Genomic Risk And Preventing Coronary Heart Disease – the GeneRISK Study and Beyond

Personalized Medicine – Sotsiaal Ministerium, Eesti

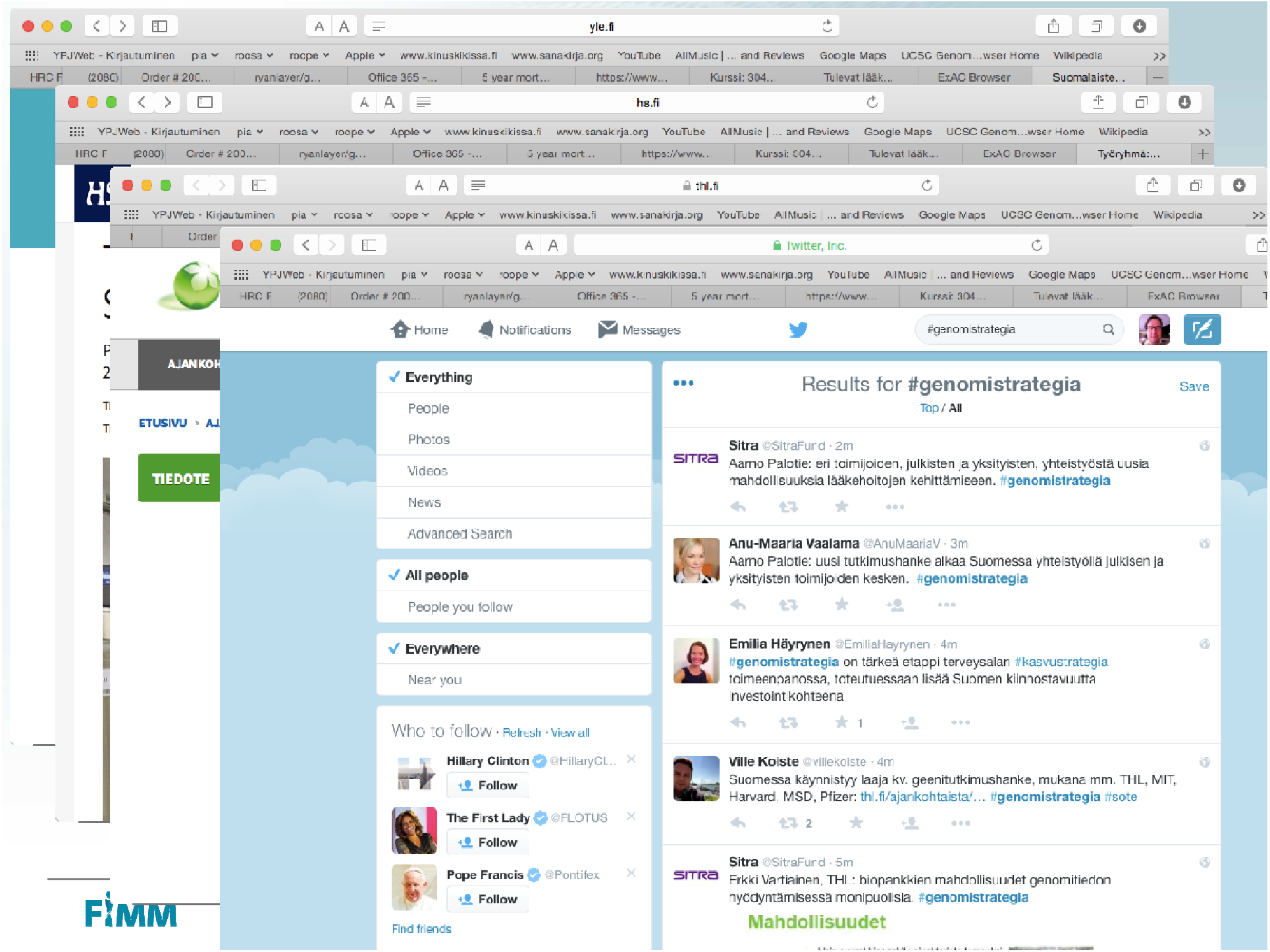
11.6. 2015

Samuli Ripatti, Professor

Public Health, University of Helsinki, Finland

Institute for Molecular Medicine Finland (FIMM)

Wellcome Trust Sanger Institute, UK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Sitra @SitraFund · 2m
Aamo Palotie: eri toimijoiden, julkisten ja yksityisten, yhteistyöstä uusia mahdollisuuksia lääkehoitojen kehittämiseen. #genomistrategia
Anu-Maaria Vaalama @AnuMaariaV · 3m
Aamo Palotie: uusi tutkimushanke alkaa Suomessa yhteistyöllä julkisen ja yksityisten toimijoiden kesken. #genomistrategia
Emilia Häyrynen @EmiliaHayrynen · 4m
#genomistrategia on tärkeä etappi terveysalan #kasvustrategia toimeenpanossa, toteutuessaan lisää Suomen kilpailukykyä investointikohteena
Ville Koiste @villekoiste · 4m
Suomessa käynnistyy laaja kv. geenitutkimushanke, mukana mm. THL, MIT, Harvard, MSD, Pfizer: thl.fi/ajankohtaista/... #genomistrategia #sote
Sitra @SitraFund · 5m
Erkki Vartiainen, THL : biopankkien mahdollisuudet genomitiedon hyödyntämisessä monipuolisia. #genomistrategia
Mahdollisuudet
TIEDOTE
FIMM

GENOMITIEDON TEHOKKAAN KÄYTÖN HYÖDYT

Finnish Genome Strategy June 11

Finland's Genome Strategy - Announced Today June 11, 2015

- Action 3: Developing national genome database
  - Pilot: SISu Project
- Action 4: Enabling translation of research results into clinical practice
- Actions 5-7: Education of genomics to health care professionals, MDs, general public
  - Pilot: First personalized medicine course for MD students at University of Helsinki
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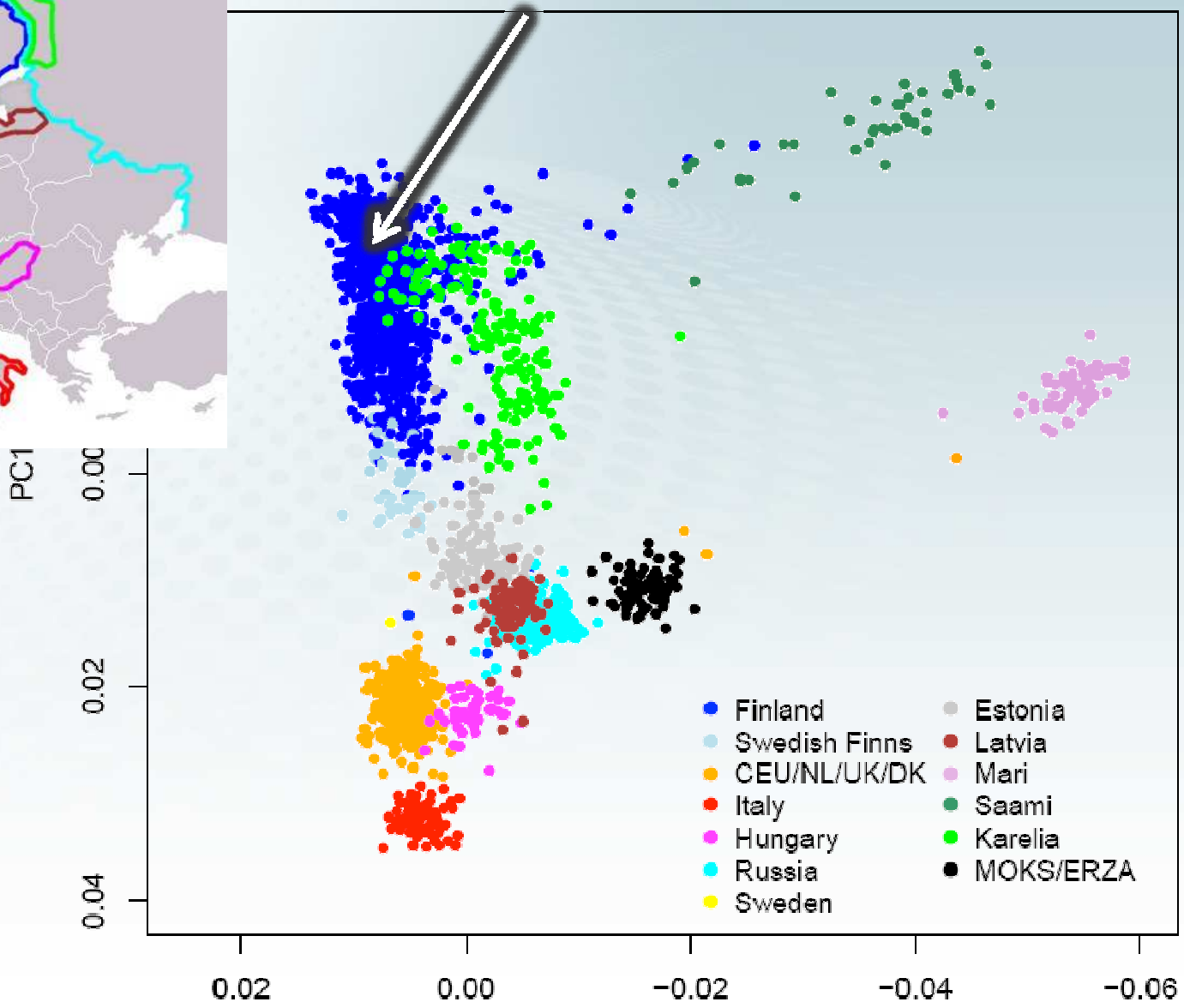
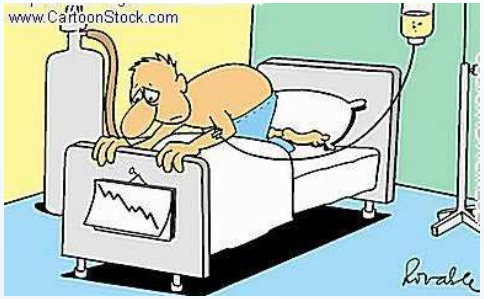
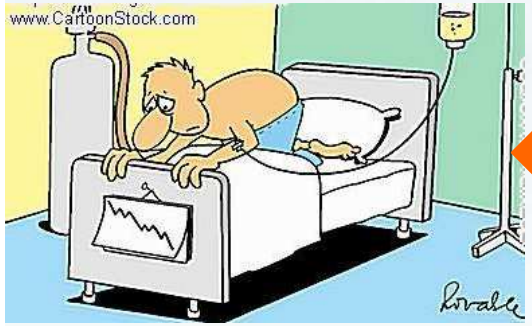
Aarno Palotie

Sequencing Initiative Suomi

Finnish genomic variation differs from the neighbors







Apply to an individual patient

Search

www.sisuproject.fi

Search | rs1570248, rs184935153, rs150680234, rs201177049, rs200920925, rs201493772 | Reset

Results

rsID	Chr	Coord	Minor	Major	RefSNP Alleles	N_minor	N_het	N_major	SISu	1000g
rs201493772	5	132015505	T	C	-	0	3	3322	0.0004511	N/A
rs200920925	5	114482990	A	G	-	0	3	3322	0.0004511	0
rs1570248	9	35751221	C	T	-	458	1557	1310	0.3719	0.332168
rs201177049	5	81613844	T	C	-	1	4	3320	0.0009023	N/A
rs150680234	2	233396060	C	A	-	0	5	3320	0.0007519	N/A
rs184935153	2	43958656	A	T	-	0	3	3322	0.0004511	N/A

query params: rs1570248, rs184935153, rs150680234, rs201177049, rs200920925, rs201493772

LPA loss-of-function variant protecting from CHD

exac.broadinstitute.org

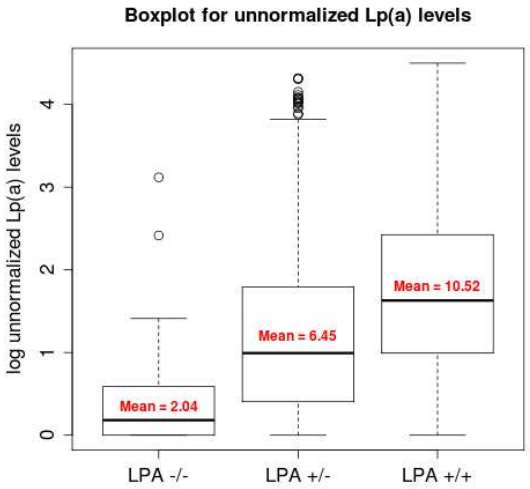
Annotations

This variant falls on 2 transcripts in 1 genes:

splice acceptor

- LPA Transcripts

Note: This list may not include additional transcripts in the same gene that the variant does not overlap.

