Centro di Eccellenza per lo Studio del Rischio Genomico in Patologie Complesse Multifattoriali – Facoltà di Medicina e Chirurgia

Improving quality of life by a translational medicine perspective

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Simple but important questions in medicine

Why some individuals get sick more easily?

Why is treatment succesful only in some individuals?

Why are some individuals more prone to adverse effects?

The Problem

- ***Every year, adverse reactions to drugs possibly kill 100,000 American patients.***
- ***Over 2 million people have serious reactions to medication***
- ***'One-size- fits-all' medication can be dangerous***

It's a frustrating realty of modern medicine — doctors know the drugs they prescribe don't work for all

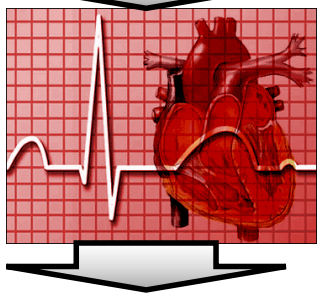
Target drugs to individuals based on their genetic makeup

Solution?

“Personalised medicine may be defined as “a medical model using molecular profiling technologies for tailoring the right therapeutic strategy for the right person at the right time, and determine the predisposition to disease at the population level and to deliver timely and stratified prevention”.

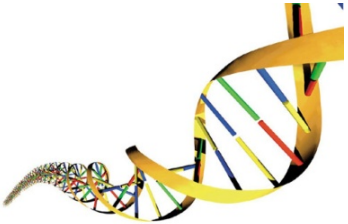
PRESENT

Smoke
hypercholesterolemia
Hypertension



CV
disease

Therapy
DNA test for individual risk

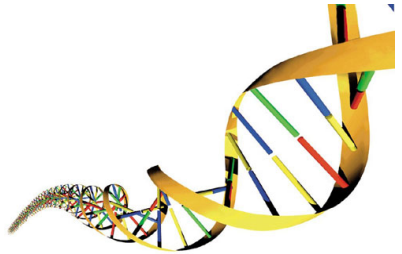


lifestyle

FUTURE

Smoke
hypercholesterolemia
Hypertension

DNA test for individual risk

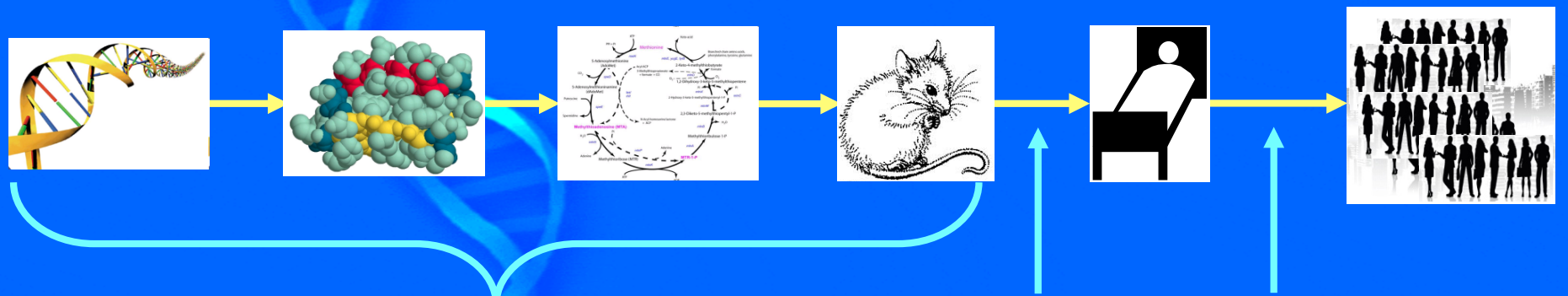


lifestyle

CV
disease

Translational Research

The application of research findings in one domain of study to another, (usually broader) domain.



