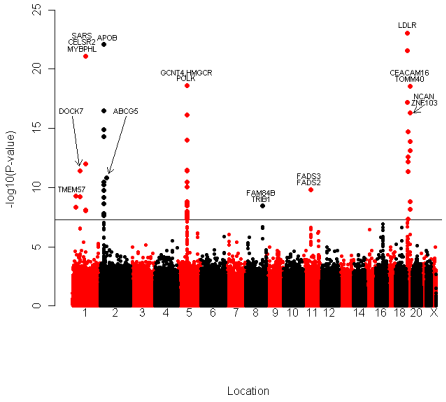
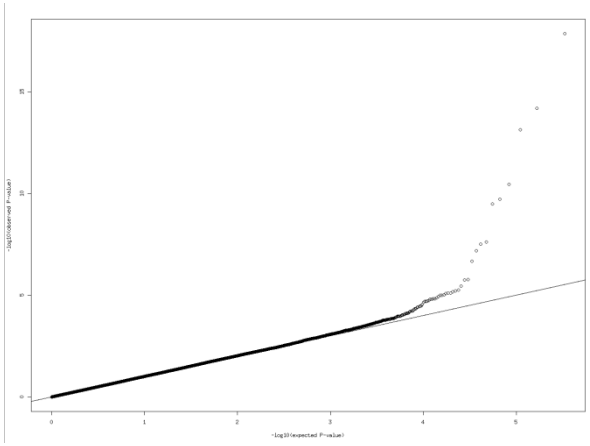
NATIONAL INSTITUTE FOR HEALTH AND WELFARE

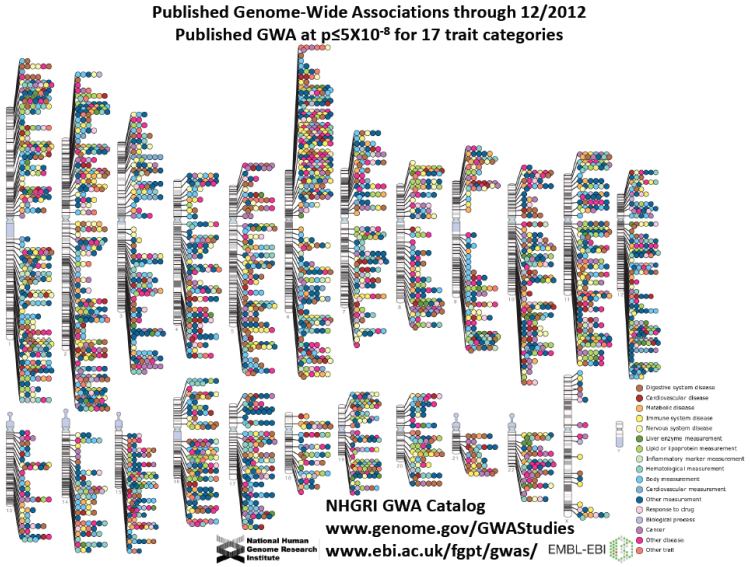
From retrospective patient cohorts into prospective patient cohorts to clinical validation

Markus Perola, MD, PhD

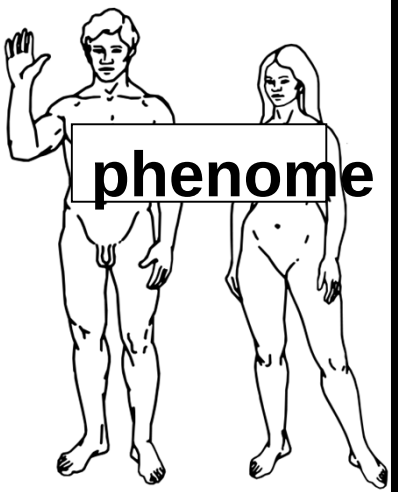
This is so exiting right now!