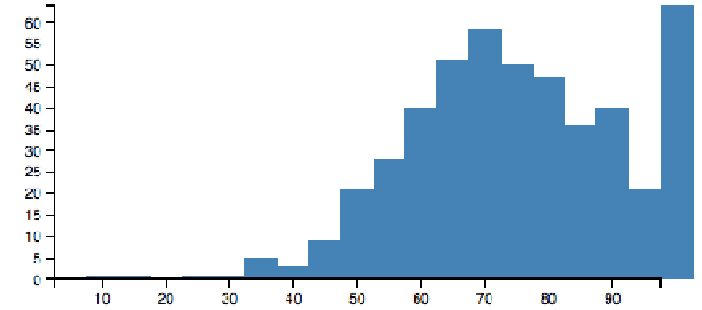


Population Frequencies

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
European (Finnish)	198	6614	1	0.02994
Other	6	904	0	0.006637
European (Non-Finnish)	228	66720	2	0.003417
Latino	30	11574	0	0.002592
African	13	9994	0	0.001301
South Asian	4	16510	0	0.0002423
East Asian	0	8650	0	0
Total	**479**	**120966**	**3**	**0.00396**

Quality Metrics

Variant carriers | All individuals | Depth | Genotype Quality



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hjelt.helsinki.fi

LL-koulutusohjelman valinnainen opintojakso keväällä 2015

mediuutiset.fi

Talentum Talouselämä Tekniikka&Talous Tivi Arvopaperi M&M MPC Mediuutiset Uratie Summa

KOULUTUS Minna Phlava,

Helsingin yliopi
henkilökohtaise

20 Helsingin yliopistor
ensimmäisen henkilök
opetetaan potilaskohta

Pilottikurssin järjestäv
molekyylilääketieteen

Lääkäri voi joutua tila
geenitestin tehnyt pot

– Tulevaisuuden lääke
osallistavaa. Potilaan t
hyvä huomioida jo kou
Elisabeth Widén Suo

Widén on suunnitellut
ylicpistonlehtori **Hann**

Opiskeljat saavat halu
kardiovaskulaaristen t
käytetään Kardiokom

sitra.fi

SITRA Medialle Yhteystiedot Tapahtumat Julkaisut På svenska In English Haku

Ekologia Hyvinvointi Talous Tulevaisuus Yhteiskunta Sitra

Ensimmäinen genomikurssi ohi: ”Pitää tietää, kuinka suuria riskit ovat” – katso video!

Uutiset 05.06.2015 12:46

Ota yhteyttä

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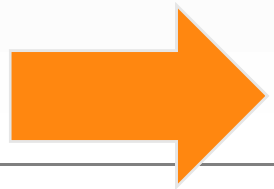
Johtava asiantuntija,
hyvinvointia tiedosta
Tuula.Tiihonen@sitra.fi
+358 294 618 269

Jukka Vahti
Asiantuntija, viestintä

The MD students…

- …tested their coronary heart disease risk using traditional risk factors and a panel of 50 risk variants
- …tested a panel of 75 pharmacogenetic markers
- …learned about P4 medicine (predictive, preventive, personalized, participatory)
- …learned to interpret risk and how to motivate high risk individuals for life style changes
- …learned how genes modify drug metabolism
- …learned how personalized cancer genetics are currently used for diagnosis and treatment and Helsinki University Hospital (HUCH)



The students' feedback:
Genomics need to be integrated in all standard teaching

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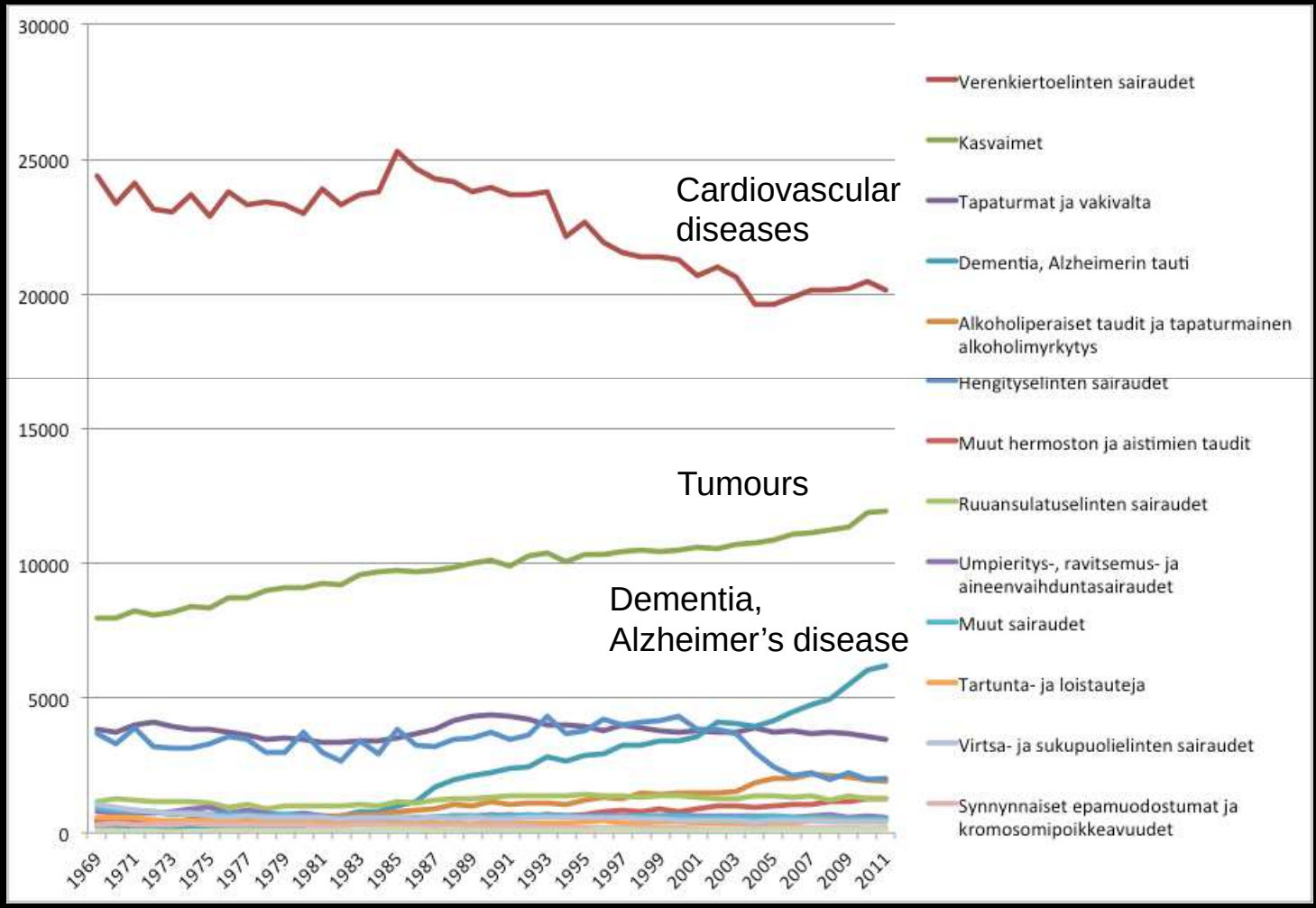
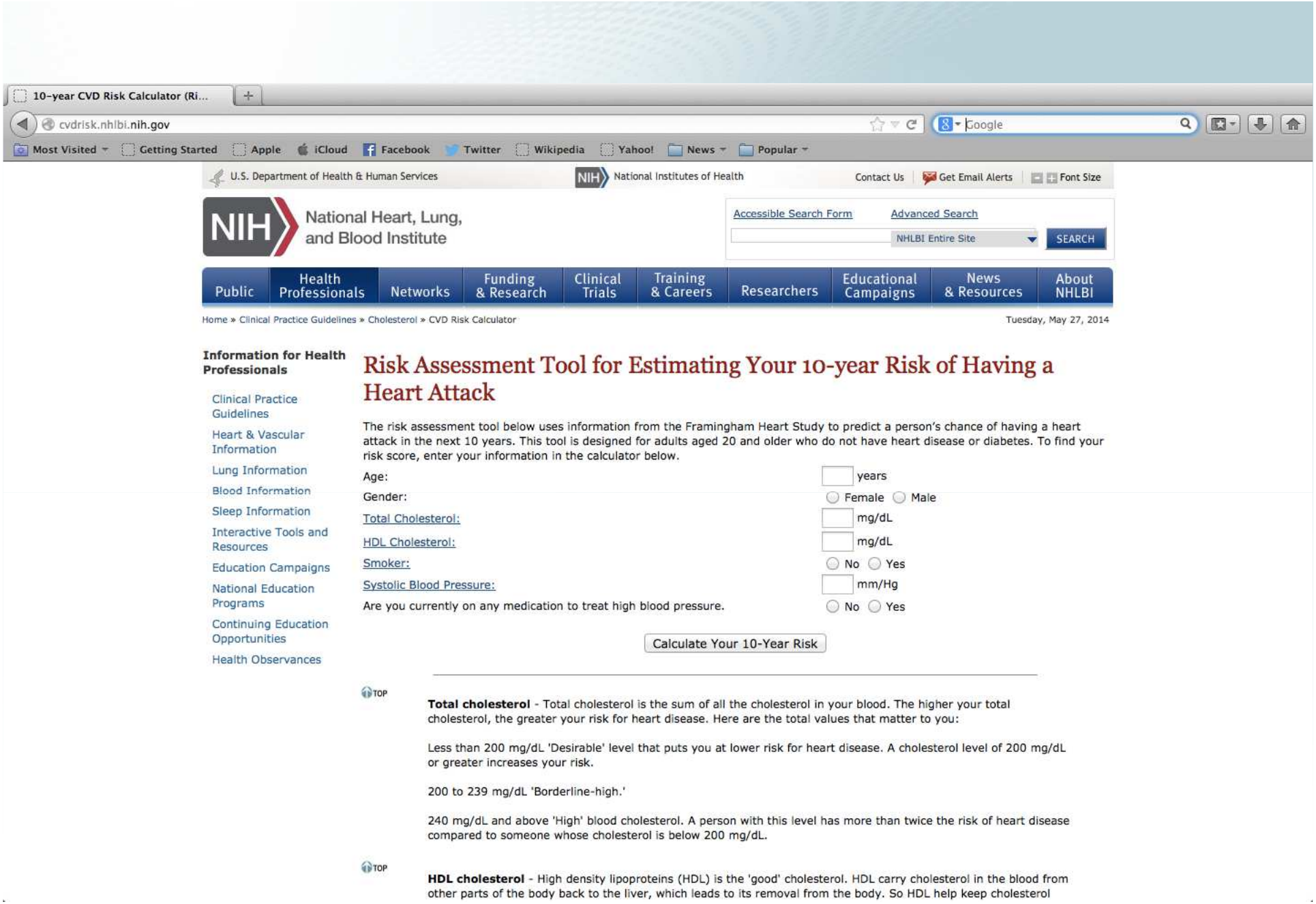
Causes of death in Finland



