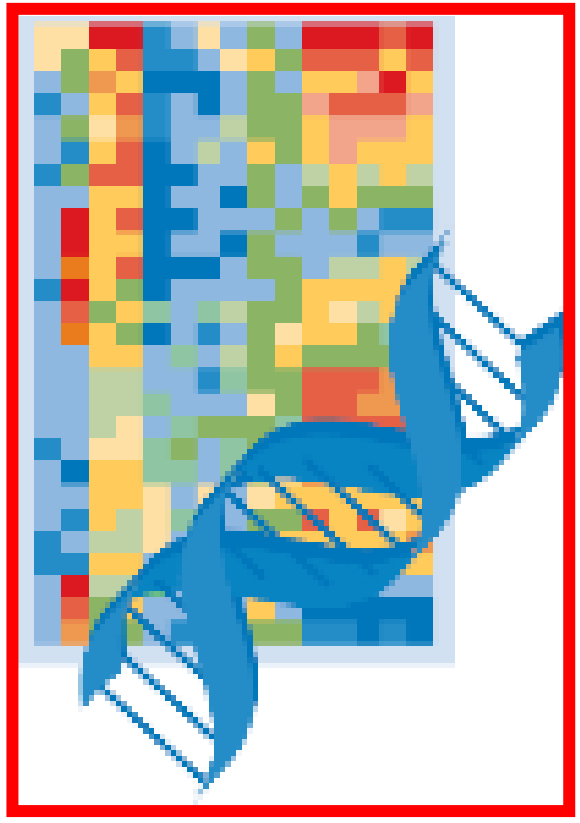
Polygenic risk scores are ready for application in routine cardiological practice – CONTRA



Heribert Schunkert

Deutsches Herzzentrum München • Technische Universität München

Polygenic risk scores are ready for application in routine cardiological practice – CONTRA

H. Schunkert
has received honoraria for consulting from AstraZeneca, MSD/Merck, Daiichi, Servier, Amgen and Takeda Pharma. He has further received honoraria for lectures and/or chairs from AstraZeneca, BayerVital, BRAHMS, Medtronic, Mitsubishi Pharma, Novartis, Sanofi and Servier

Heribert Schunkert

Deutsches Herzzentrum München • Technische Universität München

Integrating genetics in the assessment for coronary disease

pos. family history

mutations

polymorphisms

molecular basis

Common SNP versus rare FH mutation

LDLR SNP rs6511720; Effect: 6.99 mg / Allele; *P* = 4.28 x10^{-117}

Strong effect in the population

Strong effect on the individual

80.620.000 inhabitans x 0.001 allel frequency x 2 alleles x **150 mg** = **24 kg**

Genome-wide association study (GWAS)

Patients

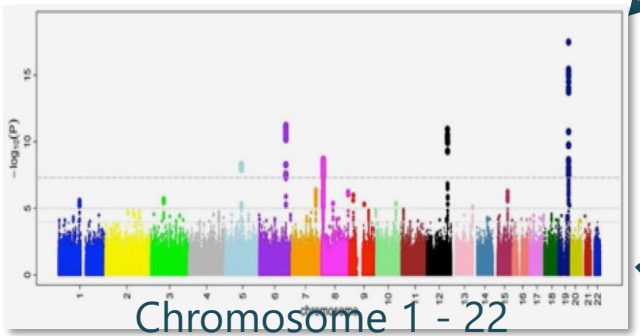
Controls

Genotyping
1 Million SNPs

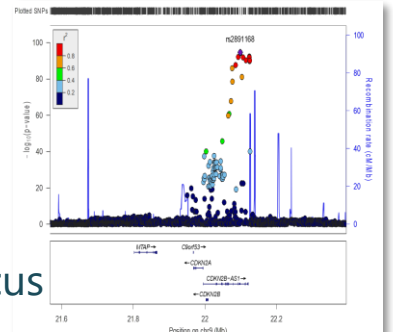
Imputation
>20 Million SNPs

Statistical comparison
for each SNP

P-Wert



Chromosome 1 - 22

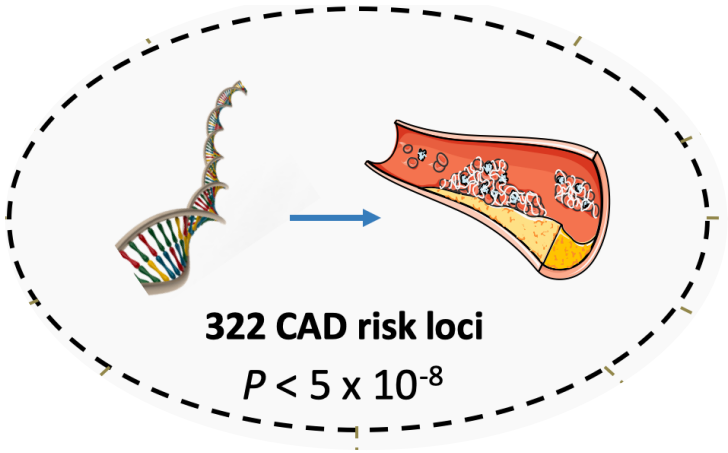


Risk-locus

322 CAD loci $P < 5 \times 10^{-8}$

Tcheandjieu C et al Nat Med 2022
Aragam K et al Nat Genet 2022

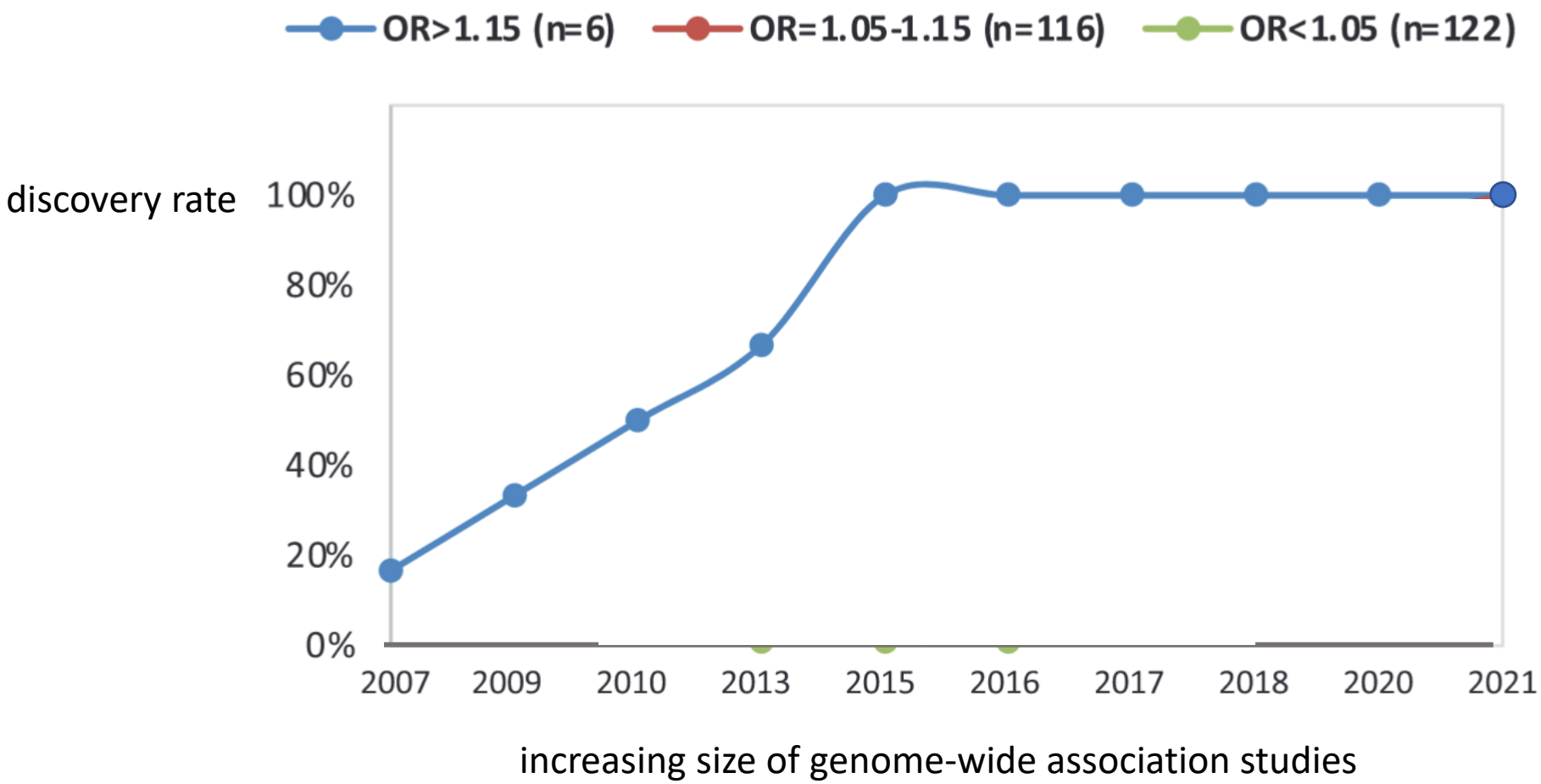
Chen & Schunkert J Intern Med. PMID: 34237186