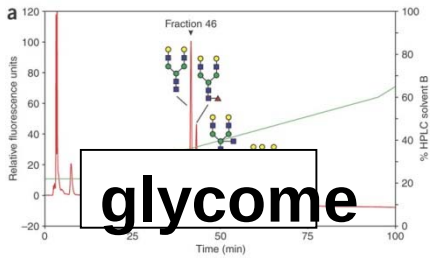


Omics approach

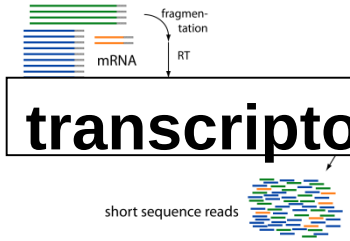


phenome

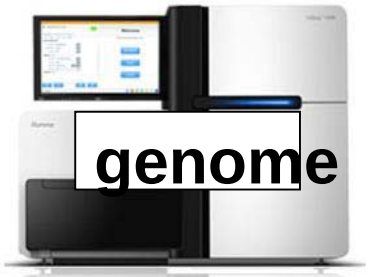
biobanks



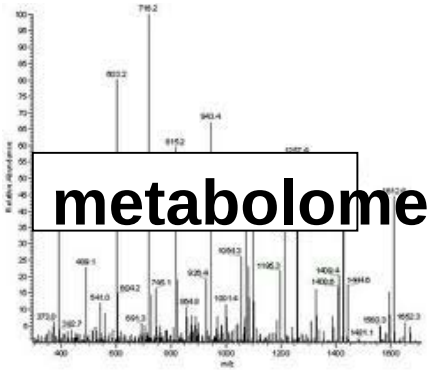
glycome



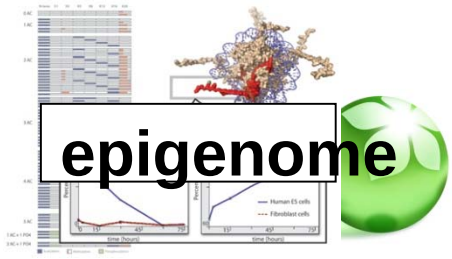
transcriptome



genome



metabolome



epigenome

Epidemiologic study designs

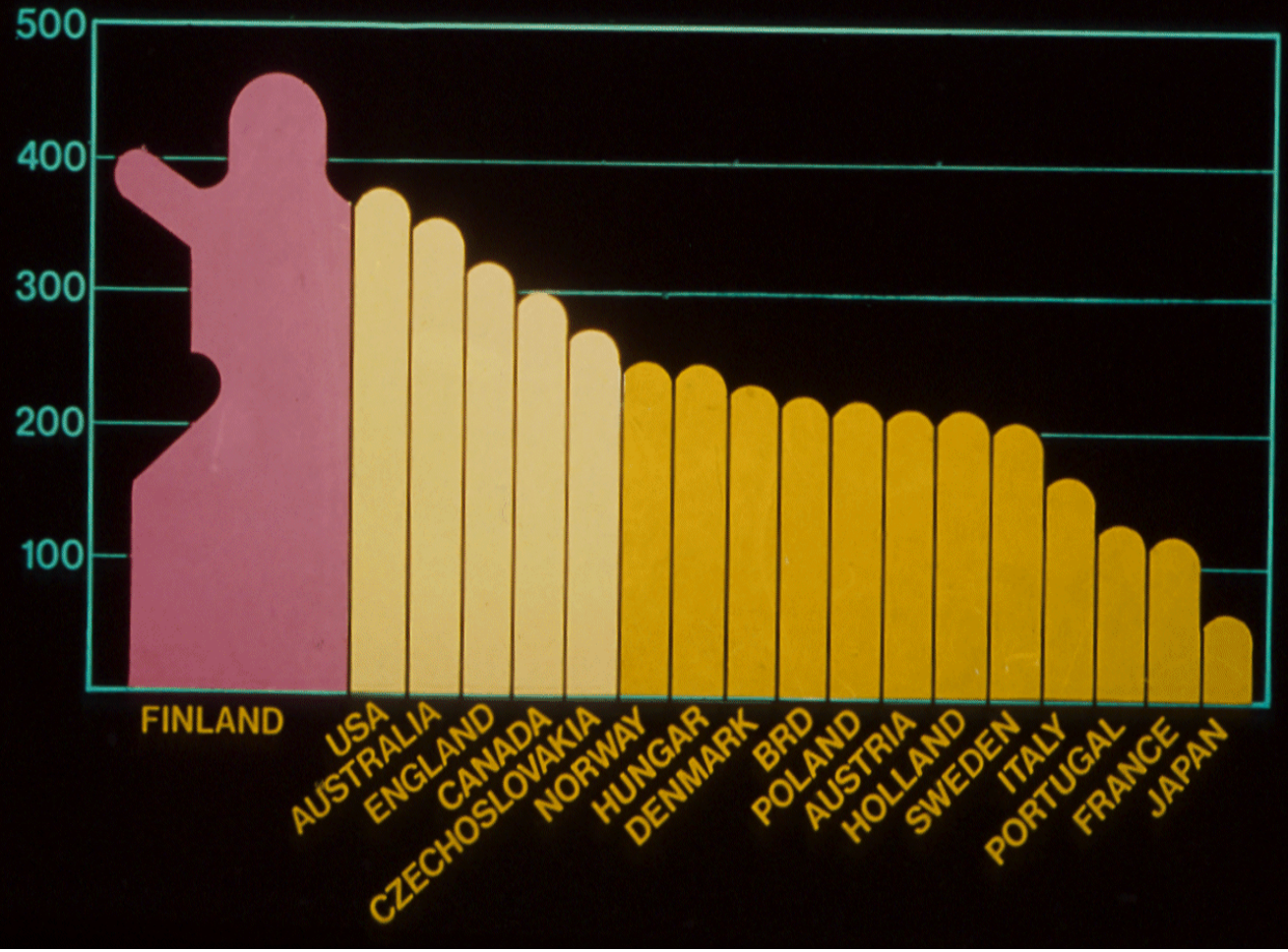
- What type of study to chose depends on:
- what is the research question/ objective
- Time available for study
- Resources available for the study
- Common/rare disease or production problem
- Type of outcome of interest
- Quality of data from various sources
- Often there are multiple approaches which will all work
- Choosing an established design gives you a huge head start in design, analysis and eliminating biases

An example from history – can we repeat this?