Suomen virallinen tilasto: Kuolemansyyt 2010


10-year CVD Risk Calculator (Ri...
cvdrisk.nhlbi.nih.gov
Google
Most Visited
Getting Started
Apple
iCloud
Facebook
Twitter
Wikipedia
Yahoo!
News
Popular
U.S. Department of Health & Human Services
National Institutes of Health
Contact Us
Get Email Alerts
Font Size
National Heart, Lung, and Blood Institute
Accessible Search Form
Advanced Search
NHLBI Entire Site
SEARCH
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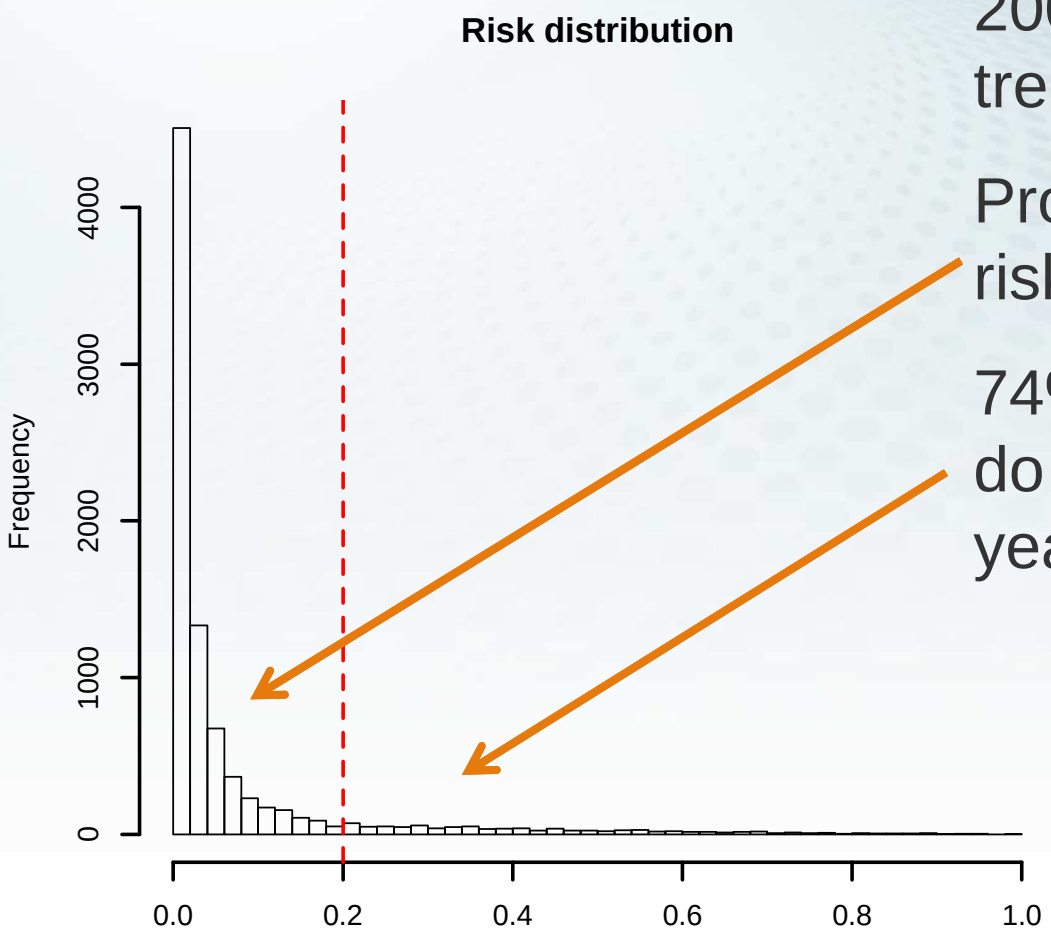
Home » Clinical Practice Guidelines » Cholesterol » CVD Risk Calculator
Tuesday, May 27, 2014
Information for Health Professionals
Clinical Practice Guidelines
Heart & Vascular Information
Lung Information
Blood Information
Sleep Information
Interactive Tools and Resources
Education Campaigns
National Education Programs
Continuing Education Opportunities
Health Observances
Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack
The risk assessment tool below uses information from the Framingham Heart Study to predict a person's chance of having a heart attack in the next 10 years. This tool is designed for adults aged 20 and older who do not have heart disease or diabetes. To find your risk score, enter your information in the calculator below.
Age: years
Gender: Female Male
Total Cholesterol: mg/dL
HDL Cholesterol: mg/dL
Smoker: No Yes
Systolic Blood Pressure: mm/Hg
Are you currently on any medication to treat high blood pressure. No Yes
Calculate Your 10-Year Risk
TOP
Total cholesterol - Total cholesterol is the sum of all the cholesterol in your blood. The higher your total cholesterol, the greater your risk for heart disease. Here are the total values that matter to you:
Less than 200 mg/dL 'Desirable' level that puts you at lower risk for heart disease. A cholesterol level of 200 mg/dL or greater increases your risk.
200 to 239 mg/dL 'Borderline-high.'
240 mg/dL and above 'High' blood cholesterol. A person with this level has more than twice the risk of heart disease compared to someone whose cholesterol is below 200 mg/dL.
TOP
HDL cholesterol - High density lipoproteins (HDL) is the 'good' cholesterol. HDL carry cholesterol in the blood from other parts of the body back to the liver, which leads to its removal from the body. So HDL help keep cholesterol

CHD prevention based on traditional risk factors



2008 guidelines: statin treatment for those >20% risk

Problem: 83% of cases have risk < 20%

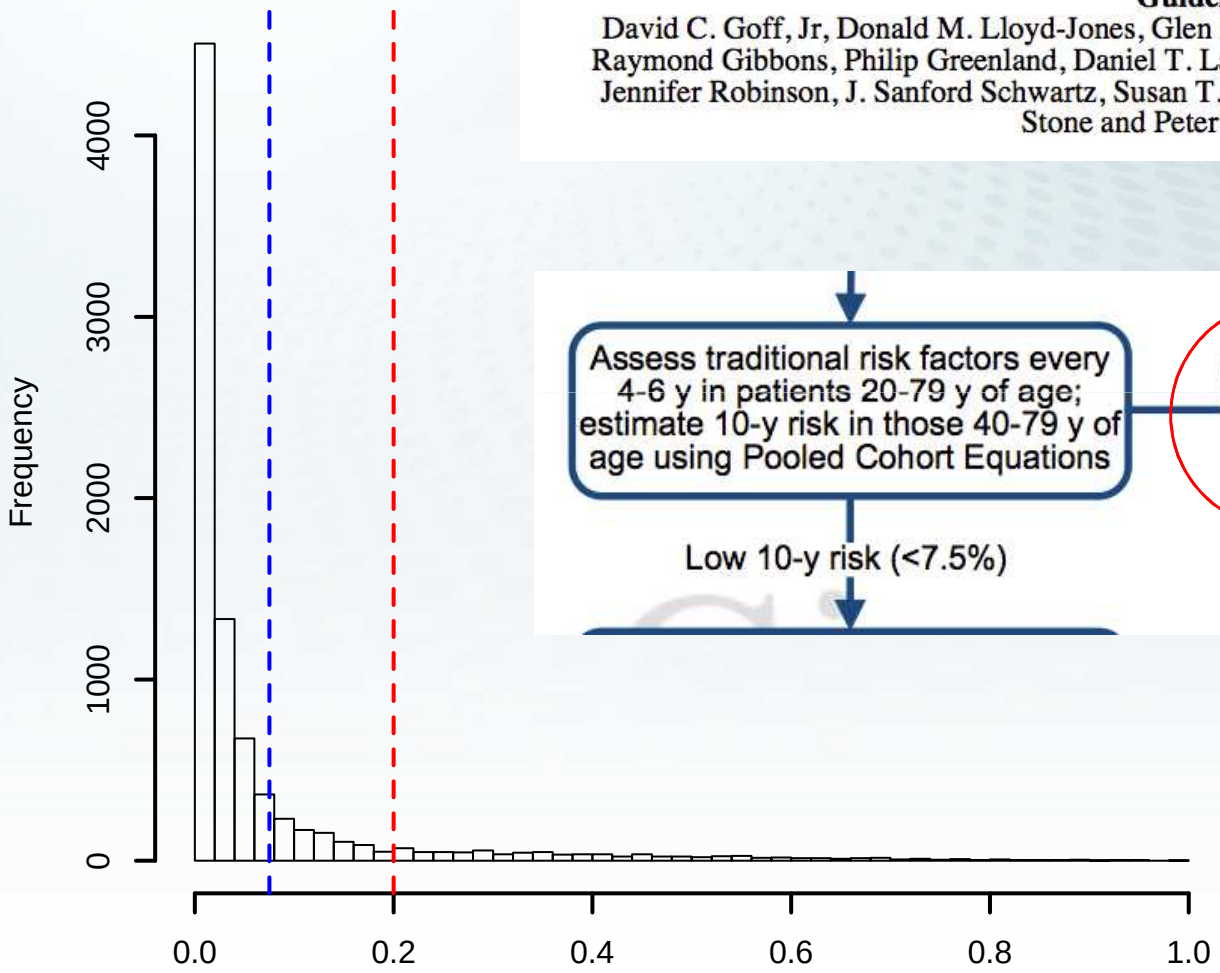
74% of those with risk >20% do not get the disease (in 10 years)

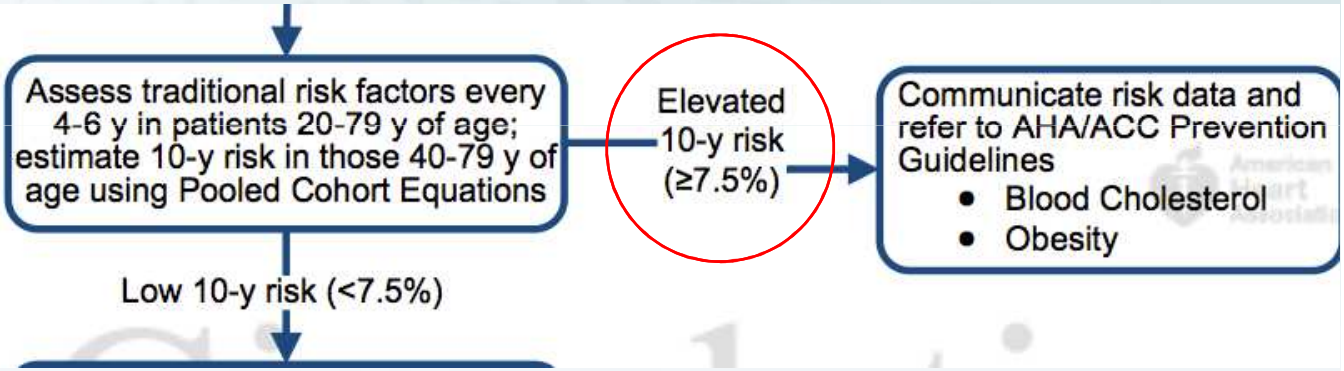
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

