UPPSALA UNIVERSITET

Karolinska Institutet

ecpc e-Science for Cancer Prevention and Control

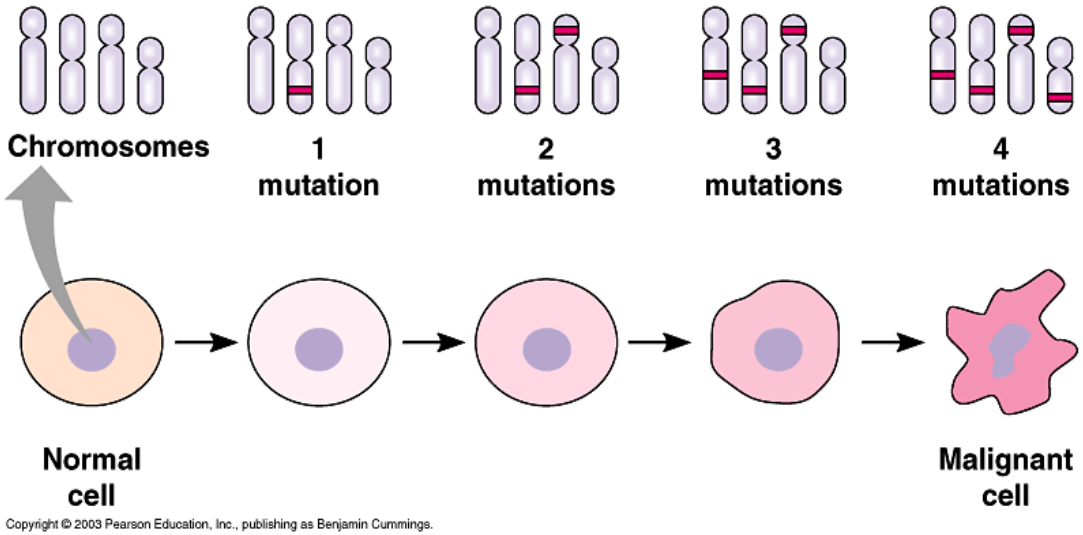
Enabling Translational Medicine with e-Science

