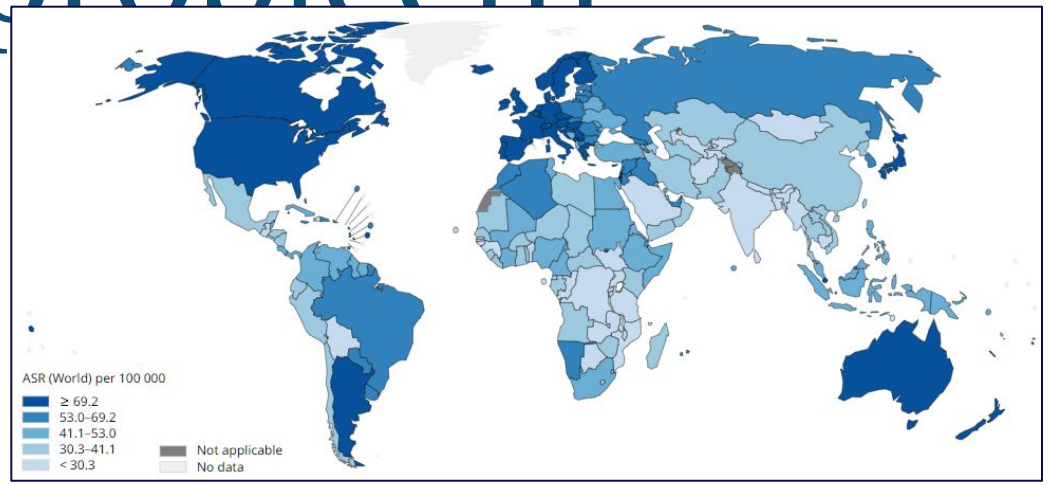
Rinnavähi personaliseeritud ennetus – Eesti ja rahvusvaheline tõenduspõhine vaade

Krista Kruuv-Käo

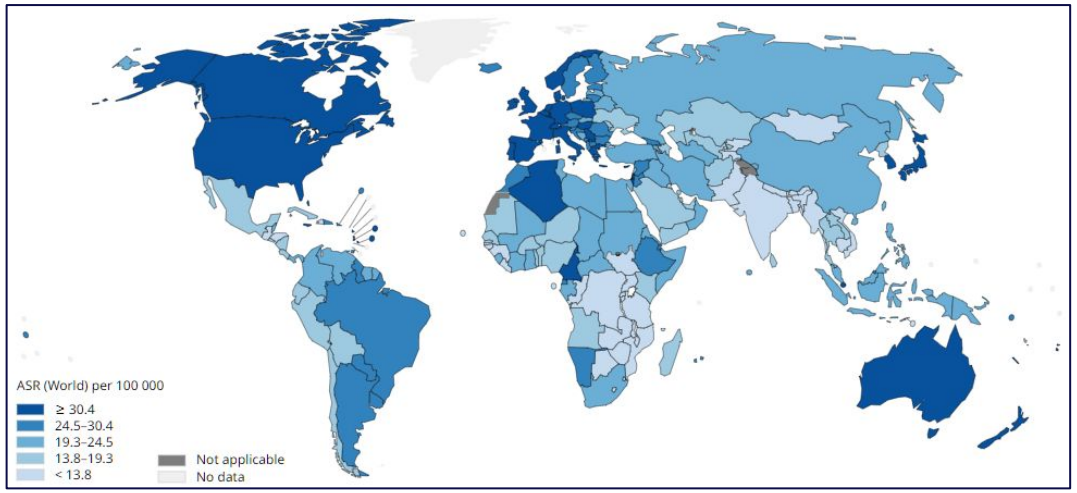
Eesti Arstide Päevad
12. aprill 2024, Tallinn