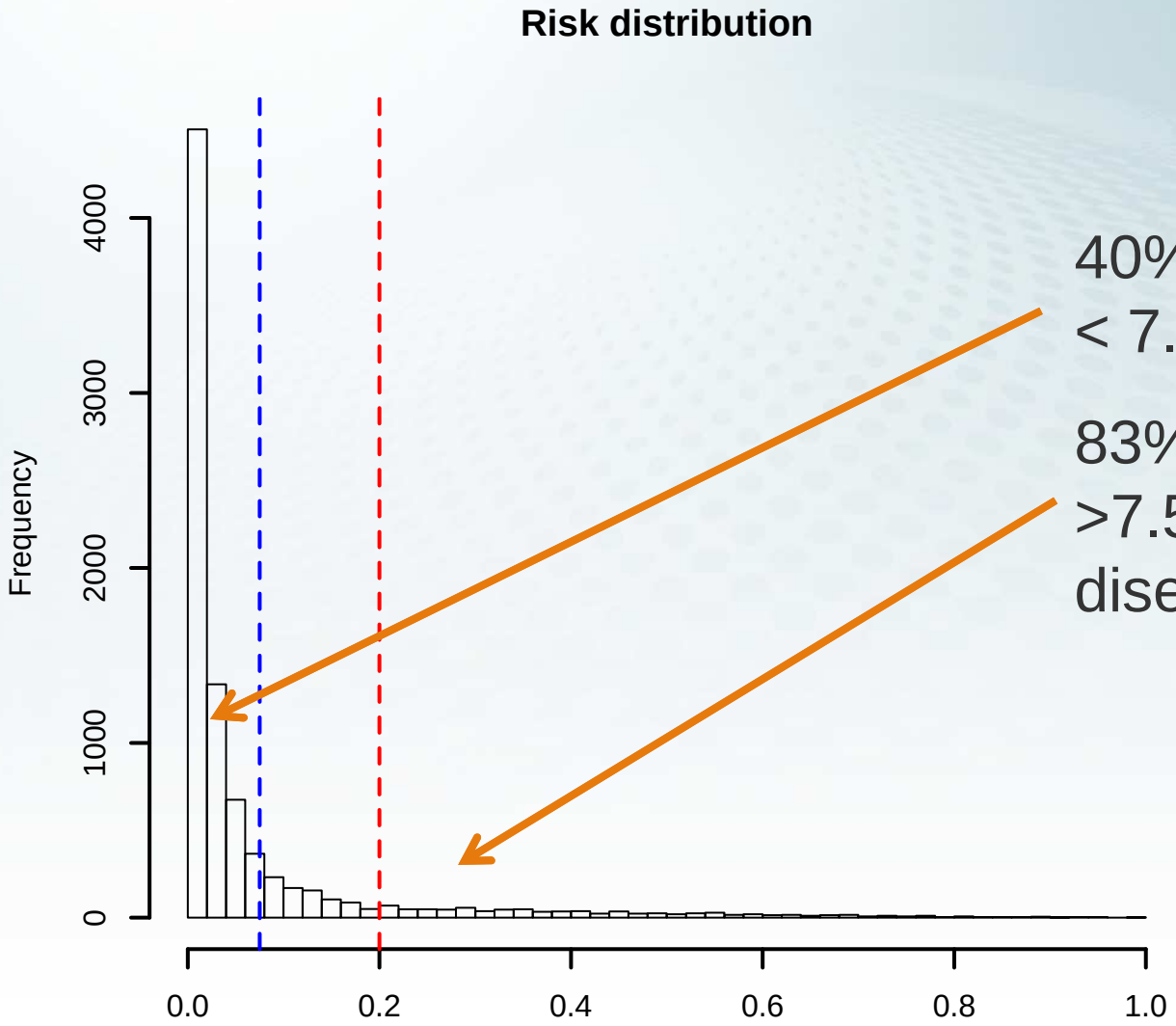
American Heart Association

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

David C. Goff, Jr, Donald M. Lloyd-Jones, Glen Bennett, Sean Coady, Ralph B. D'Agostino, Sr, Raymond Gibbons, Philip Greenland, Daniel T. Lackland, Daniel Levy, Christopher J. O'Donnell, Jennifer Robinson, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Jr, Paul Sorlie, Neil J. Stone and Peter W.F. Wilson

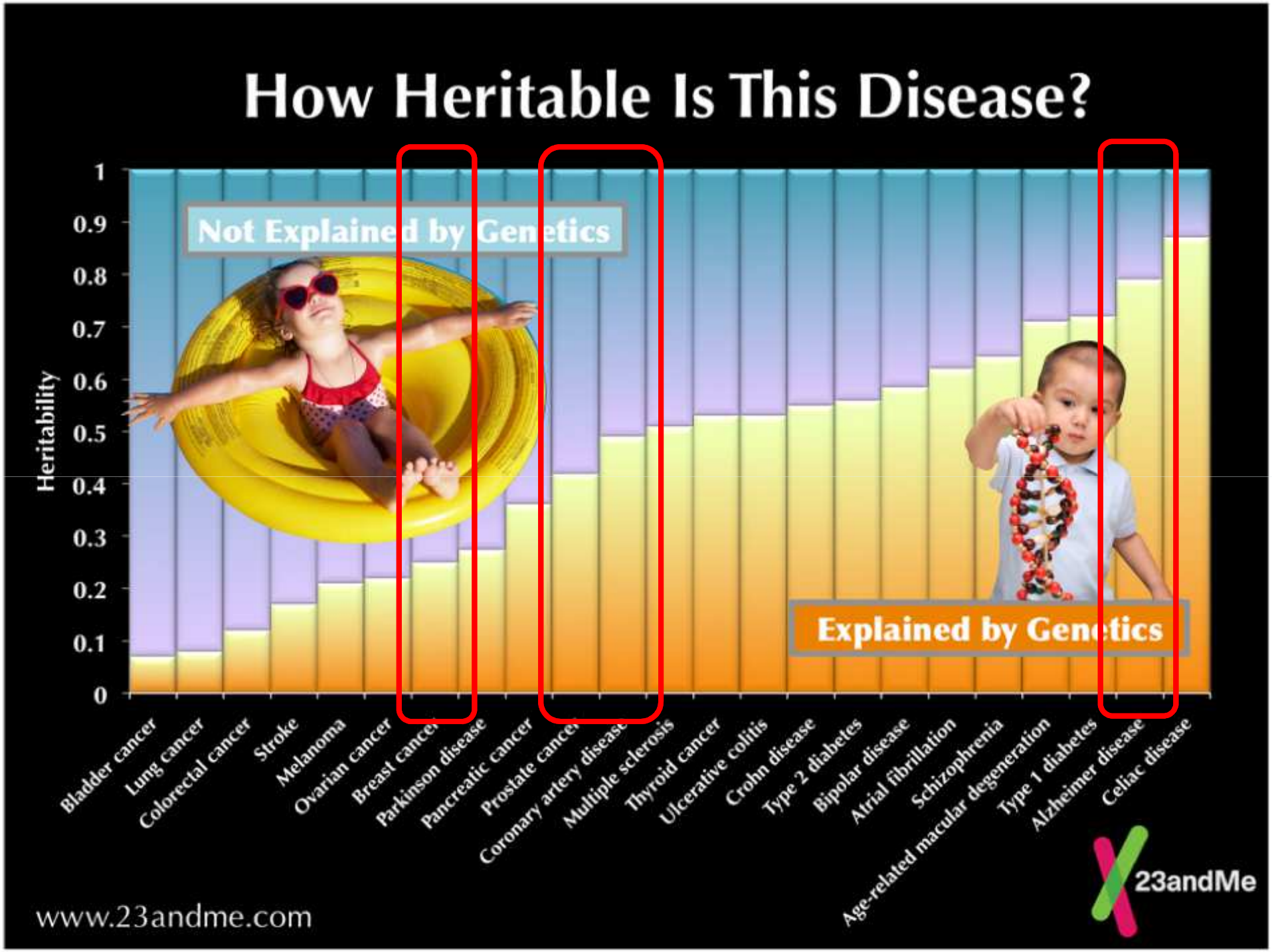




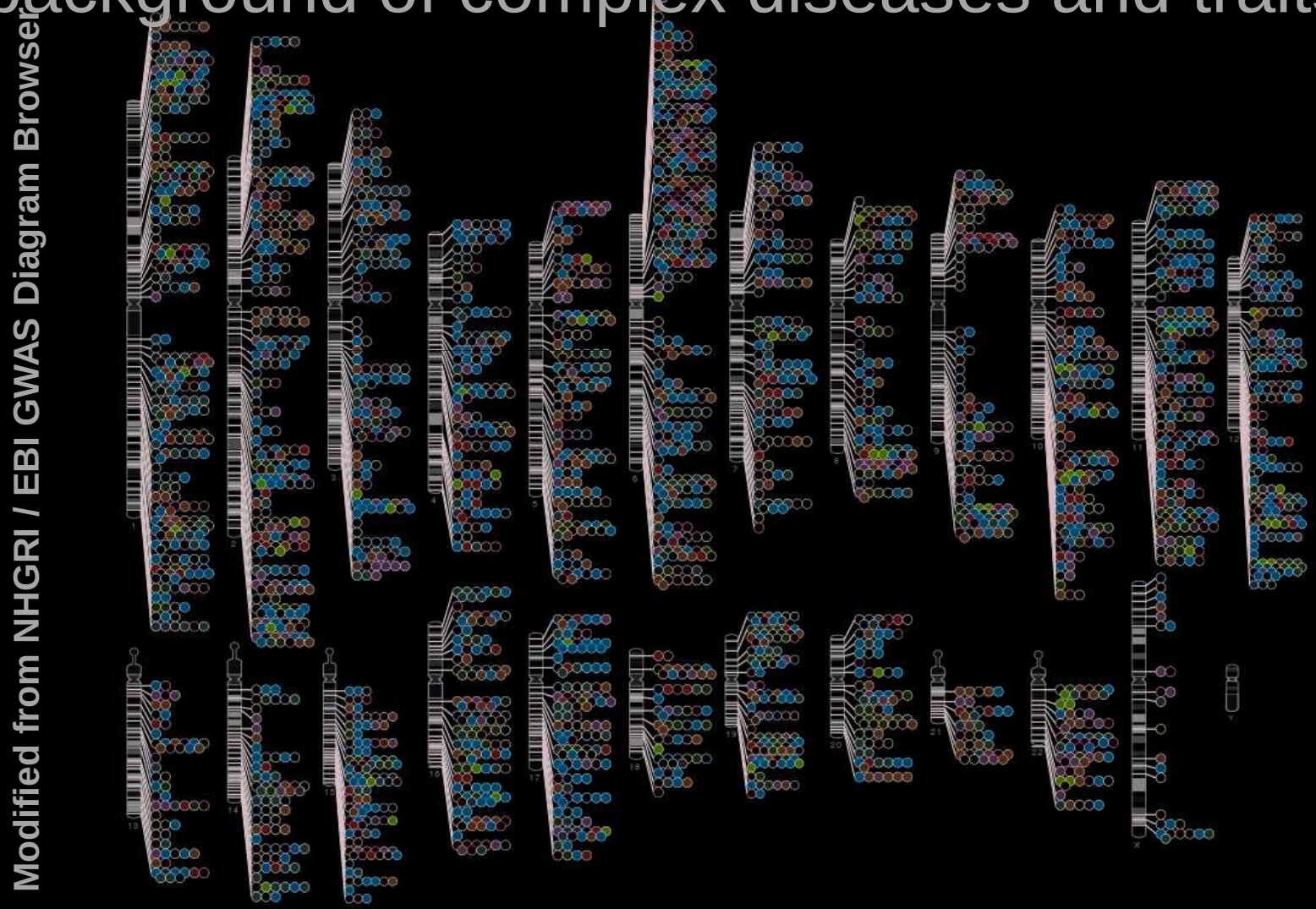


40% of cases have risk < 7.5%

83% of those with risk >7.5% do not get the disease (in 10 years)