"Type 0" Type 1 Type 2

Researchers

Clinicians

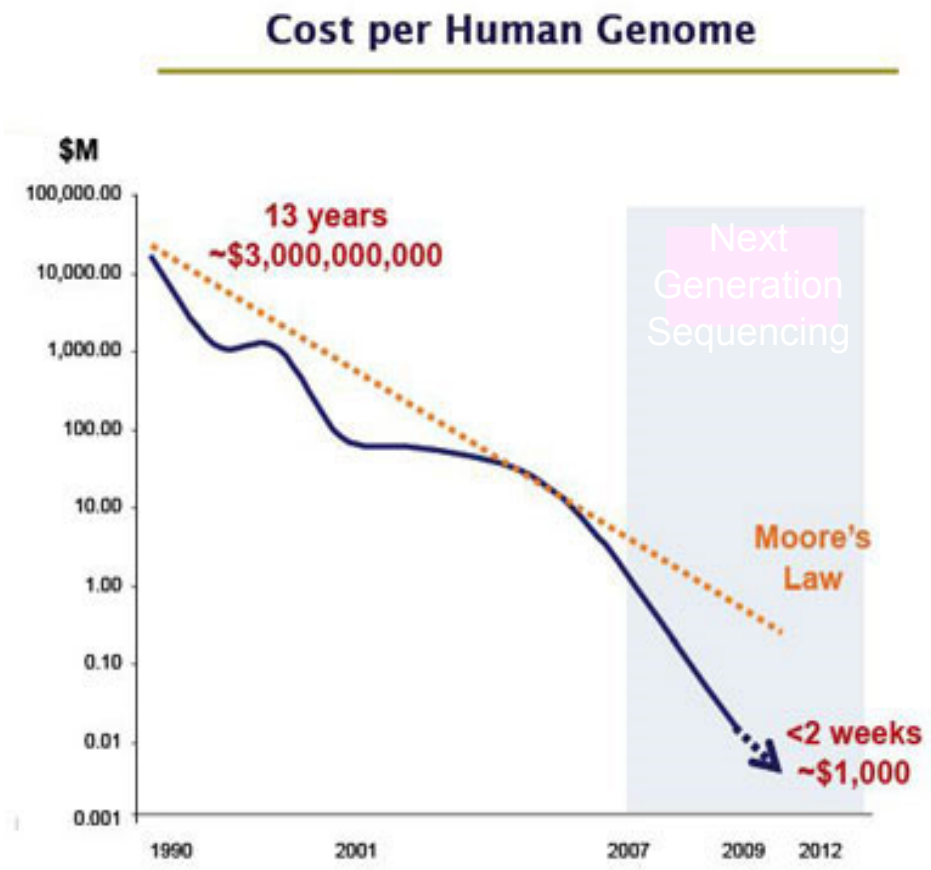
Electronic Medical Records and Genomics (eMERGE) network

- “If you have a lot of phenotypic information and genetic information, and it’s easy to have access to this database, you know there is the practical risk that some intelligent hacker might be able to figure out somebody’s identity by combing this information,”
  - Chisholm from eMERGE

