Juni Palmgren

Swedish eScience Research Centre
Annual Meeting 2014-04-23
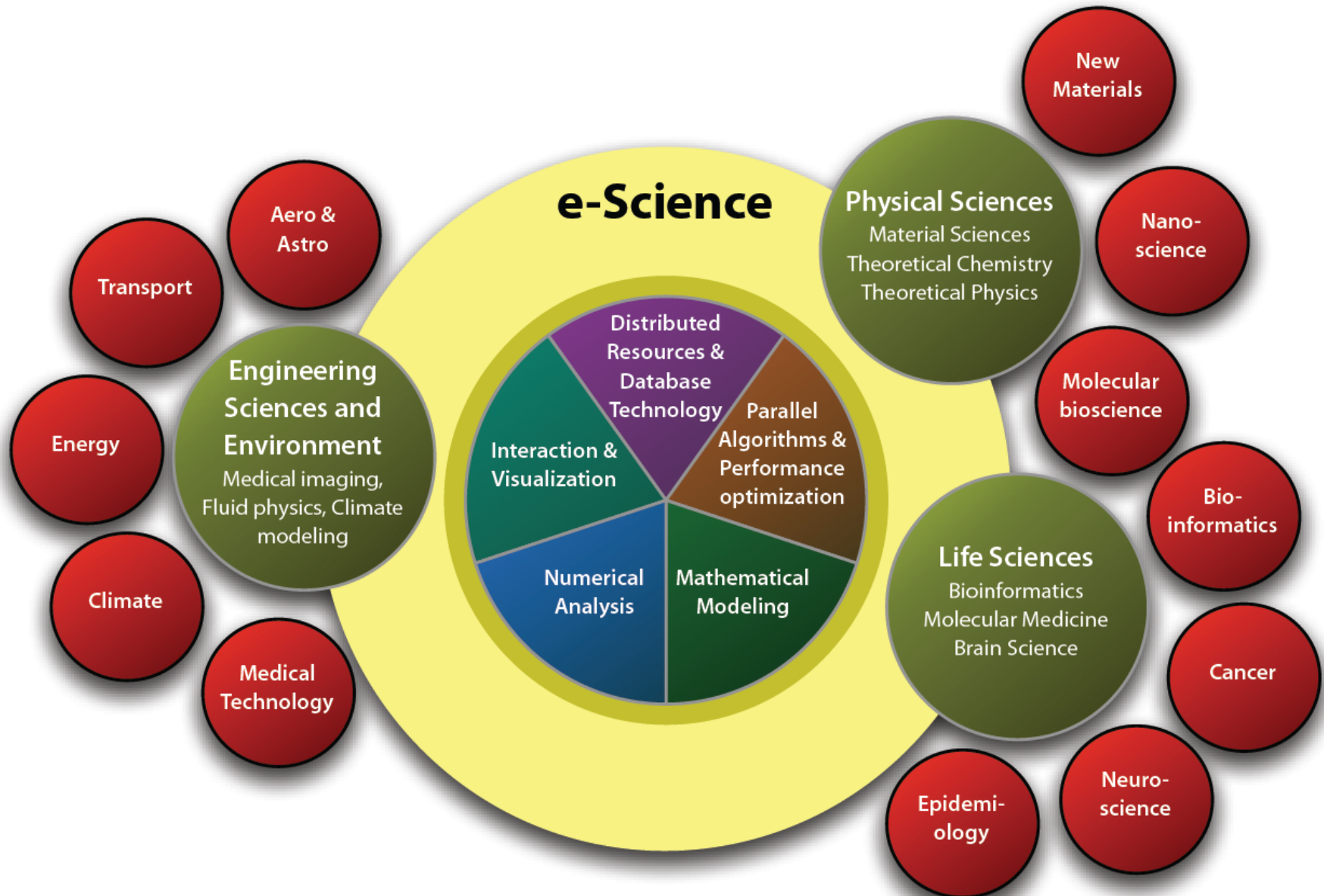
Feb 25th 2010 | From *The Economist* print edition

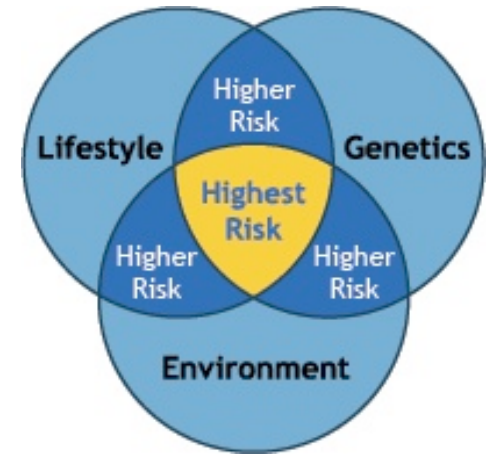*eScience for Cancer Prevention and Control, eCPC*

SeRC Complex Disease Community

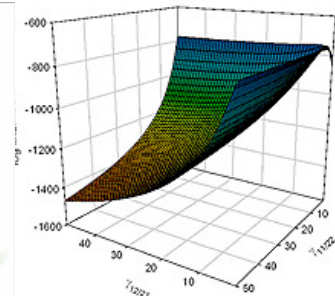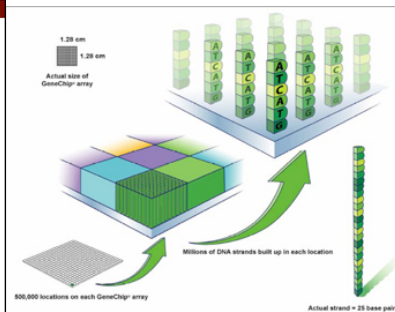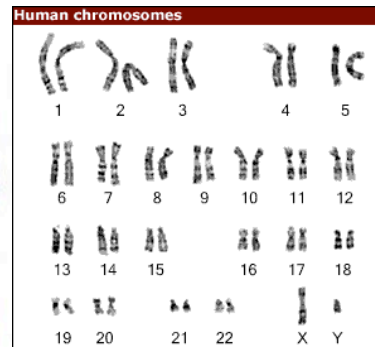# SeRC eScience Structure