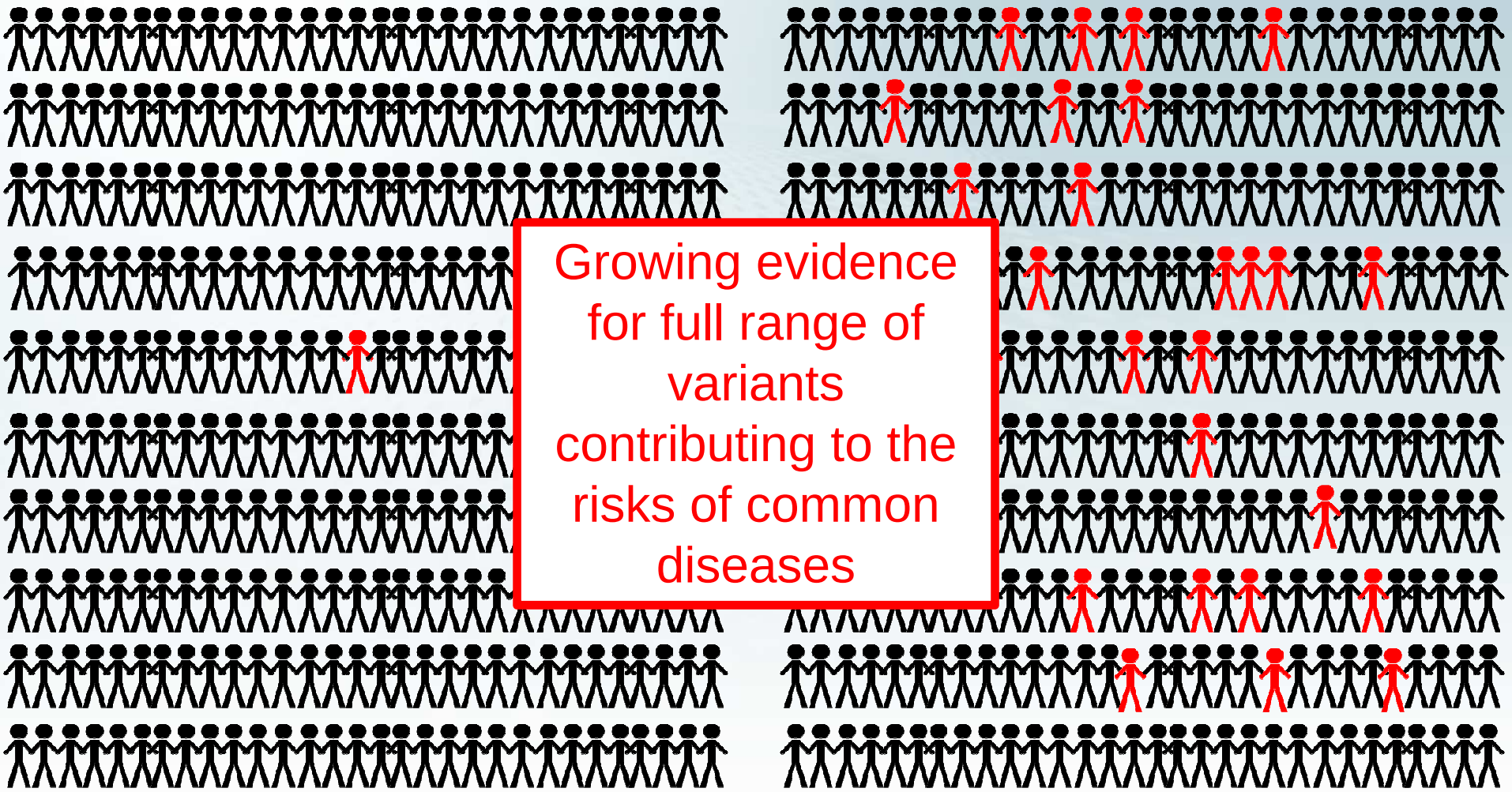

How Heritable Is This Disease?
Heritability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Not Explained by Genetics
Explained by Genetics
Bladder cancer
Lung cancer
Colorectal cancer
Stroke
Melanoma
Ovarian cancer
Breast cancer
Parkinson disease
Pancreatic cancer
Prostate cancer
Coronary artery disease
Multiple sclerosis
Thyroid cancer
Ulcerative colitis
Crohn disease
Type 2 diabetes
Bipolar disease
Atrial fibrillation
Schizophrenia
Age-related macular degeneration
Type 1 diabetes
Alzheimer disease
Celiac disease
23andMe
www.23andme.com

Genome-wide studies have provided unprecedented information about genetic background of complex diseases and traits



Modified from NHGRI / EBI GWAS Diagram Browser

Rare high-impact vs. common low-impact variants



Growing evidence for full range of variants contributing to the risks of common diseases

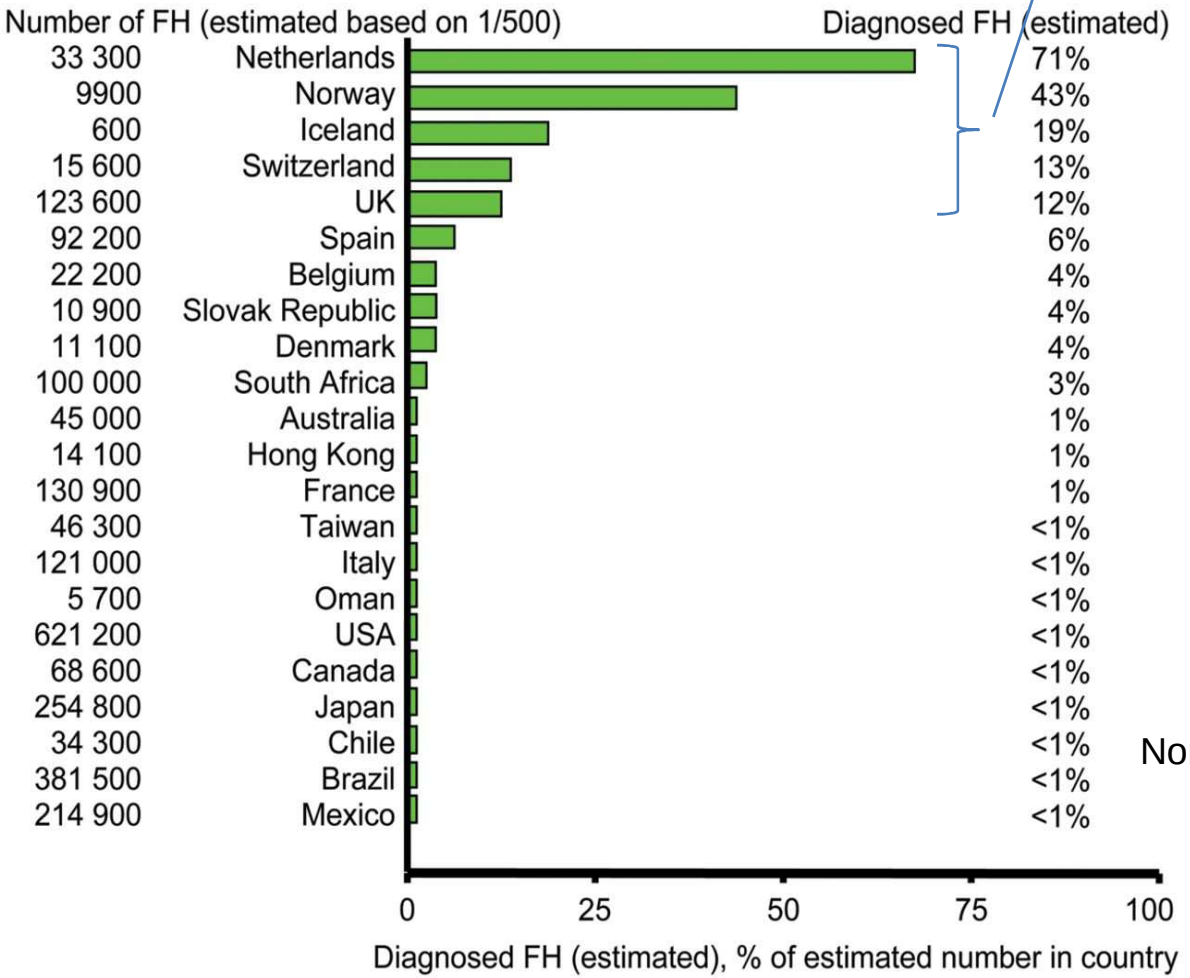
Single rare variant dominating the risk (>5 × risk, >0.5sd)

Multiple genetic and other risk factors contributing (<2 × risk, <0.2sd)

Some of the most centralized health car systems worldwide NL, NO ,IS, UK

The evidence:

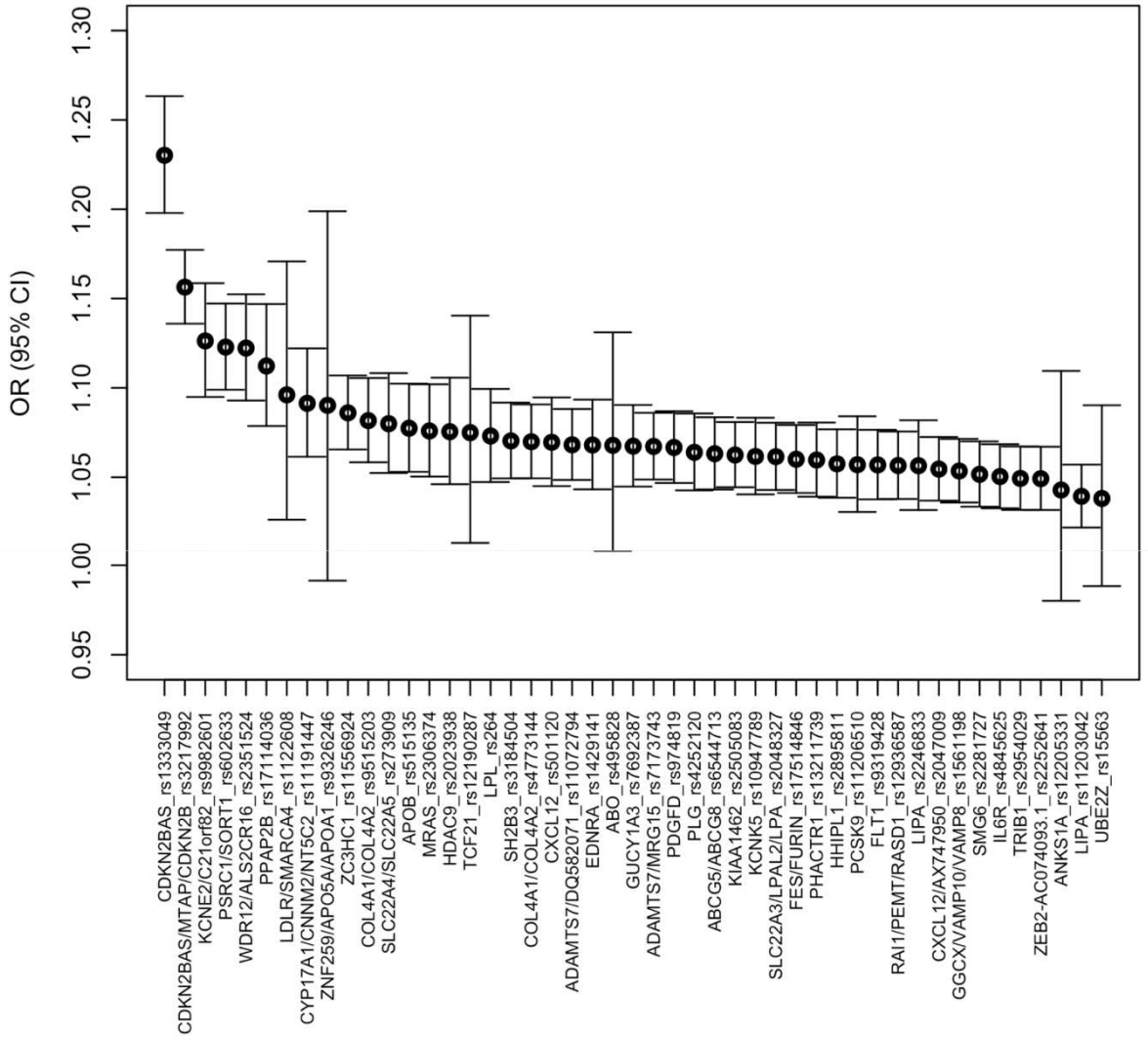
- **Familial hypercholesterolemia (FH) although frequent is underdiagnosed**