Rinnavähk kui globaalne probleem



Incidence in all age groups

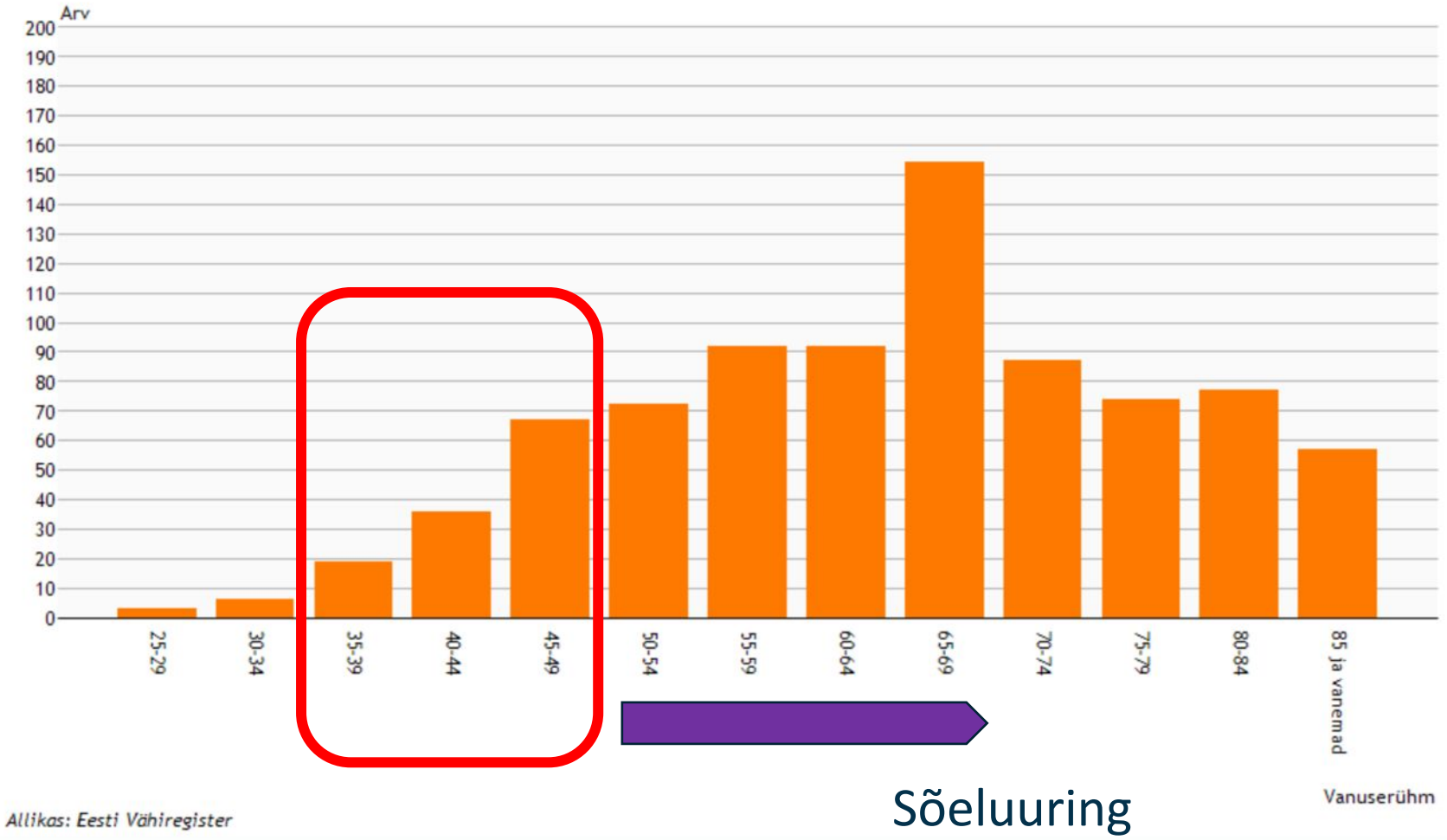
ASR - age-standardized rate



Incidence under 50Y

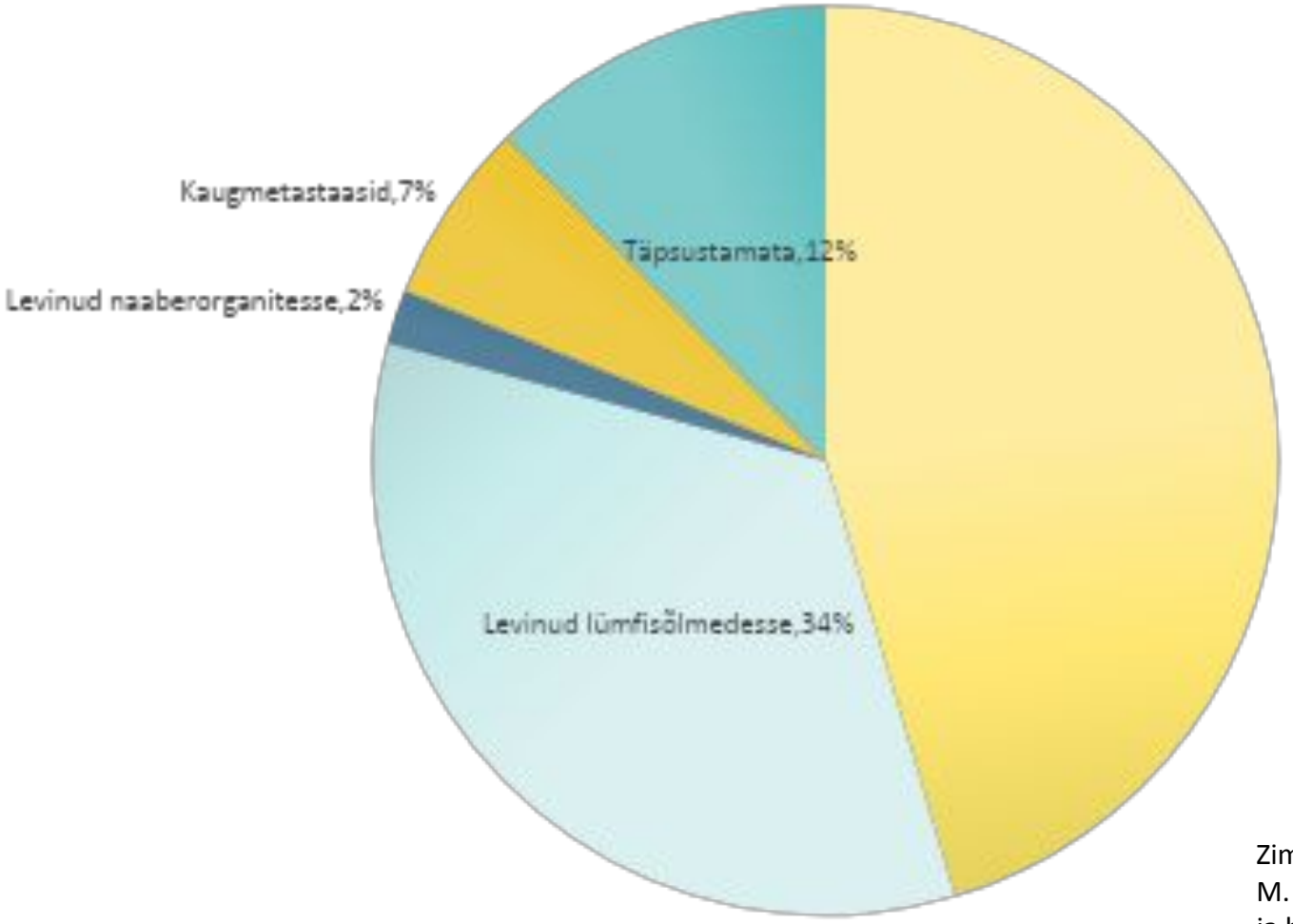
- Rinnavähk on kõige levinum pahaloomuline kasvaja naistel
- 2 miljonit juhtu aastas (WHO)
- Euroopas 58% juhtudest 50–69 aastastel naistel (IARC, 2018)
- Alla 50-aastaste naiste vähijuhud on halvasti käsitletud
- Kõige olulisem lapsorbude põhjustaja

Paljud rinnavähid diagnoositakse nooremas vanuses, osalemine alla 70%



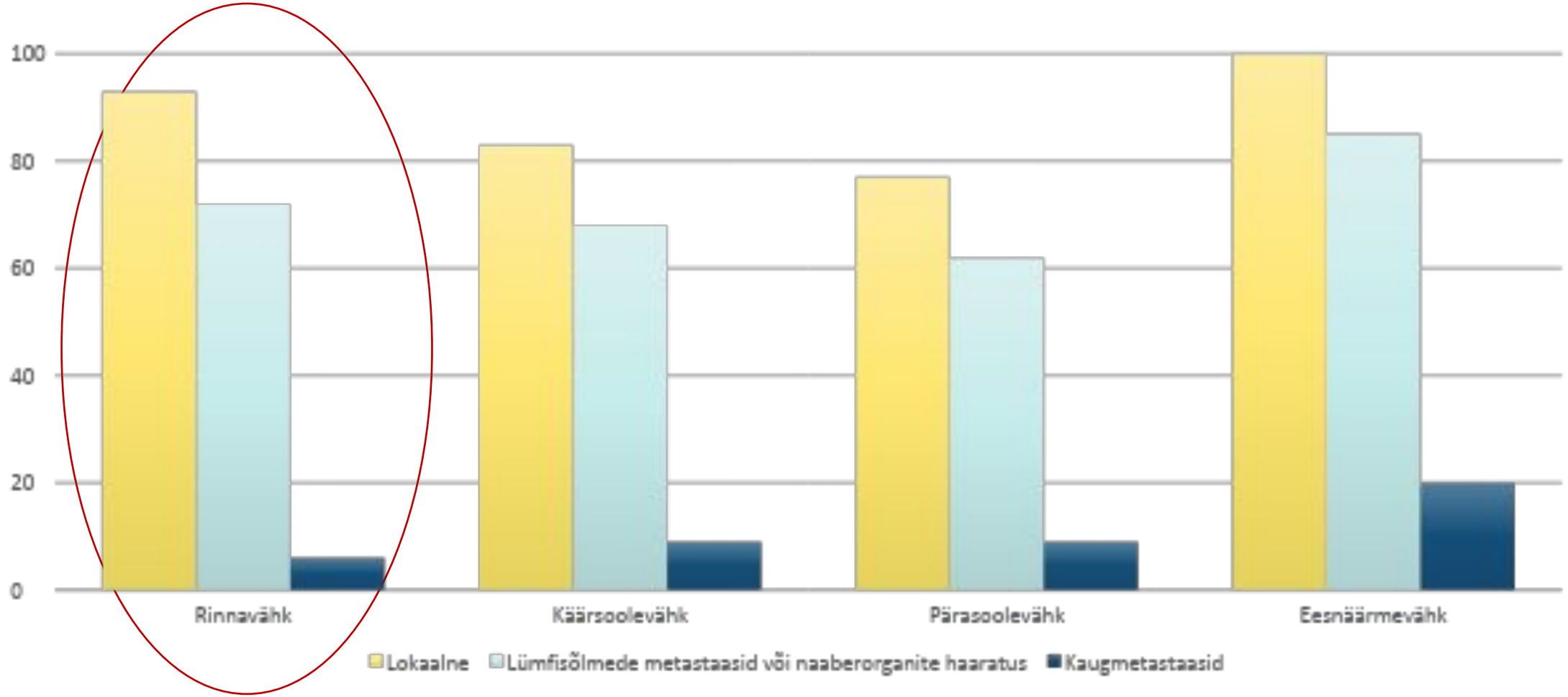
- Rinnavähi sõeluuring vanuses 50-69 aitab päästa elusid
- Alla 50aastastele naistele sõeluuringut ei tehta
- 2022. aastal osales rinnavähi sõeluuringus 63% uuringule kutsutud Eesti naistest.

Rinnavähi levik avastamisel



Zimmermann M-L, Innos K, Paapsi K, Härmaorg P, Mägi M. Vähk Eestis: haigestumus 2020, elulemus 2016-2020 ja hematoloogilised kasvajad 2011-2020. TAI 2023

10-aasta suhteline vähielulemus (%) Eestis 2016-2020



Antegenes®

Zimmermann M-L, Innos K, Paapsi K, Härmaorg P, Mägi M. Vähk Eestis: haigestumus 2020, elulemus 2016-2020 ja hematoloogilised kasvajad 2011-2020. TAI 2023