Ola Spjuth
ola.spjuth@ki.se
ola.spjuth@farmbio.uu.se

SciLifeLab essence THE e-SCIENCE COLLABORATION SeRC

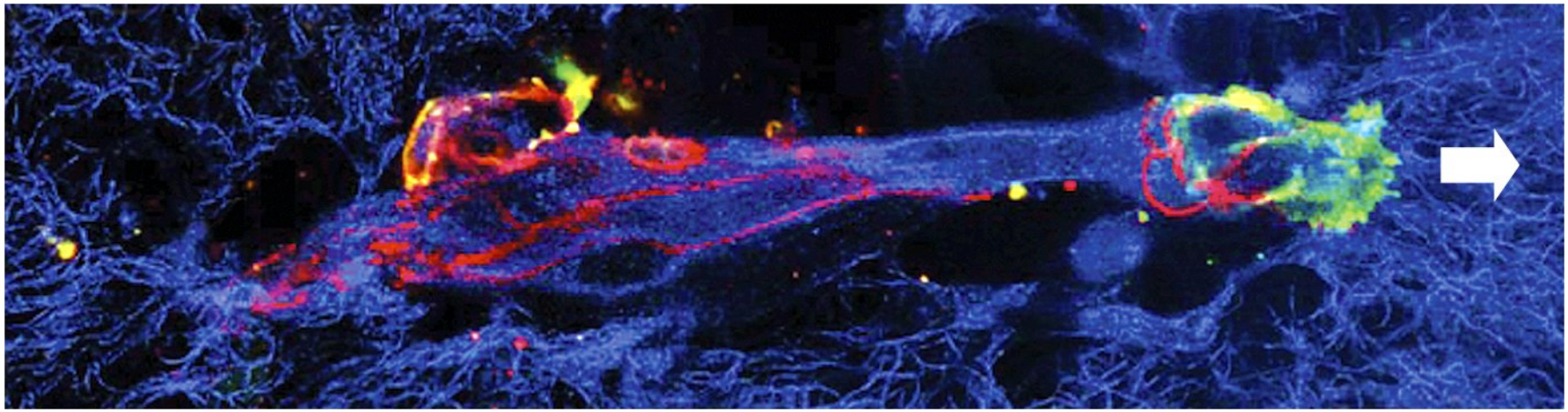
Cancer

Normal cells accumulate mutations

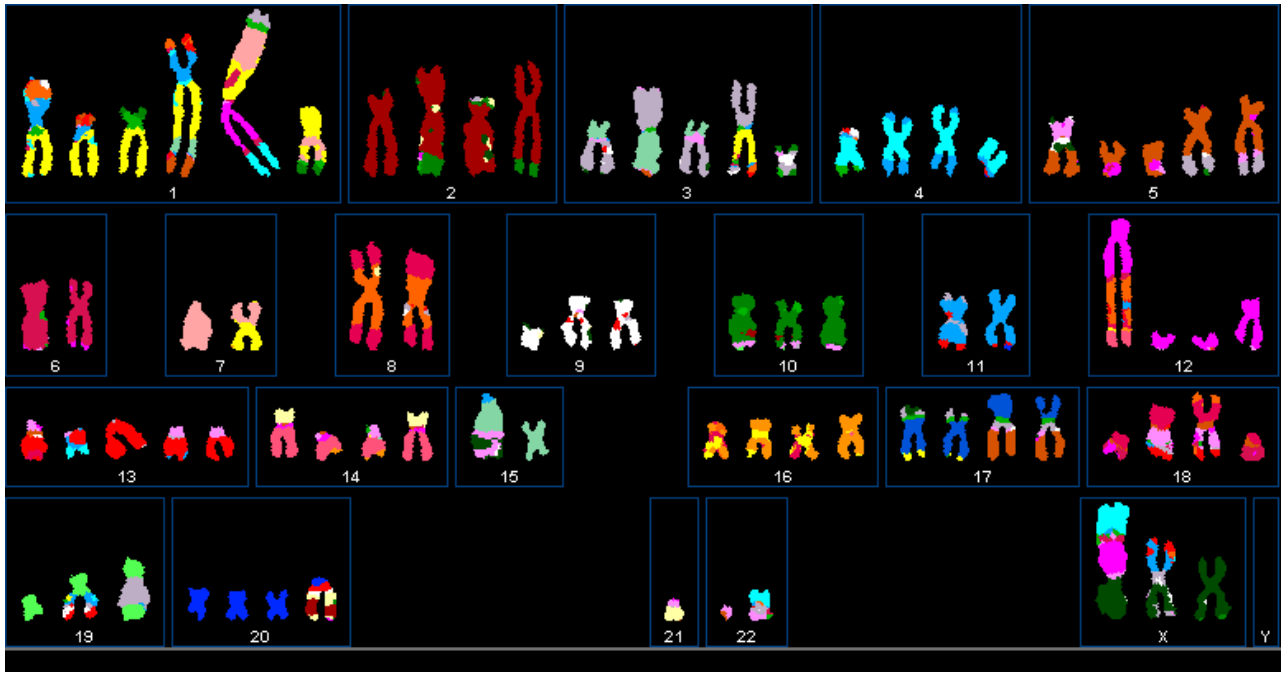


Cancer cells divide excessively and form tumors

Malignant cancer cells can invade other tissues



Cancer cells have altered genomes



- Each cancer has its own genome
  → Calls for individualized/stratified diagnostics and treatment

Source: www.path.cam.ac.uk/~pawefish/BreastCellLineDescriptions/HCC38.html

Today: We have access to high-throughput technologies to study biological phenomena

New challenges: Data management and analysis

- Storage
- Analysis methods, pipelines
- Scaling
- Automation
- Data integration, security
- etc.