Tcheandjieu C et al Nat Med 2022
Aragam K et al Nat Genet 2022

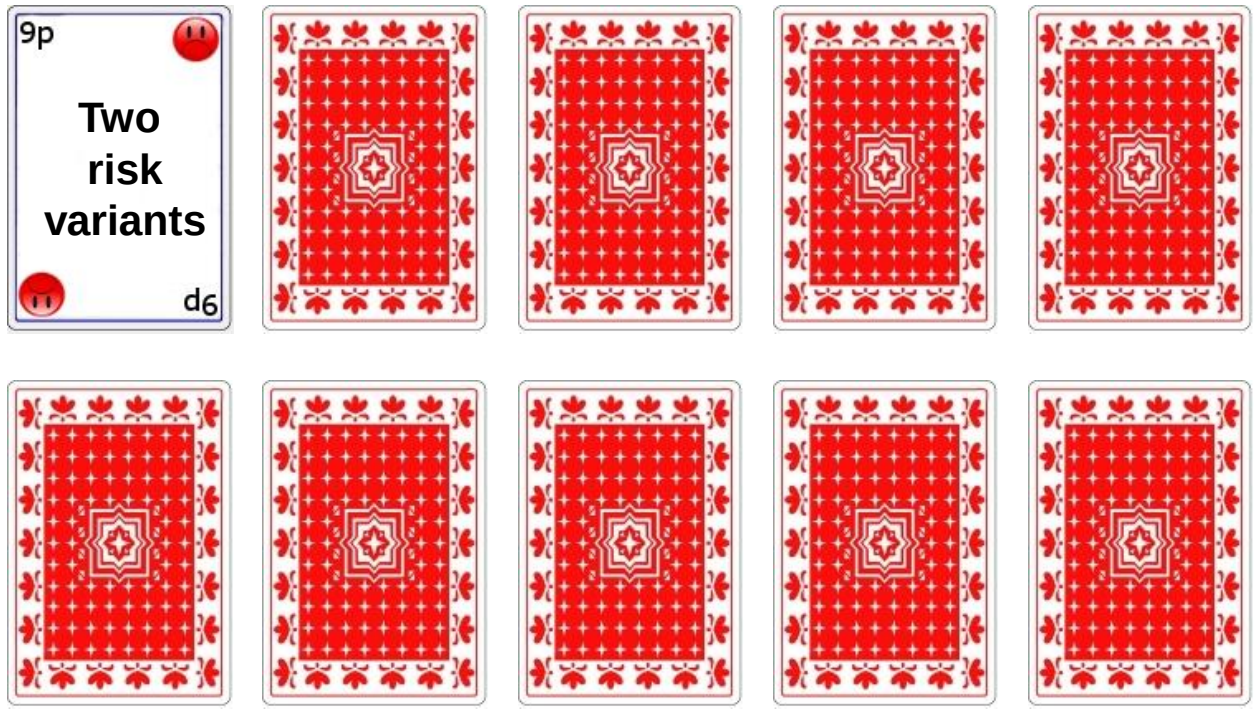
Chen & Schunkert J Intern Med. PMID: 34237186

