Tamoxifene	Teofillina Warfarin
2A6	Cumarina		
2B6	Artemisina Bupropione Ciclofosfamide *S*-mefobarbitale	*S*-Mefenitoina (N-demetilazione a nirvanolo) Propofolo	Selegina Sertralina
2C9	Esobarbitale Fenitoina Ibuprofene	Sulfafenazolo Tolbutamide Ticrinafene	Trimetadione *S*-Warfarin
2C19	Diazepam *S*-Mefenitoina	Naproxene Nirvanolo	Omeprazolo Propranololo
2D6	Antidepressivi triciclici Aloperidolo Bufuralolo Bupranololo Clorimipramina Clozapina Codeina Debrisochina Destrometorfano	Encainide Fenformina Flecainide Fluoxetina Guanossano Idrocodone Metoprololo 4-Metossi- amfetamina Mexiletina	Ossicodone Paroxetina Propafenone Propoxifene Risperidone Selegilina Sparteina Tioridazina Timololo

CYP450: enzimi e polimorfismi

Enzima	Percentuale di farmaci metabolizzati	Polimorfismi maggiori
CYP3A4	**40-45%**	**Raro**
CYP2D6	**20-30%**	***2xn, *4, *10, *17, *41**
CYP2C9	**10%**	***2, *3**
CYP2C19	**5%**	***2, *3**
CYP1A2	**5%**	***1K**
CYP2B6	**2-4%**	**-**
CYP2E1	**2-4%**	**-**
CYP2A6	**2%**	***4, *9**
CYP2C8	**1%**	***3**
CYP3A5	**<1%**	***3**

Il gene CYP 2D6 è estremamente polimorfico con più di 70 varianti alleliche descritte da tempo[1]

Ingelman-Sundberg, TRENDS in Pharmacological Sciences, Vol. 25 No.4 April 2004
[1] Dahl, Clin. Pharmacokinet 2002; 41 (7): 453-470

Farmaci metabolizzati da CYP2D6 e CYP2C19

2D6		2C19	
Antidepressivi	**Beta Bloccanti**	**Antidepressivi**	**Inibitori pompa protonica**
amitriptilina	carvedilolo	amitriptilina	omeprazolo
clomipramina	metoprololo	clomipramina	lansoprazolo
desipramina	propafenone		pantoprazolo
imipramina	timololo		
paroxetina	**Altri**	**Antiepilettici**	**Altri**
venlafaxina	atomoxetina	diazepam	ciclofosfamide
Antipsicotici	codeina	fenitoina	progesterone
aloperidolo	dextrometorfan	fenobarbital	
risperidone	flecainide		
tioridazina	mexiletina		
	ondansetron		
	tamoxifene		
	tramadolo		

Amplichip CYP450 Test package insert

Drug Details

Drug Name(s)	PROZAC (Brand Name Drug)
FDA Application No.	(NDA) 020101
Active Ingredient(s)	FLUOXETINE HYDROCHLORIDE
Company	LILLY
Original Approval or Tentative Approval Date	April 24, 1991
Chemical Type	3 New formulation
Review Classification	P Priority review drug

- There are no Therapeutic Equivalents
- Label Information
- Approval History, Letters, Reviews, and Related Documents
- Other Important Information from FDA

Products on Application (NDA) #020101

Click on a column header to re-sort the table:

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	RLD	TE Code
PROZAC	FLUOXETINE HYDROCHLORIDE	EQ 20MG BASE/5ML **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**	SOLUTION; ORAL	Discontinued	No	None

Drug Details

Drug Name(s)	PROZAC (Brand Name Drug)
FDA Application No.	(NDA) 020101
Active Ingredient(s)	FLUOXETINE HYDROCHLORIDE

Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

Drugs metabolized by CYP2D6 — Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index (see list below) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of poor metabolizers. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, propafenone, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (*see* CONTRAINDICATIONS *and* WARNINGS).

Drugs metabolized by CYP3A4 — In an in vivo interaction study involving coadministration of fluoxetine with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

FDA: VALIDI BIOMARKER

http://www.fda.gov

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZIAGEN safely and effectively. See full prescribing information for ZIAGEN.

ZIAGEN® (abacavir sulfate) Tablets and Oral Solution
Initial U.S. Approval: 1998

WARNING: HYPERSENSITIVITY REACTIONS/LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY

See full prescribing information for complete boxed warning.