eScience for complex human disease

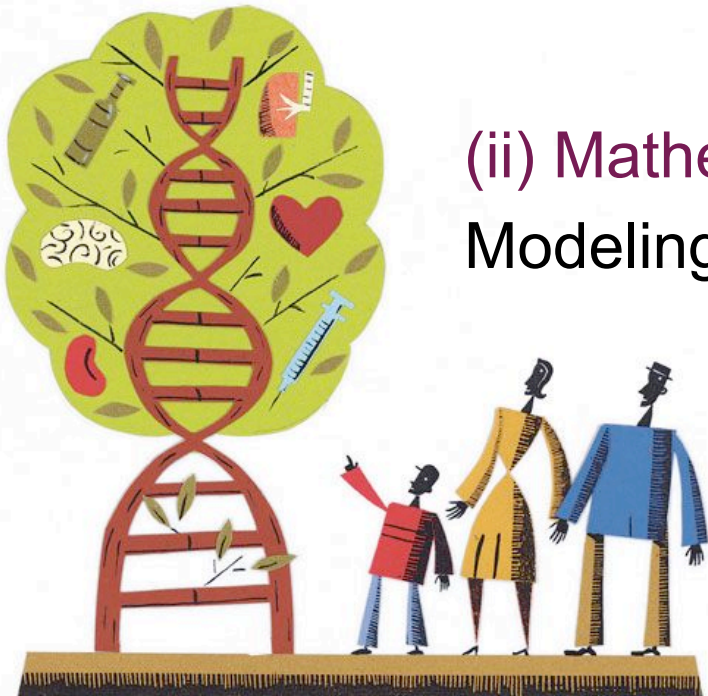Science focus: Biological mechanisms, early detection, prevention and cure

eScience tools

(i) Informatics: Data integration, secure transfer and storage

(ii) Mathematics and statistics
Modeling, simulation and inference

SeRC Complex Disease Community

- **Cancer & Data science**

Juni Palmgren
Jan-Eric Litton

- **Neuroscience**

Jeanette Hellgren
Kotalesky

- **Computational medicine**

Jesper Tegner

SeRC eScience for Cancer Prevention and Control eCPC   2012-2014

Can new screening and prevention strategies reduce morbidity, mortality, side-effects and cost?

Cervical cancer

Cytology + HPV screening + HPV vaccination

Breast cancer

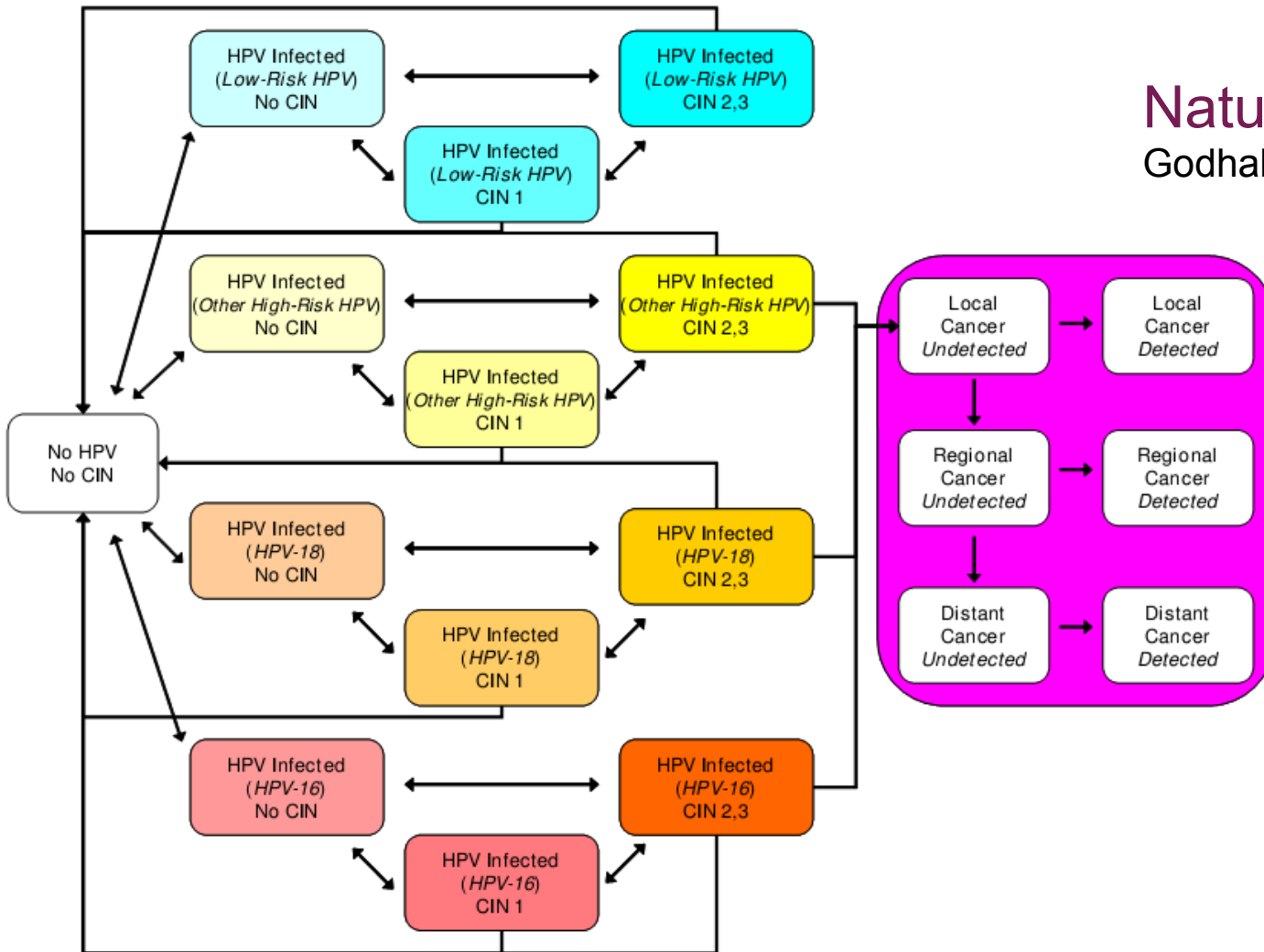Mammograms + reproductive history + genetic markers + breast density