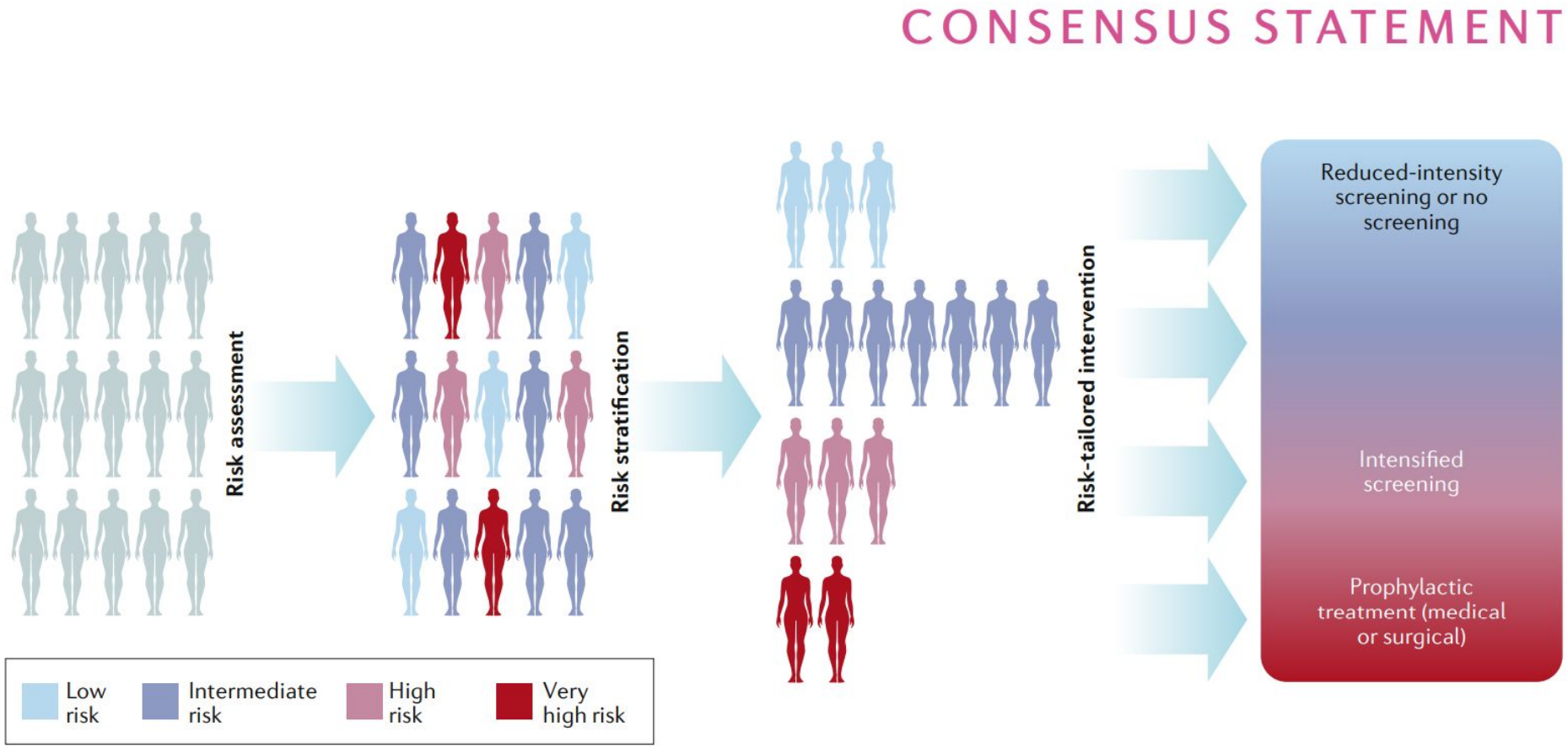
Elulemus 10 aastat pärast diagnoosi

Lokaalne ehk
I staadium

Levinud lümfisõlmedesse
ehk II-III staadium

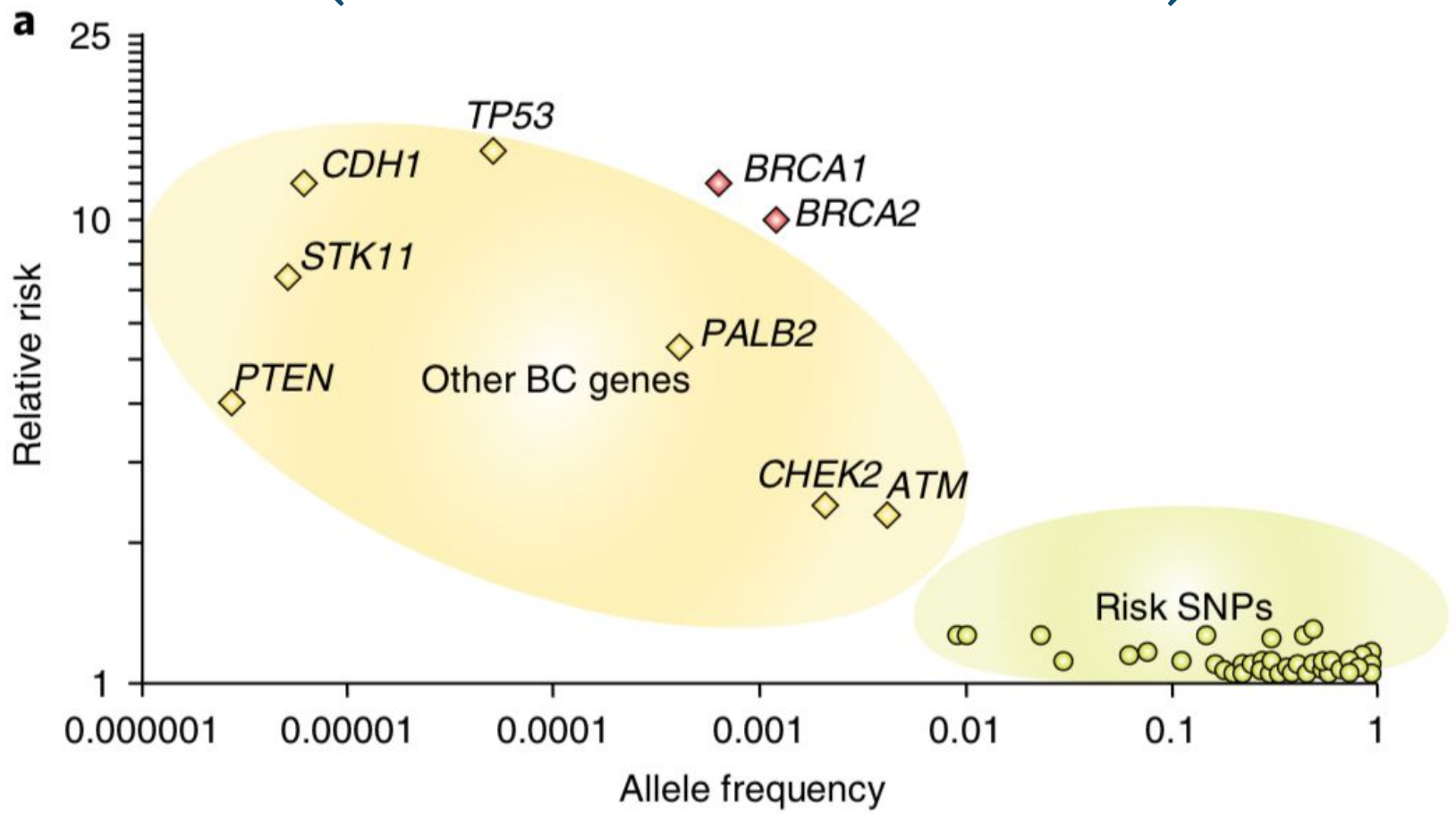
Kaugsiirded ehk
IV staadium

Rinnavähi personaliseeritud varane avastamine ja ennetamine: ENVISION consensus statement



European Collaborative on Personalized Early Detection and Prevention of Breast Cancer (ENVISION) Network. Nature Reviews Clinical Oncology. June, 2020

Pahaloomuliste kasvajate geneetiline eelsoodumus (rinnavähk näitena)

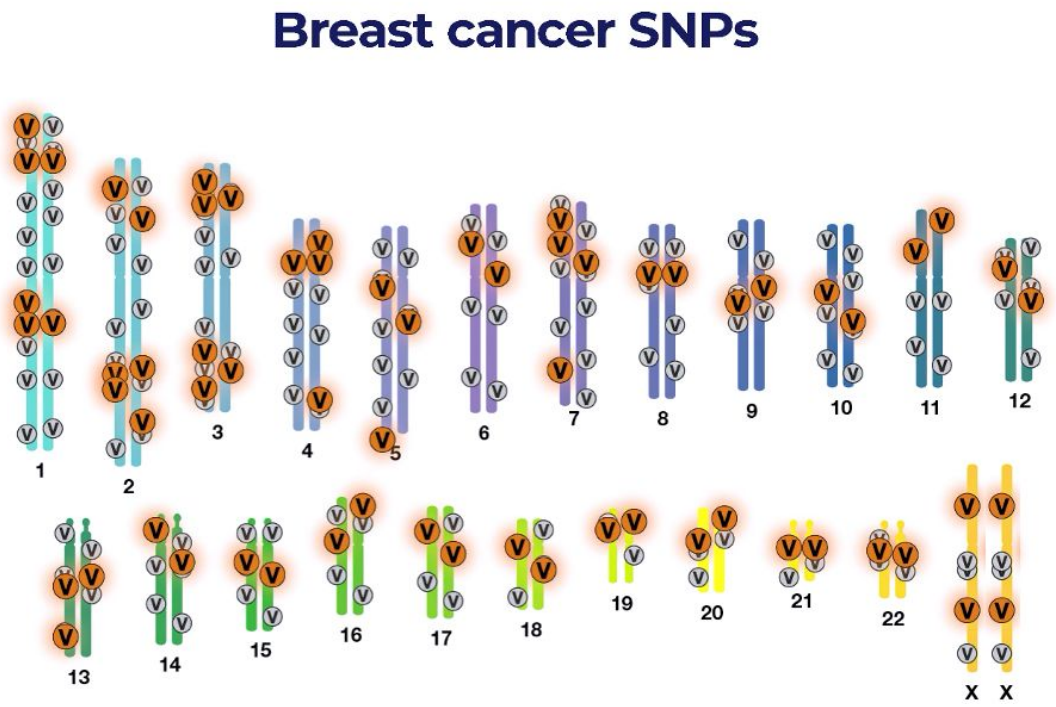


Turnbull C. et al. Cancer genetics, precision prevention and a call to action. Nature Genetics. Vol 50, Sept. 2018

Polügeenne riskiskoor

Kombineerib informatsiooni väga paljudest geneetilistest variantidest

Polügeensetel riskiskooridel põhinev geenitest aitab täpsustada geneetilist eelsoodumust erinevate kasvajate tekkeks



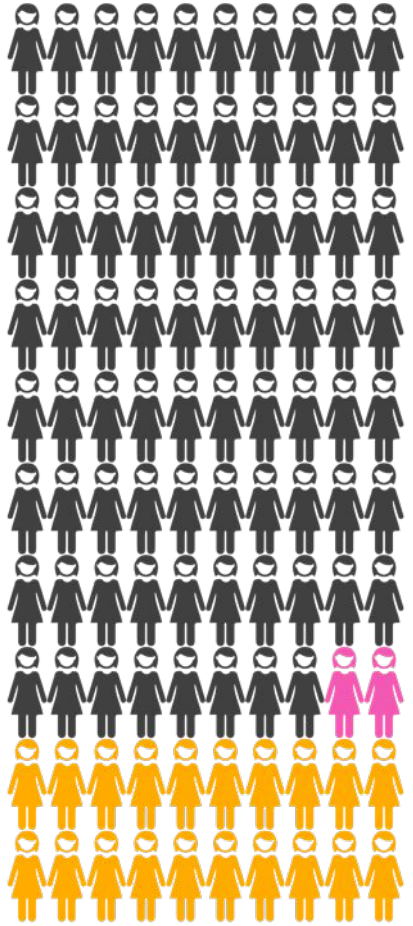
Rinnavähi geneetiline eelsoodumus Eestis

Haruldased kõrge ja mõõduka riski monogeensed variandid (*BRCA1&2, PTEN, CHEK2, PALB2, P53*, etc.)