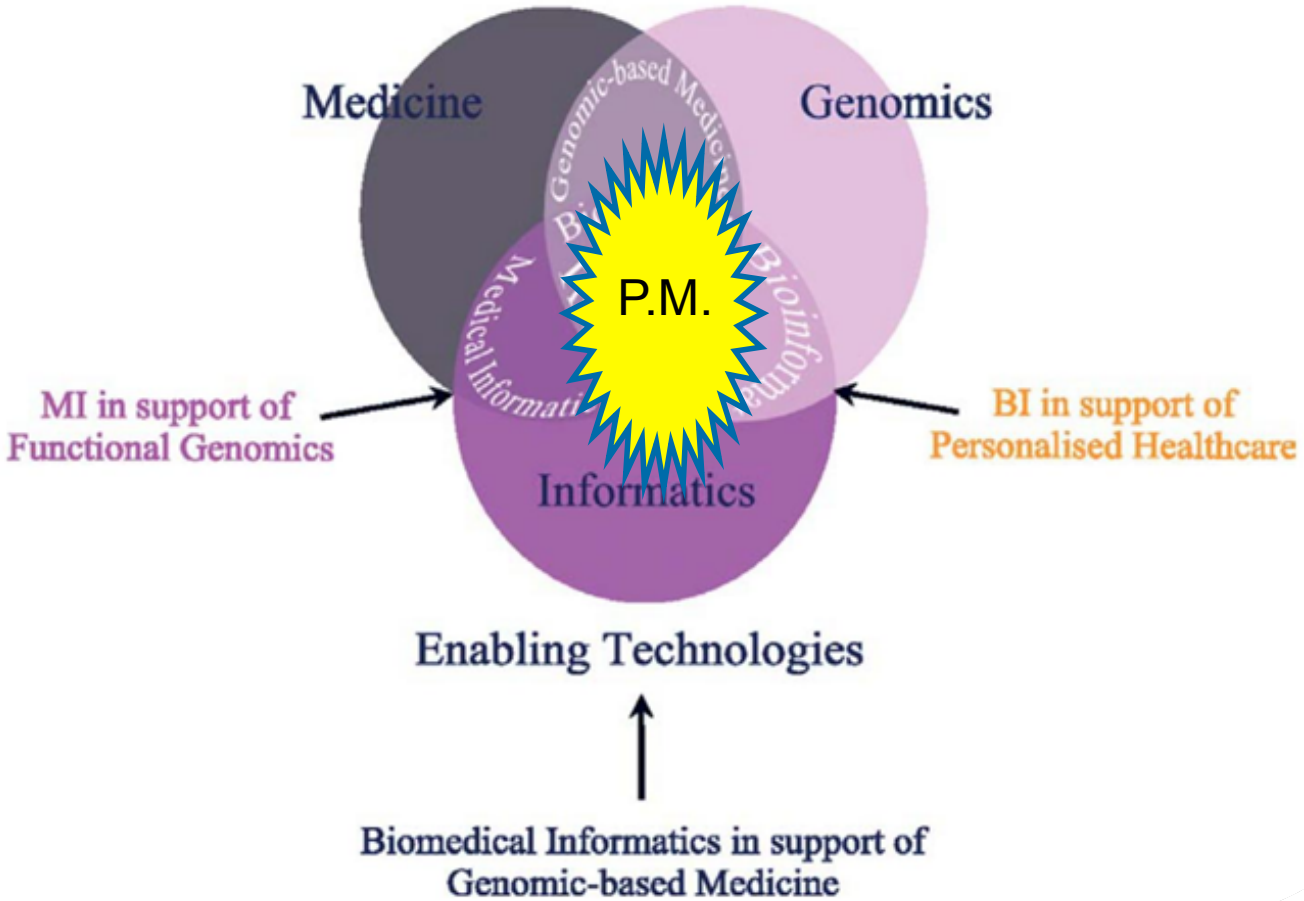
Translational Medicine

- Diseases predicted by genes
- Effectiveness of prevention
- Diseases indicated by activation
- Appropriate testing
- Drug dose, toxicity and interactions
- Drug effectiveness

ARE WE READY?


Cost per Human Genome
$M
100,000.00
10,000.00
1,000.00
100.00
10.00
1.00
0.10
0.01
0.001
13 years
~$3,000,000,000
Next Generation Sequencing
Moore's Law
<2 weeks
~$1,000
1990
2001
2007
2009
2012

F. Martin-Sanchez et al. / Journal of Biomedical Informatics 37 (2004) 30–42

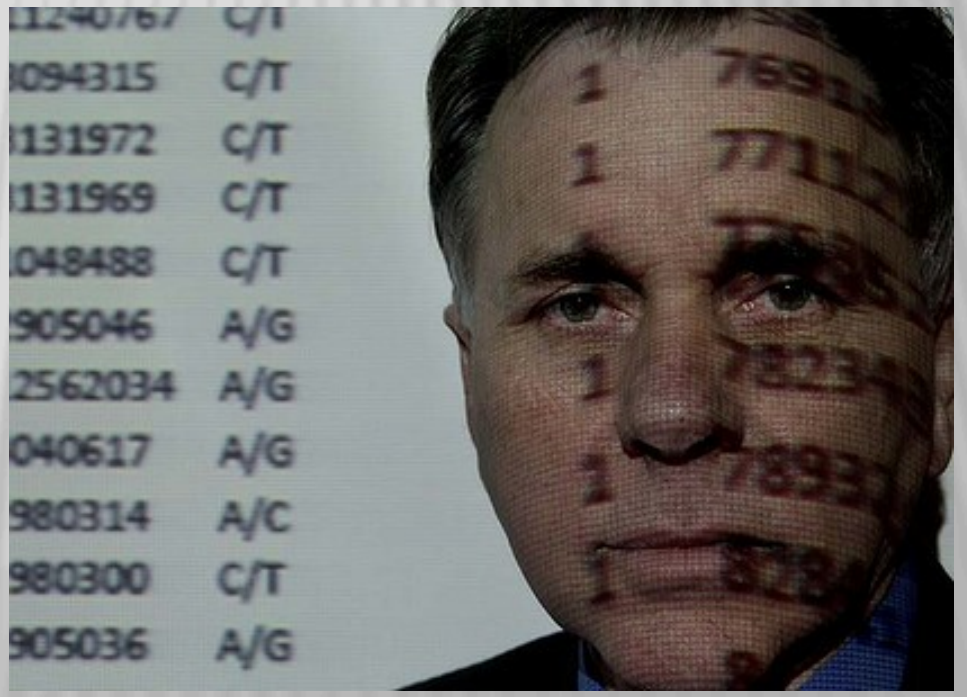


Medical information on a smartcard contains our unique molecular profile. Healthcare providers will consult the profile before treatments/drugs are prescribed.