Finland:
10,000 – 20,000 undiagnosed FH cases

Nordenstgaard et al Eur Heart J 2013

CHD risk variants



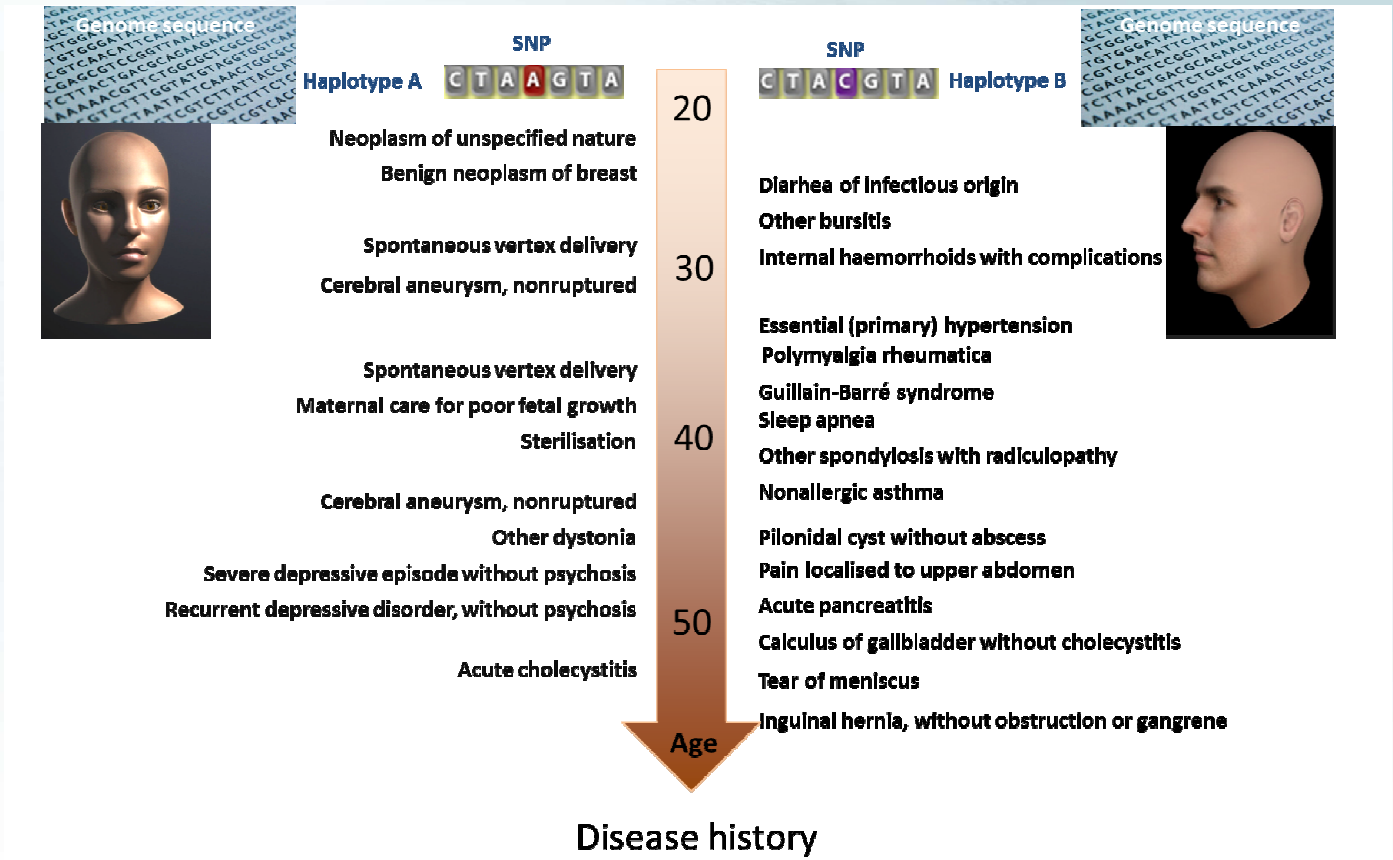
CARDIoGRAMplusC4D Consortium, Nat Genet 2013

How to use the genome in prevention?

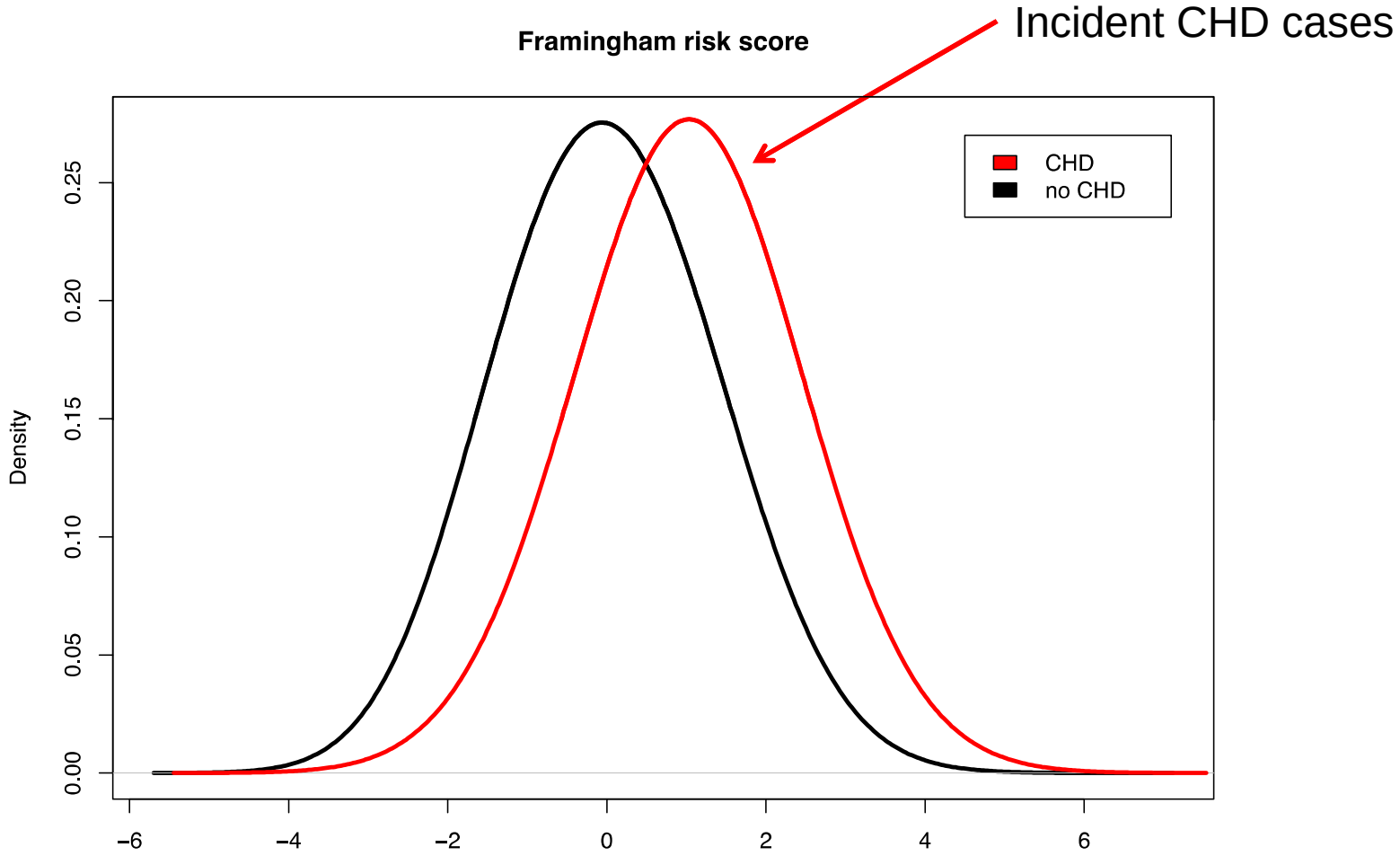
1. Database: Large-scale prospective data with genomic screen and follow-up recordings of health
2. Algorithms: to estimate the personalized risks
3. Apps: to communicate the risk to individuals