All strong common risk alleles have been found by today

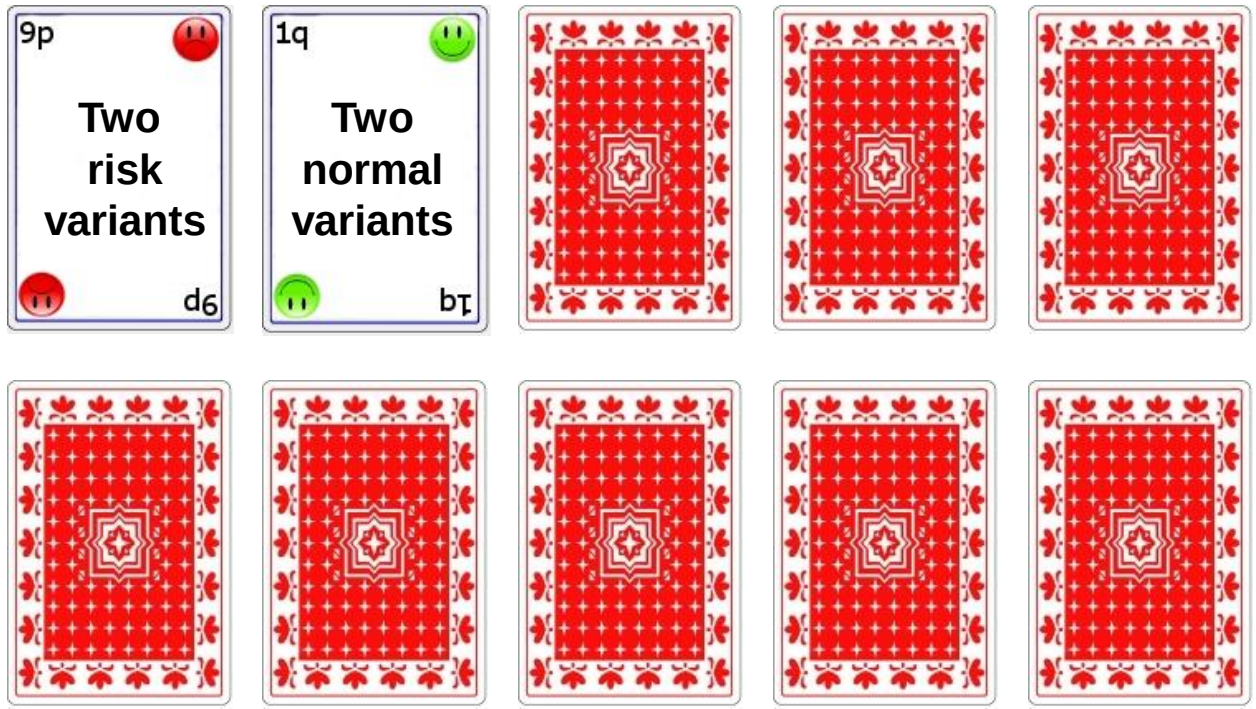


Z. Chen & H. Schunkert
J Intern Med. PMID: 34237186

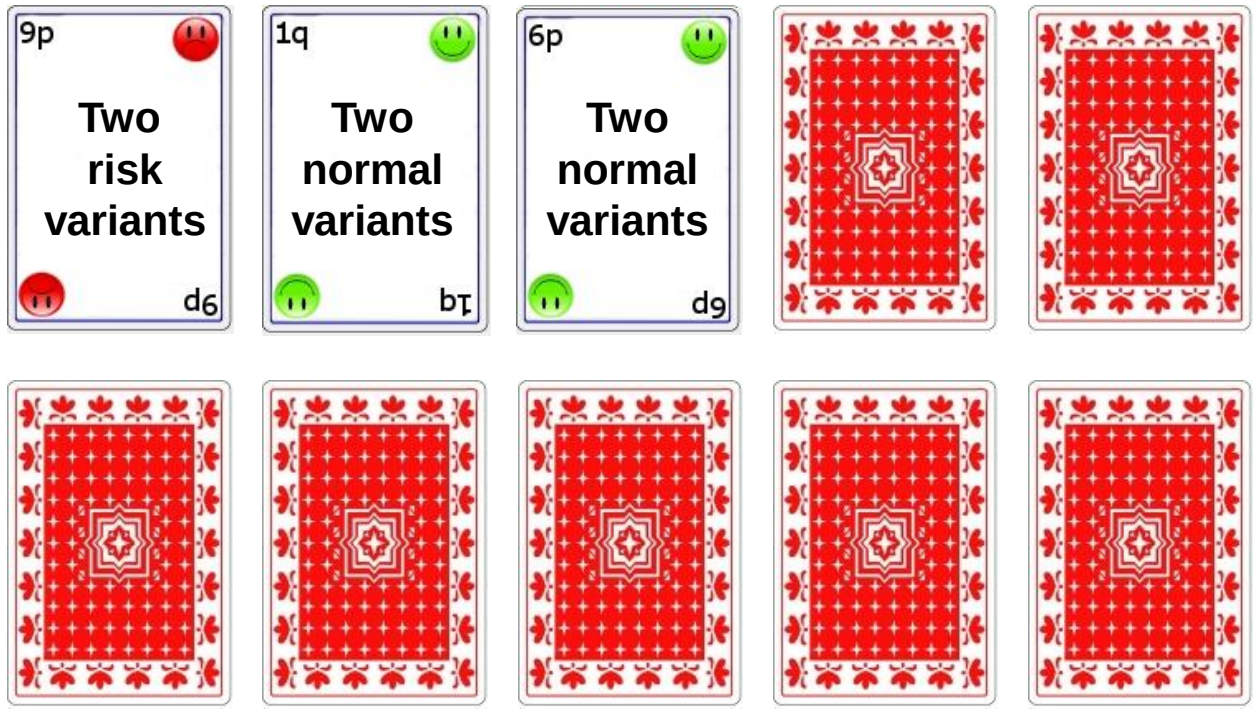
Computing individual probability



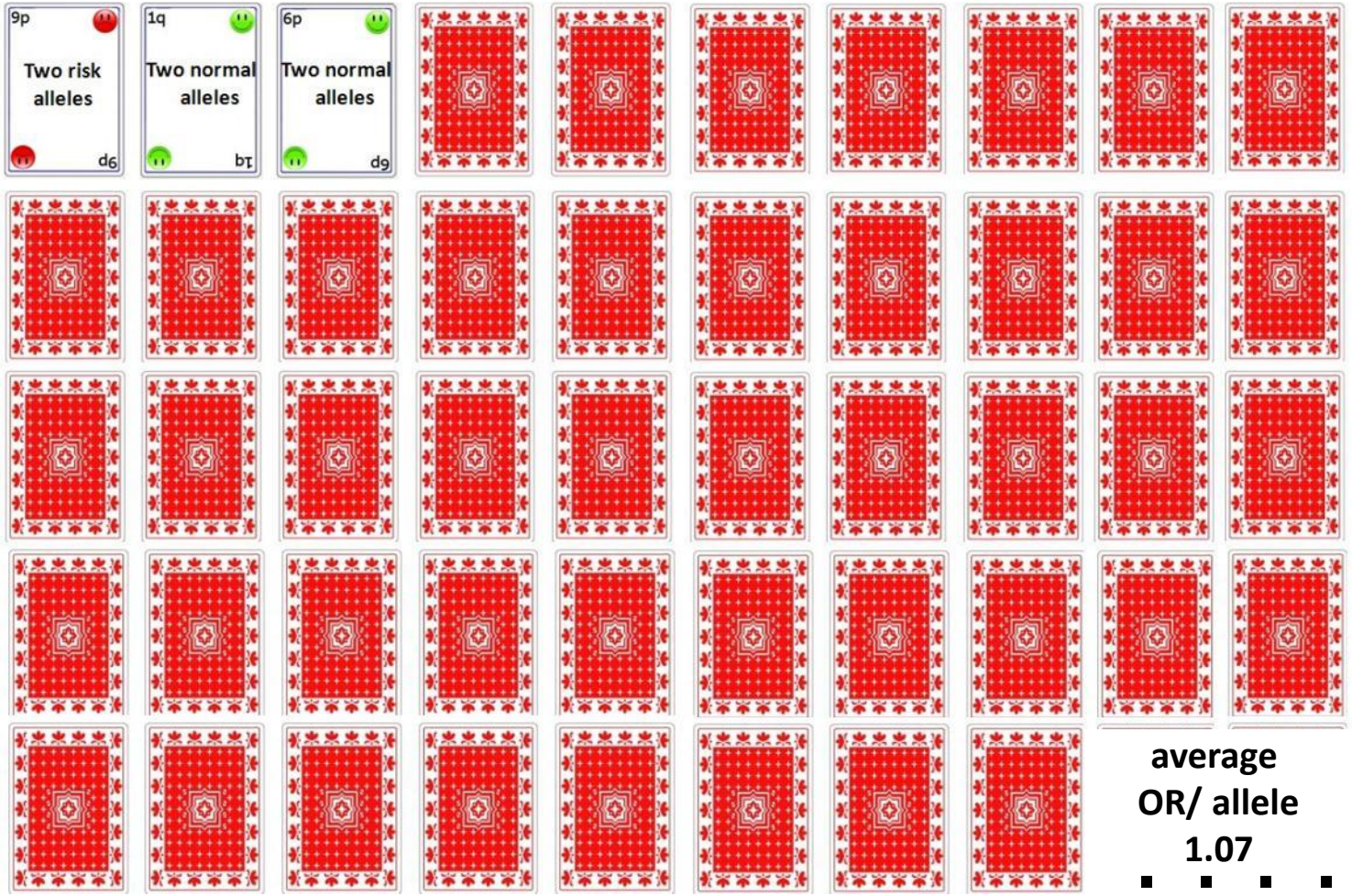
Computing individual probability



Computing individual probability

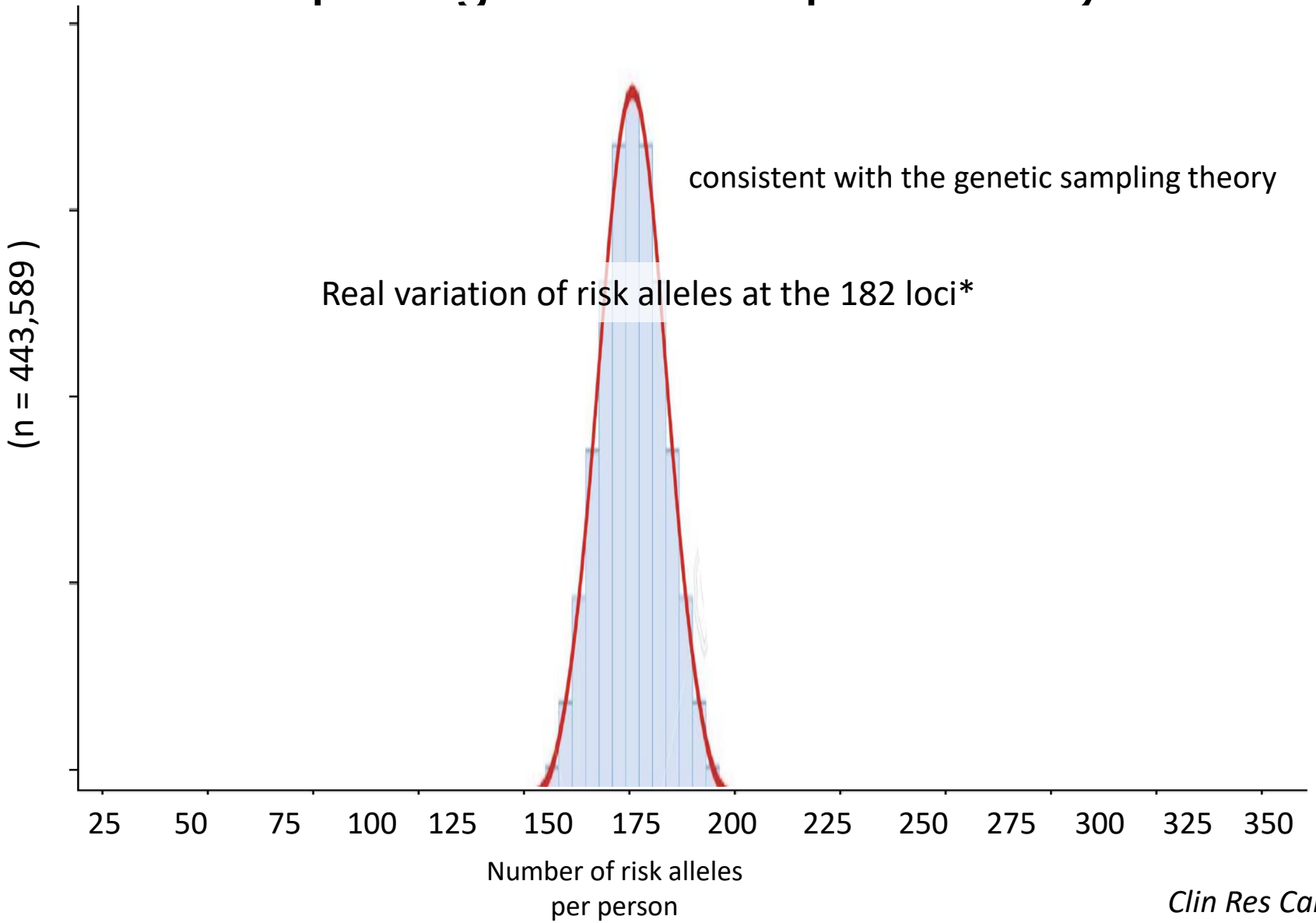


Computing individual probability



UK Biobank

Computing individual probability

