Towards personalized cardiovascular prevention

Zlatko FRAS, MD, PhD, FESC
Ljubljana, Slovenia
Vision for the Transformation of Medicine in the 21st Century = “P4 Medicine”

Predictive    Personalized    Preemptive

Comprehensive, genomics-based health care is going to become the norm with individualized preventive medicine and early detection of illnesses....

= PARTICIPATORY

Leading to Patient Empowerment!!
Personalized Medicine: Definition

“Personalized medicine is the use of diagnostic and screening methods to better manage the individual patient’s disease or predisposition toward a disease....

“Personalized medicine will enable risk assessment, diagnosis, prevention, and therapy specifically tailored to the unique characteristics of the individual, thus enhancing the quality of life and public health.”
Risk Factors, Biomarkers & Genetic Markers

- Risk Factors as predictive factors
- Risk Factors as causative factors
- Markers of pathobiological events
- Markers of target organ response/damage

- Genetic / genomic markers of disease susceptibility
- Genetic / genomic markers of therapeutic response
Pharmacogenetics:
Study of the effect of variation in a single gene

Pharmacogenomics:
Study of the effect of variation in multiple genes
What can we understand from studying variations (SNPs) ?

• Understand the risk of a child being affected by inherited disorders
  • carrier status in the case of unaffected parents

• Identify SNPs associated with disease development
  • diabetes, heart disease....addiction, Alzheimer's etc.

• Identify patients that will benefit from drugs

• Explain differential response to drugs
  • adjust doses of drugs

• Aid in therapeutic development
Clinical Application of Genetic Susceptibility Information

- **Improve disease prevention**
  - Secondary prevention in those with disease
  - Primary prevention in at-risk relatives

- **Improve disease management**
  - Earlier diagnosis
  - Better prognosis

  ➔ **Targeted treatments**
  - Pharmacogenomics
Coronary Artery Disease is a Complex Genetic Disease

- Multiple risk factors
- Estimated that traditional risk factors fail to explain up to 50% of CAD morbidity and mortality
- Novel risk factors are being described
- Interaction of risk factors
- Most traditional and novel risk factors have a genetic influence
# Candidate Genes for Lipid Traits from Genomic Studies

![Diagram of candidate genes and lipid level changes](image)

<table>
<thead>
<tr>
<th>LDL</th>
<th>HDL</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOB</td>
<td>ABCA1</td>
<td>APOA cluster</td>
</tr>
<tr>
<td><strong>APOE cluster</strong></td>
<td>CETP</td>
<td>ANGPTL3</td>
</tr>
<tr>
<td>LDLR</td>
<td>LIPC</td>
<td>MLXIPL</td>
</tr>
<tr>
<td>HMGCR</td>
<td>LIPG</td>
<td>GCKR</td>
</tr>
<tr>
<td>PCSK9</td>
<td>LPL</td>
<td>TRIB1</td>
</tr>
<tr>
<td>CSPG3</td>
<td>GALNT2</td>
<td></td>
</tr>
<tr>
<td><strong>SORT1</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The hazard ratios and 95% confidence intervals taken from the Northwick Park Heart Study, a prospective study of the risk of coronary heart disease (CHD), which has followed more than 3000 middle-aged men for over 6 years. For non-smokers all genotype groups have been pooled and the hazard ratio set at 1. In this group there were 32 CHD events and 727 event-free men. In smokers, divided on the basis of the APOE genotype, in the [epsilon]3[epsilon]3 group there were five events and 367 event-free men, in the [epsilon]4+ group there were 21 events and 163 event-free men, and for the [epsilon]2+ group there were five events and 95 event-free men.