Prostate cancer

PSA + genetic/molecular markers

Cervical cancer

ACCES Advancing Cervical Cancer Eradication Strategies
SSF 2011-2016

Natural history model
Godhaber Diebert et al 2007

eCPC Microsimulation Model

- Simulate individual event histories
- Aggregate to population level
- Assess the model fit (calibration)
- Evaluate effects of intervention

Alexander Ploner

Reduction in Cervical Cancer Incidence (Bodhager Diebert et al. 2007)

Vaccination Only

Screening Every 2 Years Only

Screening Every 2 Years with Vaccine
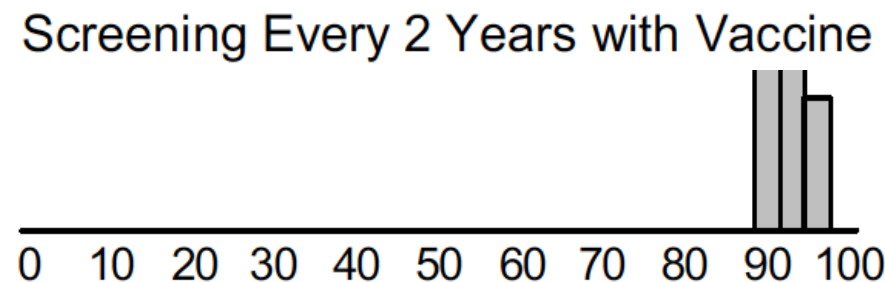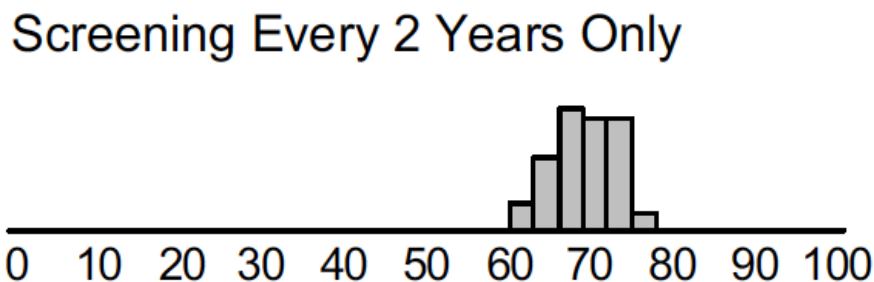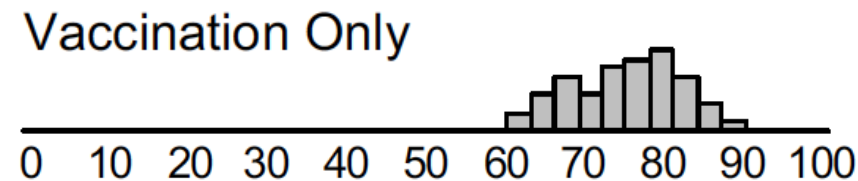
Uncertainty in model predictions due to parameter estimation, sampling variability, the selected calibration data, simulation variability etc.

eCPC Calibration
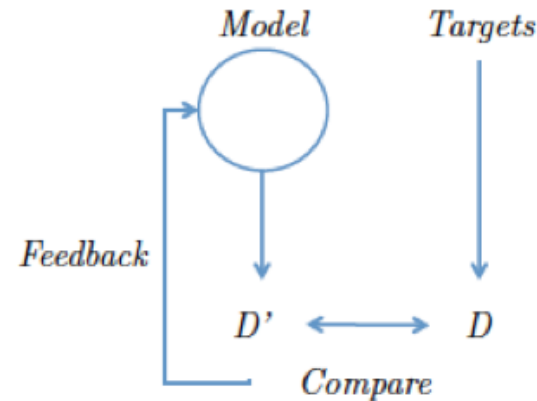
Approximate Bayesian Computation

A method to simulate observations from posterior distributions without the explicit use of likelihoods.