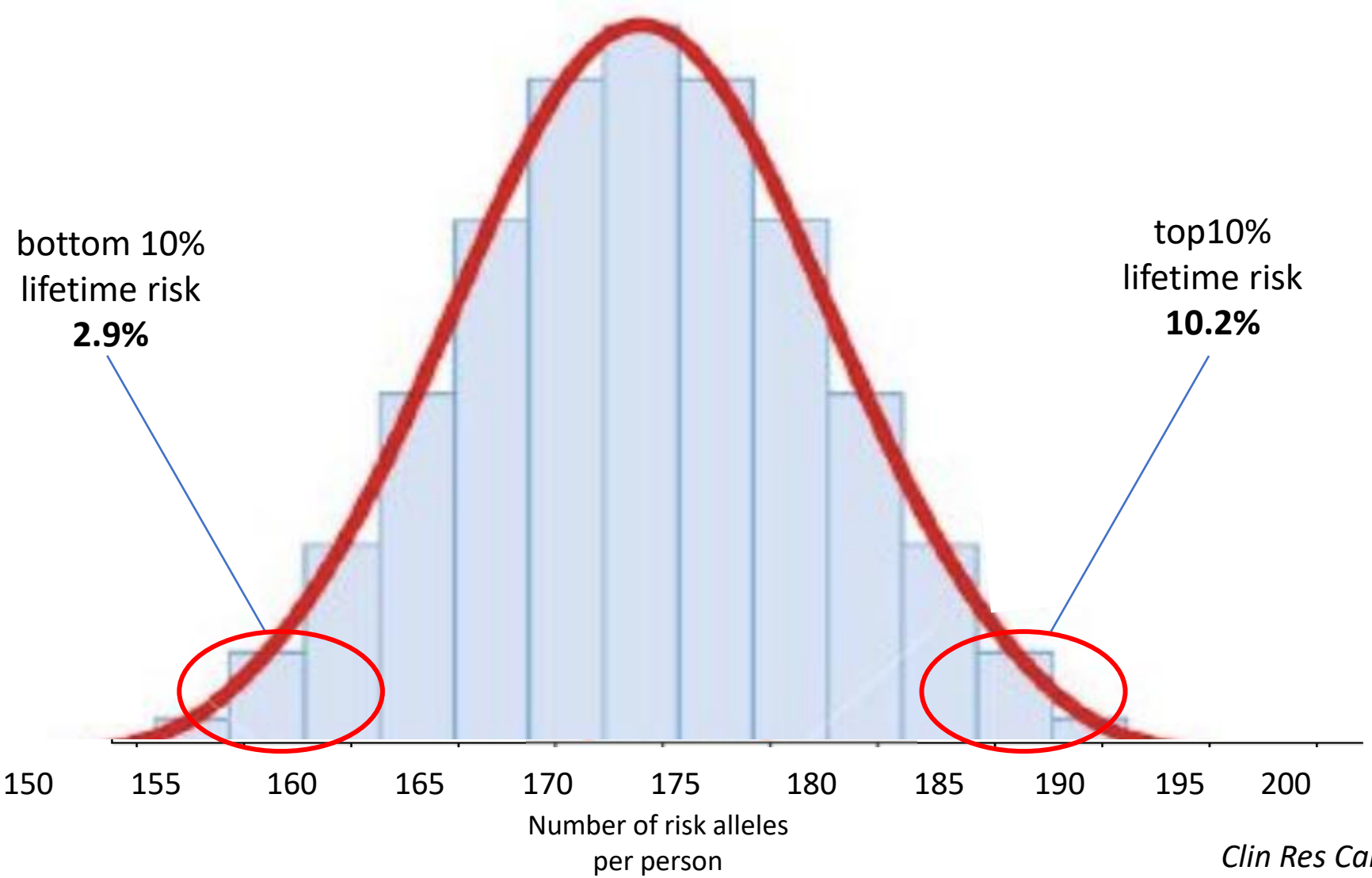


Clin Res Cardiol 2023;112:247-257

*FDR<5% prior to inclusion of UKBB in GWAS meta-analysis

UK Biobank

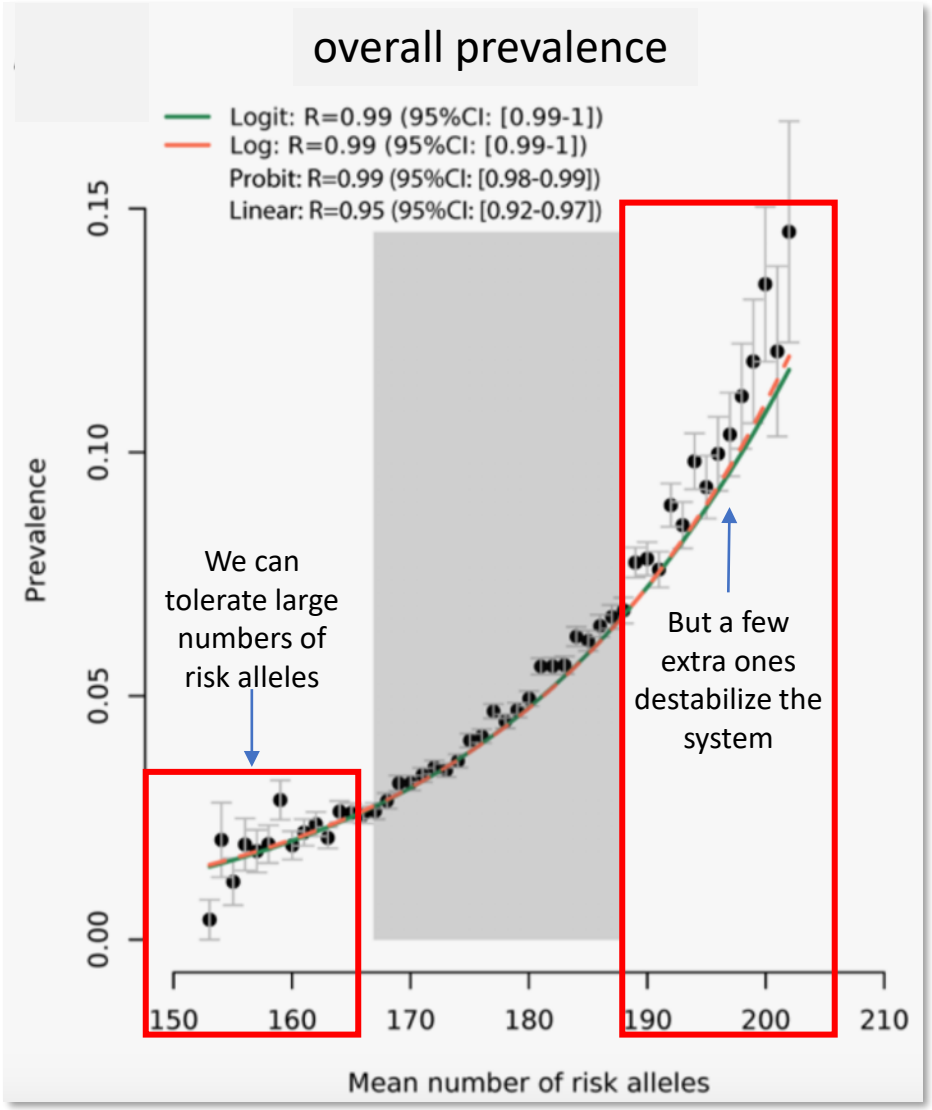
Computing individual probability



Clin Res Cardiol 2023;112:247-257

UK Biobank

Computing individual probability

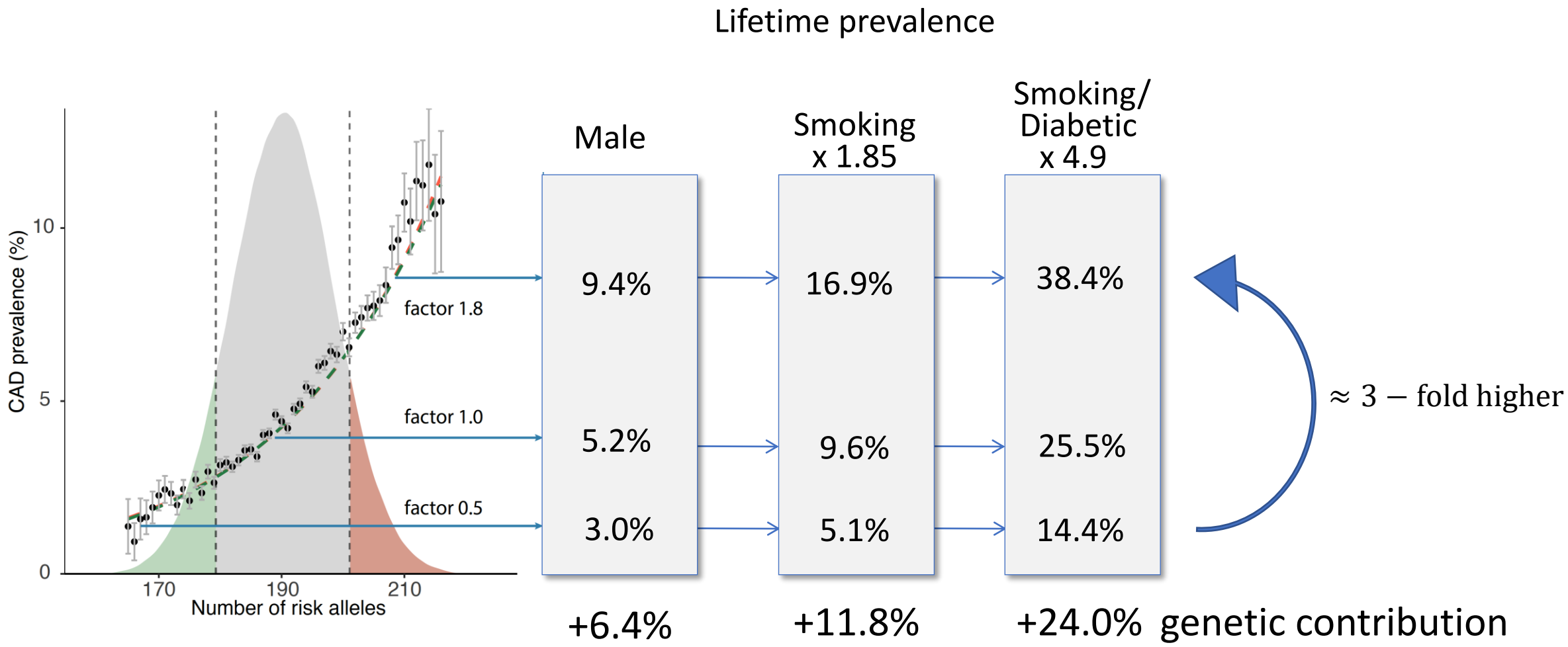


*FDR<5% prior to inclusion of UKBB in GWAS meta-analysis

Clin Res Cardiol 2023;112:247-257

UK Biobank (n=424.405)

