Personalized or Stratified Medicine ?
An epidemiological perspective

2ème colloque annuel de l'ITMO Santé Publique (2013)

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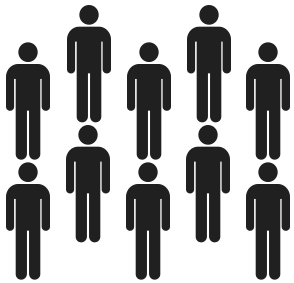
Point of View

- From a clinical epidemiologist
- Mainly developing research on how to assess treatment in chronic diseases
- Knowing nothing about genetic, genetic tests and « personalized medicine »

Personalized Medicine : A very promising concept and a « magic » word



Patients with the same diagnosis

Test diagnostic (Biomarker)

+ Benefit
No toxicity

+ Benefit
+ toxicity

No Benefit
No toxicity

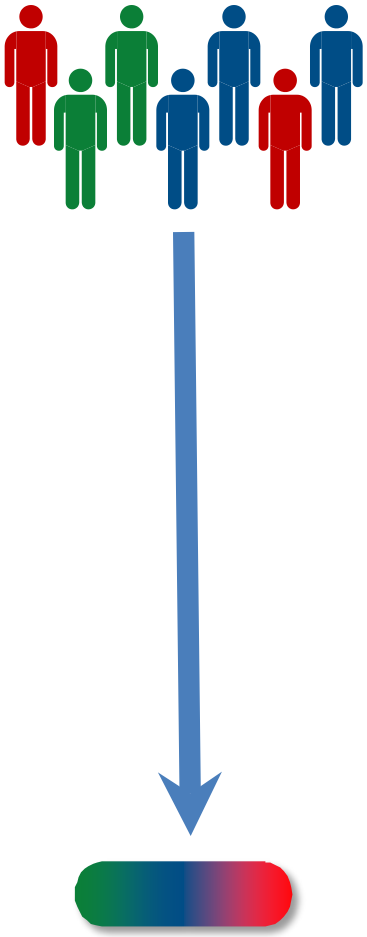
No Benefit
+ toxicity

Personalized medicine is the ability to offer :

- ❑ The right drug
- ❑ To the right patient
- ❑ For the right disease
- ❑ At the right time
- ❑ With the right dosage

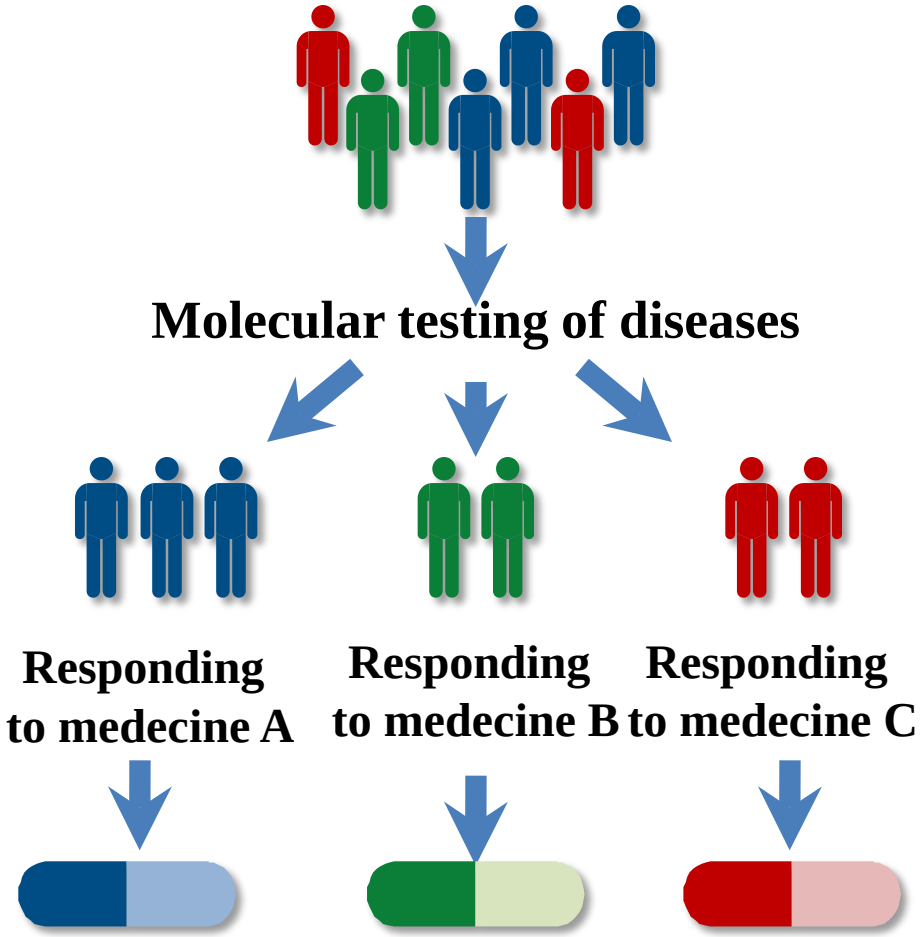
Personalized Medicine : Tailored treatments

Medicine of the present :
« one size fits all » approach



Same treatment

Medicine of the future :
Personalized Treatment



Personalized Medicine or Stratified Medicine ?

- What we are sometimes able to do :

  To determine the best treatment for a group of patients sharing some similar characteristics with the patient of interest

- Are we really able to determine the best treatment for an individual patient ?

There Is Nothing Personal

JAMA Internal Medicine
Formerly *Archives of Internal Medicine*

Ioannidis[1] nicely addressed key challenges of "personal" genetic prediction for common diseases. Expectations are huge in this domain. I argue that some of these expectations may be favored by the term *personal* and that it would be better to use the term *stratified*.[2-4]

Arnaud Chiolero,ISPM Lausanne

- Patients characteristics (e.g. genetic variants) can help to identify groups of patients who are more (or less) likely to respond to a treatment

- Probability is a group property and should not be confounded with individual determinism

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- At the individual level , you respond or do not respond to the treatment, there is no probability
- 2 patients with exactly the same characteristics (that are predictive of the response to treatment) are in the same risk stratum
- 1 of these 2 patients could respond to the treatment and not the other

There Is Nothing Personal

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Ioannidis[1] nicely addressed key challenges of "personal" genetic prediction for common diseases. Expectations are huge in this domain. I argue that some of these expectations may be favored by the term *personal* and that it would be better to use the term *stratified*.[2-4]