- Internal parameter vector: θ
- Prior distribution $\pi(\theta)$ for θ
- Data distribution $f_j(y_j; \omega_j) = f_j(y_j; g_j(\theta))$, for data $y = \{y_1, \ldots, y_m\}$
- Posterior distribution $p(\theta|y)$

Alexandra Jauhiainen

Informatics
Cervical cancer prevention database

Keyfile Pnr lopnr	Women resident in Sweden ~1960-2011 County, municipality 1968-2011

Statistics Sweden (SCB)

Women resident in Sweden ~1960-2011 County, municipality 1968-2011
Multi Generation Register -2011 Children, parents, siblings, "partners"
Migration -2011 Dates of immigration and emigration

Cervical screening data -2012 Pap smears, histological samples, invitations, HPV tests

Case-control study cervical cancer Invasive cervical cancer, CIS, controls, Pap smears, HPV

SVEVAC – 2013-06 HPV vaccination

Attitude survey adults - 2007	Attitude survey parents - 2007

External data sources

Education 1985-2011
Censuses 1960, 70, 80, 90
LISA -2011

Cancer register - 2011	Causes of Death register - 2011
Patient register - 2012	Medical Birth register - 2012

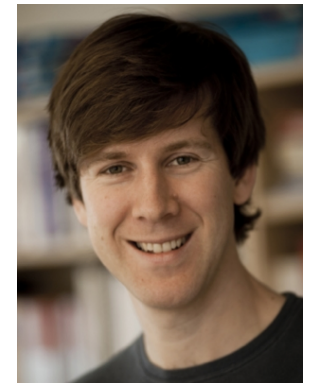| Drug prescription register -2012 |
|---|

Socialstyrelsen

SAIL – Sample Availability System

- Overview of data – what is available
- Plan studies, investigate data available for subset of patients; Security of data transfer
- SAIL: Developed in international consortium

Ola Spjuth

Jim Dowling

SeRC
Swedish e-Science Research Centre

Uniquer

EMBL-EBI

FIMM
Institute for Molecular Medicine Finland

Cancer Risk Prediction Centre, CRiSP
VR Linnaeus 2008-2018

Breast cancer is the most common cancer among women in Sweden with almost 8,000 new cases annualy. In Sweden 1,500 women die from breast cancer yearly but there is a remarkable difference between outcomes of localized vs advanced disease.

Prostate cancer is the most common cancer among men in Sweden today and yearly almost 10,000 new cases are diagnosed. Despite the old age of onset, the morbidity and mortality of this cancer is substantial with more than 2,500 deaths annually.

We know that cancer mortality can be reduced if cases are detected and treated early, but there is a problem with over-diagnosis and over-treatment. **What if we instead could predict the risk for aggressive cancers?** Our research focuses on understanding cancer risk and how to design individualized prevention strategies.

PI: Per Hall   PI: Henrik Grönberg

Personalized Cancer Prevention!

Personalized screening; Why?

Effictiveness of current practice for early detection
of breast and prostate cancer is questioned!

(Esserman et al 2009; Chowdhury et al 2013)

- Organised mammographic screening
- Widespread opportunistic PSA testing

Rates of detection of slow growing cancers increase

Beware of overdiagnosis, overtreatment,

increasing cost and increase in side effects!

Aggressive cancers and mortality do not decrease enough

Tumor growth

Source: Esserman et al (2009)
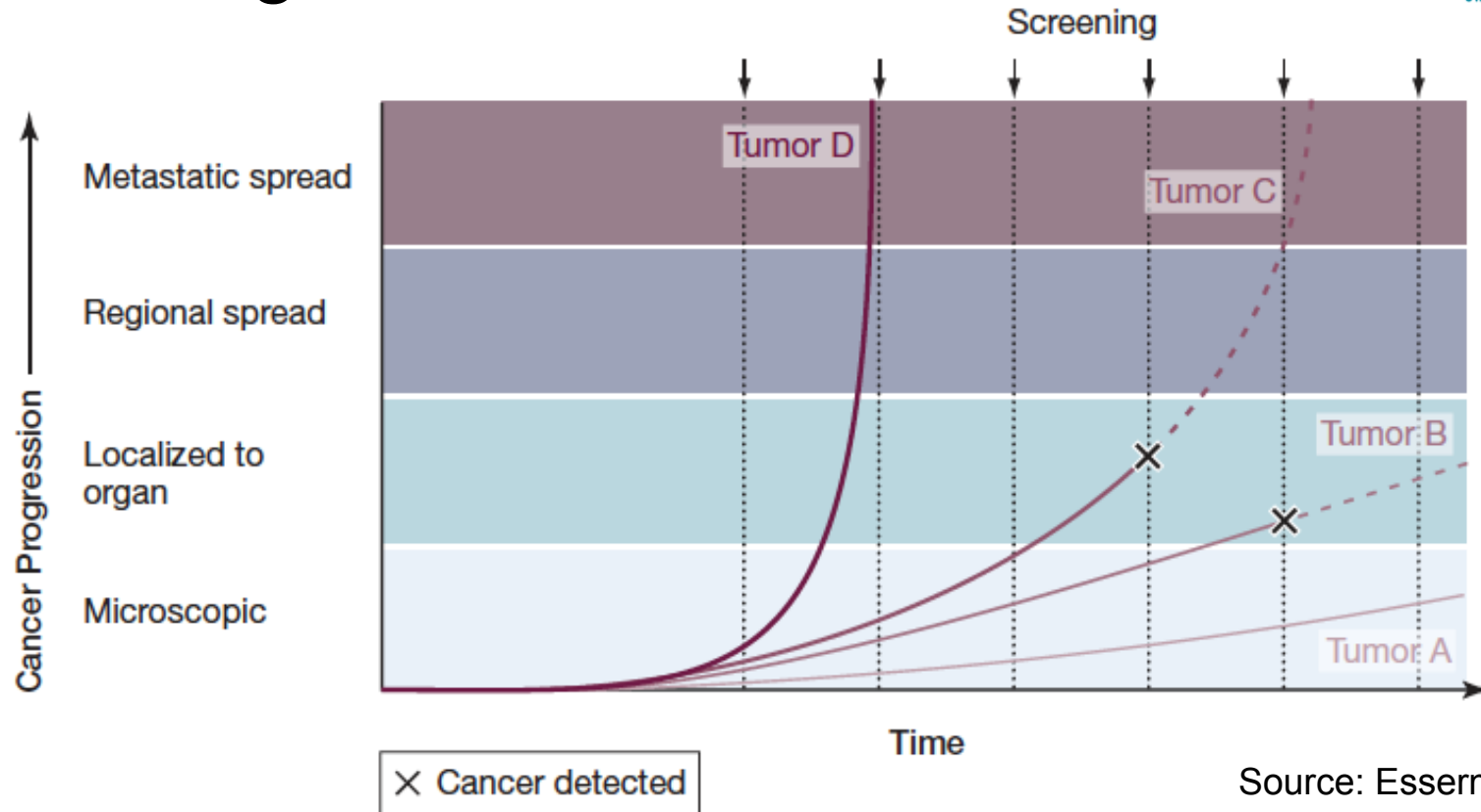
Need to

- Understand how tumors differ
- Develop novel prediction models
- Identify high and low risk individuals
- Evaluate personalized screening programmes for benefits, harm and cost