NATIO

MORTALITY RATES OF ISCHAEMIC HEART DISEASE AMONG MEN IN SELECTED COUNTRIES

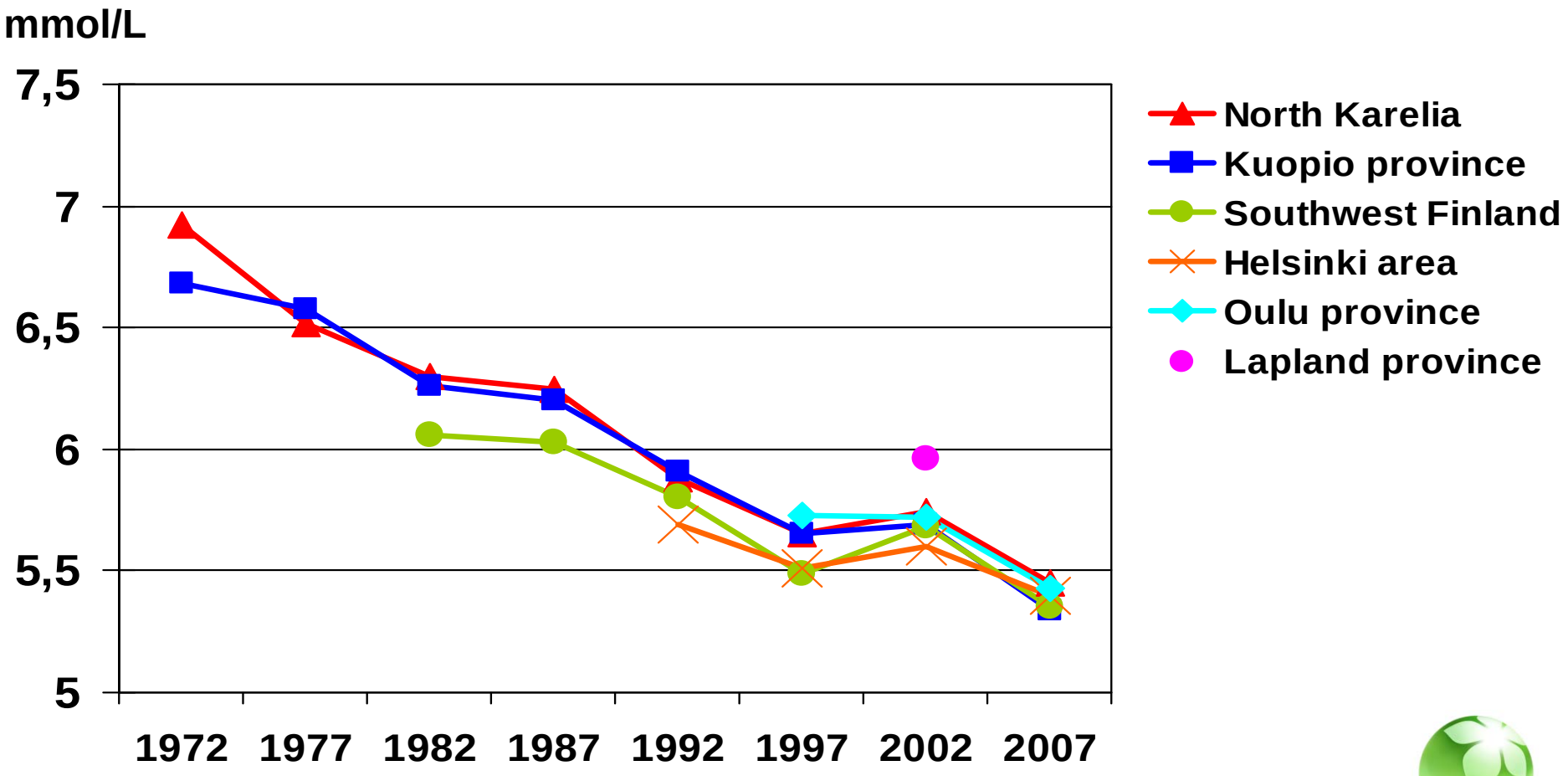
CHD mortality
per 100.000 men in 1973



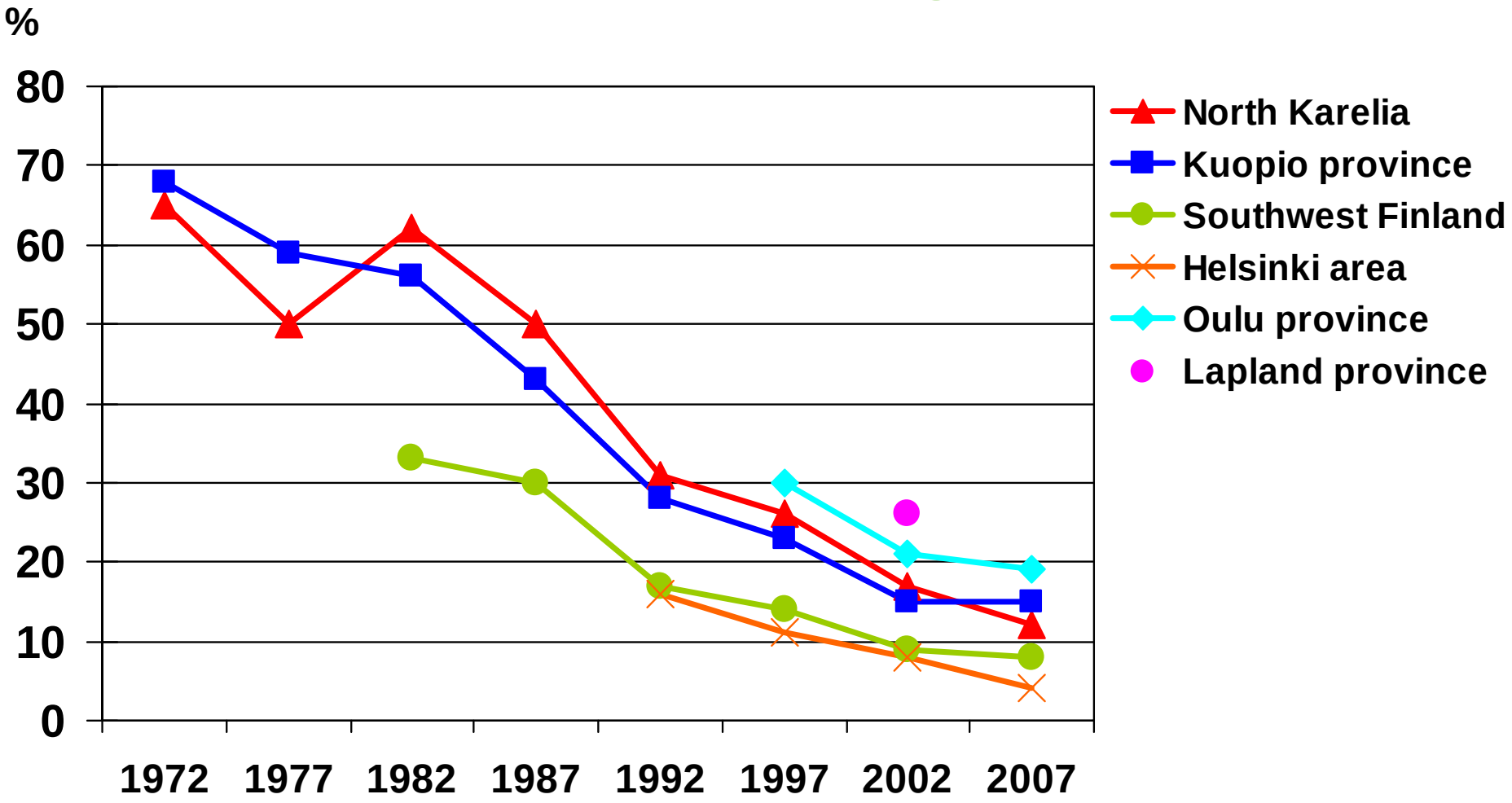
Two main questions in 1970's

- Can risk factors and behaviors be changed on population level ?
- If risk factors will reduce what will happen to the mortality?
- Survey + intervention in North Karelia