- Suhteliselt harvad
- Testimine on praegu kallis
- Testimine on praegu näidustatud küsimustiku alusel

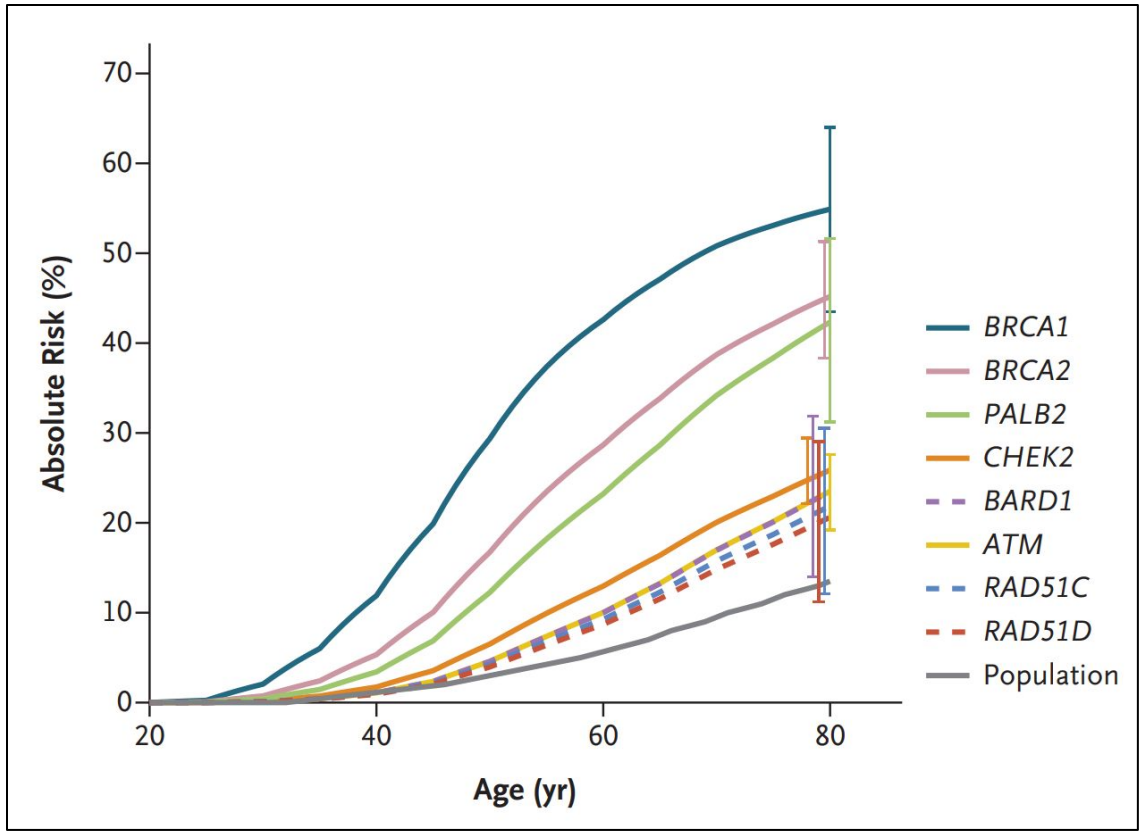
Polügeenne riskiskoor

- Testimine on odavam
- Mõõdukas kuni kõrge polügeenne risk sagedasem

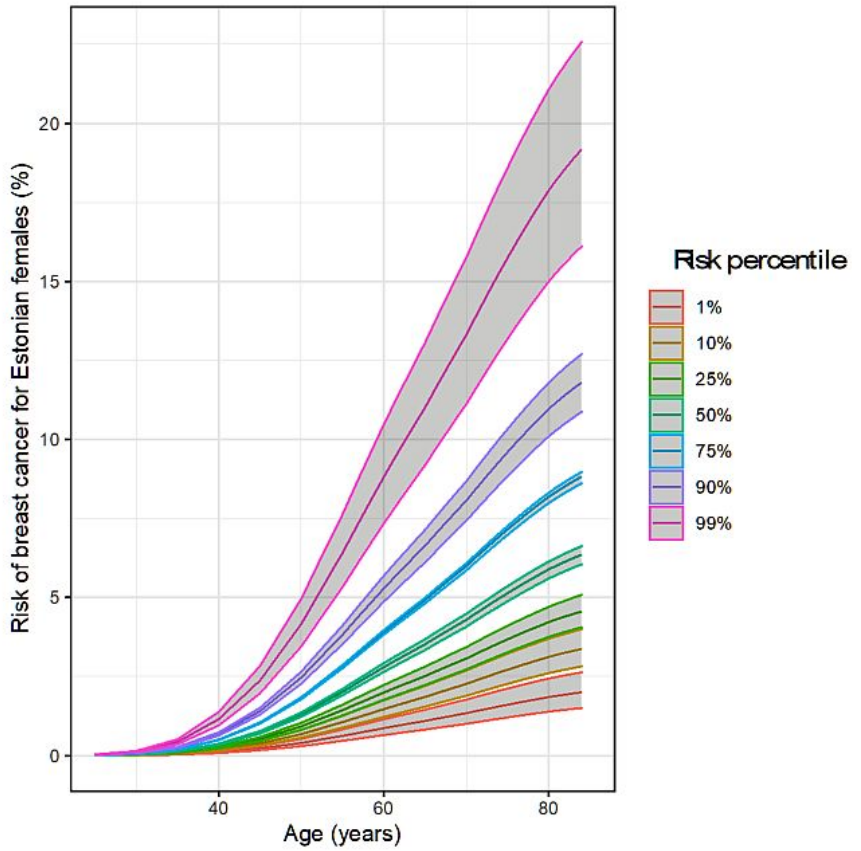


Eesti Biobank ja Antegenes andmed

PRS-i riskid on mõõduka riskiga monogeensete patogeensete variantidega (nt CHEK2) samal tasemel

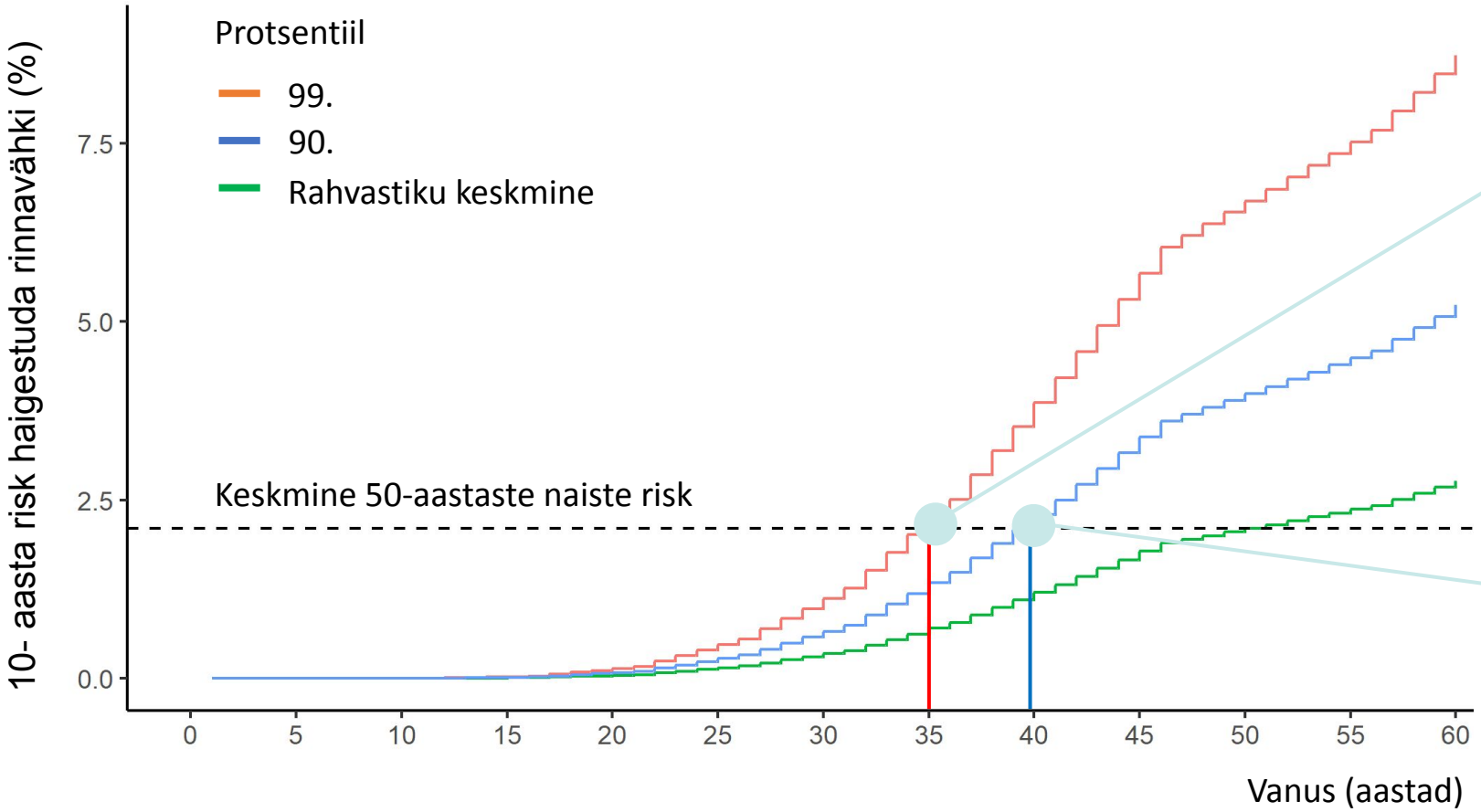


BCAC, *NEJM* ,2021



Padrik P, *et al. Breast Cancer: Basic and Clinical Research, 2023*

Osadel naistel ületab polügeenne risk elanikkonna 50-aastaste naiste riskiläve 15 aastat varem