Smoking increases the risk in the [epsilon]3[epsilon]3 group by 68%, but by over 200% in the [epsilon]4+ group.
Apo E Genotype Effects on Plasma Lipids

• Apo E3 has “normal” lipid metabolism - no genotype impact

• Apo E2 versus Apo E4 - opposing effects on plasma lipids
  o Apo E2 associated with slow conversion of IDL to LDL
    ✓ Decreases plasma cholesterol and increases triglycerides
  o Apo E4 limits HDL-binding - inhibits normal cholesterol clearance process (reverse cholesterol transport or RCT)
    ✓ Increases total cholesterol, LDL, and TG and decreases HDL

Therapeutic Implications of Apo E

- Interactions between Apo E gene polymorphism, abnormal lipid profiles, and diet and drug therapy have been documented

- Therapy targeting the lipid abnormalities resulting from the phenotypic expression of certain Apo E genotypes in response to environmental “stress” factors can mediate their impact on CVD

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Apo E2 Response</th>
<th>Apo E3 Response</th>
<th>Apo E4 Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/2</td>
<td>2/2</td>
<td>3/3</td>
<td>3/4</td>
</tr>
<tr>
<td>2/3</td>
<td>2/3</td>
<td>3/3</td>
<td>3/4</td>
</tr>
<tr>
<td>3/3</td>
<td>3/3</td>
<td>Highest Risk (↑42%)</td>
<td></td>
</tr>
<tr>
<td>3/4</td>
<td>3/4</td>
<td>Highest Risk (↑42%)</td>
<td></td>
</tr>
<tr>
<td>4/4</td>
<td>4/4</td>
<td>Highest Risk (↑42%)</td>
<td></td>
</tr>
</tbody>
</table>

- **Genotype**
  - 2/2
  - 2/3
  - 3/3
  - 3/4
  - 3/4
  - 4/4

- **Population Frequency**
  - 1%
  - 10%
  - 62%
  - 2%
  - 20%
  - 5%

- **CVD Risk**
  - Intermediate
  - Normal
  - Highest Risk (↑42%)
## Apo E Genotype Response
### Treatment Summary

<table>
<thead>
<tr>
<th>Apo E Genotype</th>
<th>Treatment</th>
<th>Surrogate Markers</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo E2</td>
<td>Statin</td>
<td>↓ LDL</td>
<td>Beneficial</td>
</tr>
<tr>
<td></td>
<td>Statin</td>
<td>↓ LDL / ↑ HDL</td>
<td>Beneficial</td>
</tr>
<tr>
<td></td>
<td>Moderate Alcohol</td>
<td>↓ LDL / ↑ HDL</td>
<td>Beneficial</td>
</tr>
<tr>
<td></td>
<td>Low Fat Diet</td>
<td>↑ Small Dense LDL / limited ↓ LDL</td>
<td>Not Recommended</td>
</tr>
<tr>
<td>Apo E4</td>
<td>Statin</td>
<td>Limited ↓ LDL</td>
<td>Limited</td>
</tr>
<tr>
<td></td>
<td>Statin</td>
<td>Limited ↓ LDL</td>
<td>Limited</td>
</tr>
<tr>
<td></td>
<td>Moderate Alcohol</td>
<td>↑ LDL / ↓ HDL</td>
<td>Not Recommended</td>
</tr>
<tr>
<td></td>
<td>Low Fat Diet</td>
<td>↓ LDL / ↓ TG / ↓ small dense LDL</td>
<td>Beneficial</td>
</tr>
</tbody>
</table>

↑ Increases
↓ decreases
Therapeutic Implications of Apo E

• When managed with treatment algorithms based on the routine CVD analytes supported by consensus guidelines (without Apo E genotype), a significant percentage of patients will be:
  o sub-optimally treated
  o managed in a limited way with a “one diet, standard drug therapy regimen fits all” approach
Apo E Genotype and CVD Management

Heterogeneity of gene-environment interaction

Heterogeneity of therapeutic response to “accepted” treatments

Establish Apo E genotyping as an important adjunct to an aggressive, targeted, and effective cardiovascular disease management program

.....allowing personalization of:

- Pharmaceutical Recommendation
- Diet Recommendation
- Alcohol Recommendation
SNP Panels for Risk Prediction – Pitfalls

• Several companies are marketing SNP panels to the general public, charging hundreds to thousands of € / $

• The premise for these panels is that they will let patients know if they are at higher risk for particular diseases

• None of these panels have yet been shown to add value to traditional risk factor algorithms, and they should not be recommended to patients at this time

• The panels do not include rare mutations that cause disease
Strategies in CVD prevention: 1. lifestyle change & 2. medical (drug) intervention.....
Drug Response Tests

- Responders
- Genetic Test

Genetic variations affect the way individuals respond to drug treatment.