Compare mutation patterns of interval and screening detected breast cancers

Emma Ivansson

Image by Klevebring and Lindberg

Breast density as risk factor
Imaging technology and computational techniques

$$h_d(x, y) = \frac{\ln\left(P(x, y) / P_{Fat}\right)}{\mu_{fat} - \mu_{dense}}$$

Thickness of Dense tissue

Attenuation coeffs. At recorded tube voltage, compressed breast thickness…

```
Volpara v1.3.0
Breast Density Assesment

Patient Name    vpaHR001
Patient ID      001
Patient DOB     06/24/1929
Accession #     0001373051
Study Date      06/24/2010

Factor                                  Right      Left
Fibroglandular Tissue Volume (cm3)      49.0       41.2
Breast Tissue Volume (cm3)              733.8      752.7
Breast Density (%)                      6.7        5.5

Volpara Density Grade (tm)                          2
```
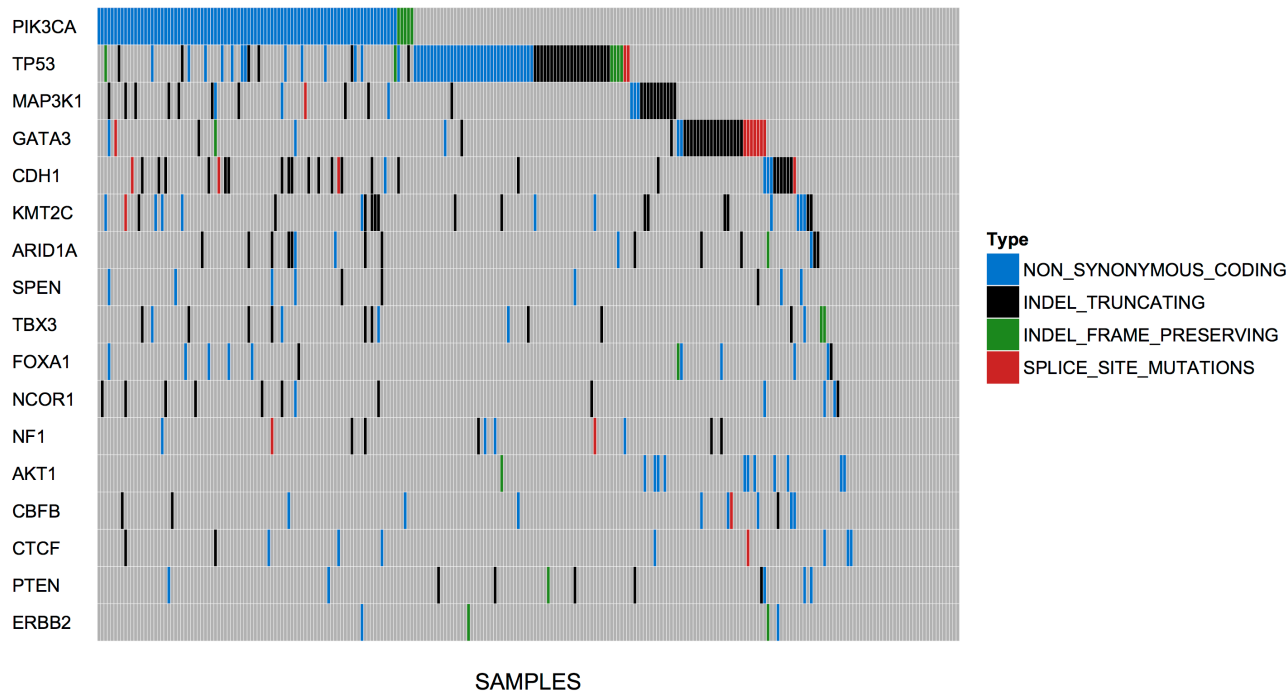
volpara™

3D Density Map
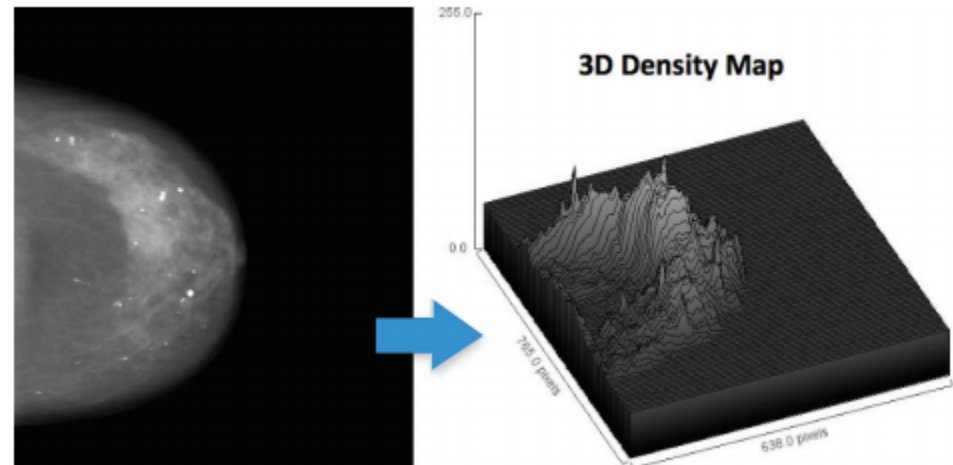
Automated measurement of volumetric mammographic density: a promising tool for

widespread breast cancer risk assessment.