Results:
Serum cholesterol in men aged 30-59 years

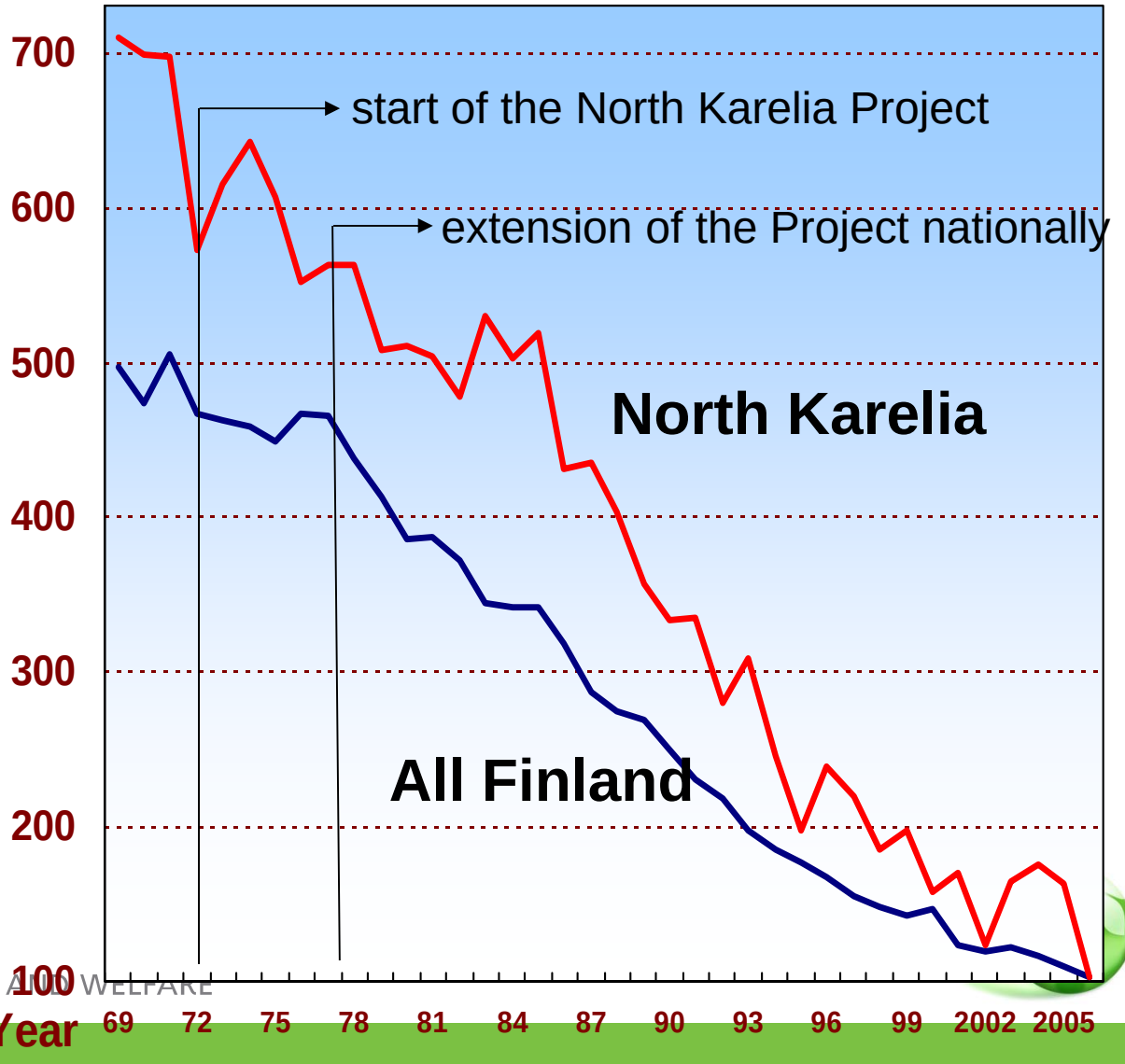


Results:
Use of butter for cooking



Mortality per 100 000 population

Age-standadized to European population



Why did diet (etc.) change?

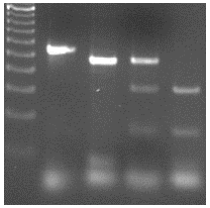
- North Karelia Project (community based CVD prevention program)
- Consensus in the medical community
- Political consensus
- Recommendations
- Cholesterol screening
- Fat debates
- Educational programs
- Business got interested

WHY SUCCESS IN NORTH KARELIA

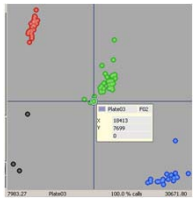
- Appropriate epidemiological and behavioural framework
- Restricted, well defined targets
- Good monitoring of immediate targets (Behaviours, process)
- Flexible intervention
- Emphasis in changing environment and social norms
- Working closely with the community
- Positive feedback, work with media
- International collaboration, support from WHO
- Close interaction with national health policy, integration with National Public Health Institute
- Long term, dedicated leadership
- **How to succeed in a similar way in 2020->?**

Revolution in Genomics → The march of technology…

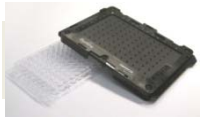
single variant
(10^0 SNPs; 10^3 genotypes)



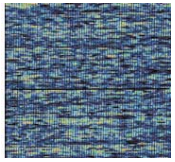
detailed study of individual genes
(10^2 SNPs; 10^{5+} genotypes)



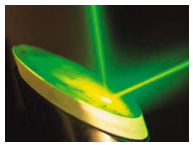
regional studies
(10^4 SNPs; 10^8 genotypes)



genome-wide association
(10^6 SNPs; 10^{10} genotypes)



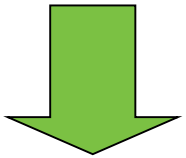
Credits to Mark McCarthy, Oxford



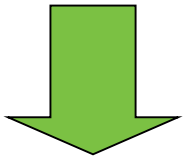
complete resequencing
(10^8 SNPs / 10^{12} genotypes)

Genome-wide Study Principles

Case-control pairs (or population cohorts)

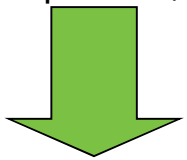


Type for ~500k SNPs



Obtain information about strength of association genome wide

(within limits of sample size, allele frequency, LD etc)