Arnaud Chiolero,ISPM Lausanne

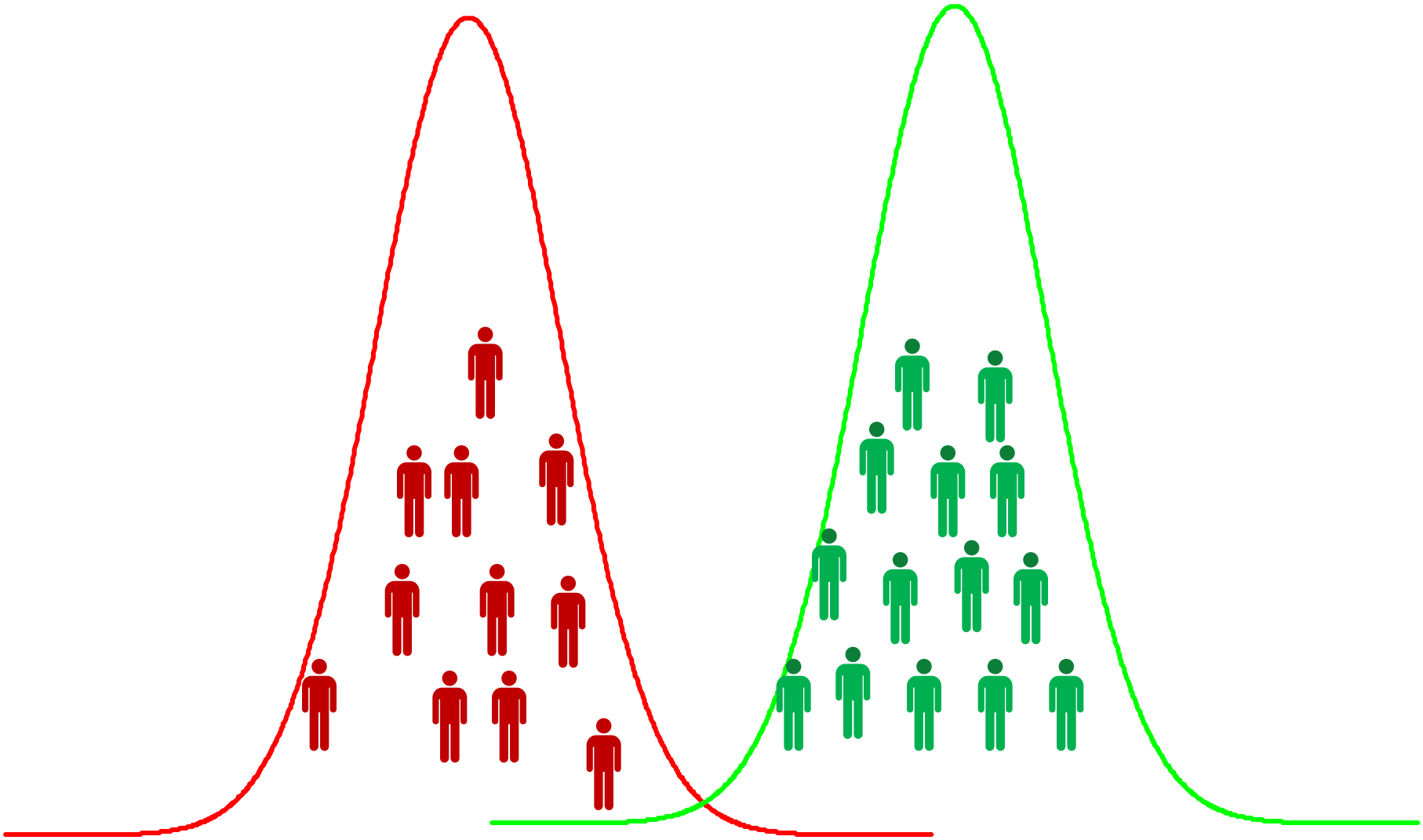
- Inference of the risk associated with the characteristics of these patients is to the corresponding group or strata level, not to the personal or individual level

- PM only reflect attempts to fractionate or stratify the larger population into smaller groups likely and not likely to benefit from specific treatments
- Therefore it would be better to use the term ***stratified medicine***

Personalized or Stratified Medicine : A new approach ?

100 Years Ago	**“Disease of the Blood”**	
80 Years Ago	**Leukemia or Lymphoma**	
60 Years Ago	**Chronic Leukemia** **Acute Leukemia** **Preleukemia**	**Indolent Lymphoma** **Aggressive Lymphoma**
Today	**~38 Leukemia types identified**: Acute myeloid leukemia (~12 types) Acute lymphoblastic leukemia (2 types) Acute promyelocytic leukemia (2 types) Acute monocytic leukemia (2 types) Acute erythroid leukemia (2 types) Acute megakaryoblastic leukemia Acute myelomonocytic leukemia (2 types) Chronic myeloid leukemia Chronic myeloproliferative disorders (5 types) Myelodysplastic syndromes (6 types) Mixed myeloproliferative/myelodysplastic syndromes (3 types)	**~51 Lymphomas identified**: Mature B-cell lymphomas (~14 types) Mature T-cell lymphomas (15 types) Plasma cell neoplasm (3 types) Immature (precursor) lymphomas (2 types) Hodgkin’s lymphoma (5 types) Immunodeficiency associated lymphomas (~5 types) Other hematolymphoid neoplasms (~7 types)

Personalized medicine requires perfect predictive accuracy :
Are genetic tests perfect ?



American Journal of Epidemiology
Vol. 159, No. 9
Printed in U.S.A.
DOI: 10.1093/aje/kwh101

Limitations of the Odds Ratio in Gauging the Performance of a Diagnostic, Prognostic, or Screening Marker

Margaret Sullivan Pepe[1,2], Holly Janes[2], Gary Longton[1], Wendy Leisenring[1,2,3], and Polly Newcomb[1]

A marker with an odds ratio of as high as 3 is in fact a very poor classification tool.