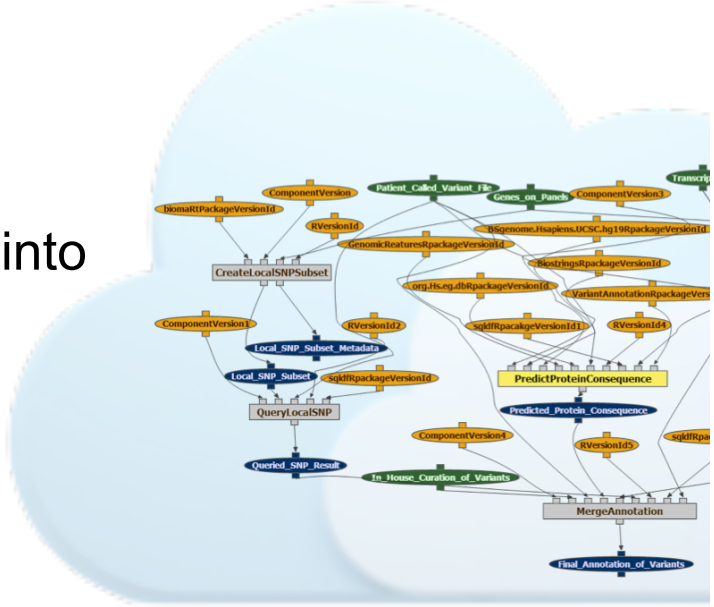
Translational medicine

- Aim: **Turn Basic Research into Medicines and Treatments**
  - → “from bench to bedside”
  - → “from laboratory to clinic”

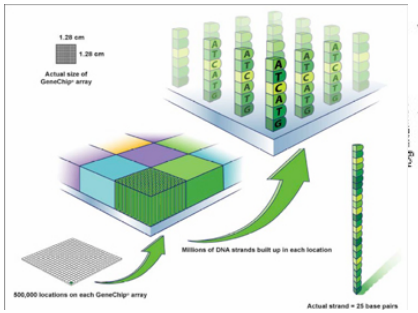
- Traditionally a slow process
  - → May take 10 -20 years for original research to translate to routine medical practice

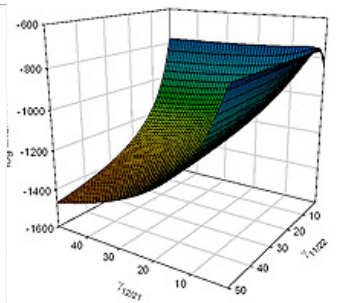
e-Science in translational medicine

- e-Science solutions are desperately needed in order to translate high-throughput technologies into clinical settings (diagnostics, treatment,…)
  - → e-infrastructure (computers, storage, networks, frameworks)
  - → Methods, workflows/pipelines
  - → Operations, experience and expertise



- e-Science can aid translational medical research
  - → Simulation and prediction models
  - → Large-scale collaborative, integrative research





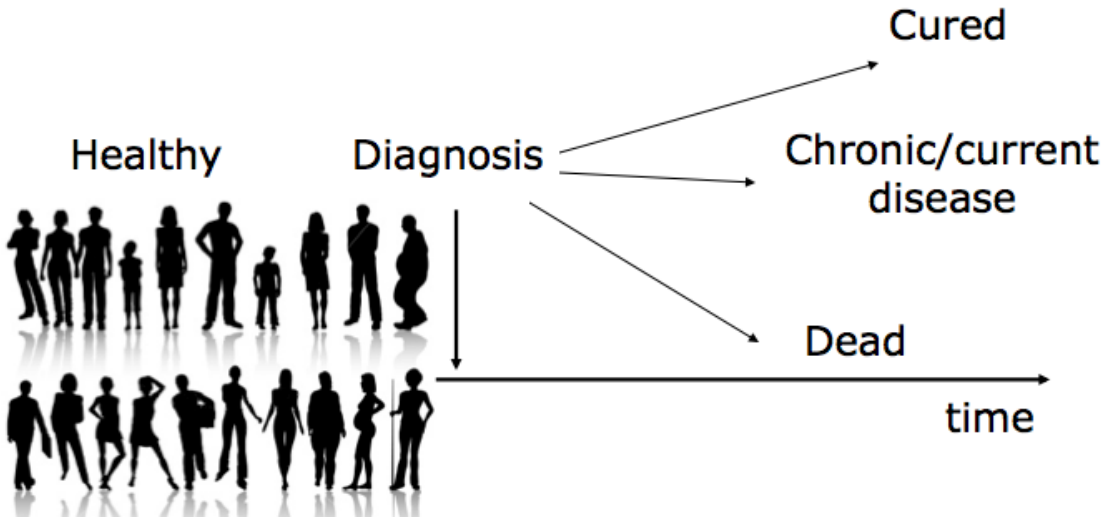
2012-2014:
e-Science for Cancer Prevention and Control
- a SeRC flagship project

Use statistical modeling and data integration in cancer research:

→Individualized prevention strategies

→Individualized treatments

PIs: Juni Palmgren & Jan-Eric Litton



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?