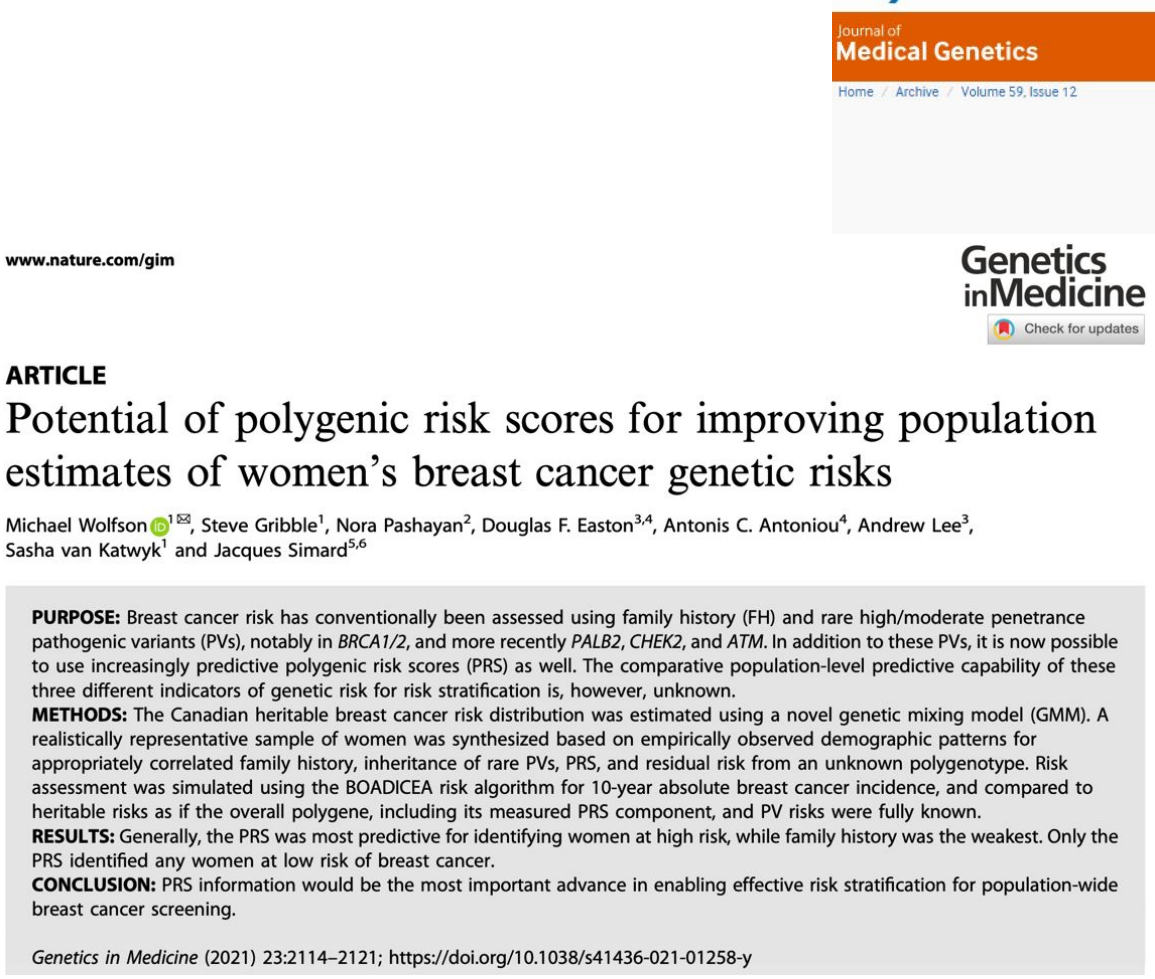
NÄIDE 1 (punane, protsentiil 99)

1% kõrge riskiga **naistes**t ületab juba **35-aastaselt** keskmise 50-aastase naise riskiläve.

NÄIDE 2 (sinine, protsentiil 90)

10% kõrge riskiga **naistest** ületab **40. eluaastaks** 50-aastase naise keskmise riskiläve.

PRS – kõige olulisem edasiminek, mis võimaldab kasutada riskide põhist kihistamist rahvastikku hõlmavas rinnavähi sõeluuringus



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Genetics in Medicine

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ARTICLE

Potential of polygenic risk scores for improving population estimates of women's breast cancer genetic risks

Michael Wolfson[1]✉, Steve Gribble[1], Nora Pashayan[2], Douglas F. Easton[3,4], Antonis C. Antoniou[4], Andrew Lee[3], Sasha van Katwyk[1] and Jacques Simard[5,6]

PURPOSE: Breast cancer risk has conventionally been assessed using family history (FH) and rare high/moderate penetrance pathogenic variants (PVs), notably in *BRCA1/2*, and more recently *PALB2*, *CHEK2*, and *ATM*. In addition to these PVs, it is now possible to use increasingly predictive polygenic risk scores (PRS) as well. The comparative population-level predictive capability of these three different indicators of genetic risk for risk stratification is, however, unknown.
METHODS: The Canadian heritable breast cancer risk distribution was estimated using a novel genetic mixing model (GMM). A realistically representative sample of women was synthesized based on empirically observed demographic patterns for appropriately correlated family history, inheritance of rare PVs, PRS, and residual risk from an unknown polygenotype. Risk assessment was simulated using the BOADICEA risk algorithm for 10-year absolute breast cancer incidence, and compared to heritable risks as if the overall polygene, including its measured PRS component, and PV risks were fully known.
RESULTS: Generally, the PRS was most predictive for identifying women at high risk, while family history was the weakest. Only the PRS identified any women at low risk of breast cancer.
CONCLUSION: PRS information would be the most important advance in enabling effective risk stratification for population-wide breast cancer screening.

Genetics in Medicine (2021) 23:2114–2121; https://doi.org/10.1038/s41436-021-01258-y

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Prospective validation of the BOADICEA multifactorial breast cancer risk prediction model in a large prospective cohort study

Xin Yang[1], Mikael Eriksson[2], Kamila Czene[2], Andrew Lee[1], Goska Leslie[1], Michael Lush[1], Jean Wang[1], Joe Dennis[1], Leila Dorling[1], Sara Carvalho[1], Nasim Mavaddat[1], Jacques Simard[3], Marjanka K Schmidt[4, 5], Douglas F Easton[1, 6], Per Hall[2, 7], Antonis C Antoniou[1]

Correspondence to Professor Antonis C Antoniou, Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge CB1 8RN, Cambridgeshire, UK; aca20@medschl.cam.ac.uk

Abstract

Background The multifactorial Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) breast cancer risk prediction model has been recently extended to consider all established breast cancer risk factors. We assessed the clinical validity of the model in a large independent prospective cohort.

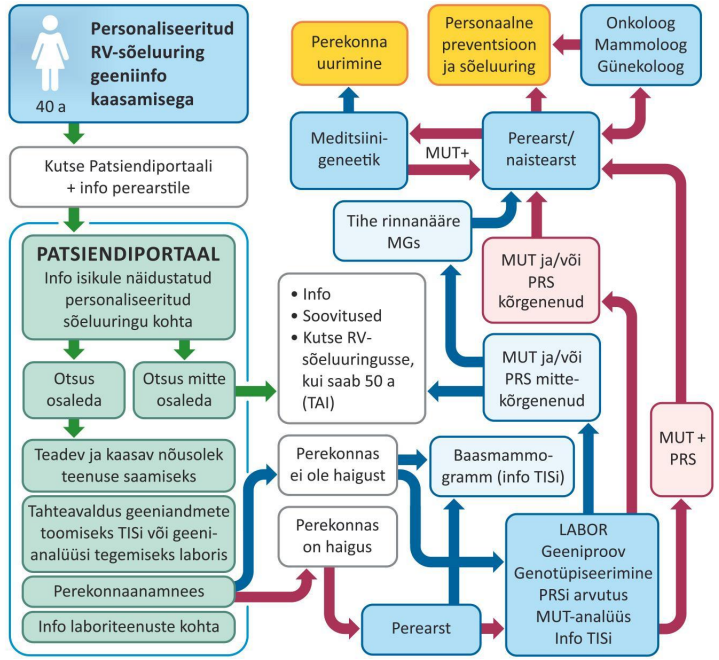
Methods We validated BOADICEA (V.6) in the Swedish KARolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA) cohort including 66 415 women of European ancestry (median age 54 years, IQR 45–63; 816 incident breast cancers) without previous cancer diagnosis. We calculated 5-year risks on the basis of questionnaire-based risk factors, pedigree-structured first-degree family history, mammographic density (BI-RADS), a validated breast cancer polygenic risk score (PRS) based on 313-SNPs, and pathogenic variant status in 8 breast cancer susceptibility genes: *BRCA1, BRCA2, PALB2, CHEK2, ATM, RAD51C, RAD51D* and *BARD1*. Calibration was assessed by comparing observed and expected risks in deciles of predicted risk and the calibration slope. The discriminatory ability was assessed using the area under the curve (AUC).

Results Among the individual model components, the PRS contributed most to breast cancer risk stratification. BOADICEA was well calibrated in predicting the risks for low-risk and high-risk women when all, or subsets of risk factors are included in the risk prediction. Discrimination was maximised when all risk factors are considered (AUC=0.70, 95% CI: 0.66 to 0.73; expected-to-observed ratio=0.88, 95% CI: 0.75 to 1.04; calibration slope=0.97, 95% CI: 0.95 to 0.99). The full multifactorial model classified 3.6% women as high risk (5-year risk ≥3%) and 11.1% as very low risk (5-year risk <0.33%).

Conclusion The multifactorial BOADICEA model provides valid breast cancer risk predictions and a basis for personalised decision-making on disease prevention and screening.