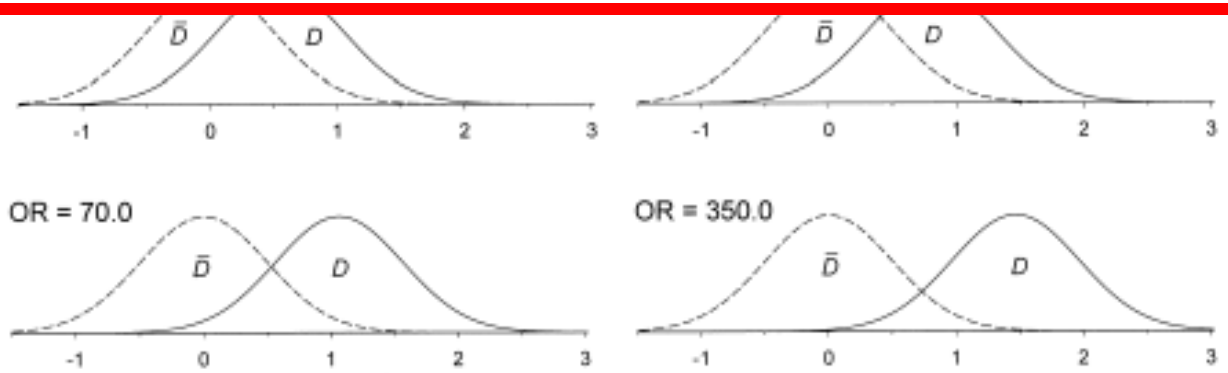
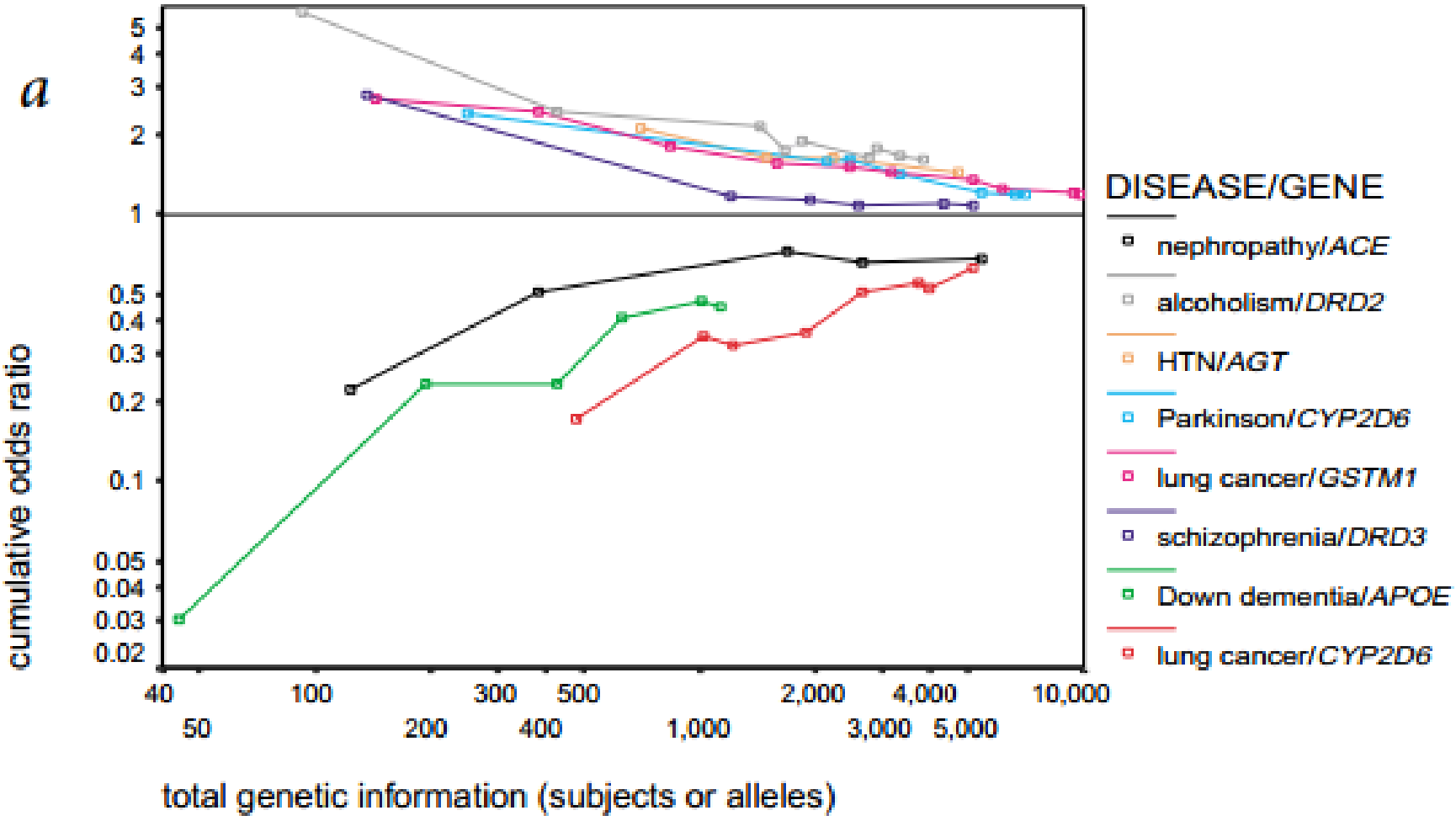


FIGURE 2. Probability distributions of a marker, X, in cases (solid curves) and controls (dashed curves) consistent with the logistic model $\text{logit}P(D = 1|X) = \alpha + \beta X$. It has been assumed that X has a mean of 0 and a standard deviation of 0.5 in controls so that a unit increase represents the difference between the 84th and 16th percentiles of X in controls. The marker is normally distributed, with the same variance in cases. The odds ratio (OR) per unit increase in X is shown.