- Early detection is important.
- Efficiency of current practice for early detection of breast and prostate cancer is questioned!

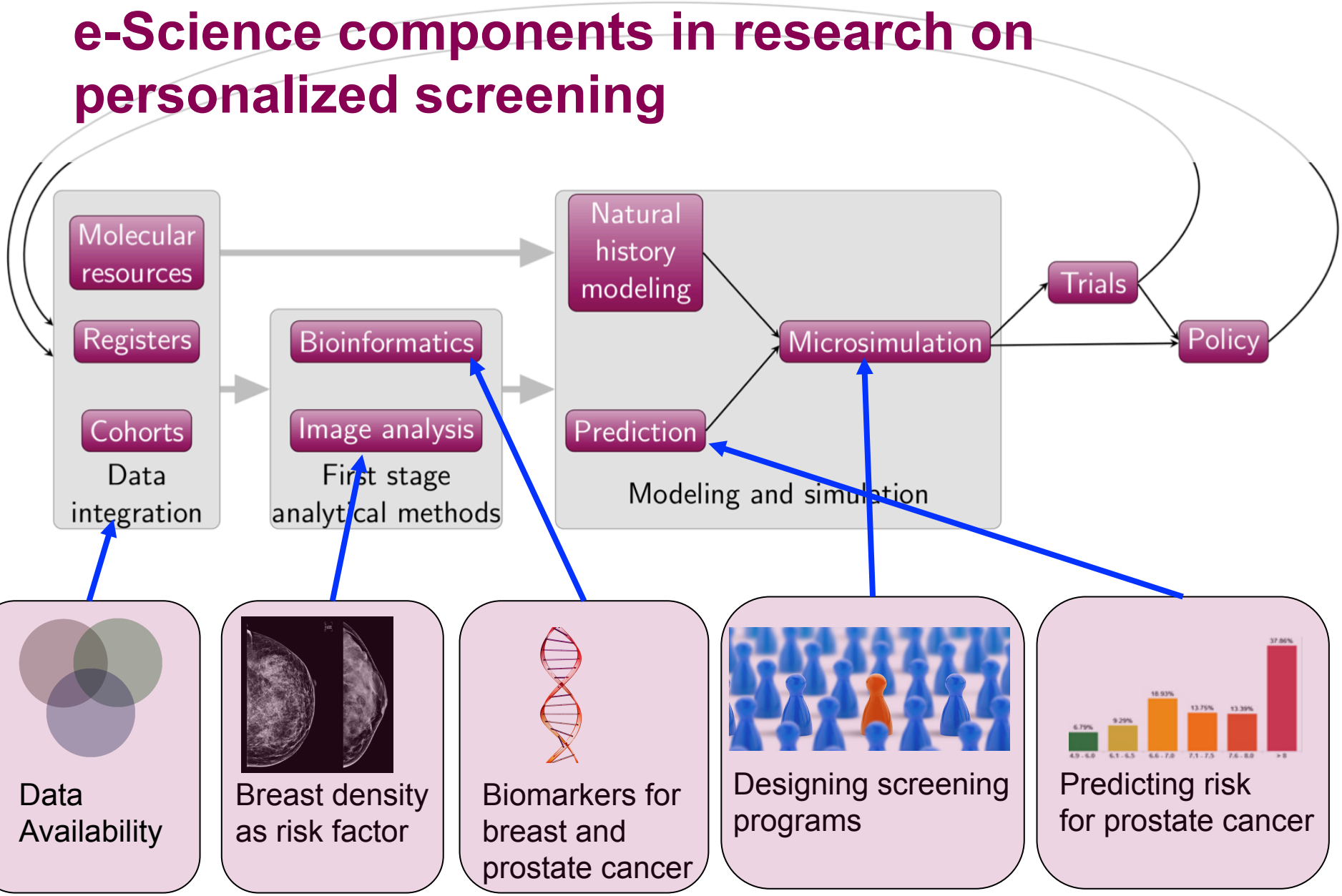
We have:

→ Organized mammographic screening

→ Widespread opportunistic PSA testing

- Rates of detection of slow growing cancers increase
  → Beware of over-diagnosis, overtreatment, increasing cost and increase in side effects!
- Aggressive cancers and mortality do not decrease enough

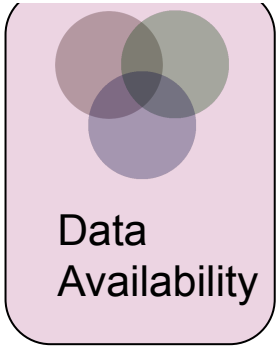
e-Science components in research on personalized screening



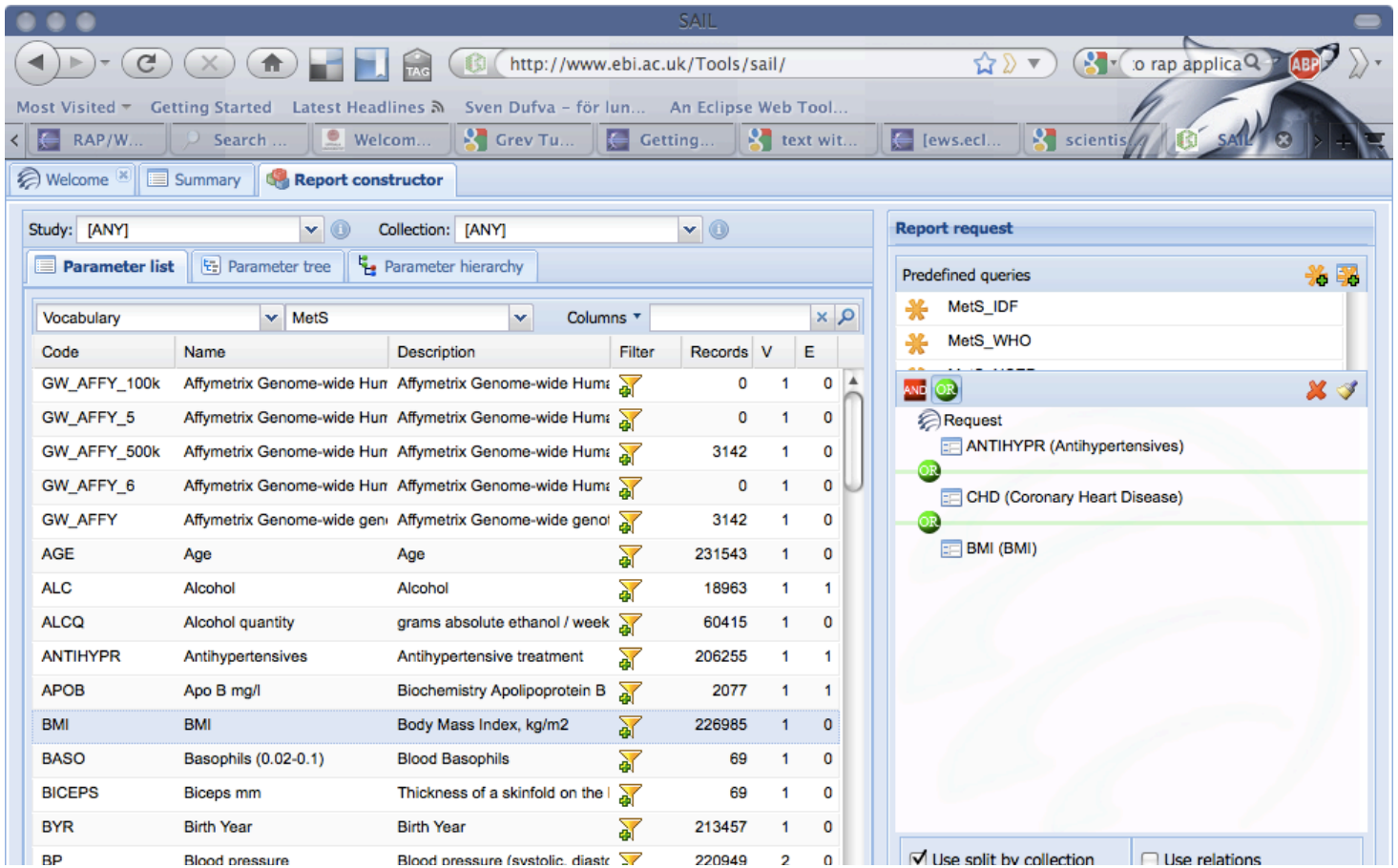
highlight 5 eCPC case studies

Data Integration

SAIL – Sample Availability System



- Overview of data – what is available
- Plan studies, investigate data available for subset of patients/samples across data archives such as biobanks



