Genomics from bench to bedside:
A change in perspective

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Inserm - Cermes 3
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Use genetic and epidemiology methods to get insight into the biology of complex diseases

– Non actionable risk factors
– But should be involved in the biology of the pathogenic process.
Identifying them could open the way to future therapy
Theoretical and technological advances in genetic epidemiology methodologies

Candidate gene studies

Case-Control setting

Segregation analysis

Family setting

Whole genome linkage studies

Genome Wide Association Studies (GWAS)
Identification of disease risk factors, stable over a lifetime and easy to measure at the individual level
BREAKTHROUGH OF THE YEAR

Human Genetic Variation
It's All About Me

Along with the flood of discoveries in human genetics, 2007 saw the birth of a new industry: personal genomics. Depending on your budget, you can either buy a rough scan of your genome or have the whole thing sequenced. The companies say the information will help customers learn about themselves and improve their health. But researchers worry that these services open up a Pandora's box of ethical issues.
With the advent of chip-based genome-wide association studies, the era of personalized genomics is finally here. It is now possible for individuals to obtain their own genotypes with the same technologies as those used in large association studies, then compare their genotypes to those discussed in the scientific literature.

Genotypes relate to the incidence of a disease, condition, or trait. You can also see a list of the associations we currently report in our Gene Journal, along with excerpts from the scientific content that will be provided to our customers.

Because new association studies are being published weekly, even daily, we expect to add many more traits, diseases and conditions to our Gene Journal in the coming months and years. As we do so, we intend to strike a balance by reporting the latest scientific discoveries as they come, but linking them to our customers' personal data only after they meet our standards of power and replication.

Just a few years ago, the technology to perform genome-wide association studies did not even exist. Now we are at the forefront of a revolution in personalized genetics and medicine, thanks to a community of geneticists and other
We will then be in a circumstance where risk-predicting genotypes will be available for lots of people, initially as part of research and ultimately as part of clinical care.
Genetic epidemiology of Crohn’s disease

Chronic inflammatory bowel disease
Prevalence in western countries : 0.001

Familial recurrence : 10-40
Concordance rates in Twins :
   Monozygotes : 20%-50%
   Dizygotes : 0%-6%

NOD2, first genetic risk factor identified in 2001 (Hugot et al)
Genome-wide meta-analysis increases to 71 the number of confirmed Crohn’s disease susceptibility loci

Franke et al.
Genetic risk factor characteristics

Franke et al.

minor allele frequency of the 71 associated SNPs
Franke et al.

Genetic risk factor characteristics

Maximum OR = 2.66

95% of ORs in [1.05-1.37]
Meta-analysis Confirmed 71 Susceptibility Loci for Crohn’s Disease

Prediction power is very poor

Franke et al, Nat. Genet. 2010
From GWAS to individual prediction

- **OR** estimated from GWAS may be **overestimated**
- **SNPs** are only surrogates, rarely « causal » variation, that **imperfectly reflect the effect of DNA variation**
- Integration of information from multiple variants assumes small additive effects (polygenic model)
- GWAS studies don’t detect **strong GxG and GxE interactions between SNPs**
- Rely on a **simple linear approximation** of risk factor effects \( \text{Phenotype (P)} = \text{Genotype (G)} + \text{Environment (E)} \) without including Environment in the model
From individual prediction to clinical action?

More than knowledge. Knowing what to do.

By knowing more about your underlying health risks, you and your doctor can make more informed decisions about your healthcare.

Main recommendation from genetic testing: “Lifestyle changes to reduce risk”

➔ Act on risk factors that are not included in the prediction model...
Warfarin: poster child or problem child?

- Most widely used anticoagulant (vitamin K antagonist) to prevent thrombosis and thromboembolic events.

- Warfarin dosing is challenging: large interindividual variability in effective dose and serious bleeding events (5% of patients).

- Drug level influenced by diet; compliance; demographic and clinical factors.

![Warfarin Dose Distribution](image)

No. of Patients

<table>
<thead>
<tr>
<th>Warfarin Dose (mg/day)</th>
<th>No. of Patients</th>
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<tbody>
<tr>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>&gt;2, 10-25</td>
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<td>&gt;3, 10-40</td>
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<td>&gt;7, 10-120</td>
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<tr>
<td>&gt;8</td>
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</tbody>
</table>
Warfarin: poster child or problem child?

- Genetic variants in genes VKORC1 and CYP2C9 explain 50% of the interindividual effective dose variation
- Confirmation by GWAS
Warfarin: poster child or problem child?

- 2008-2012: observational studies, small clinical trials...support inclusion of genomic information
- 2007: FDA relabel warfarin to include references to the genetic variants
- 2008/2009: rejection by professional bodies (ACMG) and payors (CMS) for lack of clinical evidence
- 2010: FDA relabel with pharmacogenetics-based dosage guidance
Publication of three large randomized clinical trials on pharmacogenomics of Vitamin K antagonist dosing

The NEW ENGLAND JOURNAL of MEDICINE

November 19th 2013

% of time that a patient is within the therapeutic range during the initial phase of treatment

A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing

Kimmel et al. (COAG, partly promoted by NIH)

A Randomized Trial of Genotype-Guided Dosing of Warfarin

Pirmohamed et al. (EU-PACT, partly promoted by EU)

A Randomized Trial of Genotype-Guided Dosing of Acenocoumarol and Phenprocoumon

Verhoef et al. (EU-PACT, partly promoted by EU)
Publication of three large randomized clinical trials on pharmacogenomics of Vitamin K antagonist dosing

The NEW ENGLAND JOURNAL of MEDICINE

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A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing

Kimmel et al. (COAG, partly promoted by NIH)

1015 patients

Compare 2 groups. Initial dosing defined by an algorithm based -on clinical and genetic information
-on clinical information

After 4 weeks, results in the two groups are identical
Publication of three large randomized clinical trials on pharmacogenomics of Vitamin K antagonist dosing

The New England Journal of Medicine

November 19th 2013

A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing

A Randomized Trial of Genotype-Guided Dosing of Warfarin

455 patients
Compare 2 groups. Initial dosing defined by
- an algorithm based on clinical and genetic information
- standard dosing method

After 12 weeks, significant though very modest improvement over standard care
Publication of three large randomized clinical trials on pharmacogenomics of Vitamin K antagonist dosing

The New England Journal of Medicine

A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing

A Randomized Trial of Genotype-Guided Dosing of Warfarin

A Randomized Trial of Genotype-Guided Dosing of Acenocoumarol and Phenprocoumon

548 patients

Compare 2 groups. Initial dosing defined by an algorithm based on clinical and genetic information. After 12 weeks, results in the two groups are identical.
Do Pharmacogenetics Have a Role in the Dosing of Vitamin K Antagonists?

Bruce Furie, M.D.

« This pharmacogenetic testing has either no usefulness in the initial dosing of vitamin K antagonists or, at best, marginal usefulness, given the cost and effort required to perform testing. »

« Perhaps we should concentrate on improvements in the infrastructure for INR testing, including better communication; in the use of formal algorithms for dosing, without concern for genotype; in patient adherence to therapy ... »
Genomics from bench to bedside...

Two examples, not representative of all cases

The substantial findings recently obtained in the genetic study of many complex traits should not make us forget the simple models on which they rely

This reductionism, efficient in a highly technological research setting, reaches its limits in a clinical setting, in the absence of major effects