NEXT

…….will also push genomic discoveries back into the EMRs to support clinical decisions……

"That's six billion letters of information. No physician is going to look at six billion letters and say"



We need to develop new solutions to provide physicians with a clinical decision support.

For example, if a pop-up on an EMR could inform a physician that his patient has a genetic variant that affects the processing of a particular drug, the physician could then use an alternative drug, increase the dosage of that drug, or do nothing.

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

Gene or Gene Product	Medication	Drug Effect Associated with Polymorphism
ACE	ACE inhibitors (e.g., enalapril) Fluvastatin	Renoprotective effects, blood-pressure reduction, reduction in left ventricular mass, endothelial function[32-40] Lipid changes (e.g., reductions in low-density lipoprotein cholesterol and apolipoprotein B); progression or regression of coronary atherosclerosis[41]
Arachidonate 5-lipoxygenase	Leukotriene inhibitors	Improvement in FEV_1[42]
β_2-Adrenergic receptor	β_2-Agonists (e.g., albuterol)	Bronchodilatation, susceptibility to agonist-induced desensitization, cardiovascular effects[43-50]
Bradykinin B2 receptor	ACE inhibitors	ACE-inhibitor–induced cough[51]
Dopamine receptors (D2, D3, D4)	Antipsychotics (e.g. haloperidol, clozapine)	Antipsychotic response (D2, D3, D4), antipsychotic-induced tardive dyskinesia (D3), antipsychotic-induced acute akathisia (D3)[52-56]
Estrogen receptor-α	Conjugated estrogens Hormone-replacement therapy	Increase in bone mineral density[57] Increase in high-density lipoprotein cholesterol[58]
Glycoprotein IIIa subunit of glycoprotein IIb/IIIa	Aspirin or glycoprotein IIb/IIIa inhibitors	Antiplatelet effect[59]
Serotonin (5-hydroxytryptamine) transporter	Antidepressants (e.g., clomipramine, fluoxetine, paroxetine)	5-Hydroxytryptamine neurotransmission, antidepressant response[60-62]

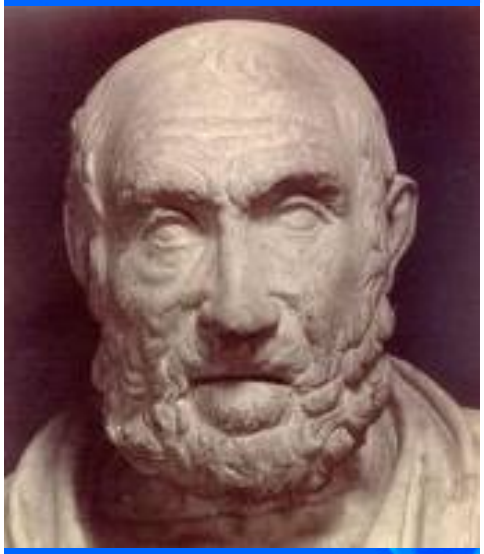
* The examples shown are illustrative and not representative of all published studies, which exceed the scope of this review. ACE denotes angiotensin-converting enzyme, and FEV_1 forced expiratory volume in one second.