SeRC
Swedish e-Science Research Centre

Uniquer

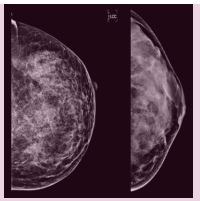
EMBL-EBI

FIMM
Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine

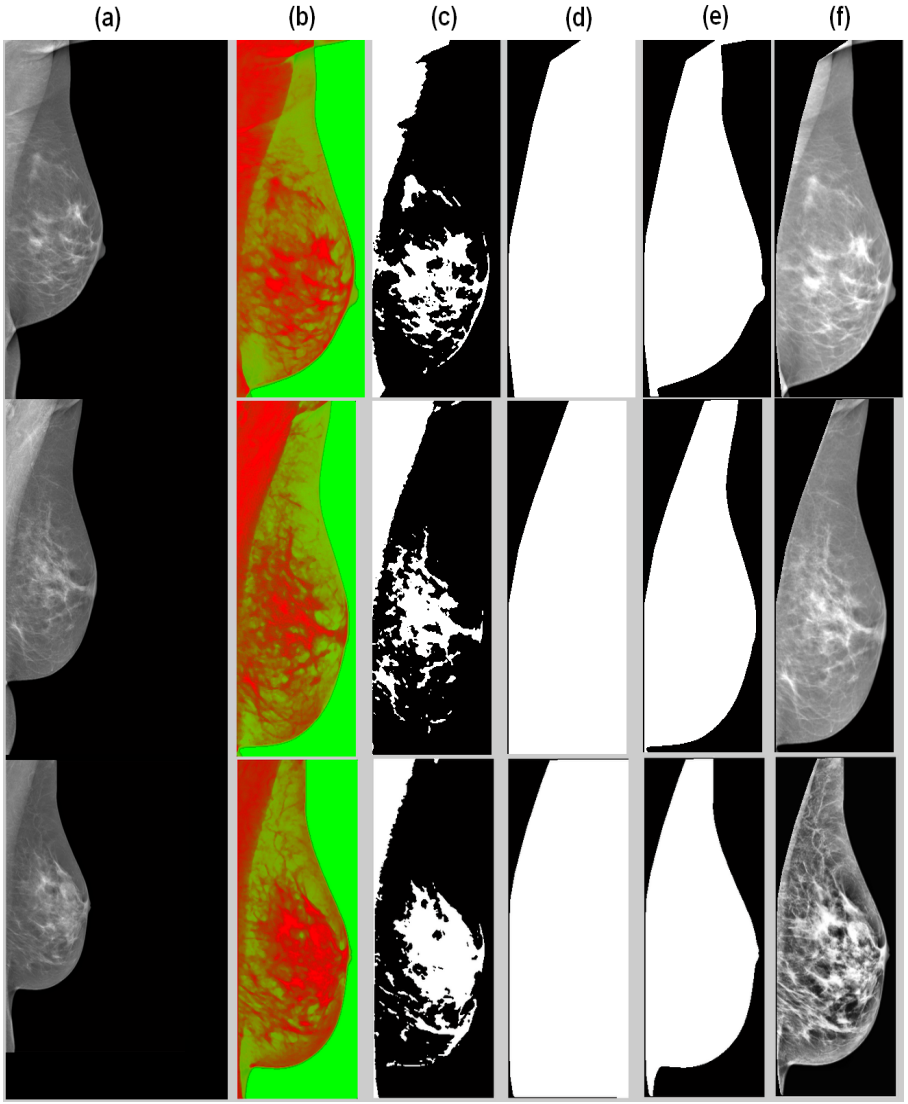
O. Spjuth et al. "Enabling integrative cross-biobank research: the SAIL method for harmonizing and linking biomedical and clinical data across disparate data archives" *Eur J Hum Genet*. 2015 Aug 26. [Epub ahead of print]