Judith S. Brand [1*], Kamila Czene [1], John A. Shepherd [1], Karin Leifland [2], Boel Heddson [3],

Ann Sundbom [4], Mikael Eriksson [1], Jingmei Li [5], Keith Humphreys [1], Per Hall [1].

Breast cancer screening
Models for screening sensitivity and tumor growth accounting for mammographic density
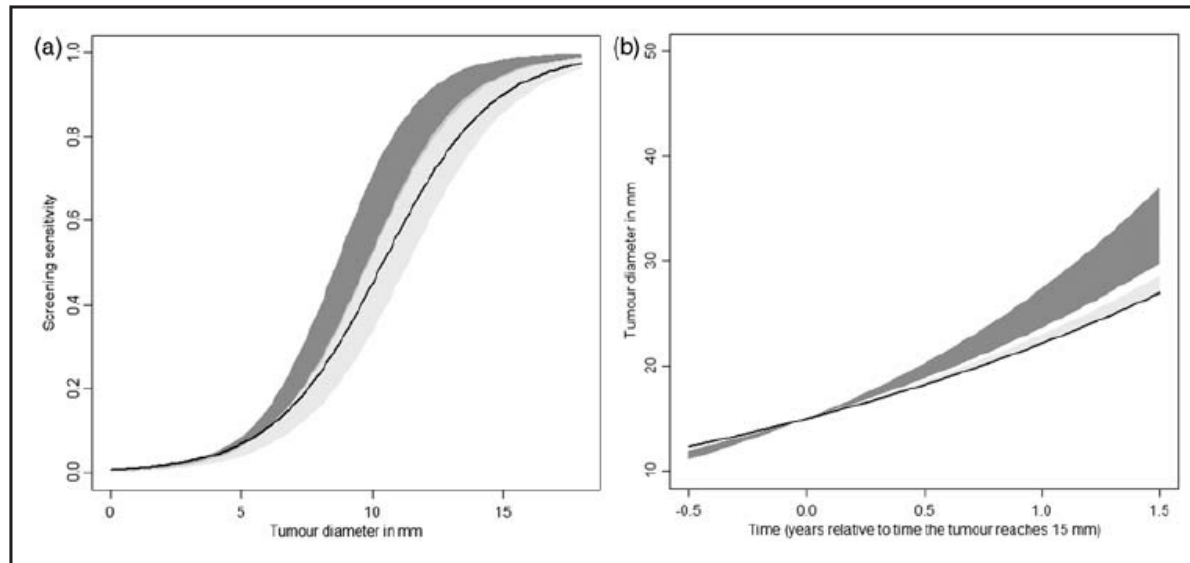

Figure 1. Estimated sensitivity functions (left) and median growth functions (right) for the corrected and uncorrected methods.
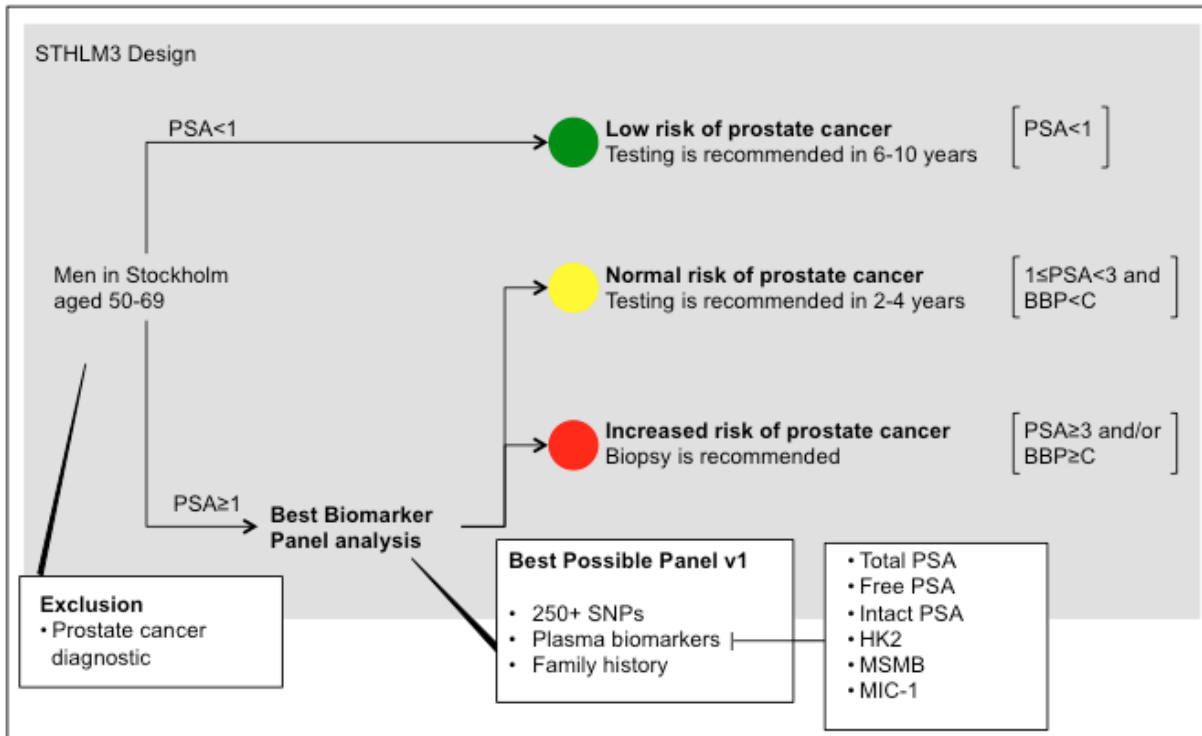
Abrahamsson & Humphreys, SMMR 2013

$$V(t) = V_{cell}e^{t/r},$$

ll and r is the inverse growth rate. Ind
he inverse growth rate as an outc
ter τ_1 and an inverse scale parameter

$$f_R(r) = \frac{\tau_2^{\tau_1}}{\Gamma(\tau_1)} r^{\tau_1-1} e^{-\tau_2 r}, r \geq 0.$$