Replication validity of genetic association studies

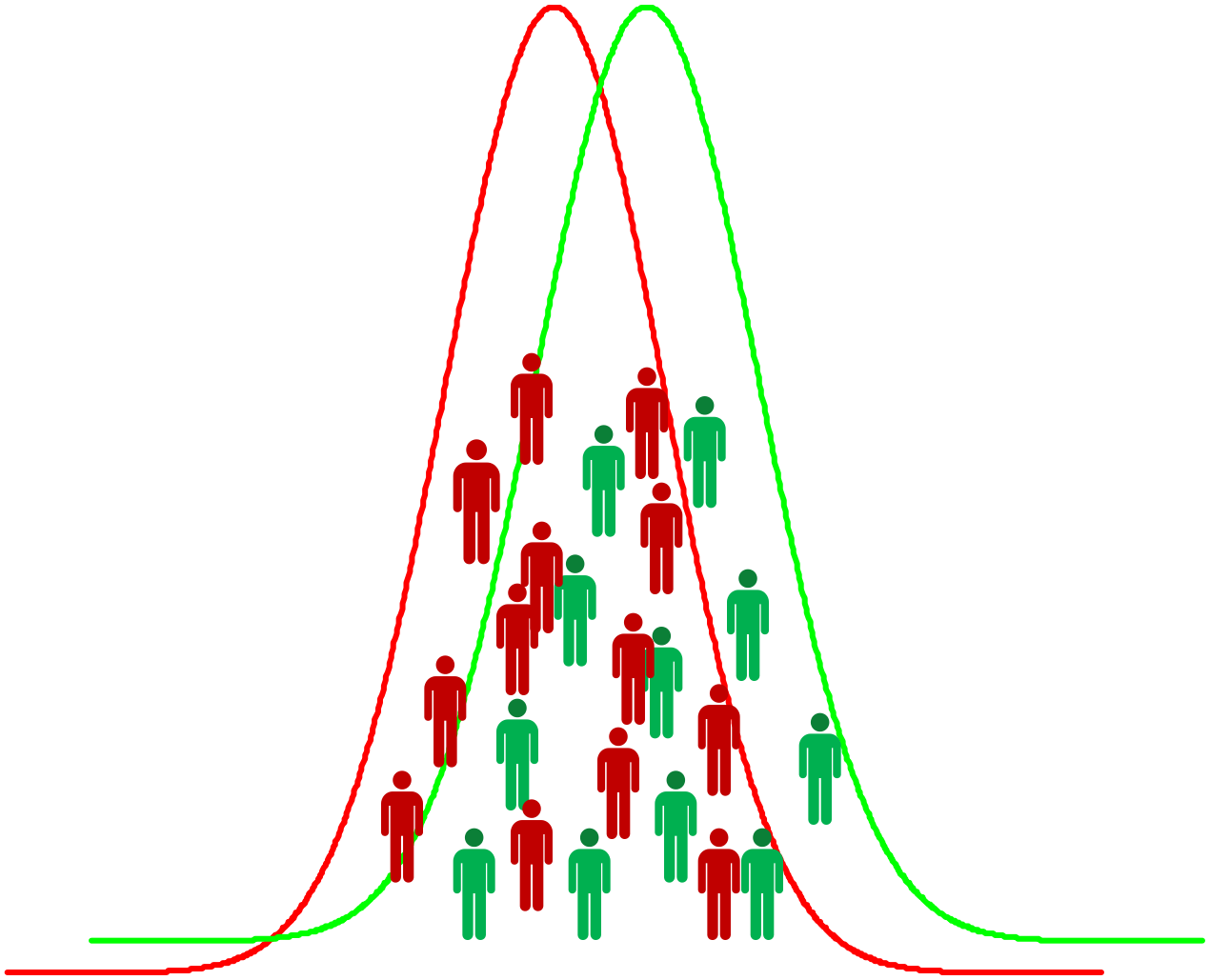
nature genetics

John P.A. Ioannidis[1–3], Evangelia E. Ntzani[1], Thomas A. Trikalinos[1] & Despina G. Contopoulos-Ioannidis[1,4]



Evolution of the strength of an association as more information is accumulated

Predictive Accuracy : Most of the genetic tests are probably not perfect !