Computing individual probability



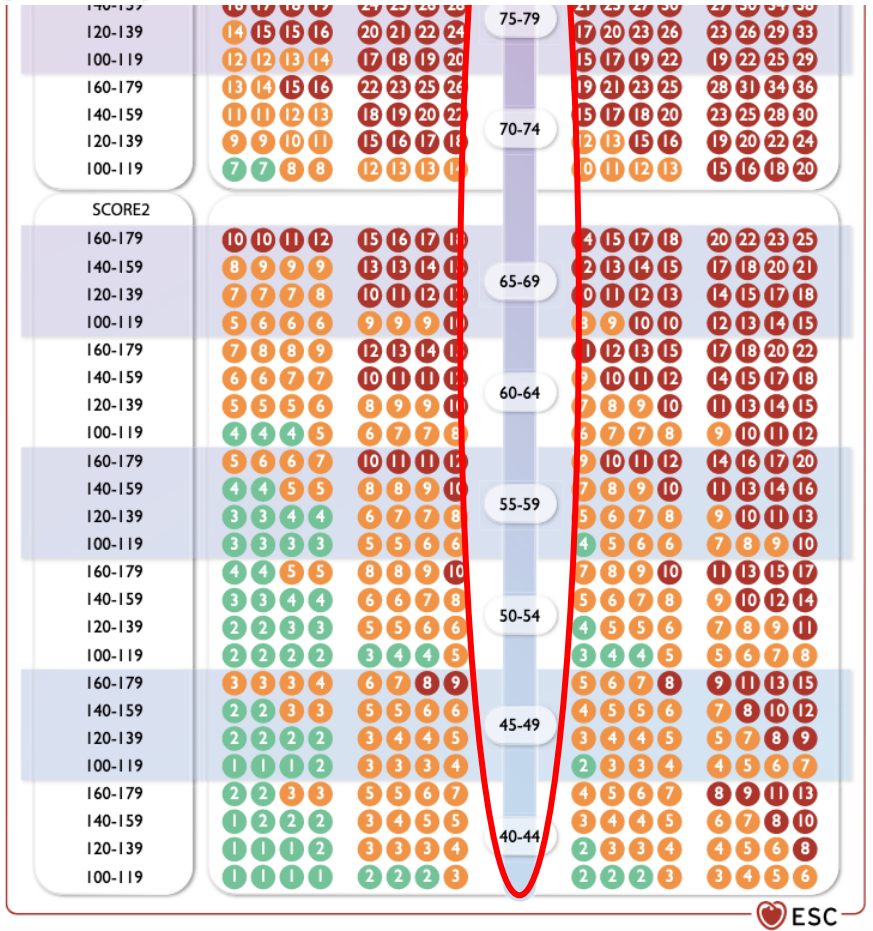
Seemingly a paradox:
Genetics have the strongest effect in people with the most non-genetic risk factors

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3227–3337
doi:10.1093/eurheartj/ehab484

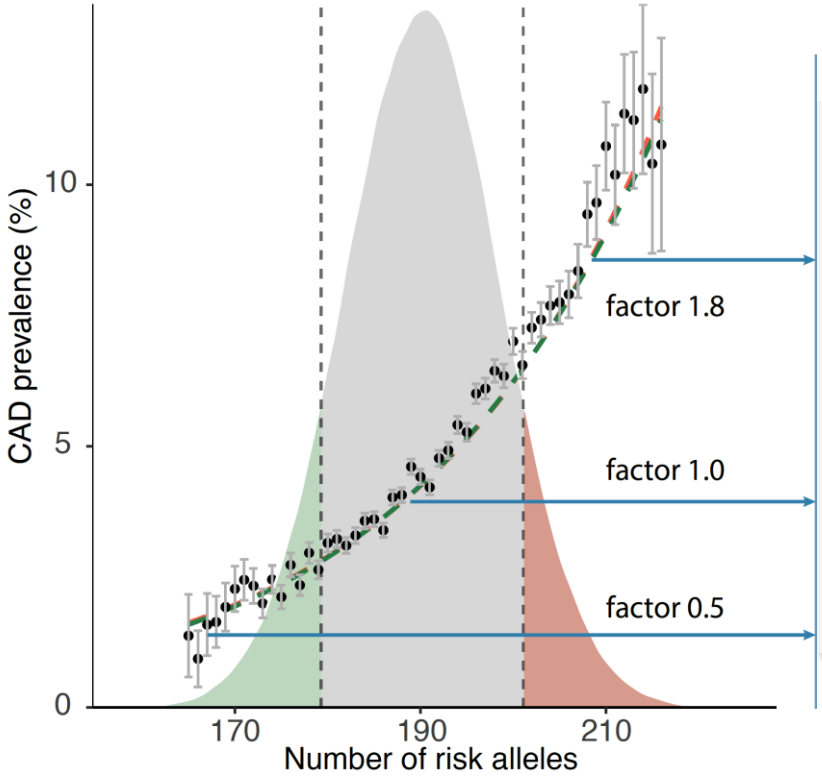
ESC GUIDELINES

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

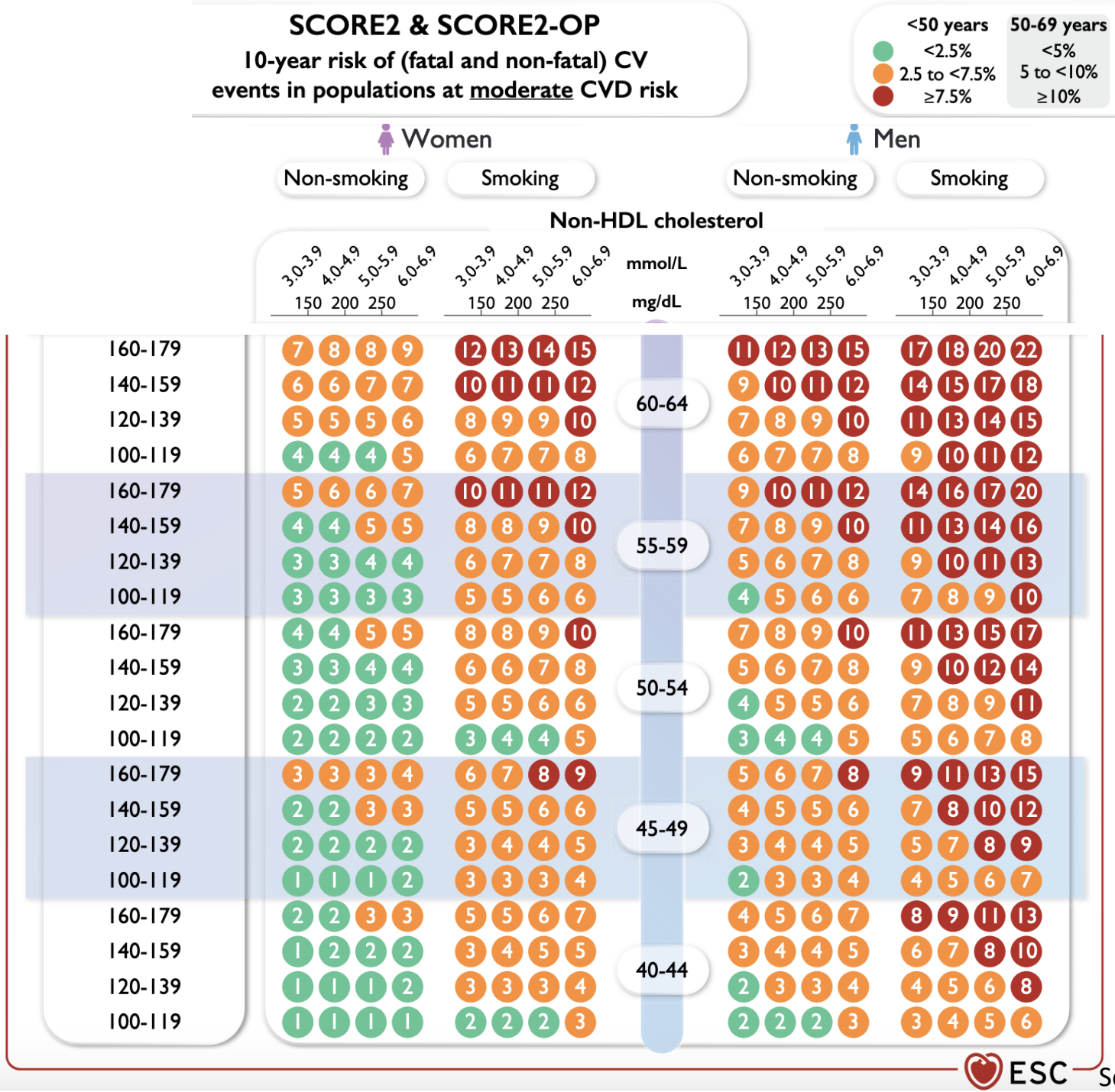
With the special contribution of the European Association of Preventive Cardiology (EAPC)



European Heart Journal
September 2021;42:3227–3337



Is it possible to use the position on the PRS distribution curve as a factor in conjunction with conventional risk factors to predict total risk?