Personaalmeditsiini kliinilised juhtprojektid rinnavähi ja südame-veresoonkonna haiguste täppisennetuses 2018-2021

- Praegusest sõeluuringueast noorematele naistele vanuses 40-49
- Kulutõhus teenusemudel riskipõhiseks sõelumiseks:
  - PRS test kõigile
  - Monogeensete patogeensete variantide (MPV) testimine vastavalt perekonna vähianamneesile
- Päästab Eestis 14-22 elu aastas



Geneetikast lähtuv rinnavähi ennetamise projekt 2022-2024

- 2400 tervet naist: Eestis (vanuses 35–49), Portugalis (vanuses 35–49) ja Rootsis (vanuses 30–49)
- Digitaalne, kombineeritud või kohal osutatav teenusemudel
- PRS-i testimine kõigile
- MPV testimine näidustuse põhjal
- Personaliseeritud riskipõhine sõeluuring
- Kõrgenenud rinnavähi riskiga naistele intensiivistatud sõeluuringusoovitused koos mammograafia saatekirjaga

BRIGHT projekti Eesti haru AnteBC testi tulemused (avaldamisel)

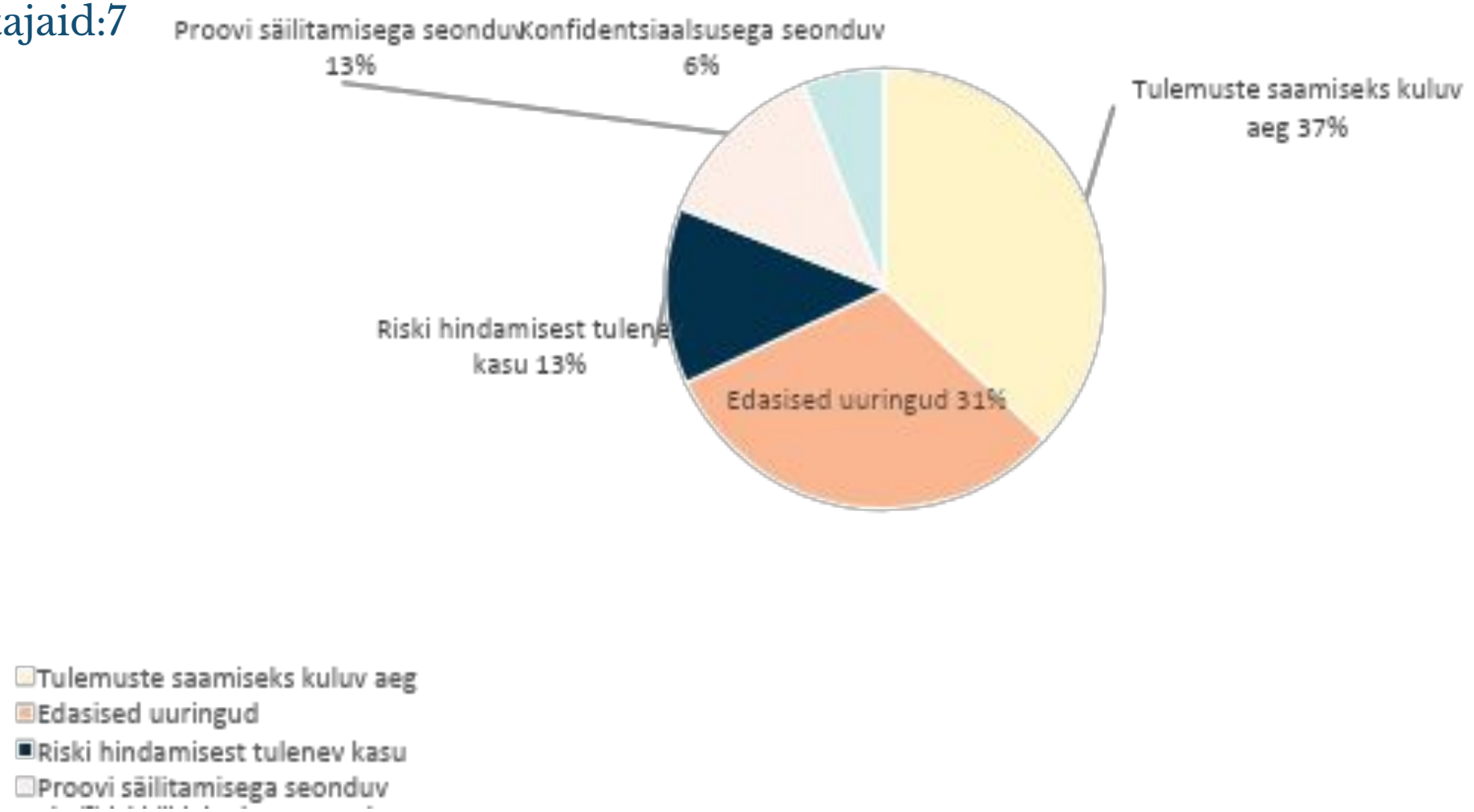
800 naist, vanus 35-49, keskmine 41

Riskigrupp PRS alusel	Riskitõus kordades	Arv	%
Keskmine risk	alla 1,5 X	658	82,2
Mõõdukalt kõrgem risk	1,5 – 2,7 X	134	**16,8**
Kõrge risk	üle 2,7 X	8	**1,0**

- 124 naist (15,5 %) peaks alustama MG sõeluuringut sel aastal
- 72 naist testiti MPV-de suhtes vastavalt kriteeriumidele
- 5 monogeense patogeense variandi leidu

BRIGHT uurijate tagasiside
Testi-eelsel konsultatsioonil enim küsitud küsimused

vastajaid:7



Testijärgsel konsultatsioonil enim küsitud küsimused

vastajaid:11

Testijärgsel konsultatsioonil valmistas uurijale raskusi:

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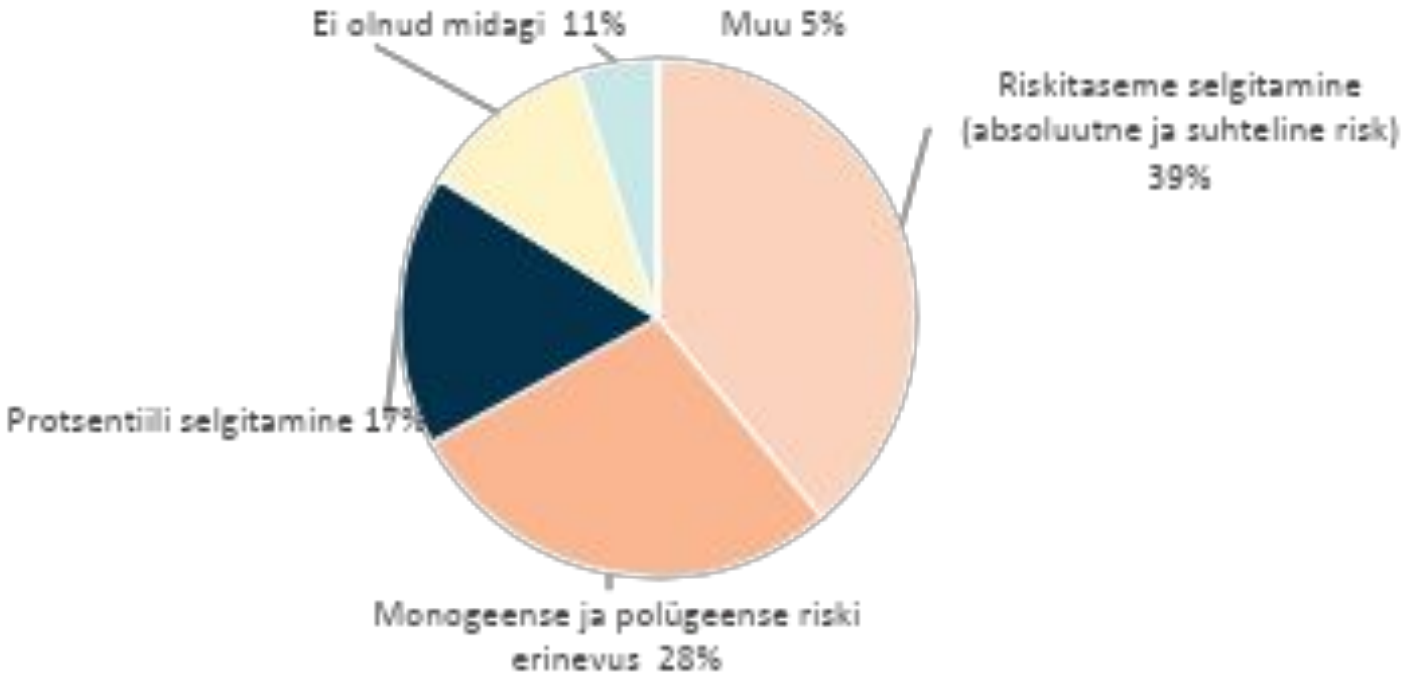