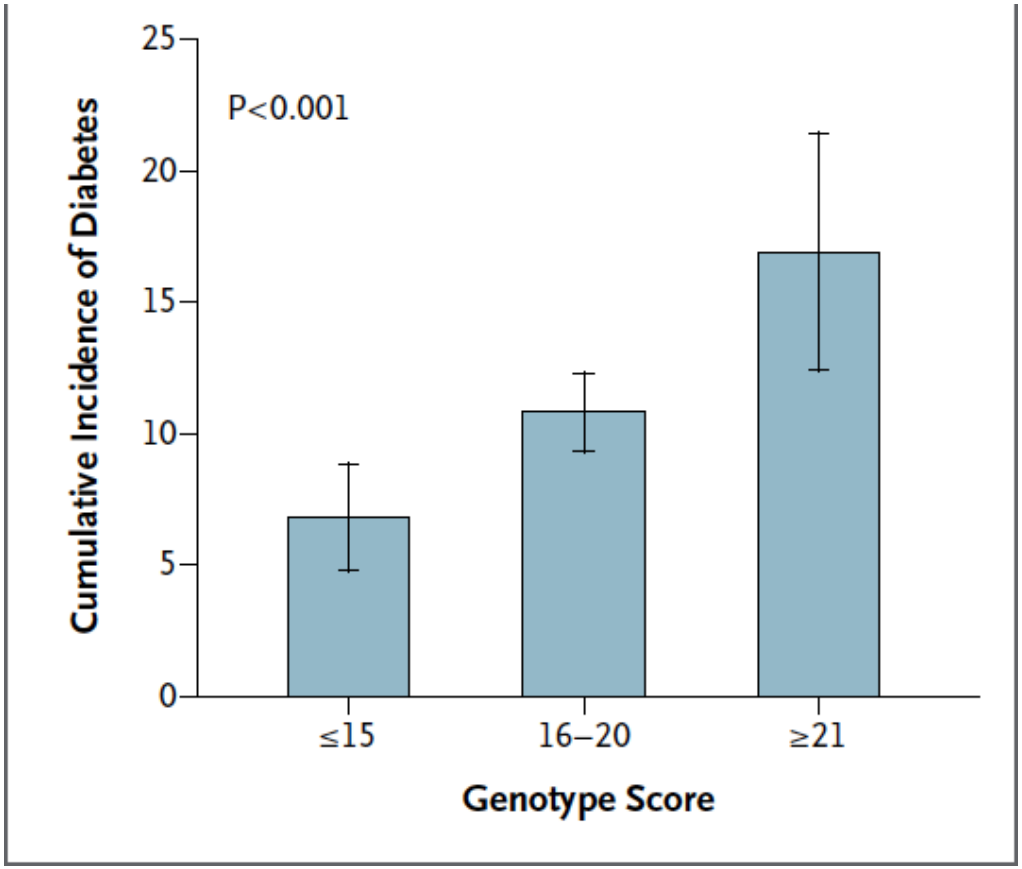


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

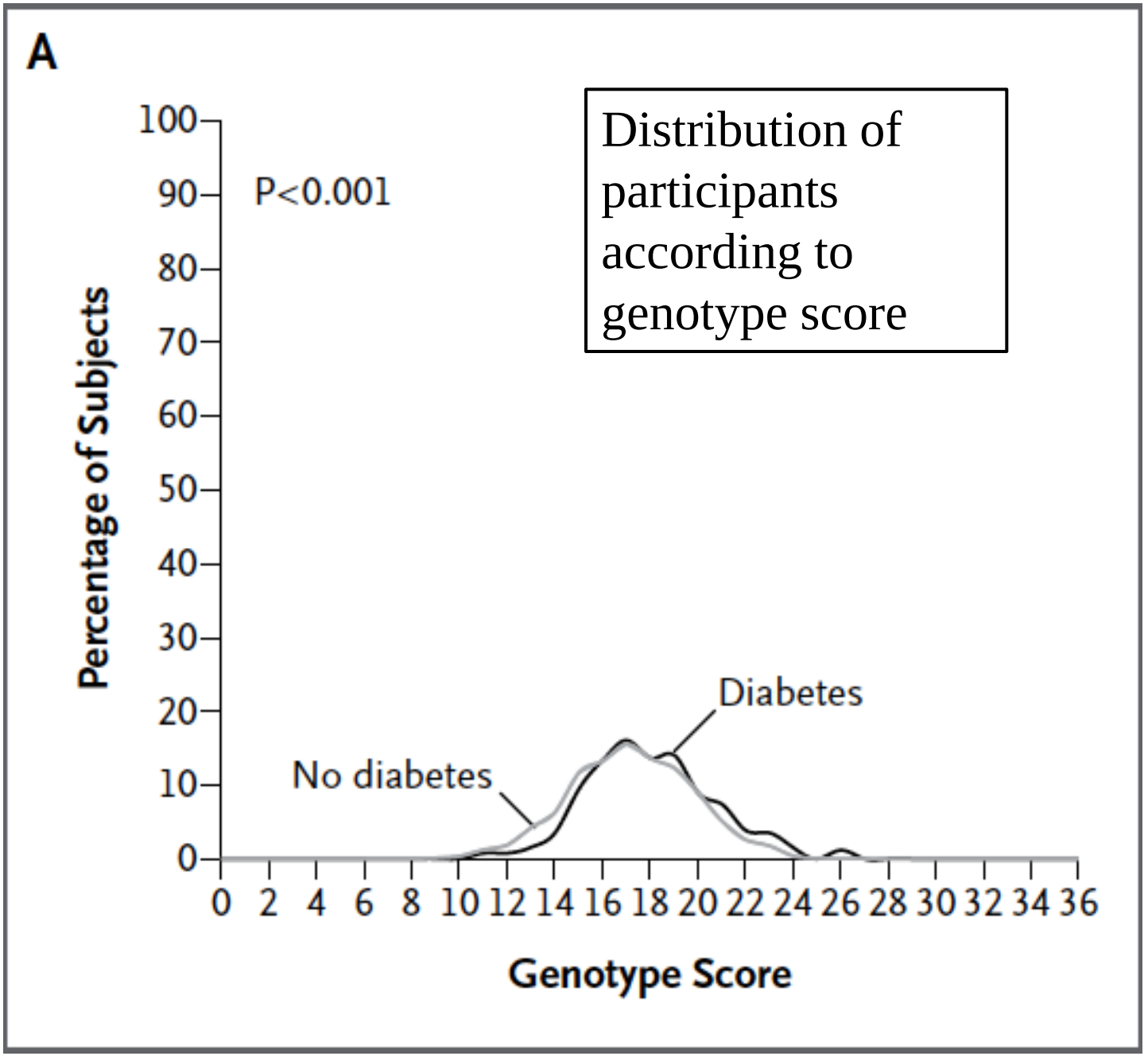
Genotype Score in Addition to Common Risk Factors for Prediction of Type 2 Diabetes

James B. Meigs, M.D., M.P.H., Peter Shrader, M.S., Lisa M. Sullivan, Ph.D., Jarred B. McAteer, B.A., Caroline S. Fox, M.D., M.P.H., Josée Dupuis, Ph.D., Alisa K. Manning, M.A., Jose C. Florez, M.D., Ph.D., Peter W.F. Wilson, M.D., Ralph B. D'Agostino, Sr., Ph.D., and L. Adrienne Cupples, Ph.D.



28-year cumulative incidence of type 2 diabetes in the Framingham Offspring Study grouped according to the genotype score

Meigs JB, **Shrader** P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, Manning AK, Florez JC, Wilson PW, D'Agostino RB Sr, Cupples LA. Genotype score in addition to common risk factors for prediction of type 2 diabetes. N Engl J Med. 2008 Nov 20;359(21):2208-19



Meigs JB, **Shrader** P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, Manning AK, Florez JC, Wilson PW, D'Agostino RB Sr, Cupples LA. Genotype score in addition to common risk factors for prediction of type 2 diabetes. N Engl J Med. 2008 Nov 20;359(21):2208-19

Additional value of genetic tests

From: **Genetic Polymorphisms for Estimating Risk of Atrial Fibrillation in the General Population: A Prospective Study**

Arch Intern Med. 2012

Table. Prediction of Atrial Fibrillation With Genetic Polymorphisms and Conventional Risk Factors[a]

	Cross-sectional Results		Prospective Results	
Risk Factor	**OR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Age	2.12 (1.75-2.57)	<.001	2.77 (2.57-2.98)	<.001
Male sex	1.94 (1.48-2.54)	<.001	1.79 (1.63-1.97)	<.001
BMI	1.21 (1.03-1.42)	.07	1.29 (1.22-1.37)	<.001
Hypertension	2.91 (1.89-4.49)	<.001	1.46 (1.29-1.65)	<.001
History of diabetes	1.80 (1.13-2.87)	.02	1.25 (1.01-1.54)	.04
History of MI	1.59 (0.95-2.67)	.04	1.63 (1.31-2.02)	<.001
History of HF	18.55 (9.86-34.91)	<.001	3.22 (1.88-5.53)	<.001
4q25 (rs2200733)	2.15 (1.69-2.74)	<.001	1.47 (1.33-1.62)	<.001
16q22 (rs2106261)	1.28 (1.02-1.61)	.03	1.13 (1.04-1.12)	.003
KCNH2 (rs1805123)	0.86 (0.68-1.09)	.22	1.08 (1.00-1.17)	.06

Model	**C Statistic**	**Calibration**	***P* Value**	**C Statistic**	**Calibration**	***P* Value**
Basic model						
Age, sex	0.737 (0.711-0.763)	14.5	.07	0.738 (0.728-0.748)	15.2	.08
Age, sex, and genetic polymorphisms						
rs22700733	0.751 (0.724-0.779)	11.7	.17	0.742 (0.732-0.753)	15.9	.07
rs2106261	0.740 (0.713-0.767)	9.5	.30	0.739 (0.729-0.750)	18.8	.03
rs22700733, rs2106261	0.751 (0.724-0.779)	5.8	.67	0.743 (0.733-0.754)	14.4	.11
Age, sex, and conventional risk factors						
Hypertension	0.755 (0.730-0.779)	4.1	.85	0.743 (0.733-0.753)	19.9	.02
BMI	0.745 (0.719-0.771)	6.0	.65	0.747 (0.737-0.756)	8.4	.49
Diabetes	0.738 (0.711-0.765)	13.0	.11	0.738 (0.727-0.748)	17.4	.04
History of MI	0.743 (0.717-0.769)	16.6	.03	0.740 (0.730-0.750)	22.7	.007
History of HF	0.750 (0.724-0.777)	14.5	.07	0.739 (0.730-0.749)	17.2	.05
All conventional risk factors	0.776 (0.750-0.802)	2.1	.98	0.750 (0.741-0.762)	10.5	.31
Age, sex, conventional risk factors, and genetic polymorphisms						
rs22700733	0.784 (0.757-0.812)	3.2	.92	0.754 (0.743-0.765)	10.4	.32
rs2106261	0.776 (0.749-0.804)	8.1	.42	0.751 (0.741-0.762)	4.0	.91
Both polymorphisms	0.785 (0.757-0.813)	5.2	.73	0.755 (0.744-0.766)	9.6	.39

Abbreviations: BMI, body mass index; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio.