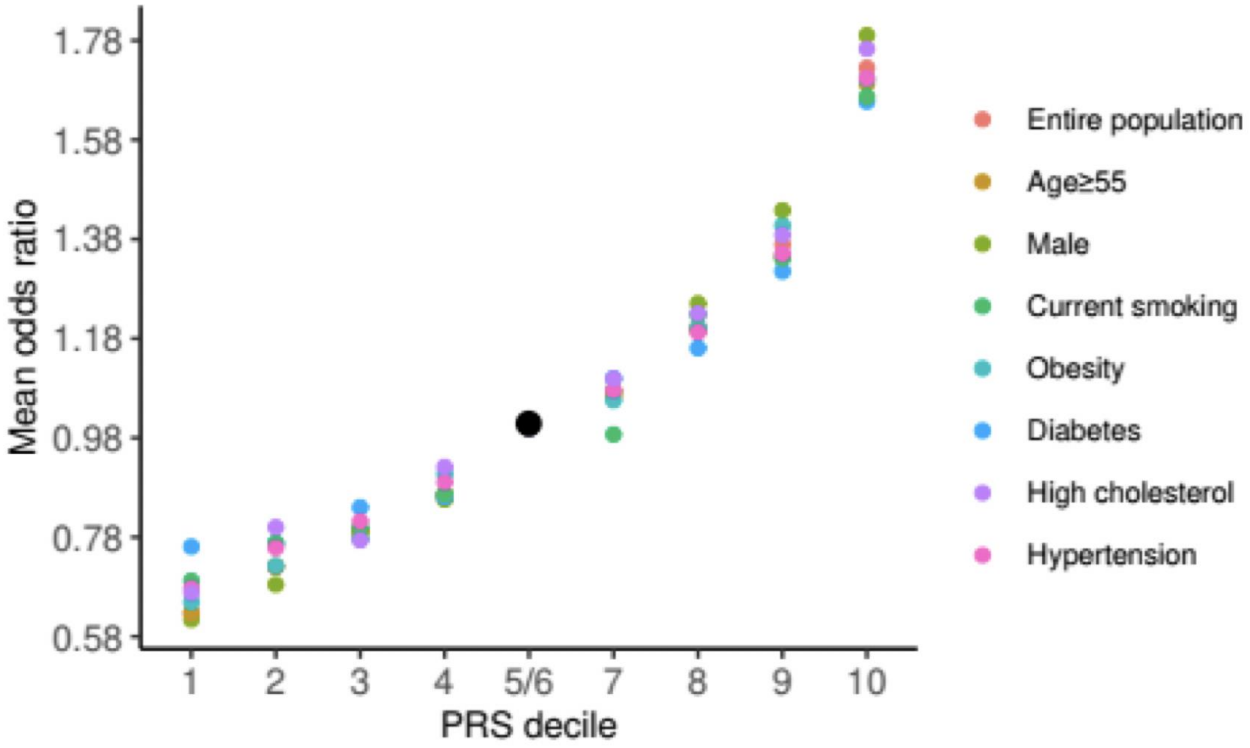
- **the individual**
- *** PRS-factor (0.6 – 2.2)**

European Heart Journal
September 2021;42:3227–3337

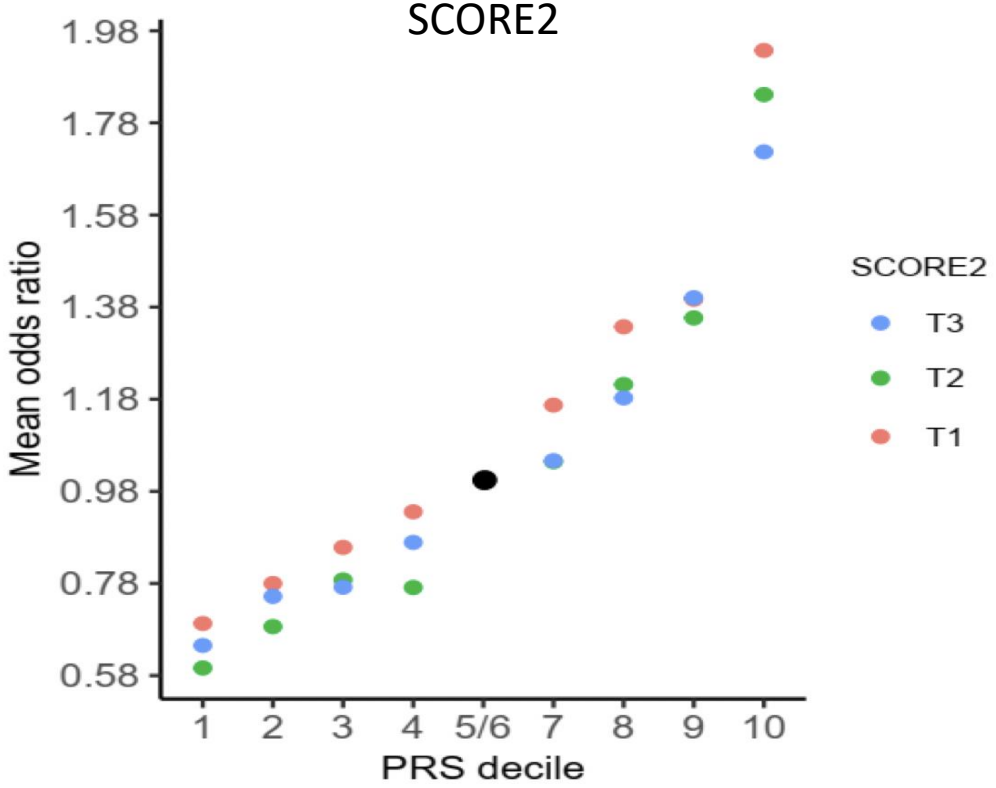
The relative effects at any position of the PRS on risk are fairly the same

UK Biobank (n=424.405)

rel. risk is independent from risk factors



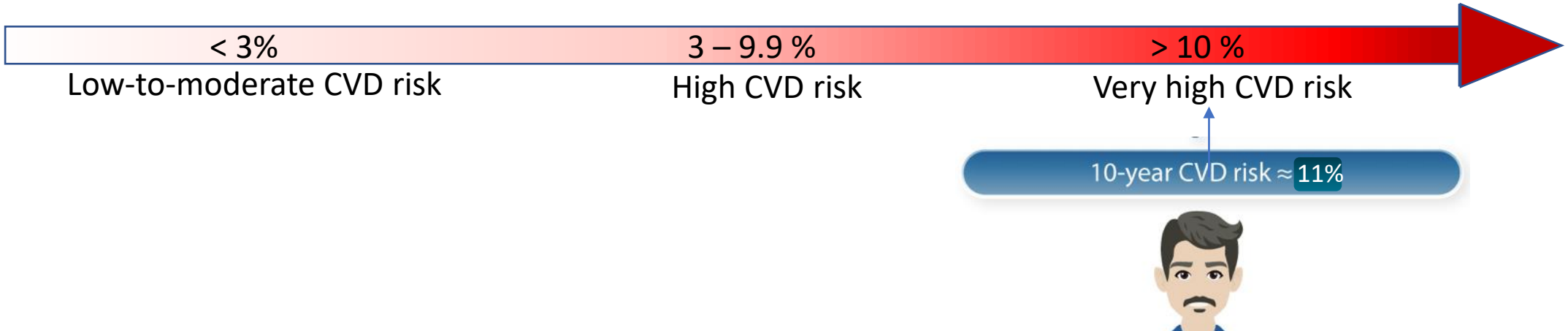
rel. risk is independent from tertiles of SCORE2



Ling Li and H. Schunkert et al, unpublished

Who has a benefit from genotyping?

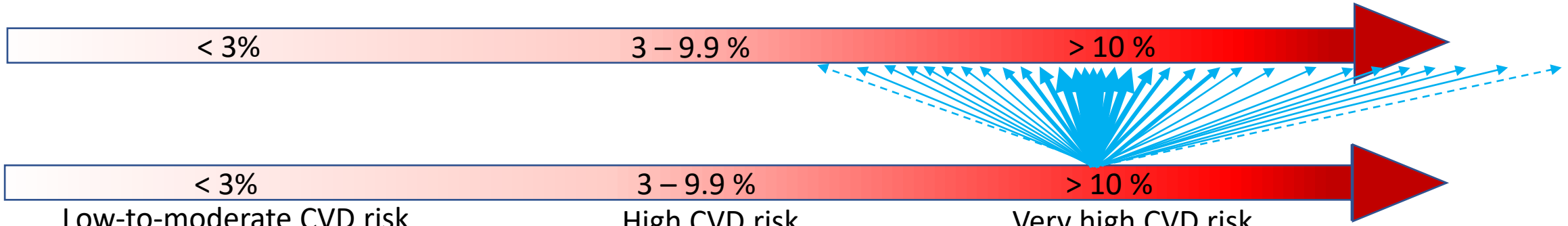
Who has a benefit from genotyping?



Who has a benefit from genotyping?

People with high CVD risk need treatment – but no genotyping

Re-adjustment of Risk by a CAD-PRS



10-year CVD risk ≈ 11%

Who has a benefit from genotyping?