Breast density as risk factor

Imaging technology and computational techniques



Breast density as risk factor



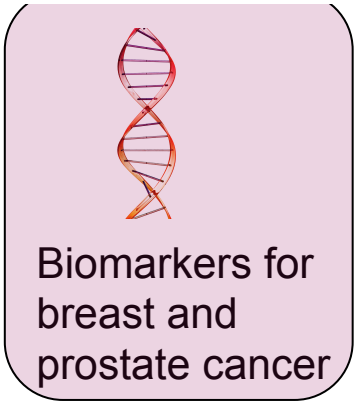
- Applying e-Science methods to image analysis data can feed into prediction modeling and help guide screening and preventative strategies.
- eCPC developed new measures of mammographic density, with the aim of providing stronger risk factors for breast cancer.

Stora nationella bröstcancerstudien:

Karma

Keith Humphreys

Biomarker discovery and validation



- Validated genetic and protein markers conveying prostate cancer risk
- Studied genomic profile of breast cancers

→Data-intensive bioinformatics making use of national HPC e-Infrastructures (SNIC)

Stora prostata-cancerstudien:

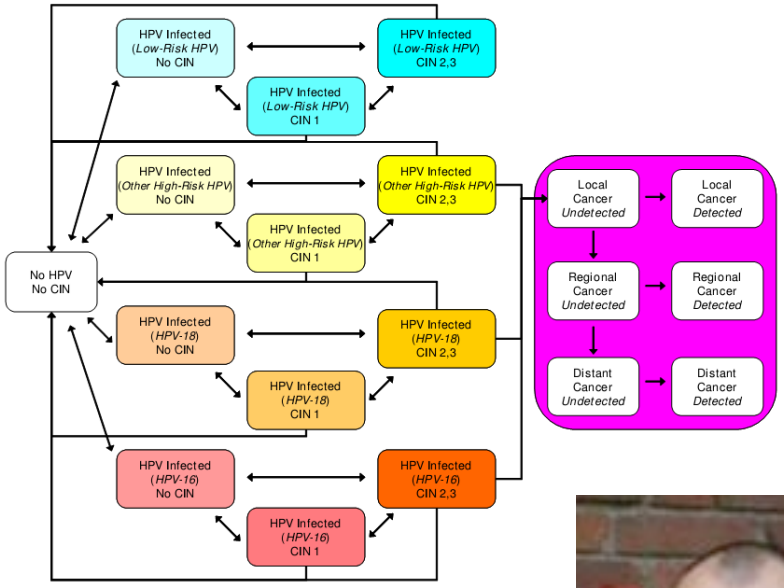
STHLM 2

Stora nationella bröstcancerstudien:

Karma

eCPC Microsimulation Model

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

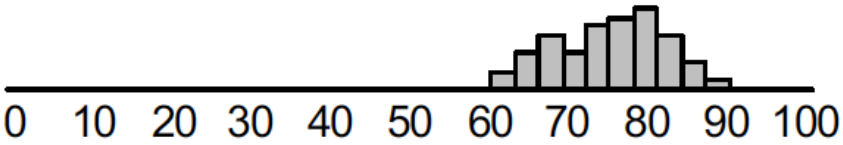


Mark Clements

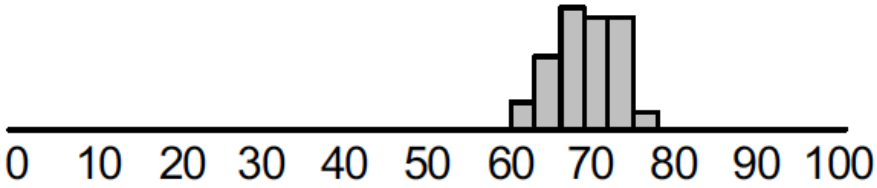
Example: **Reduction in Cervical Cancer Incidence**

(Bodhager Diebert et al. 2007)