- **Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN (abacavir sulfate). (5.1)**
- **Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)**
- **Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)**
- **Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)**
- **Following a hypersensitivity reaction to abacavir, NEVER restart ZIAGEN or any other abacavir-containing product. (5.1)**
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.1, 5.5) July 2008

ABACAVIR

Terapia antiretrovirale
pazienti HIV positivi

Reazioni di ipersensibilità

RASH cutaneo

manifestazioni gastrointestinali
manifestazioni respiratorie
talvolta fatali

FDA: VALIDI BIOMARKER

*Risk Factor: HLA-B*5701 Allele:* Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir.

CNA106030 (PREDICT-1), a randomized, double-blind study, evaluated the clinical utility of prospective HLA-B*5701 screening on the incidence of abacavir hypersensitivity reaction in abacavir-naive HIV-1-infected adults (n = 1,650). In this study, use of pre-therapy screening for the HLA-B*5701 allele and exclusion of subjects with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66/847) to 3.4% (27/803). Based on this study, it is estimated that 61% of patients with the HLA-B*5701 allele will develop a clinically suspected hypersensitivity reaction during the course of abacavir treatment compared with 4% of patients who do not have the HLA-B*5701 allele.

Screening for carriage of the HLA-B*5701 allele is recommended prior to initiating treatment with abacavir. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. For HLA-B*5701-positive patients, initiating or reinitiating treatment with an abacavir-containing regimen is not recommended and should be considered only with close medical supervision and under exceptional circumstances where potential benefit outweighs the risk.

Skin patch testing is used as a research tool and should not be used to aid in the clinical diagnosis of abacavir hypersensitivity.

In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision-making. Even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not [illegible] hypersensitivity reaction cannot be ruled out on clinical grounds, d[illegible] or even fatal reaction.

ABACAVIR

AVVERTENZA:

“lo screening per la presenza dell’allele HLA -B*5701 è raccomandato prima di iniziare la terapia” …

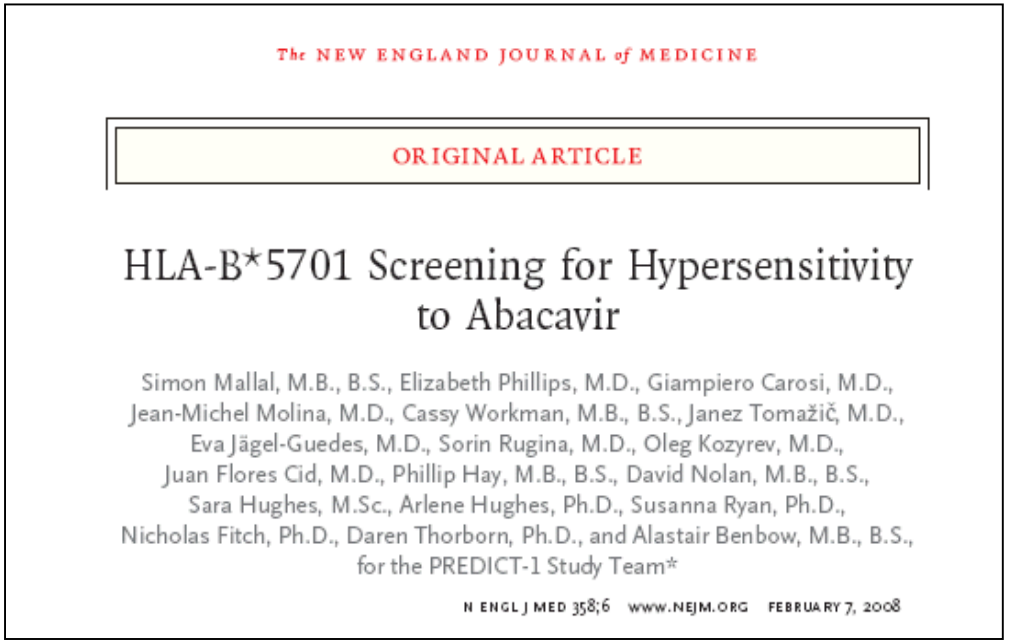
.. il trattamento a base di abacavir è sconsigliato nei pazienti HLA -B*5701 positivi …

Individui HLA-B*5701 positivi predisposti a reazioni di ipersensività (HSR) se trattati con ABACAVIR (ABC)

Uno screening capace di individuare pazienti HLA-B*5701 riduce l'incidenza della HSR da ABC prima della somministrazione della terapia

valore predittivo negativo 100%

- **risultati attendibili in tempi rapidi e costi ridotti**



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S., for the PREDICT-1 Study Team*

N ENGL J MED 358;6 www.NEJM.ORG FEBRUARY 7, 2008