Keith Humphreys Linda Abrahamsson Abbas Cheddad

Prostate cancer
CRiSP STHLM3 Diagnostic study

STHLM3 Design

Men in Stockholm aged 50-69

PSA<1 → **Low risk of prostate cancer** — Testing is recommended in 6-10 years [PSA<1]

PSA≥1 → **Best Biomarker Panel analysis** → **Normal risk of prostate cancer** — Testing is recommended in 2-4 years [1≤PSA<3 and BBP<C]

→ **Increased risk of prostate cancer** — Biopsy is recommended [PSA≥3 and/or BBP≥C]

Exclusion
• Prostate cancer diagnostic

Best Possible Panel v1
• 250+ SNPs
• Plasma biomarkers
• Family history

• Total PSA
• Free PSA
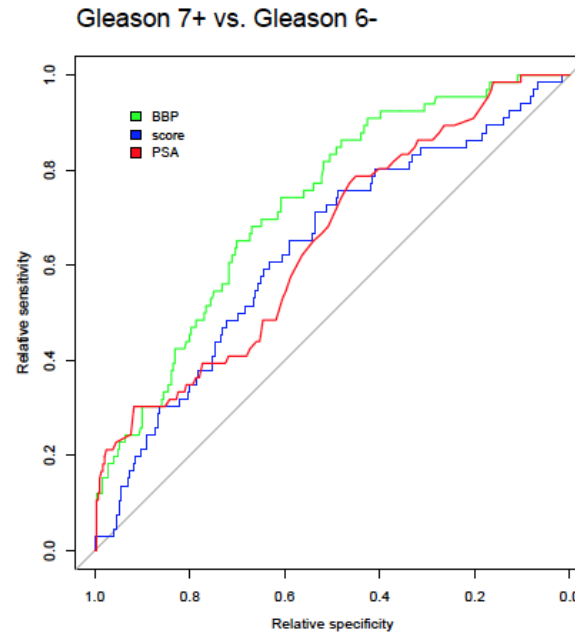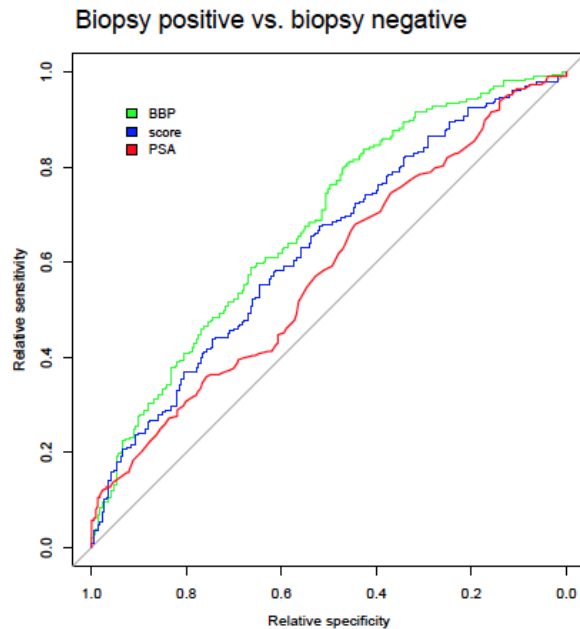• Intact PSA
• HK2
• MSMB
• MIC-1

Stockholm County Council

- 50 000 men in Study Q1 2015
- Best-Biomarker Panel BBP 2012
- Thermo Fisher customized chip

Design of STHLM3. STHLM3 uses a paired design, where all men with a PSA over 1 also are tested with BBP. Referral to biopsy will be determined by either PSA ≥ 3 ng/ml and/or BPP ≥ c where c is calculated as to have the same sensitivity as PSA ≥ 3 ng/ml to find aggressive cancers (Gleason ≥ 7).

Relative ROC curves

(Relative to the test PSA>3)