People with low CVD risk need no treatment and no genotyping

in any case

Re-adjustment of Risk by a CAD-PRS

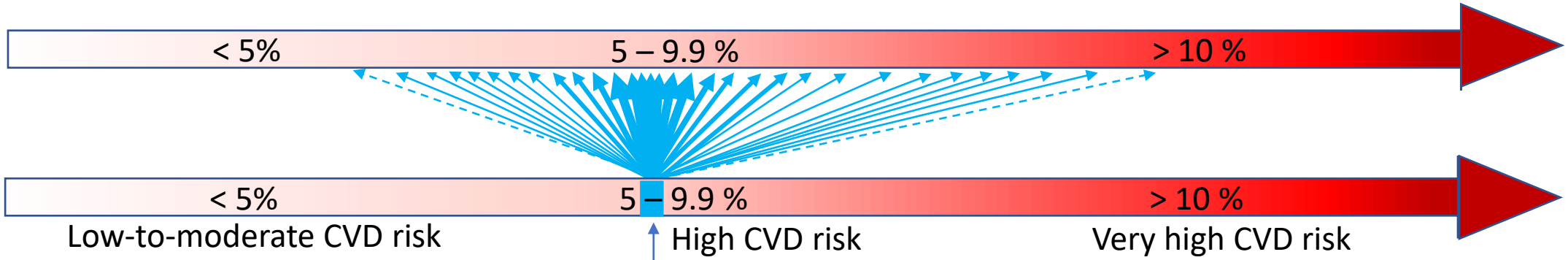
< 3%	3 – 9.9 %	> 10 %
< 3%	3 – 9.9 %	> 10 %
Low-to-moderate CVD risk	High CVD risk	Very high CVD risk

10-year CVD risk ≈ 1%

Who has a benefit from genotyping?

a person with a lower risk by PRS needs
no change in preventive treatment

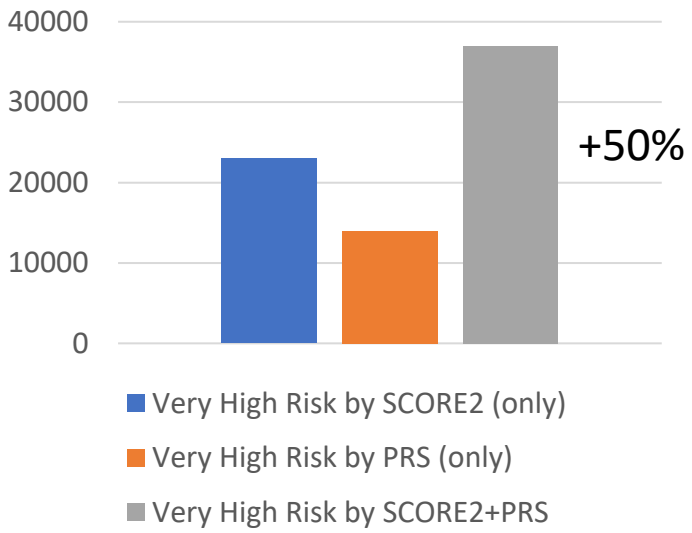
Re-adjustment of Risk by a CAD-PRS



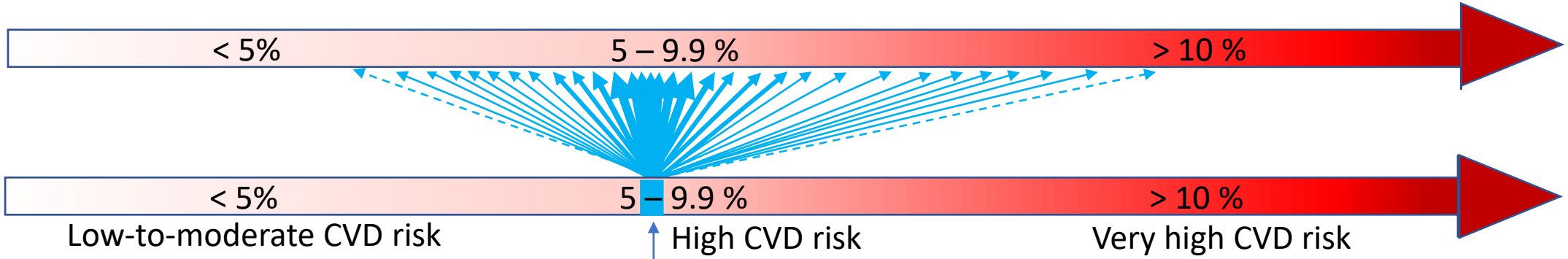
10-year CVD risk ≈ 7%

Who has a benefit from genotyping?

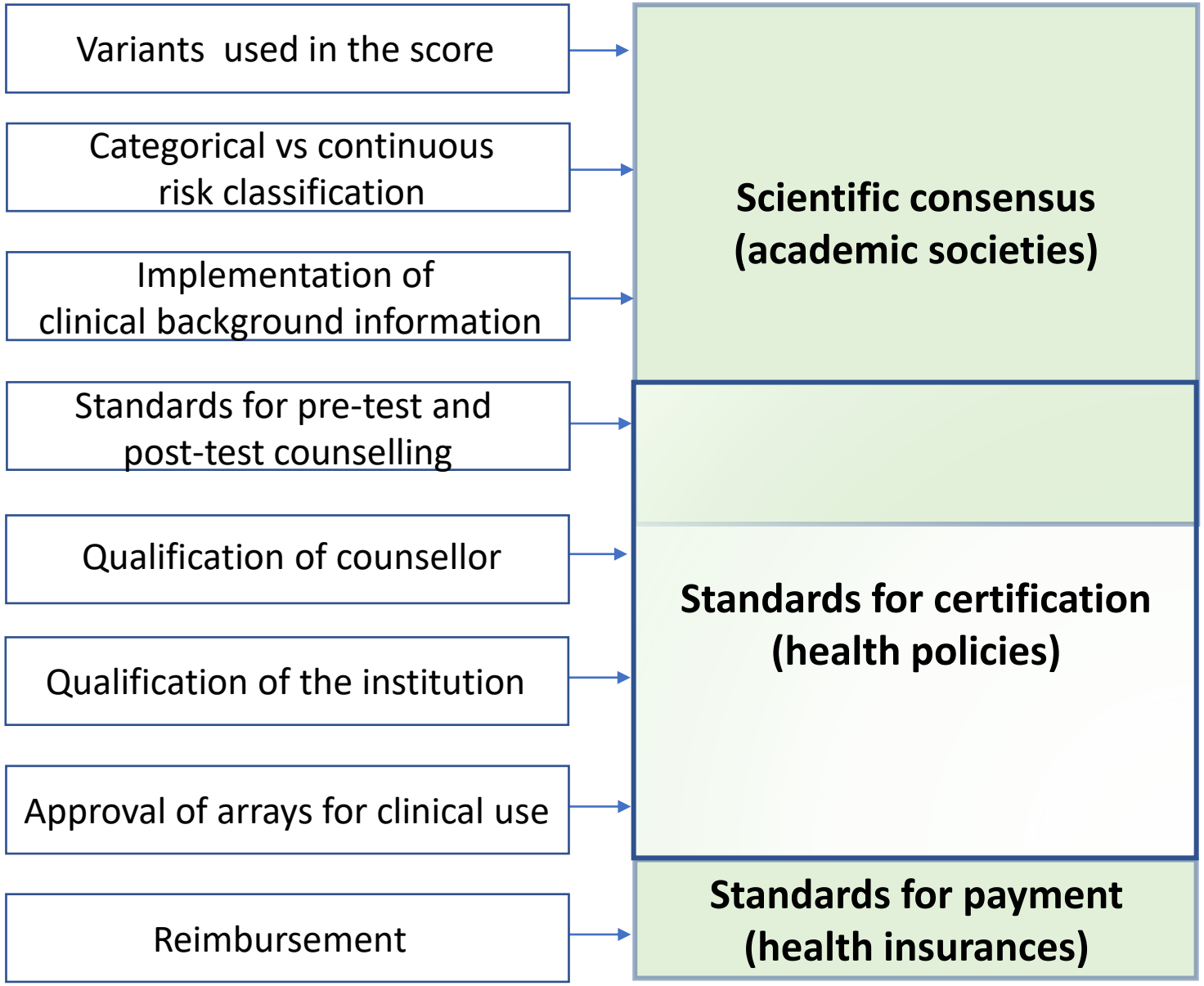
a person with a lower risk by PRS needs
no change in preventive treatment



Re-adjustment of Risk by a CAD-PRS



Requirements for implementation of PRS-based counselling for cardiovascular risk



Deutsches Herzzentrum,
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Prof. Dr. H. Sager
Dr. M. von Scheidt
Shichao Pang, PhD