- Certain variations contribute to Adverse Drug Reaction (ADR)
  - Can at times be fatal

- ADR incidence is a major cause of hospital admissions
  - Median hospitalization due to ADR is ~5 days
  - Cost INR 6197/- (USD 150) per patient.

- Testing for the variations that are linked to adverse drug reaction prior to treatment will help doctors adjust the dose of a drug or opt for an alternate treatment.

- Identify responders
- Treat with drug

- Identify at-risk for ADR patients
- Alter drug dosage
- Treat with different drug
The Challenge

Two different “phenotypes” – i.e., survival rates

Individuals with personal profile A

Individuals with personal profile B
Residual Cardiovascular Risk in Major Statin Trials

<table>
<thead>
<tr>
<th></th>
<th>Secondary</th>
<th>High Risk</th>
<th>Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>4S</td>
<td>LIPID</td>
<td>CARE</td>
</tr>
<tr>
<td>N</td>
<td>4444</td>
<td>9014</td>
<td>4159</td>
</tr>
<tr>
<td>ΔLDL</td>
<td>-36%</td>
<td>-25%</td>
<td>-28%</td>
</tr>
</tbody>
</table>

Pharmacogenomics — Ready for Prime Time
Susan B. Shurin, M.D., and Elizabeth G. Nabel, M.D.

Pharmacogenomics — Drug Disposition, Drug Targets, and Side Effects
William E. Evans, Pharm.D., and Howard L. McLeod, Pharm.D.

Pharmacogenomics of statin response
Lara M. Mangravite and Ronald M. Krauss

Purpose of review
Although statin therapy has been shown to reduce

Introduction
Statins are prescribed for primary and secondary
cardiovascular disease (CVD) and act primarily in plasma LDL-cholesterol — a
VD [1–3]. The LDL-cholesterol

Statin pharmacogenomics: what have we learned, and what
remains unanswered?
Kouji Kajinami, Mizuho Okabayashi, Ryoko Sato, Eliana Polisecki and
Ernst J. Schaefer
KIF6 Trp719Arg and CHD

- Up to 50% increased risk of CHD in carriers of a common KIF6 variant
  - KIF6 719Arg is the risk variant
  - ~60% of Caucasians carry one or two risk variant of the gene
  - KIF6 encodes a kinesin, a molecular motor protein

- Statin therapy can provide substantial and significant benefit in carriers
Previous Genetic Studies of KIF6 719Arg
Risk of CHD in 5 Prospective Studies (>49,000 participants)

Carriers of the *KIF6 719Arg* variant (60% of Caucasians) are at greater risk (approx. 50%) of coronary events compared with noncarriers.

WHS: Shiffman et al. *J Am Coll Cardiol* 2008; 51:444
CHD Event Reduction by Pravastatin

According to KIF6 719Arg Carrier Status

- Carriers of the 719Arg risk allele received significant benefit from pravastatin therapy.
- In WOSCOPS, risk reduction was significantly greater in carriers than in noncarriers (P_interaction = 0.003).

<table>
<thead>
<tr>
<th></th>
<th>CARE</th>
<th>WOSCOPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-carriers</td>
<td>3.5%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Carriers</td>
<td>0%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

*P = 0.005  P < 0.0001
Number Needed to Treat

*NNT for KIF6 in CARE and WOSCOPS*

- For prevention of coronary events with pravastatin in CARE:
  - NNT KIF6 carriers: 20
  - NNT noncarriers: 72

- In WOSCOPS, the projected NNT was:
  - 18 for KIF6 carriers
  - >100 for noncarriers
Among patients with prior vascular disease, carriers of KIF6 719Arg risk allele received substantial and significant reduction of coronary events, whereas noncarriers did not – 34% relative risk reduction in carriers.

Among patients without prior vascular disease, no significant event reduction.
In PROSPER, substantial and significant difference in reduction of events between carriers and noncarriers was observed despite similar reduction of LDL-C levels.

A similar observation was made in PROVE IT–TIMI 22.