Biopsy positive vs. biopsy negative

- BBP
- score
- PSA

Relative sensitivity / Relative specificity

Gleason 7+ vs. Gleason 6-

- BBP
- score
- PSA

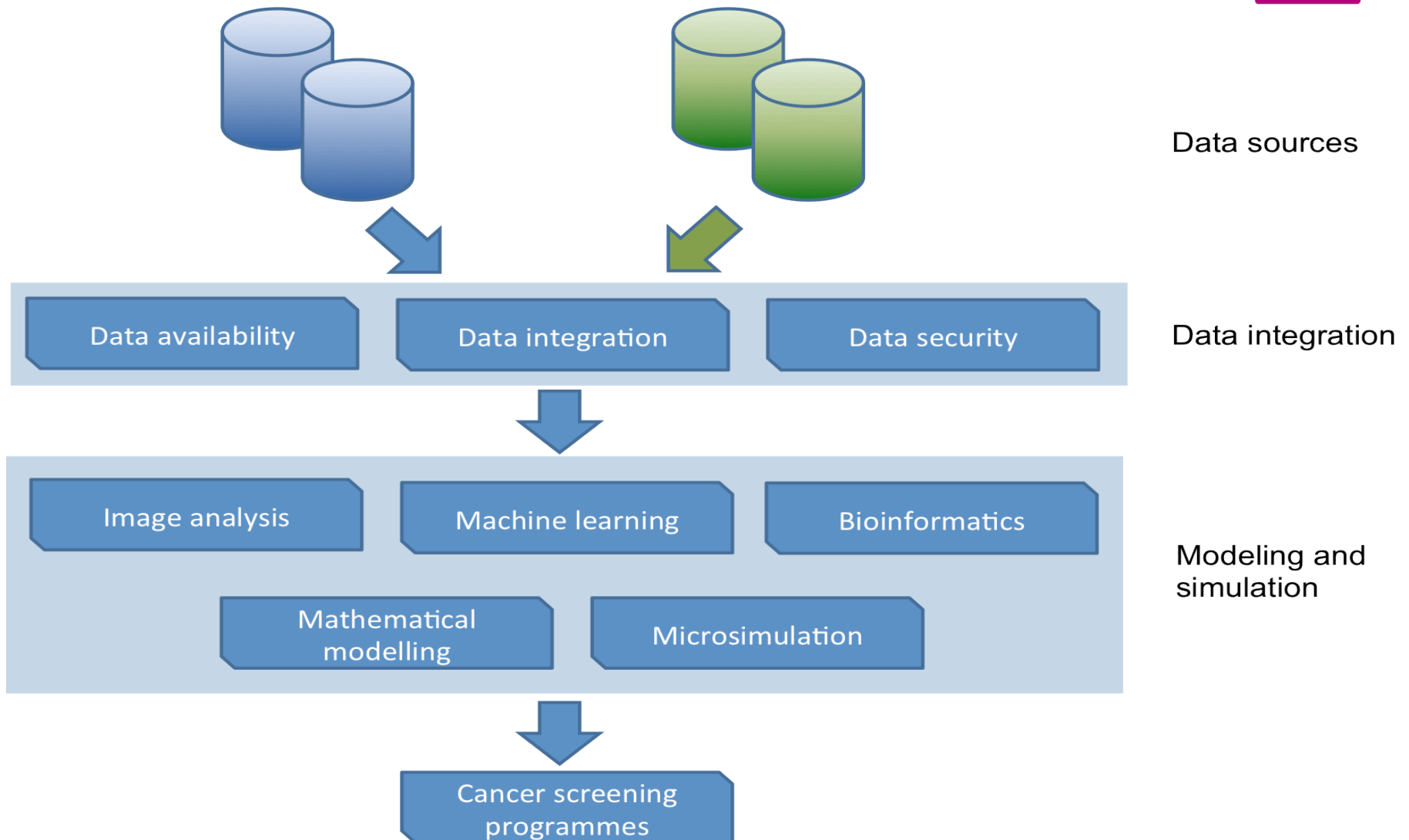Relative sensitivity / Relative specificity

STHLM2 data for design and estimation

Expectation:

- Relative false positive fraction rFPF(c) <0.8
- Relative true positive fraction rTPF(c)=1

Stockholm may move towards organized screening!

Mark Clements   Martin Eklund   Andreas Karlsson   Karl Landström

eCPC - eScience modules

Data sources

Data availability　**Data integration**　**Data security**

Data integration

Image analysis　**Machine learning**　**Bioinformatics**

Mathematical modelling　**Microsimulation**

Modeling and simulation

Cancer screening programmes

Sweden and Norden

Enormous potential for eScience in medical research
(data integration, computation modelling and simulation)
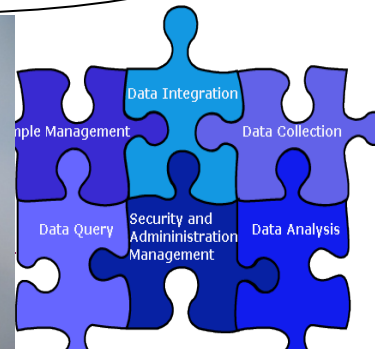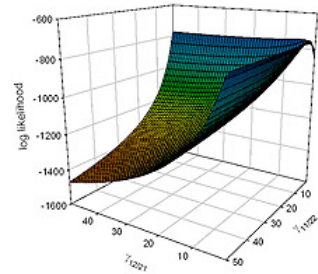

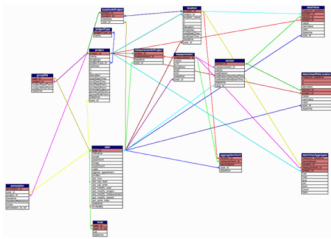- Reliable demographics and healthcare registers
- Clinical and population cohorts
- National biobanks
- Biotechnology and Information technology
- High quality epidemiology and clinical research
- Bioinformatics, computational biology, biostatistics

www.escience4cancer.net

Acknowledgments

CRiSP and ClinSeq

- Henrik Grönberg
- Per Hall
- Kamila Czene
- Johan Lindberg
- Daniel Klevebring
- Mattias Rantalainen
- Johanna Holm

SAIL – Sample Availability System

- Maria Krestyaninova
- Jani Heikkinen

ACCES Cervical Cancer

- Pär Sparen
- Joakim Dillner
- Lisen Arnheim
- Karin Sundström

SeRC Core and Communities

- Erwin Laure
- Olivia Eriksson
- Jeanette Hellgren Kotalesky
- Bengt Persson

Strangeways Research Lab

USCF School of Medicine

Fred Hutchinson Cancer Centre

Nordic NIASC eScience Center

eCPC kick-off 2012

Participants in the eCPC kickoff meeting at Sandhamn, May 9-10 2012. The meeting featured presentations from all work package leaders as well as invited speakers.