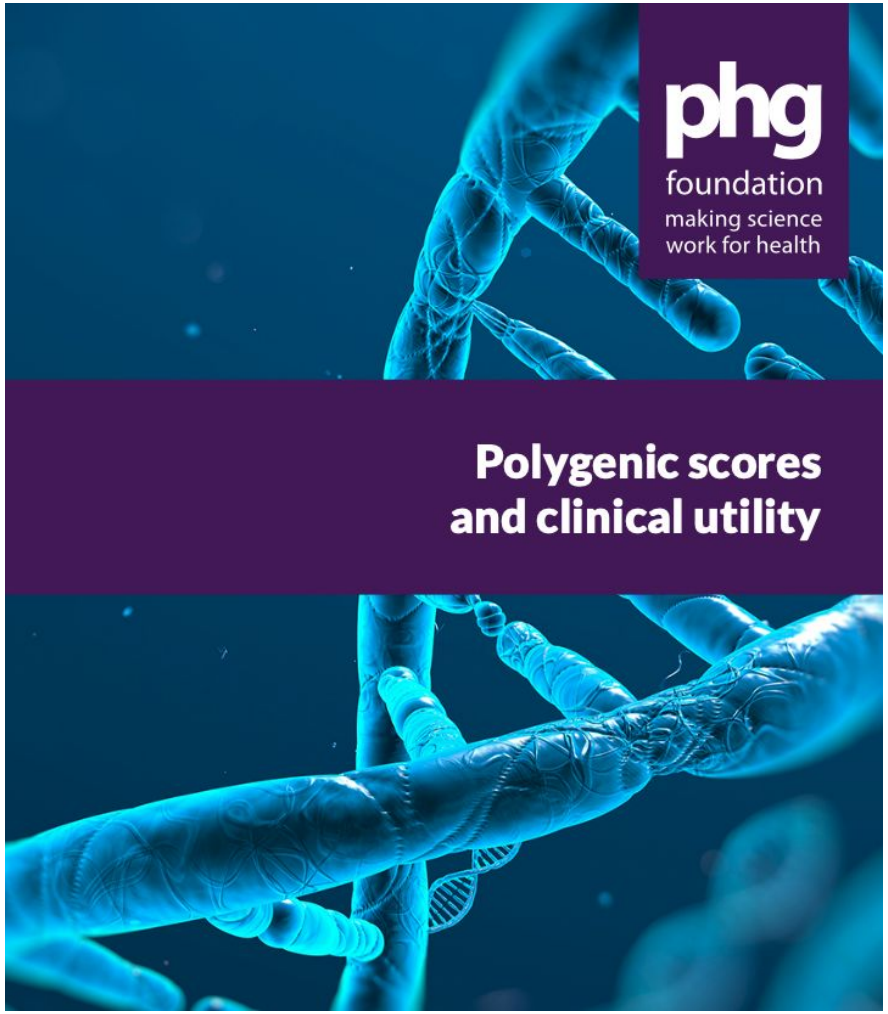
Riskitaseme selgitamine (absoluutne ja suhteline risk)
Monogeense ja polügeense riski erinevus
Protsentiili selgitamine
Ei olnud midagi
Muu

PRS-i tõhusus rinnavähi riskide põhisel stratifitseerimisel

- Kasutades sõeluuringu andmeid, demonstreerib uuring rinnavähi PRS-i efektiivsust riskide kihitamisel üksi ja kombineerituna vähi perekonna anamneesi ning monogeensete patogeensete variantidega.

- Ühel naisel kümnest on võrreldes ülejäänud elanikkonnaga oluliselt suurem risk rinnavähi tekkeks. Uuringu tulemuste põhjal oleks neil kasulik alustada rinnavähi sõeluuringuga ligi kümme aastat varem kui praegu.

- Uuringus uuriti ka geneetilise riskiprofiili seost rinnavähi diagnooside esinemisega sõeluuringute vahel. Kõrge riskiga naistel diagnoositi rinnavähk sõeluuringute vahel oluliselt sagedamini kui teistel naistel.



CONSENSUS
STATEMENT

OPEN

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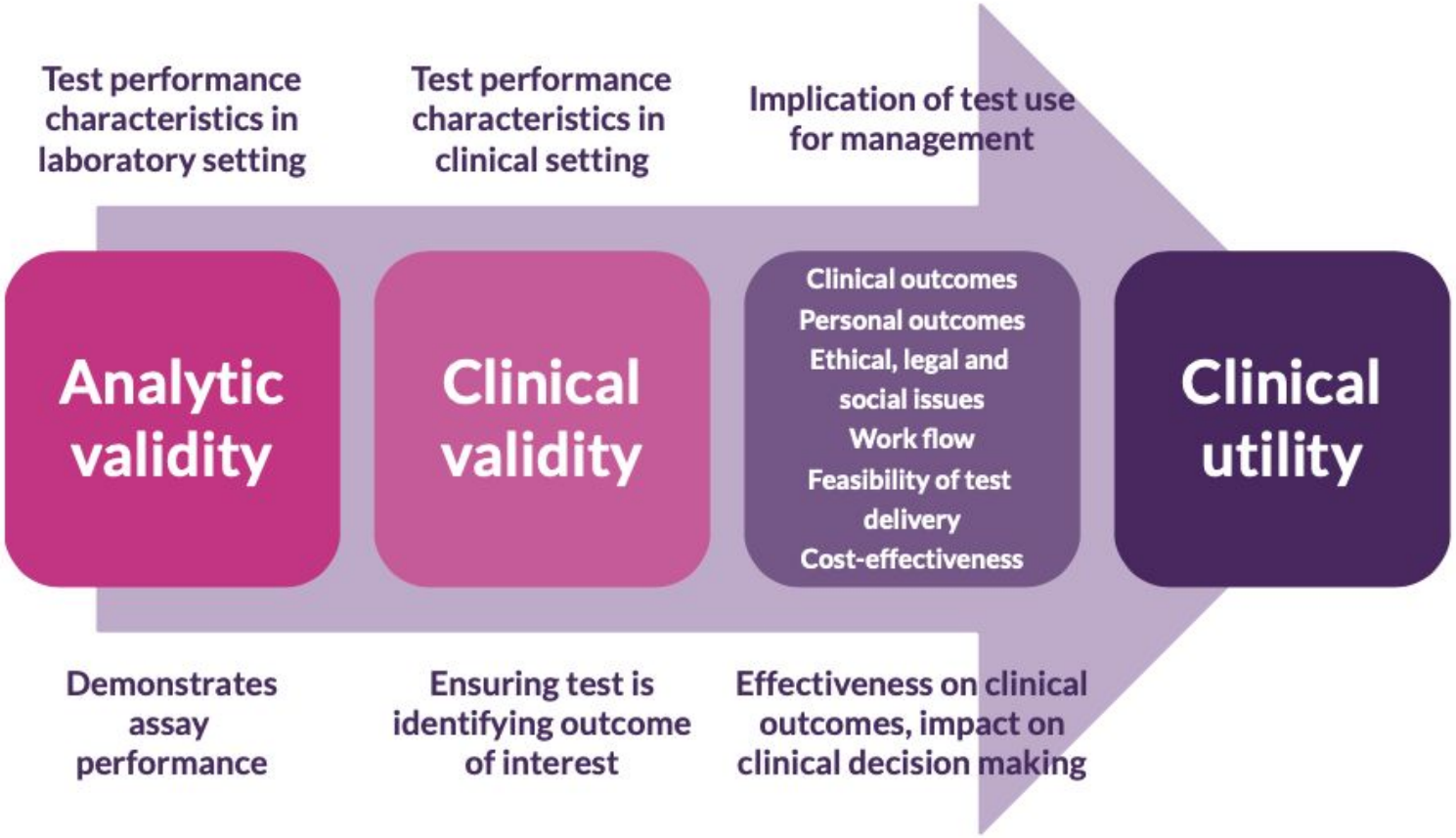
Personalized early detection and prevention of breast cancer: ENVISION consensus statement

Nora Pashayan[1], Antonis C. Antoniou[2], Urska Ivanus[3], Laura J. Esserman[4], Douglas F. Easton[2], David French[5], Gaby Sroczynski[6,7], Per Hall[8,9], Jack Cuzick[10], D. Gareth Evans[11], Jacques Simard[12], Montserrat Garcia-Closas[13], Rita Schmutzler[14], Odette Wegwarth[15], Paul Pharoah[2,16], Sowmiya Moorthie[17], Sandrine De Montgolfier[18], Camille Baron[19], Zdenko Herceg[20], Clare Turnbull[21], Corinne Balleyguier[22], Paolo Giorgi Rossi[23], Jelle Wesseling[24], David Ritchie[25], Marc Tischkowitz[26], Mireille Broeders[27], Dan Reisel[28], Andres Metspalu[29], Thomas Callender[1], Harry de Koning[30], Peter Devilee[31], Suzette Delaloge[32], Marjanka K. Schmidt[24] and Martin Widschwendter[28,33,34]✉

https://www.phgfoundation.org/report/polygenic-scores-and-clinical-utility

https://doi.org/10.1038/s41571-020-0388-9

Kliiniline kasulikkus



Polügeensete riskiskooride tervishoidu rakendamise printsiibid

- Tervishoiuteenustena, geenitestidena
- Tõenduspõhiselt
- Kliinilise kasulikkuse ja väärtuspakkumisega
- Kulutõhusalt
- Vastavuses tervishoiu regulatsioonidele

Polügeense riskiskoori arendamise võib jagada kolme etappi

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01767-6

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Development of a clinical polygenic risk score assay and reporting workflow

Limin Hao[1], Peter Kraft[2], Gabriel F. Berriz[1], Elizabeth D. Hynes[1], Christopher Koch[1], Prathik Korategere V Kumar[1], Shruti S. Parpattedar[1], Marcie Steeves[1,3], Wanfeng Yu[1,15], Ashley A. Antwi[4], Charles A. Brunette[4], Morgan Danowski[4], Manish K. Gala[5,6], Robert C. Green[6,7,8,9], Natalie E. Jones[4,7], Anna C. F. Lewis[10], Steven A. Lubitz[11,12,13], Pradeep Natarajan[6,11,12], Jason L. Vassy[4,6,8,9,16] ✉ and Matthew S. Lebo[1,6,14,16]

Implementation of polygenic risk scores (PRS) may improve disease prevention and management but poses several challenges: the construction of clinically valid assays, interpretation for individual patients, and the development of clinical workflows and resources to support their use in patient care. For the ongoing Veterans Affairs Genomic Medicine at Veterans Affairs (GenoVA) Study we developed a clinical genotype array-based assay for six published PRS. We used data from 36,423 Mass General Brigham Biobank participants and adjustment for population structure to replicate known PRS–disease associations and published PRS thresholds for a disease odds ratio (OR) of 2 (ranging from 1.75 (95% CI: 1.57–1.95) for type 2 diabetes to 2.38 (95% CI: 2.07–2.73) for breast cancer). After confirming the high performance and robustness of the pipeline for use as a clinical assay for individual patients, we analyzed the first 227 prospective samples from the GenoVA Study and found that the frequency of PRS corresponding to published OR > 2 ranged from 13/227 (5.7%) for colorectal cancer to 23/150 (15.3%) for prostate cancer. In addition to the PRS laboratory report, we developed physician- and patient-oriented informational materials to support decision-making about PRS results. Our work illustrates the generalizable development of a clinical PRS assay for multiple conditions and the technical, reporting and clinical workflow challenges for implementing PRS information in the clinic.