Follow-up what looks interesting

nature genetics

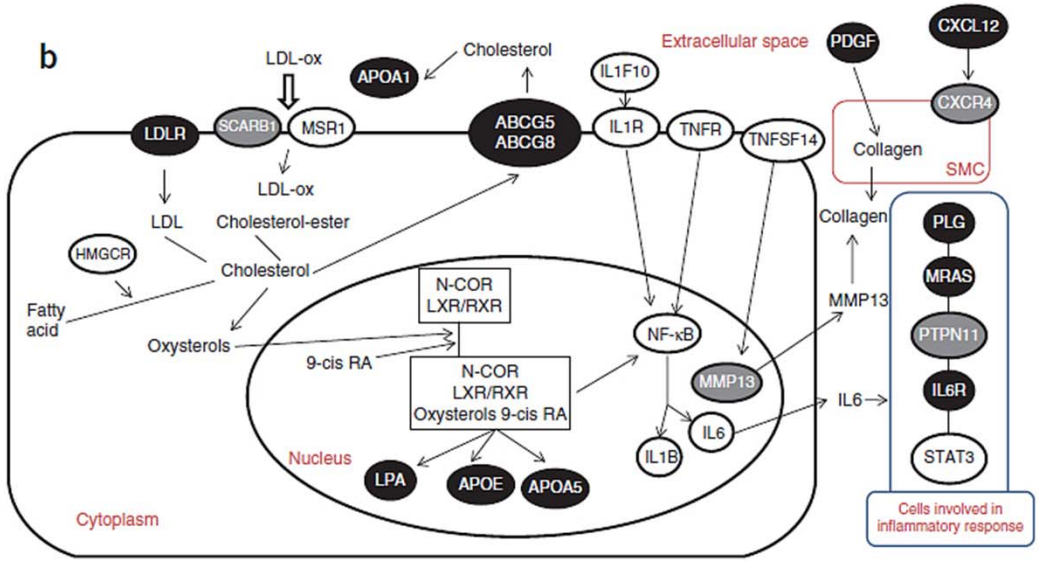
Large-scale association analysis identifies new risk loci for coronary artery disease

The CARDIoGRAMplusC4D Consortium[1]

Coronary artery disease (CAD) is the commonest cause of death. Here, we report an association analysis in 63,746 CAD cases and 130,681 controls identifying 15 loci reaching genome-wide significance, taking the number of susceptibility loci for CAD to 46, and a further 104 independent variants ($r^2 < 0.2$) strongly associated with CAD at a 5% false discovery rate (FDR). Together, these variants explain approximately 10.6% of CAD heritability. Of the 46 genome-wide significant lead SNPs, 12 show a significant association with a lipid trait, and 5 show a significant association with blood pressure, but none is significantly associated with diabetes. Network analysis with 233 candidate genes (loci at 10% FDR) generated 5 interaction networks comprising 85% of these putative genes involved in CAD. The four most significant pathways mapping to these networks are linked to lipid metabolism and inflammation, underscoring the causal role of these activities in the genetic etiology of CAD. Our study provides insights into the genetic basis of CAD and identifies key biological pathways.

CARDIoGRAMplusC4D Consortium

- 60.000 Coronary heart disease ja 130.000 controls
- 46 new CVD-loci



A Genetic Risk Score Is Associated With Incident Cardiovascular Disease and Coronary Artery Calcium

The Framingham Heart Study

George Thanassoulis, MD; Gina M. Peloso, MA; Michael J. Pencina, PhD; Udo Hoffmann, MD; Caroline S. Fox, MD, MS; L. Adrienne Cupples, PhD; Daniel Levy, MD; Ralph B. D'Agostino, S

OPEN ACCESS Freely available online

PLoS one

Genetic Markers Enhance Coronary Risk Prediction in Men: The MORGAM Prospective Cohorts

Maria F. Hughes[1]*, Olli Saarela[2], Jan Stritzke[3], Frank Kee[1], Kaisa Silander[2,4], Norman Klopp[5], Jukka Kontto[2], Juha Karvanen[2], Christina Willenborg[3], Veikko Salomaa[2], Jarmo Virtamo[2], Phillippe Amouyel[6], Dominique Arveiler[7], Jean Ferrières[8], Per-Gunner Wiklund[9], Jens Baumert[5], Barbara Thorand[5], Patrick Diemert[3], David-Alexandre Trégouët[10], Christian Hengstenberg[11], Annette Peters[5], Alun Evans[1], Wolfgang Koenig[12], Jeanette Erdmann[3], Nilesh J. Samani[13], Kari Kuulasmaa[2☯], Heribert Schunkert[3☯]

Multilocus Genetic Risk Scores for Coronary Heart Disease Prediction

Andrea Ganna, Patrik K.E. Magnusson, Nancy L. Pedersen, Ulf de Faire, Marie Reilly, Johan Ärnlöv, Johan Sundström, Anders Hamsten, Erik Ingelsson

Genetic Risk Prediction and a 2-Stage Risk Screening Strategy for Coronary Heart Disease

Emmi Tikkanen, Aki S. Havulinna, Aarno Palotie, Veikko Salomaa, Samuli Ripatti

Objective—Genome-wide association studies have identified several genetic variants associated with coronary heart disease (CHD). The aim of this study was to evaluate the genetic risk discrimination and reclassification and apply the results for a 2-stage population risk screening strategy for CHD.