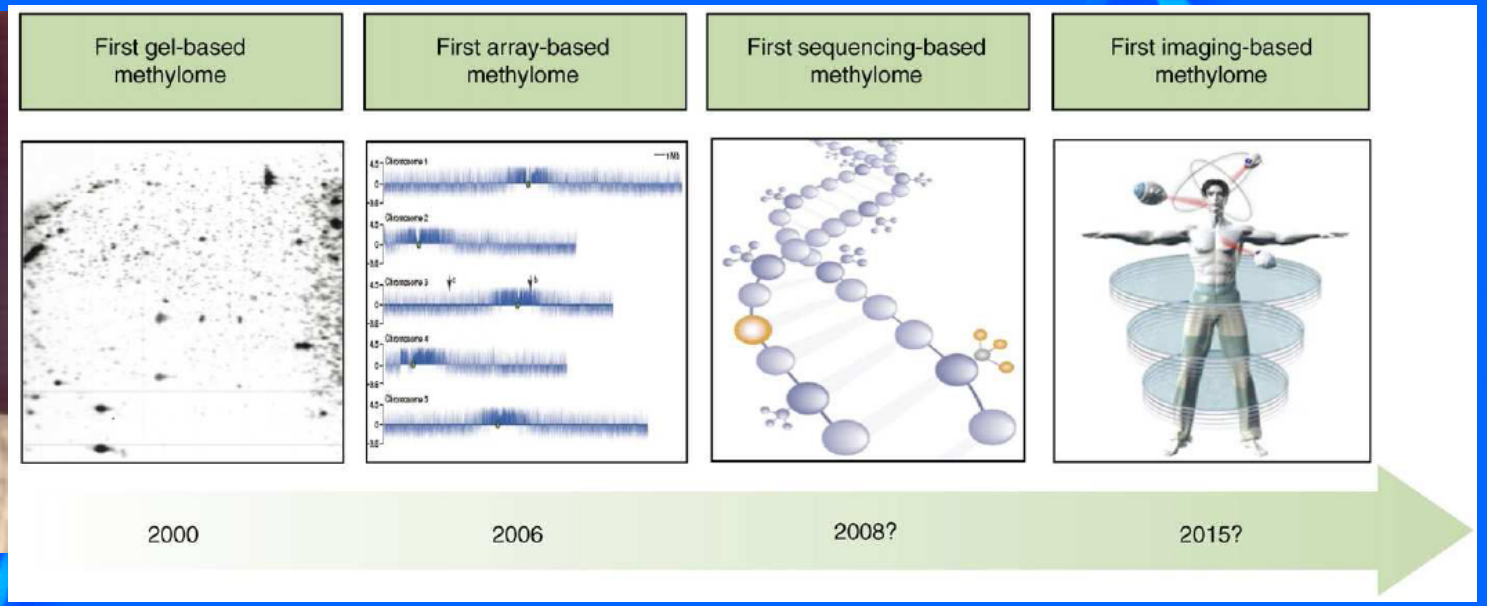
Table 2. Genetic Polymorphisms in Disease-Modifying or Treatment-Modifying Genes That Can Influence Drug Response.*

Gene or Gene Product	Disease or Response Association	Medication	Influence of Polymorphism on Drug Effect or Toxicity
Adducin	Hypertension	Diuretics	Myocardial infarction or strokes[69]
Apolipoprotein E (APOE)	Progression of atherosclerosis, ischemic cardiovascular events	Statins (e.g., simvastatin)	Enhanced survival[70,71]
Apolipoprotein E (APOE)	Alzheimer's disease	Tacrine	Clinical improvement[72]
HLA	Toxicity	Abacavir	Hypersensitivity reaction[73,74]
Cholesterol ester transfer protein (CETP)	Progression of atherosclerosis	Statins (e.g., pravastatin)	Slowing of progression of atherosclerosis by pravastatin[75]
Ion channels (HERG, KvLQT1, Mink, MiRP1)	Congenital long-QT syndrome	Erythromycin, terfenadine, cisapride, clarithromycin, quinidine	Increased risk of drug-induced torsade de pointes[76-78]
Methylguanine methyltransferase (MGMT)	Glioma	Carmustine	Response of glioma to carmustine[63]
Parkin	Parkinson's disease	Levodopa	Clinical improvement and levodopa-induced dyskinesias[79]
Prothrombin and factor V	Deep-vein thrombosis and cerebral-vein thrombosis	Oral contraceptives	Increased risk of deep-vein and cerebral-vein thrombosis with oral contraceptives[80]
Stromelysin-1	Atherosclerosis progression	Statins (e.g., pravastatin)	Reduction in cardiovascular events by pravastatin (death, myocardial infarction, stroke, angina, and others); reduction in risk of repeated angioplasty[81]

What are the anticipated benefits of PM?

- More Powerful Medicines
- Better, Safer Drugs the First Time
- More Accurate Methods of Determining Appropriate Drug Dosages
- Advanced Screening for Disease
- Better Vaccines
- Improvements in the Drug Discovery and Approval Process
- Decrease in the Overall Cost of Health Care





- ***"Its far more important to know what person the disease has than what disease the person has"***

Hippocrates