An indication of the pleiotropic effect of statins among 719Arg carriers.
Statin Intensity and CHD Event Reduction

According to KIF6 719Arg Carrier Status

KIF6 Carriers

Noncarriers

Death or major CV events

Months of follow-up

KIF6 Carriers

Pravastatin

Atorvastatin

p≤0.001

Pravastatin

Atorvastatin

P=1.0

NNT for atorvastatin vs pravastatin:

– 10 for KIF6 carriers

– 125 for noncarriers

KIF6 carriers received greater benefit from 80mg atorvastatin, compared with 40mg pravastatin, than did noncarriers.
LDL-C Lowering by Statin Therapy

Similar Reduction in KIF6 Carriers and Noncarriers

- Similar reduction of LDL-C levels in carriers and noncarriers
- However, event reduction was significantly greater in carriers
KIF6 719Arg Variant and CHD

Summary

- Associated with risk of CHD in 5 prospective studies
  - ARIC, WHS, CHS, CARE, and WOSCOPS
- 60% of Caucasians carry the risk allele, carriers are at up to 50% higher risk
- Risk estimate unchanged after adjustment for traditional risk factors
- Carriers received significant event reduction from statin therapy
  - Standard-dose pravastatin vs placebo
  - High-dose atorvastatin vs standard-dose pravastatin

![Graph showing relative risk reduction for WOSCOPS, CARE, and PROVE-IT studies]

- WOSCOPS: 50 carriers, 9 noncarriers
- CARE: 37 carriers, 20 noncarriers
- PROVE-IT: 41 carriers, 6 noncarriers

*p<0.005 for each*
1. Pharmacogenetics of CETP, PCSK9 (statins)...

2. AT and BK receptors polymorphisms (ACE-i, ARBs)...

3. Variable response to warfarin – CYP2C9 and VKORC1 variants...

4. Resistance to clopidogrel pharmacogenetics...
Health care (reforms?) into the future

- Integrated health care
  - Primary
  - Secondary
  - Tertiary

- e-Health
  - Integrated data management
  - Electronic medical records
  - Population level planning and resource allocation

- Personalized Medicine

“back to the future”?
Personal genomics in medicine – The future

• **Cost of sequencing genomes dropping - $1000 genome**
  - Analysis and understanding will remain expensive

• **Every child born or patient will likely have his or her genome sequenced fully**

• **This genome record should allow physicians to make treatment decisions based on patients genotypes:**
  - will allow individuals to make appropriate lifestyle choices (food, exercise... etc)
  - will allow to use appropriate drugs

• **Genome data will allow rapid drug development**
Personalized Medication in the Future

In the future (? years), doctors will be able to select the best drug to treat your disease and the appropriate dose based on knowledge of your specific genetic makeup!
Patient requires Treatment

Examination by the Physician

Genomic testing

Traditional investigations

EXPERT SYSTEM

Decision making by Physician, assisted by an Expert System (interactive interpretation)

Prescribes individualized drug treatment
The Promise of Pharmacogenomics

1. "Pharmacogenomics will radically change the manner in which we develop drugs."

2. "Soon, we will be able to get the right drug into the right patient.

3. "Applying pharmacogenomics to drug development will cut cycle times to 1.5 - 2 years."

4. "Pharmacogenomics will be able to bring removed drugs back on the market, by predicting who is susceptible to adverse events."

How close we really are?
Conclusions

We look to a future in which medicine will be predictive, preventive, preemptive and *(again)* personalized...

This will immediately lead to *(very) significant changes of some common and also very fashionable current concepts (e.g. evidence-based medicine, guidelines with “one-size fits for all” recommendations, etc.)*...
Two Ethically Important Distinctions

You know these, but it is important not to forget them…

Research/therapy and subject/patient

- research is aimed at developing new knowledge that may or may not benefit individual human subjects (it may even harm them); benefits usually enjoyed, if at all, by future patients

- therapy is aimed at benefiting an individual patient

- research supporting the development of personalized medicine, in particular, tends to blur the distinction between subject and patient
Disclaimer

Personalized medicine in the framework of narrower, “contemporary” sense (using genetics studies and treatment guidance) remains a research concept – it is not yet ready for clinical practice...

...but....is it really so?