› Possibility to lower the risks through intervention

40 year health event follow-up through health registries

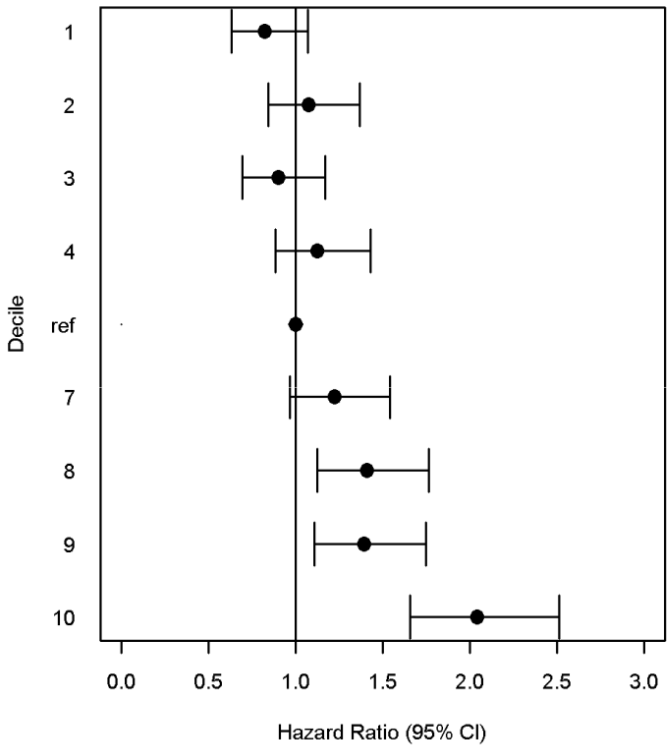


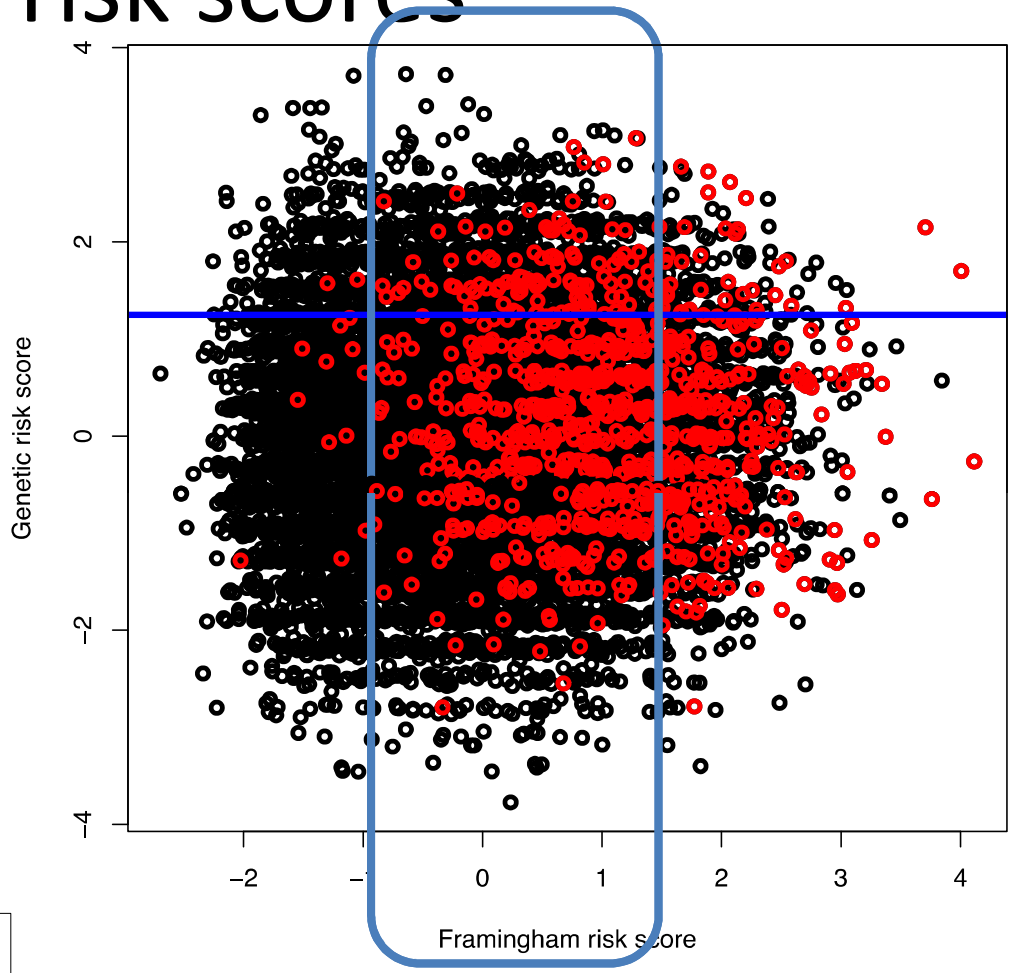
Risk factor distributions overlapping

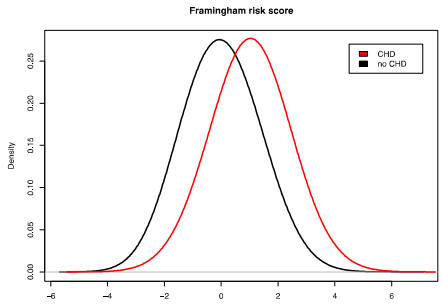


Framingham risk score at baseline:
age, sex, total cholesterol, HDL, BMI, systolic blood pressure, blood pressure treatment, current smoking status, diabetes mellitus, family history of CHD

Predicting heart disease risk with genetic risk scores







Incident cases

Non-cases

Refining the risk estimates using genetic data

Ripatti Lancet 2010

Tikkanen ATVB 2013

Examples

- Using GRS on top of traditional risk factors

58-year-old female

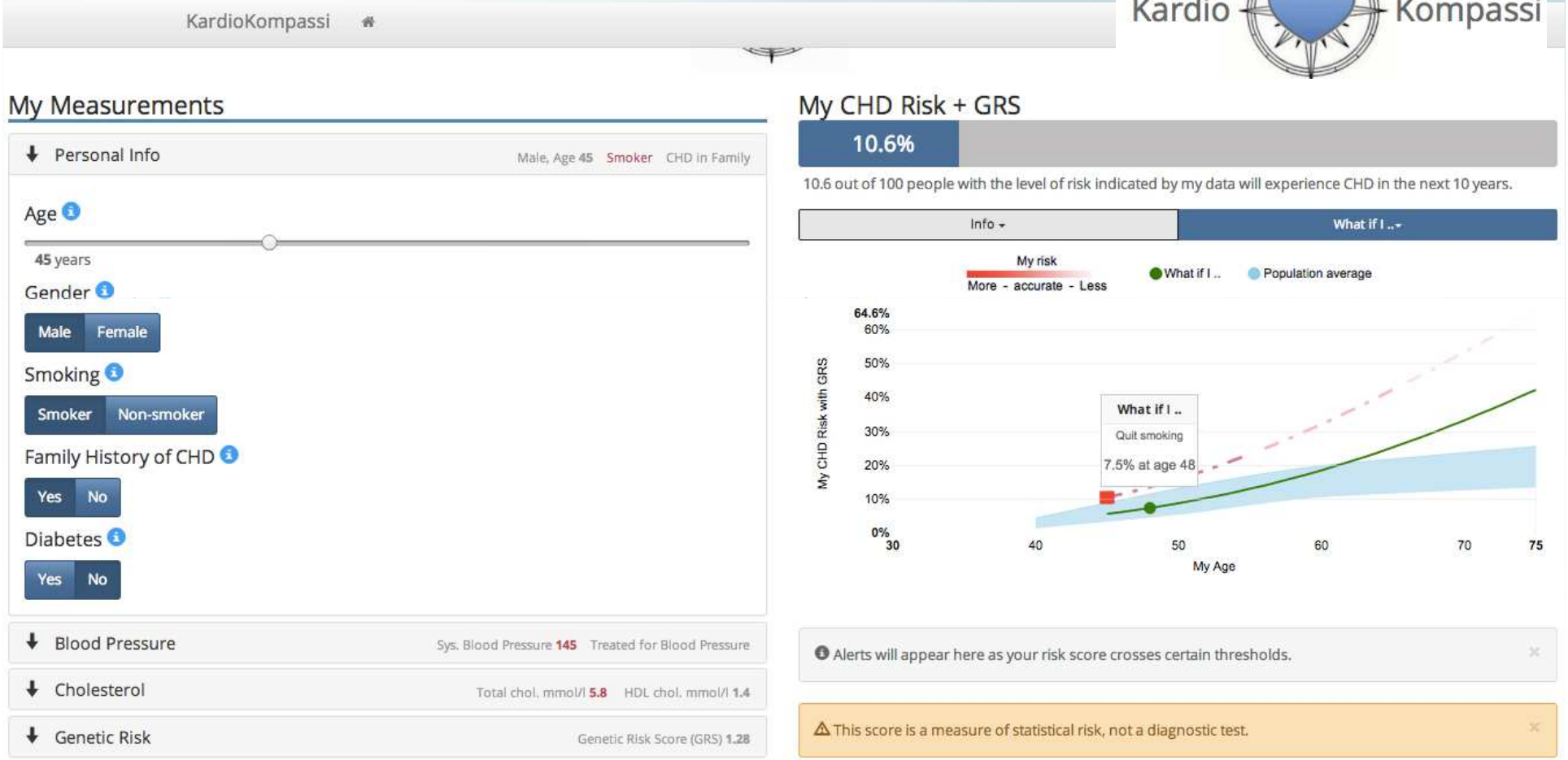
AGE

58 **Baseline examination**
Total cholesterol 5.0
HDL cholesterol 1.4
Systolic blood pressure 169, treated
Non-smoker
No diabetes
No family history of CVD
→CHD risk 13.7%
High genetic risk score
→CHD risk 21%

70 S422 Fracture of upper end of humerus

73 N179 Acute kidney failure, unspecified
I2141 Non-ST elevation (NSTEMI) myocardial infarction
I509 Heart failure, unspecified

KardioKompassi: communicating risk to citizens



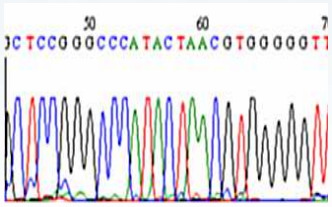
Pilot: Communicating the risk

200 healthy volunteers
FIMM, SITRA,
Finnish Red Cross

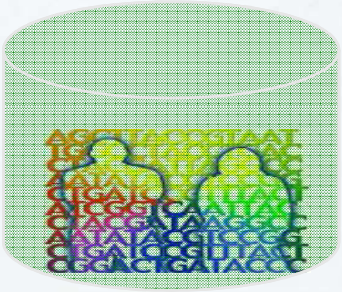
Participant X

- *Consent*
- *Assessment of cardiovascular disease risk*
- *Ordering DNA-test*

Blood sampling



DNA-test

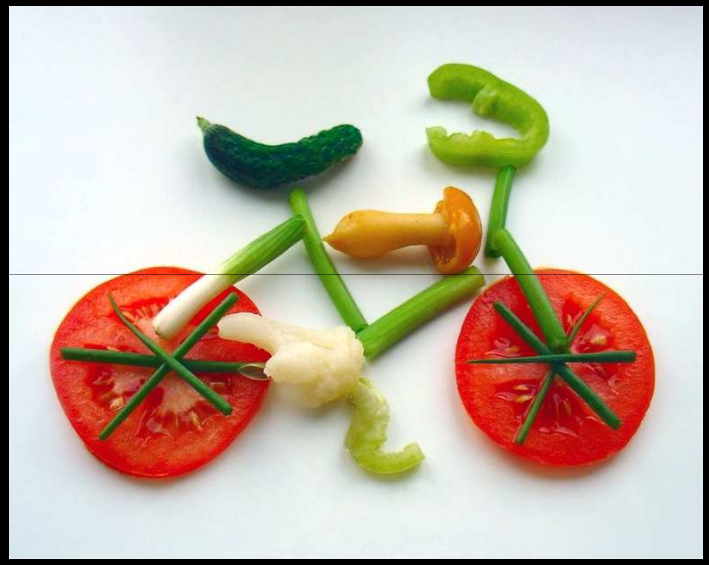


Kardiokompassi web-service

Traditional risk factors

Kardio Kompassi

OPINIONS ABOUT THE KARDIOKOMPASSI APPLICATION		Disagree (%)	No opinion (%)	Agree (%)
I learned useful information regarding my health	males	16	4	**80**
	females	12.7	12.7	**74.5**
My personal disease risk information was reassuring	males	12	28	60
	females	26.5	25.5	48.1
My personal disease risk information motivated me to take better care of my health	males	12	24	64
	females	11.8	25.5	62.6
The information I received was worrying	males	64	32	4
	females	65.7	16.7	17.7
The information I received was interesting	males	0	4	**96**
	females	3.9	5.9	**90.2**
My personal genetic risk information was confusing	males	52	32	16
	females	60.8	24.5	14.7
I was indifferent to the information provided on my personal genetic risk	males	84	12	4
	females	83.3	9.8	6.9
The information on my genetic risk, in particular, motivated me to take better care of my health	males	12	24	**64**
	females	16.7	18.6	**64.7**



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Rx only
Lipitor
80
80 mg*
Parke-Davis