[a] The upper part of the table presents effect estimates with 95% CIs per risk factor from multivariable models, including conventional risk factors and genetic polymorphisms. Cross-sectional results refer to logistic regression models of prevalent cases at baseline, and prospective results refer to Cox proportional hazards models of incident cases during follow-up. Effect estimates for genetic polymorphisms are shown per risk allele for age per 10 years and for BMI (calculated as weight in kilograms divided by height in meters squared) per 5 U. *P* values refer to Wald χ^2 tests. The lower part of the table presents C statistics with 95% CIs and calibration statistics with corresponding *P* values for each model. Calibration refers to Hosmer-Lemeshow tests for cross-sectional analyses and Groennesby-Borgan likelihood ratio tests for prospective analyses.

Classical model : 0.750

Classical model plus genetic polymorphisms : 0.755

Influence of other parameters on treatment effect : Adherence ?

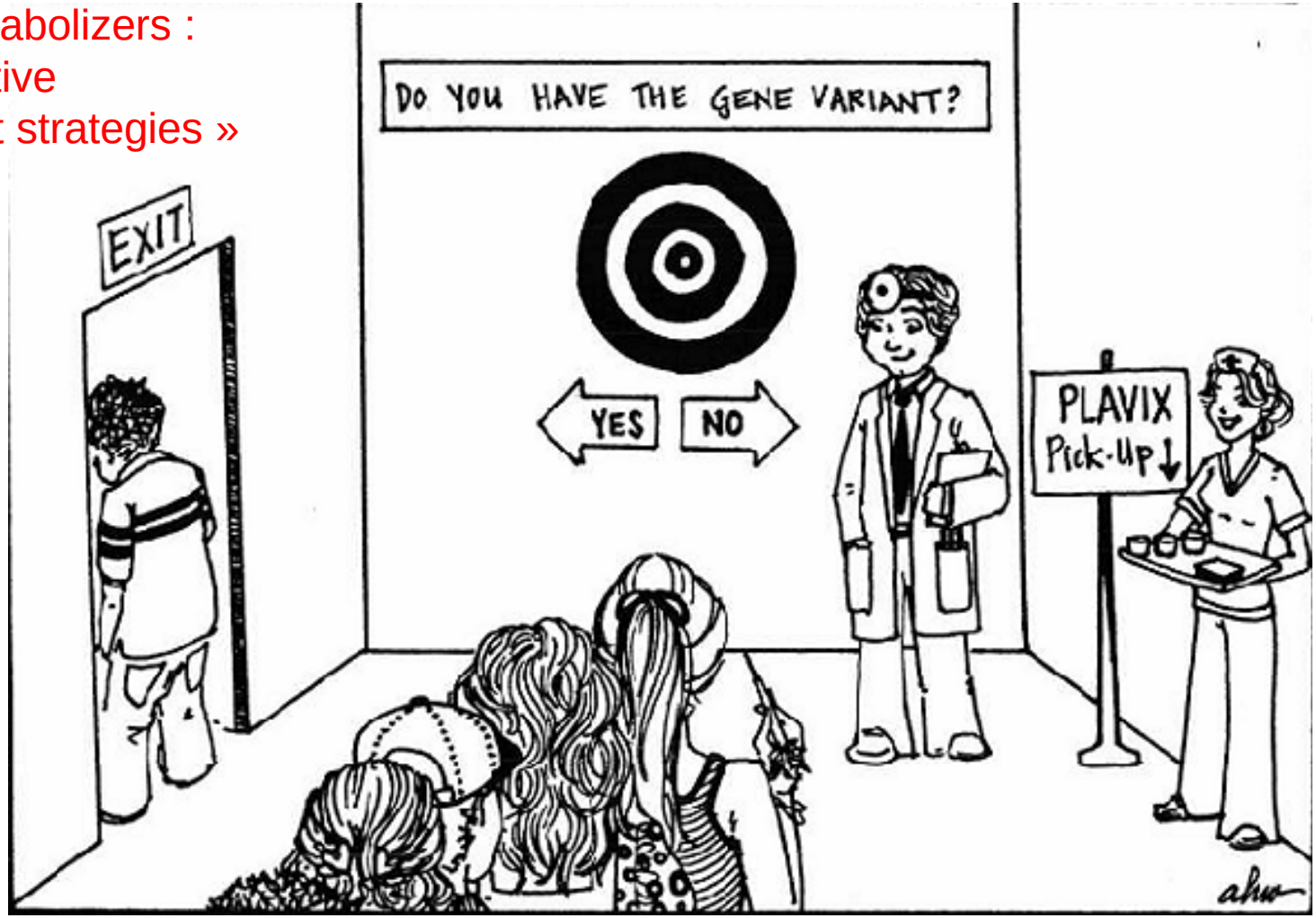
- The adherence rates to prescribed Highly Active Antiretroviral Therapies vary from 22% to 80%, in both clinical trials and clinical practice settings

- These rates of poor medication adherence are remarkably similar for various chronic diseases

- Adherence is probably poorly explained by genetic testing

Sometimes a test does not fulfill its promises in real life : CYP2C19 genotyping

Slow metabolizers : « alternative treatment strategies »



Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial

Jason D Roberts, George A Wells, Michel R Le May, Marino Labinaz, Chris Glover, Michael Froeschl, Alexander Dick, Jean-Francois Marquis, Edward O'Brien, Sandro Goncalves, Irena Druce, Alexandre Stewart, Michael H Gollob, Derek Y F So

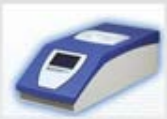
"Black Box" warning for the clopidogrel label in March of 2010

Rapid *CYP2C19* Tests

The Verigene® *CYP2C19 Testing*

CYP2C19 alleles: *1A wild-type, *2A, *3, *4, *5A, *6, *7, *8, *9, *10, and *17.

The Spartan*RX*™ *CYP2C19 Testing*



*CYP2C19*2* allele (additional polymorphisms to be added).