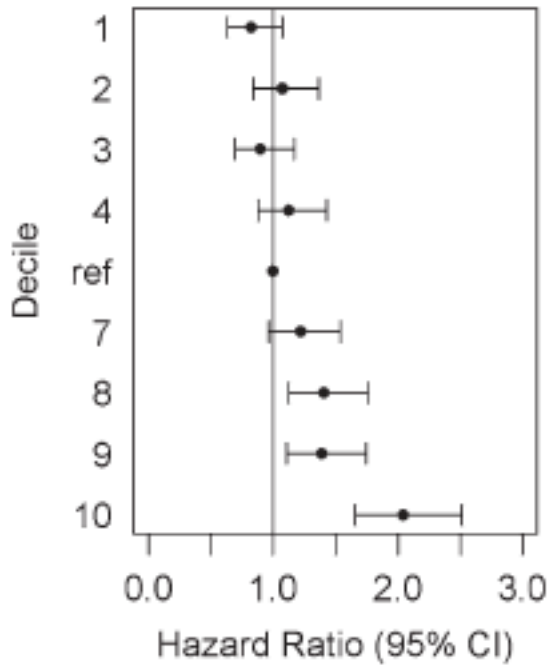
Approach and Results—We genotyped 28 genetic variants in 24 124 participants in 4 Finnish population-based, prospective cohorts (recruitment years 1992–2002). We constructed a multilocus genetic risk score and evaluated its association with incident cardiovascular disease events. During the median follow-up time of 12 years (interquartile range 8.75–15.25 years), we observed 1093 CHD, 1552 cardiovascular disease, and 731 acute coronary syndrome events. Adding genetic information to conventional risk factors and family history improved risk discrimination of CHD (C-index 0.856 versus 0.851; P=0.0002) and other end points (cardiovascular disease: C-index 0.840 versus 0.837, P=0.0004; acute coronary syndrome: C-index 0.859 versus 0.855, P=0.001). In a standard population of 100 000 individuals, additional genetic screening of subjects at intermediate risk for CHD would reclassify 2144 subjects (12%) into high-risk category. Statin allocation for these subjects is estimated to prevent 135 CHD cases over 14 years. Similar results were obtained by external validation, where the effects were estimated from a training data set and applied for a test data set.

Conclusions—Genetic risk score improves risk prediction of CHD and helps to identify individuals at high risk for the first CHD event. Genetic screening for individuals at intermediate cardiovascular risk could help to prevent future cases through better targeting of statins. (***Arterioscler Thromb Vasc Biol*. 2013;33:2261-2266.**)

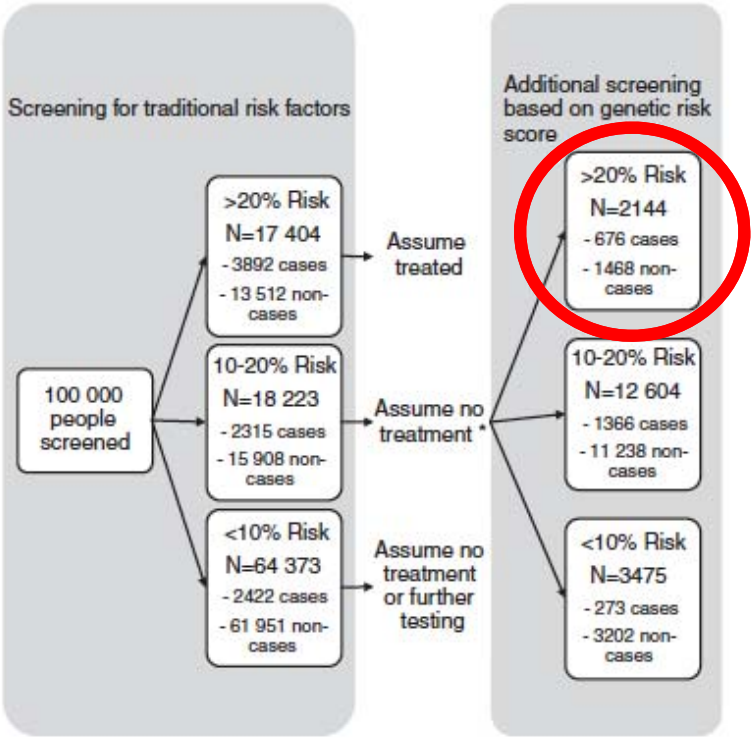
Key Words: cardiovascular genomics ■ genetic association ■ genetic epidemiology ■ risk factor ■ risk prediction

- 28 loci, 24.000 participants
  - The most significants fro Cardiogram
- 12 years' follow-up
- 1093 CHD, 1552 CVD, 731 ACS

The risk of coronary event



Prevented deaths?



By treating 2144 persons who have >20% risk when the genetic information is known 135 deaths would be prevented in 10 years!

Diagnostic value?

- Most identified omics risk factors are of no diagnostic relevance
  - Explain only a small proportion of the variance
  - Highly prevalent in the population
  - Low penetrance a rule
- Family history still surpasses most variants as most informative diagnostic method
- Albeit large (100Ks of GWAS) meta-analyses, only a small proportion of the phenotypic variation is explained
  - Even for traits with high heritability
- How to change this?

Challenges in personalised medicine

- Biocomputing
- Training
  - Interpretation
  - Professionals
- ELSI
- Clinical testing

Has genetics transformed medical practice?

- Already in practice:
  - High-impact variants with large effect and penetrance
    - More coming all the time, for example ACMG list
      - Genome ”durability” vs. knockout animals
        - » JAMA Jan 5
  - Sequecing helps in diagnostics
    - Rare diseases /inverse genetics
  - Pharmacogenetics
    - Underused?
  - Many working examples
    - Come to effect through normal clinical pathways

When will (gen)omic info transform medical practice?