IIEG, Lübeck
Prof. J. Erdmann

TUM
Prof. Dr. T. Meitinger

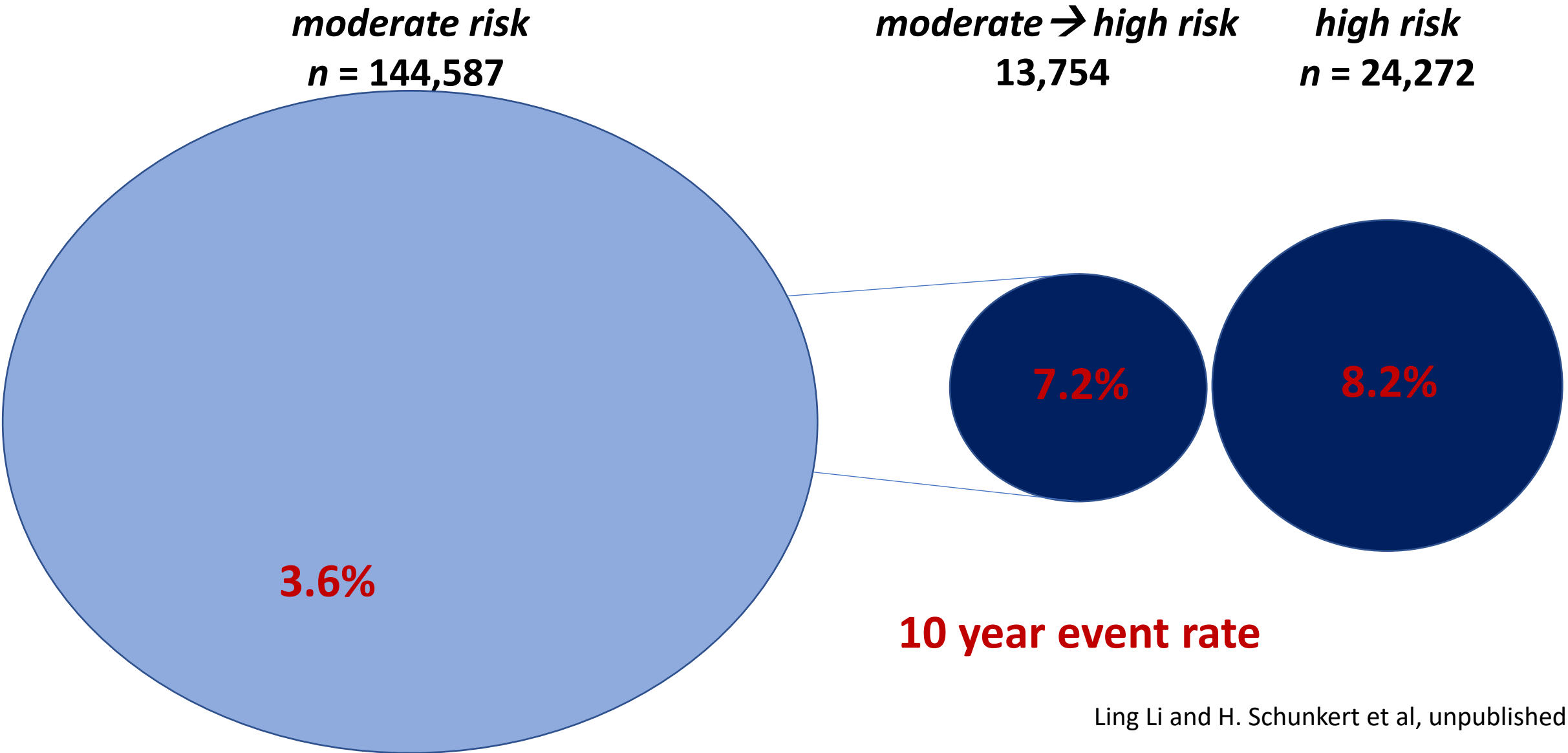
International
Prof. Sir N.J. Samani
Dr. S. Kathiresan
Dr. J. Lusis
Prof. Dr. H. Watkins
Dr. J. Björkegren
Prof. P. Visscher

Munich, Lübeck, Leicester, Boston, Brisbane, LA, NYC…

Open questions	Potential solutions
● No consensus on the type of PRS (e.g. millions vs significant-only variants, continuous vs categorical classification of PRS)	● At least all genome-wide significant lead SNPs; weighted by effect size ● preferably continuous risk classification
● No consensus on calibration across ethnically diverse groups	● Predictive testing of individuals requires calibration of the PRS in respective ethnic groups
● Clinical background information requested	● PRS for CVD risk prediction is only meaningful together with clinical background information (e.g. a risk score)
● No consensus on the contents of counselling	● If PRS used only as adjunct to a risk score: – counselling on CVD risk prediction and its medical implications is sufficient. ● If used for identification of other common diseases and of incidental findings: – genetic counselling before and after PRS.
● Predominantly commercial providers	● Extension to academic institutions and specialized preventive care centers may be useful ● A reimbursement modality may be needed
● Poor scientific evaluation of the merits of PRS-based counselling	● Systematic exploration of medical benefits/harms as well as costs benefit ratio is needed.

Application of the PRS to individuals with moderate risk

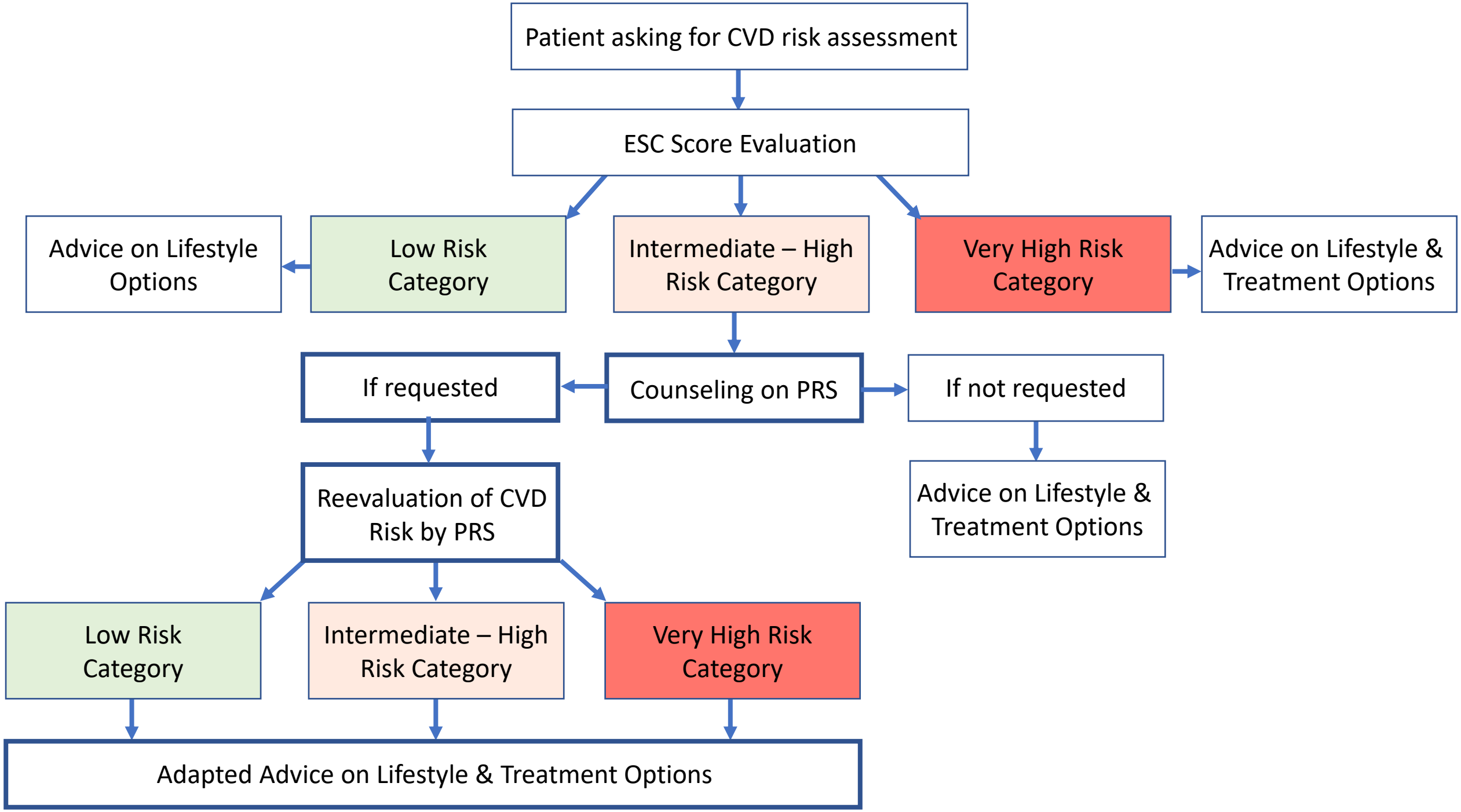
UK Biobank (n=296,001)



Ling Li and H. Schunkert et al, unpublished

Challenges for the use of PRS in predicting CVD risk

- Optimal number of SNPs to build the PRS (hundreds, thousands, millions)
- Input (SNPs) from other types of atherosclerosis (peripheral arterial disease, large artery stroke)
- Calibration across various geographical and ancestral groups
- Precise quantification of effect sizes in subgroups (e.g. young vs. old, males vs. females, diabetics etc.)
- Optimal integration into other prediction tools (SCORE2, Framingham, Pooled Cohort Equations)
- Optimal graphical presentations of test results
- Training tools for counselors of the PRS need to be developed
- Education tools for users of the PRS need to be developed
- Medico-legal aspects need to be resolved (e.g. implications for health insurance)


Patient asking for CVD risk assessment
ESC Score Evaluation
Advice on Lifestyle Options
Low Risk Category
Intermediate – High Risk Category
Very High Risk Category
Advice on Lifestyle & Treatment Options
If requested
Counseling on PRS
If not requested
Reevaluation of CVD Risk by PRS
Advice on Lifestyle & Treatment Options
Low Risk Category
Intermediate – High Risk Category
Very High Risk Category
Adapted Advice on Lifestyle & Treatment Options