Evidence for strong statin response in high genetic risk group

High genetic risk

Risk reduction

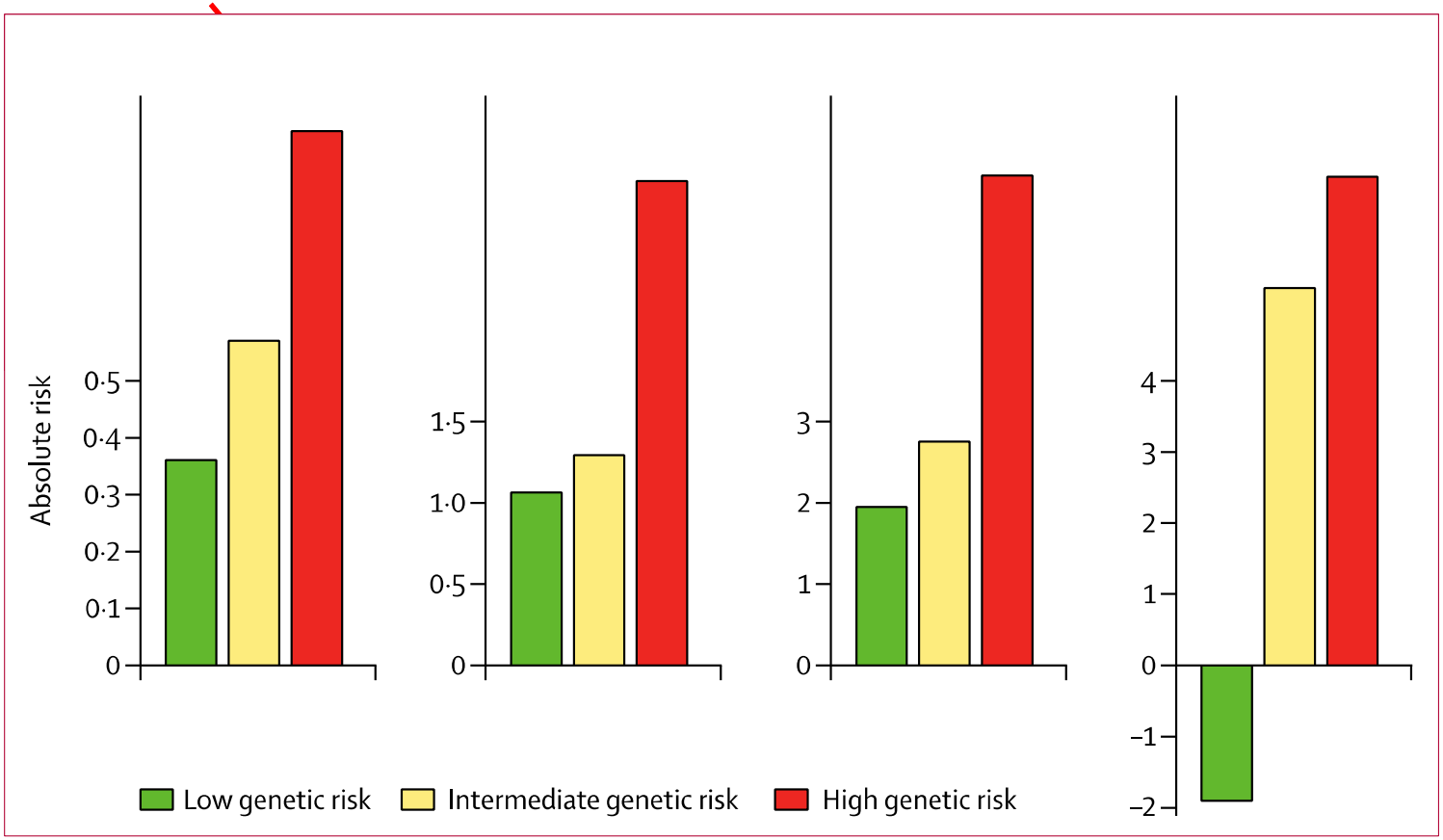
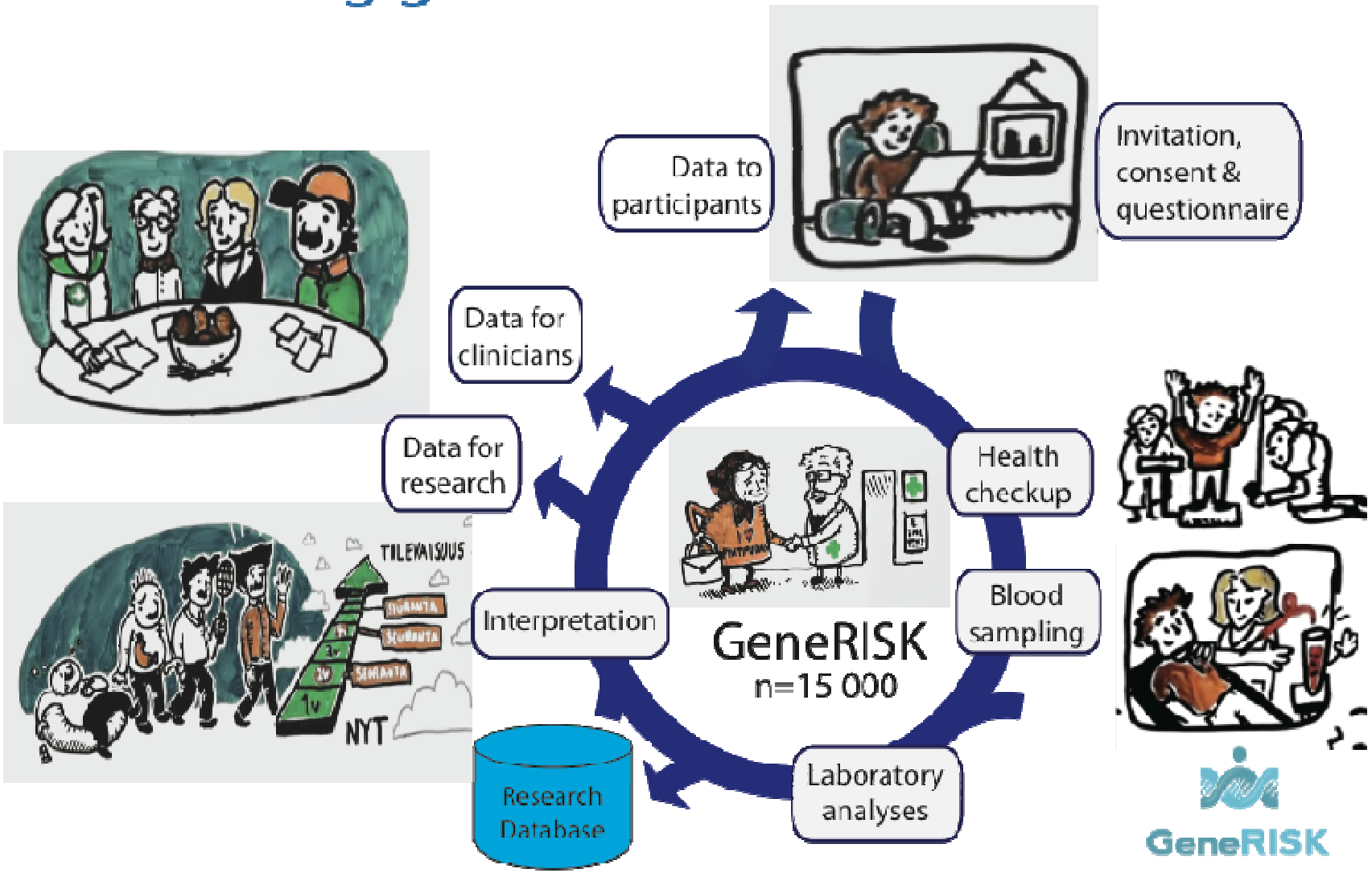


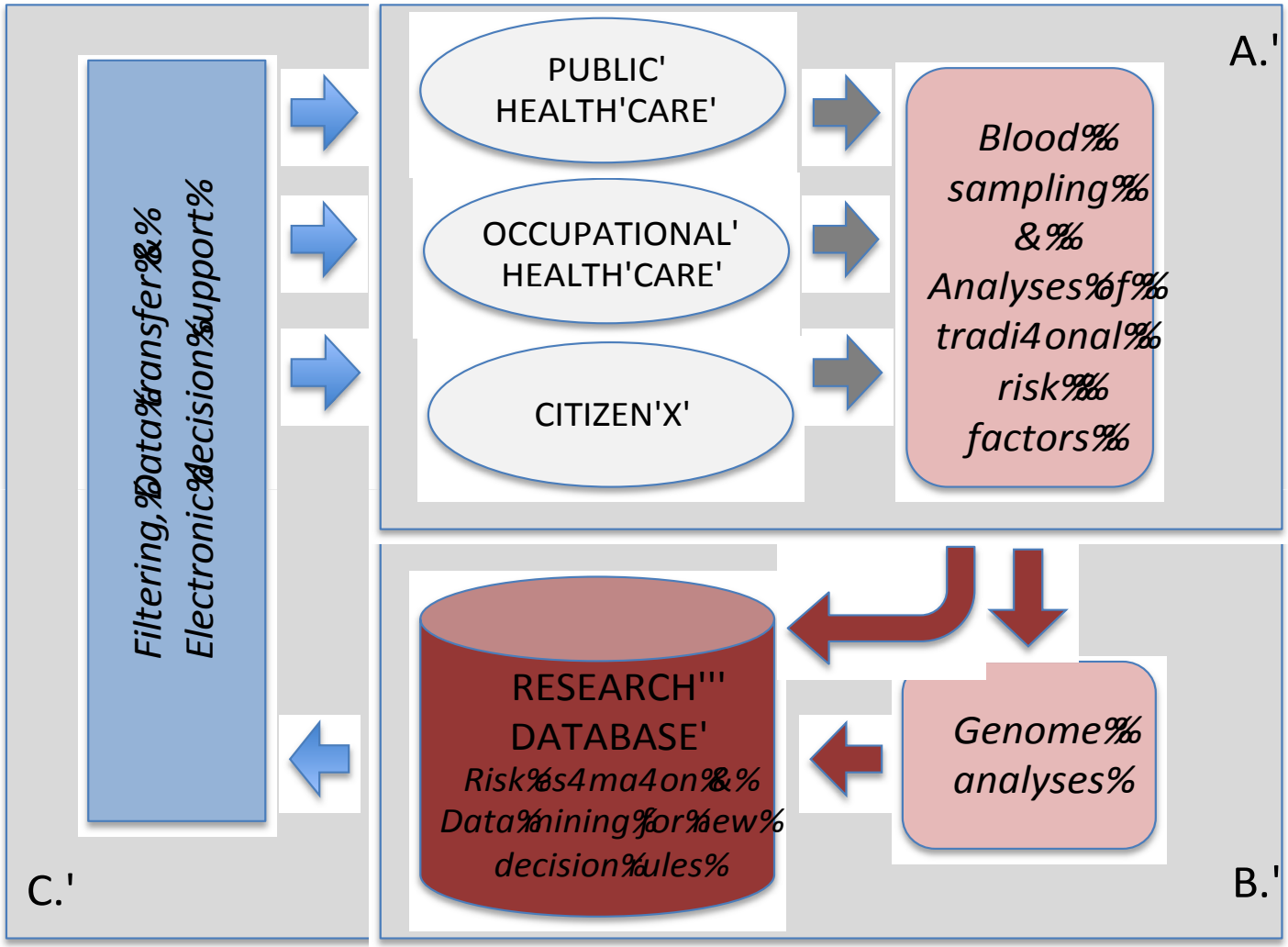
Figure 3: **Absolute risk reductions of coronary heart disease events with statin therapy across genetic risk score categories**

Mega et al, Lancet 2015

Translating genomic risk into health care



GeneRISK
Genomeista terveyttä



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