- Per-patient Cost according to FDA : $60 to $500

- 40 millions patient treated worldwide

Box. Boxed Warning Appearing at the Top of the Product Label Approved by the US Food and Drug Administration for Clopidogrel

Warning: Diminished Effectiveness in Poor Metabolizers. (See full prescribing information for complete boxed warning.)

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally *CYP2C19*.
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal *CYP2C19* function.
- Tests are available to identify a patient's *CYP2C19* genotype and can be used as an aid in determining therapeutic strategy.
- Consider alternative treatment or treatment strategies in patients identified as *CYP2C19* poor metabolizers.

CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events

A Systematic Review and Meta-analysis

Michael V. Holmes, MBBS, MSc
Pablo Perel, PhD
Tina Shah, PhD
Aroon D. Hingorani, PhD

JAMA The Journal of the American Medical Association

- 32 studies of 42 016 patients, 6 studies were randomized trials ("effect modification" design) and the remaining 26 reported individuals exposed to clopidogrel ("treatment-only" design).

- **Association between the CYP2C19 genotype and clopidogrel responsiveness based on surrogate markers (Levels of Clopidogrel metabolites or Platelet Reactivity)**

- **No significant association of CYP2C19 genotype with a modification of the effect of clopidogrel on any important cardiovascular outcomes or bleeding**

- Usual methodological limits (**use of surrogate markers, selective outcome reporting, small study effect and strong evidence of publication bias**)

Pharmacogenomics and Clopidogrel

Irrational Exuberance?

Steven E. Nissen, MD

JAMA The Journal of the American Medical Association

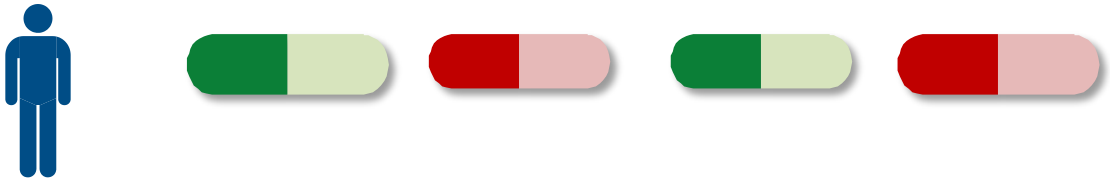
- FDA Warning reflected a case of « irrational exuberance »
- « Overzealous adoption based on limited biochemical data does not serve the public interest »

The n-of-1 clinical trial: the ultimate strategy for individualizing medicine?

Elizabeth O Lillie[1,2], Bradley Patay[1,2], Joel Diamant[1,2], Brian Issell[1,2], Eric J Topol[1,2,3,4], and Nicholas J Schork[1,2,3,†]

Personalized Medicine, 2011

- N-of-1 or single subject clinical trials consider an individual patient as the sole unit of observation in a study investigating the efficacy or side-effect of different interventions (e.g., A or B).



- An n-of-1 trial is a randomized, multiple crossover evaluation performed in a single patient

- The ultimate goal of an n-of-1 trial is to determine the optimal or best intervention for an individual patient

N-of-1 Trials

- Can be used to compare
  - Active vs. Placebo
  - Low dose vs. High dose
  - Treatment A vs. Treatment B

- Can only be used for chronic, stable conditions

- Can only be used for treatments with rapid onset/termination of effect

- The number and length of the crossover periods would be dictated by the nature of the outcome and interventions

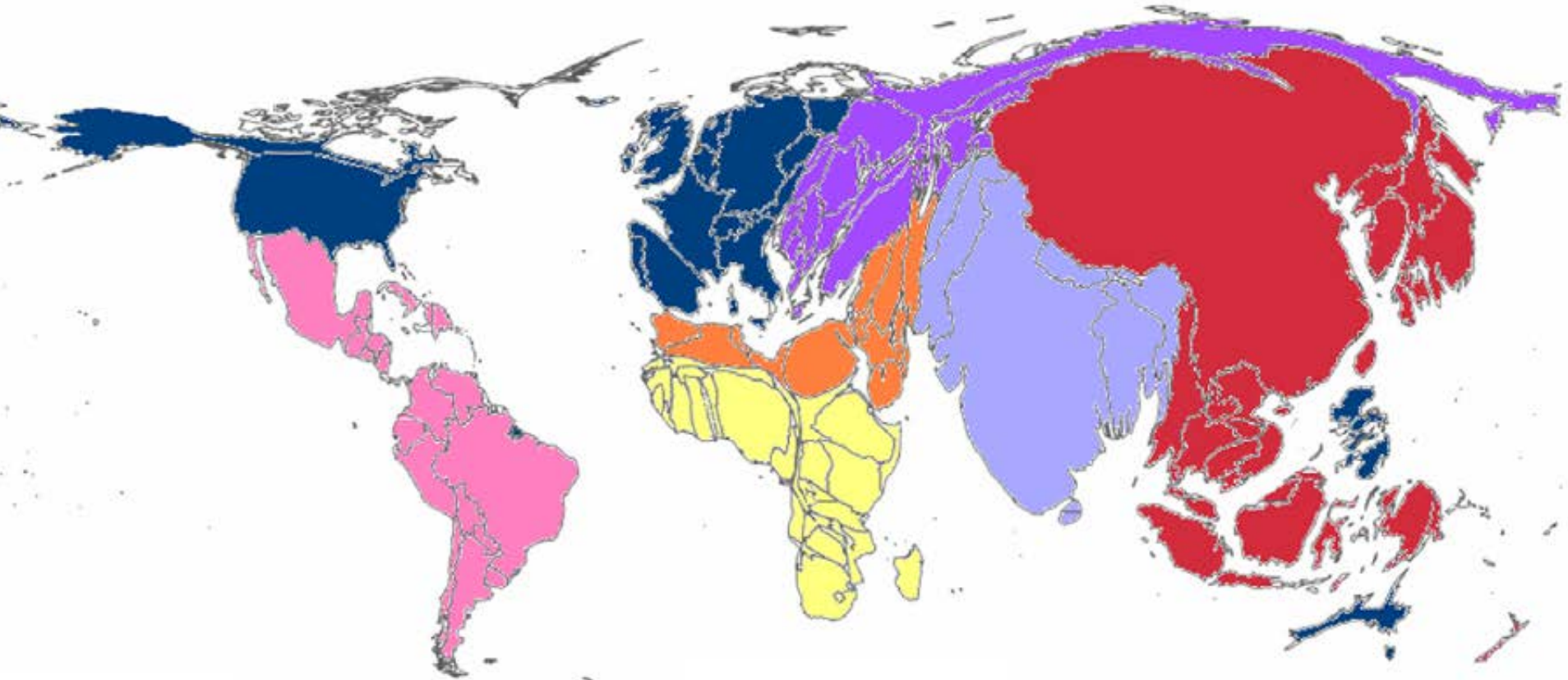
OPEN ACCESS Freely available online

PLoS one

Geographical Representativeness of Published and Ongoing Randomized Controlled Trials. The Example of: Tobacco Consumption and HIV Infection