- Sequencing price goes down (a lot) and the quality gets better
- Validated information about the applicability of the findings
- (Gen)omics-data has been interpreted and can be used by the health professional upfront when she sees the patient/customer
  - Needed:
    - Data investgated and interpreted
    - Decision supporting systems
    - Training

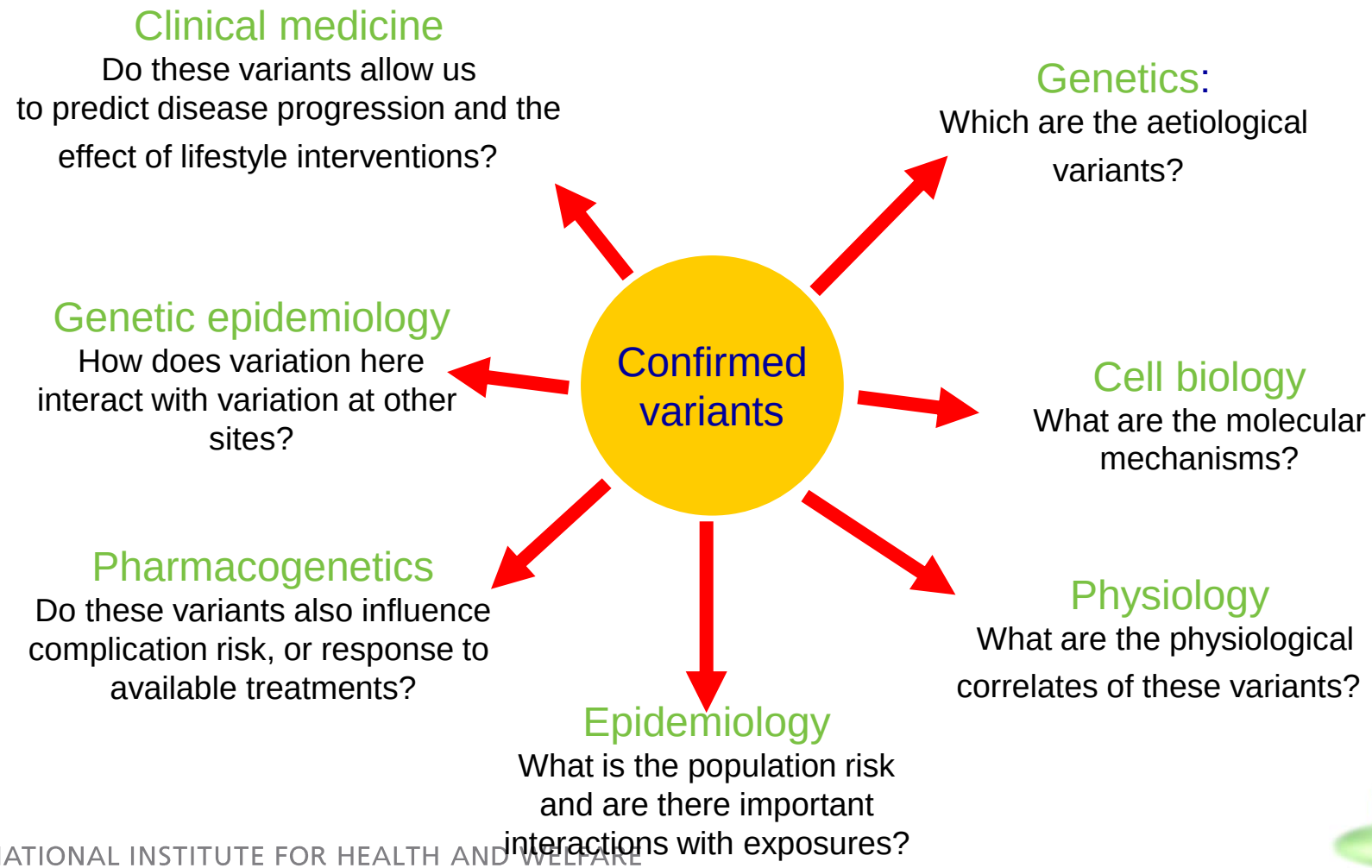
Well?

- Will Medicine be transformed?
  - Can we change risky behaviour?
    - Regression to the mean
  - Costs
    - Increased follow-ups, examinations
      - PSA
    - Increased medication
      - Primary prevention - hard
  - ”Surprises”, genetic technology
    - iPs
    - Crispr/Cas9

Yet to be covered...

- Epigenomics
- Structural variation
- Phenomics
- Non-autosomal genome (Sic!)
- Interactions
- …

Further studies needed



Thanks to Mark McCarthy

BIOLOGY

- This is basic science and whether clinically good comes out of it, remains to be seen, as for any basic science
  - All findings will need through clinical investigation, etc etc which is not cheap
- There will be expections
- New knowledge is good!!!


PHASE TWO: INTERPRETATION
SHERMAN ©HERMAN
I THINK I FOUND A CORNER PIECE.
3 BILLION PIECES
GENOME