I Epidemioloogia / statistiline geneetika

- Arvutusmeetodeid rakendatakse GWAS-i andmetele, et arendada ja kinnitada PRS-i suurtes populatsioonides

II Labor

- Laboratooriumis töötatakse välja analüütiliselt ja kliiniliselt kehtiv analüüs ja tegevuste voog PRS-i arvutamiseks, tõlgendamiseks ja aruandluseks indiviidi jaoks.

III Patsiendi ravi

- Arst kontekstualiseerib PRS-i tulemused, et teha meditsiinilisi sekkumisotsuseid

Tervishoius kasutatavate diagnostiliste testide ohutuse ja tõhususe tagamiseks peavad need olema kinnitatud ja sertifitseeritud vastavalt in vitro diagnostikameditsiiniseadmete määrusele (IVDR) “Notified Body” poolt.

AnteBC test

CE-IVD taseme rinnavähi polügeense riski test kliiniliseks kasutuseks

AnteBC

BREAST cancer

HEALTH BOARD
MEDICAL DEVICES DEPARTMENT

06.03.2020

Notice of the medical device added to database

Applicant of data:
Berit Kolk
OÜ Antegenes
Estonia

Hereby we confirm that following medical device is added to Estonian Medical Devices Database (EMDDB)

Manufacturer:	**OÜ Antegenes**
Product name:	**AnteBC, polygenic risk score test for breast cancer**
Class:	**IVD**
EMDDB code:	**14726**

DNV·GL

MANAGEMENT SYSTEM CERTIFICATE

Certificate No: 10000353679-MSC-FINAS-EST
Initial certification date: 19 August 2020
Valid: 19 August 2020 - 18 August 2023

This is to certify that the management system of

ANTEGENES OÜ
Raatuse 77, 50605 Tartu, Estonia

has been found to conform to the Quality Management System standard:
ISO 13485:2016

This certificate is valid for the following scope:
MANUFACTURING POLYGENIC RISK SCORE (PRS) TESTS FOR CANCERS AND OTHER COMPLEX DISEASES.

- Valideeritud UK Biopanga ja Eesti Geenivaramu andmetega

Esimene eelretsenseeritud artikkel, mis kirjeldab PRS-testi kasutuselevõttu rutiinsesse kliinili

Rinnavähi PRS-ide täiendaval valideerimisel EstBB-s ja UKBB-s näitas 2803 SNP-ga mudel paremat toimivust võrreldes väiksema SNP-de arvuga mudelitega.

PRS-test eraldab erinevad BC riskitasemed ja seda on võimalik kliinilises praktikas rakendada riskide põhiseks stratifitseerimiseks rinnavähi sõeluuringus.

Implementation of Risk-Stratified Breast Cancer Prevention With a Polygenic Risk Score Test in Clinical Practice

Breast Cancer: Basic and Clinical Research
Volume 17: 1–13
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DOI: 10.1177/11782234231205700
Sage

Peeter Padrik[1,2], Mikk Puustusmaa[1], Neeme Tõnisson[1,3,4], Berit Kolk[1], Regina Saar[1], Anna Padrik[1] and Tõnis Tasa[1]

[1]OÜ Antegenes, Tartu, Estonia. [2]Clinic of Hematology and Oncology, Tartu University Hospital, Tartu, Estonia. [3]Institute of Genomics, University of Tartu, Tartu, Estonia. [4]Genetics and Personalized Medicine Clinic, Tartu University Hospital, Tartu, Estonia.

ABSTRACT

BACKGROUND: Breast cancer (BC) screening with mammography reduces mortality but considers currently only age as a risk factor. Personalized risk-based screening has been proposed as a more efficient alternative. For that, risk prediction tools are necessary. Genome-wide association studies have identified numerous genetic variants (single-nucleotide polymorphisms [SNPs]) associated with BC. The effects of SNPs are combined into a polygenic risk score (PRS) as a risk prediction tool.

OBJECTIVES: We aimed to develop a clinical-grade PRS test suitable for BC risk-stratified screening with clinical recommendations and implementation in clinical practice.

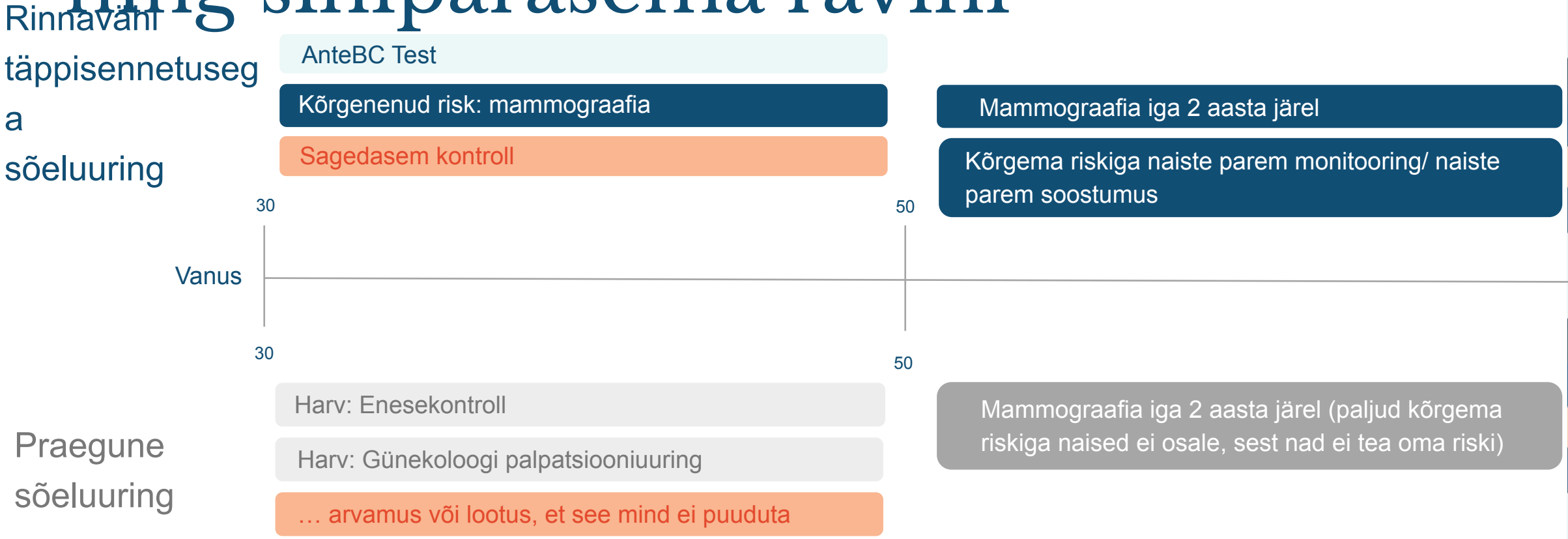
DESIGN AND METHODS: In the first phase of our study, we gathered previously published PRS models for predicting BC risk from the literature and validated them using the Estonian Biobank and UK Biobank data sets. We selected the best performing model based on prevalent data and independently validated it in both incident data sets. We then conducted absolute risk simulations, developed risk-based recommendations, and implemented the PRS test in clinical practice. In the second phase, we carried out a retrospective analysis of the PRS test's performance results in clinical practice.

RESULTS: The best performing PRS included 2803 SNPs. The C-index of the Cox regression model associating BC status with PRS was 0.656 (SE = 0.05) with a hazard ratio of 1.66. The PRS can stratify individuals with more than a 3-fold risk increase. A total of 2637 BC PRS tests have been performed for women between the ages 30 and 83. Results in clinical use overlap well with expected PRS performance with 5.7% of women with more than 2-fold and 1.4% with more than 3-fold higher risk than the population average.

CONCLUSION: The PRS test separates different BC risk levels and is feasible to implement in clinical practice.

KEYWORDS: breast cancer, polygenic risk score, screening, personalized prevention, genetic predisposition

Polügeense riski teadmine ja kasutamine viib tõhusama ennetuse ning sihipärasema ravini



Tõenditel põhinevad kliinilised stsenaariumid PRS testi kasutamiseks

1. Tervete naiste riskikäsitlus päriliku vähiga tegelevates kliinikutes

   Monogeensete patogeensete variantideta naised

   Naised, kellel on diagnoositud monogeensed patogeensed variandid (eriti ATM, CHEK 2)

2. Kliiniline teenus personaliseeritud rinnavähi ennetuseks (oportunislik skriining) – väljaspool rahvastikupõhiseid sõeluuringuprogramme

   Praegu rakendatud Antegenese poolt era- ning kombineerituna Tervisekassa teenusega

3. Rinnavähi rahvastikupõhise sõeluuringuprogrammi täpsemaks ja tõhusamaks muutmiseks

   Personaliseeritud sõeluuring 40. aastastele naistele Tervisekassa poolt käivitamisel

Tänan!

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