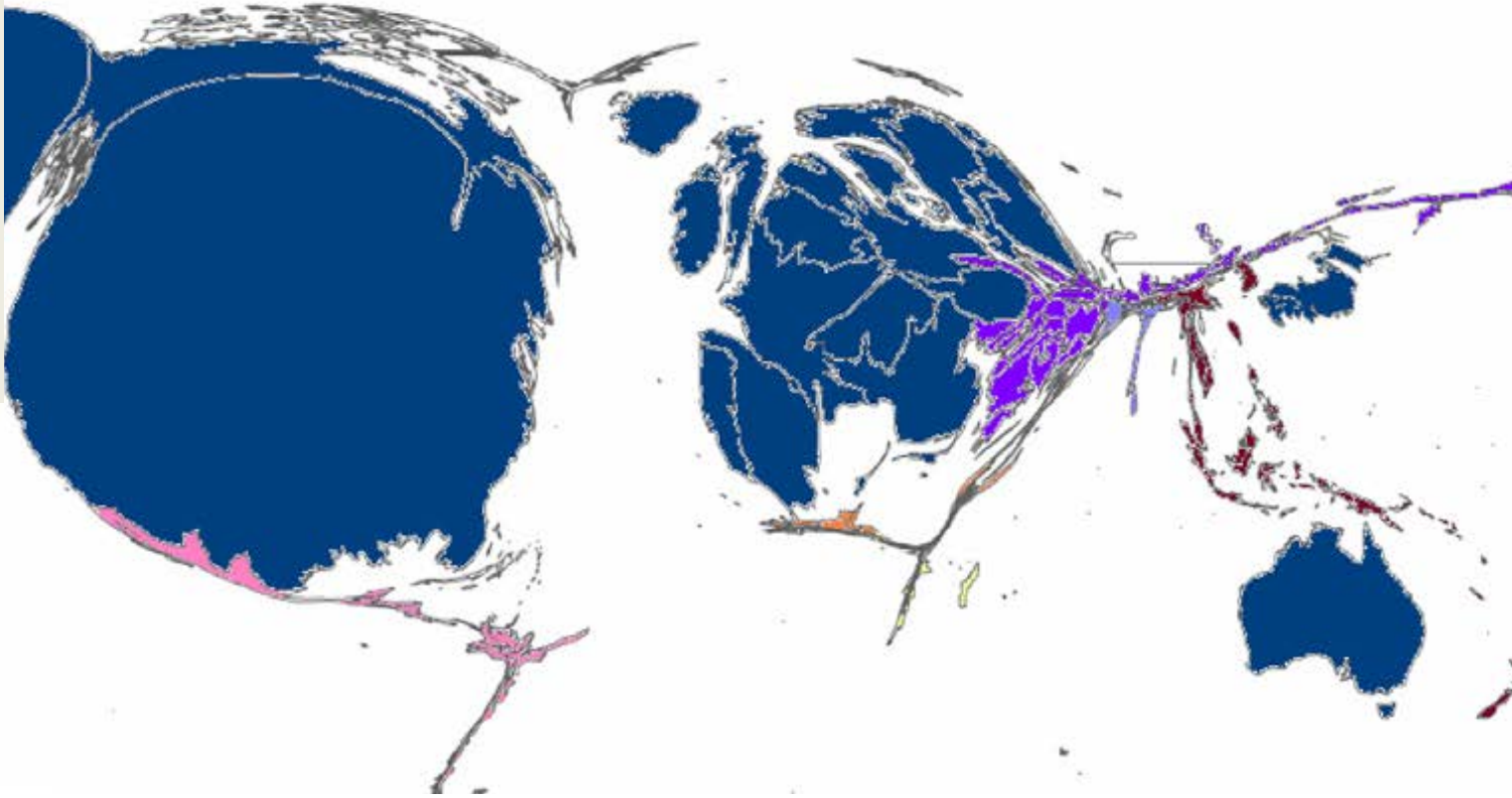
Nizar Ahmad[1,2,3*], Isabelle Boutron[1,2,3], Agnes Dechartres[1,2,3], Pierre Durieux[4,5], Philippe Ravaud[1,2,3,4]

Area cartograms showing the sizes of countries in proportion to the number of smokers



Generalizability of trials aimed at stopping tobacco use? Could trials performed in USA or EU inform decisions in India or China ?!

Area cartograms showing the sizes of countries in proportion to the number of trials



From a Public Health point of view **,**
« Continent-personalized » Medicine would be a huge step forward

Conclusions

- The term « personalized medicine » is excellent from a marketing point of view but potentially misleading
- The term stratified is in my view more accurate
- PM fuels frequently unrealistic expectations of predictive accuracy
- No matter how promising genetic markers must (as any other diagnostic or pronostic or screening markers) be assessed carefully to demonstrate their utility in clinical practice

CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events

A Systematic Review and Meta-analysis

Michael V. Holmes, MBBS, MSc
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Aroon D. Hingorani, PhD
Juan P. Casas, PhD

Context The US Food and Drug Administration recently recommended that *CYP2C19* genotyping be considered prior to prescribing clopidogrel, but the American Heart Association and American College of Cardiologists have argued evidence is insufficient to support *CYP2C19* genotype testing.

Objective To appraise evidence on the association of *CYP2C19* genotype and clopidogrel response through systematic review and meta-analysis.

- **In Treatment-only analysis (Cohorts)**, individuals with 1 or more CYP2C19 alleles associated with lower enzyme activity had lower levels of active clopidogrel metabolites, less platelet inhibition, lower risk of bleeding and higher risk of CVD events (but small study effect , selective reporting)

- **In Effect modification studies (RCTs)**, CYP2C19 genotype was not associated with modification of the effect of clopidogrel on CVD end points or bleeding

Personalized medicine according to Wikipedia

- **Personalized medicine** or **PM** is a medical model that proposes the customization of healthcare - with medical decisions, practices, and/or products being tailored to the individual patient. The use of genetic information has played a major role in certain aspects of personalized medicine, and the term was even first coined in the context of genetics (though it has since broadened to encompass all sorts of personalization measures). To distinguish from the sense in which medicine has always been inherently "personal" to each patient, **PM** commonly denotes the use of some kind of technology or discovery enabling a level of personalization not previously feasible or practical.