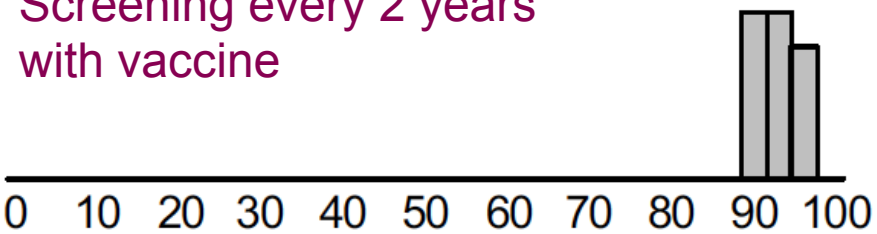
Vaccination only



Screening every 2 years only



Screening every 2 years with vaccine



eScience and eCPC microsimulation

- Used OpenMP/MPI or PGAS for Bayesian calibration of the microsimulation on HPC
- Compared HPC with MapReduce for the microsimulation
- Trans-compile from C++ to WebAssembly/JavaScript for microsimulation on the browser
- Compared client-server and client-only web interfaces for the microsimulation

Microsimulation and STHLM-2

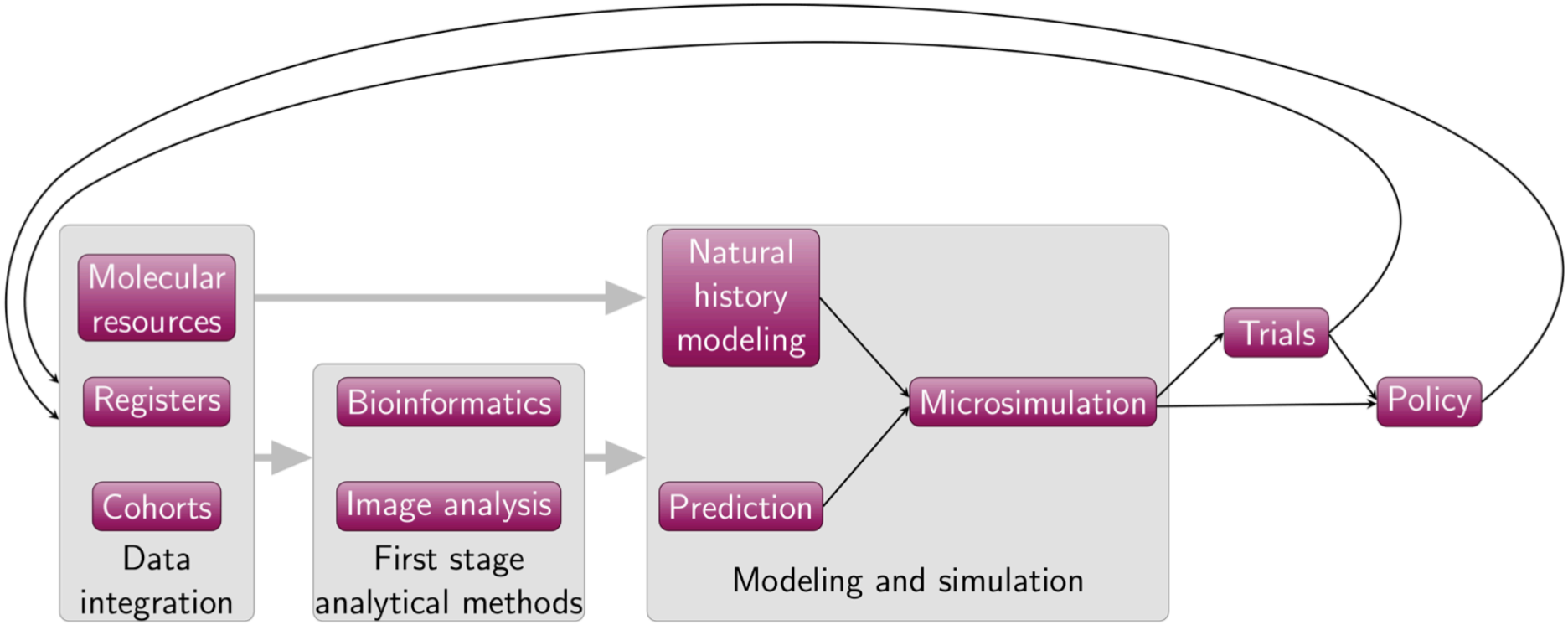
Designing screening programs

- **Stockholm 2 study:** Find out how heredity, environment and genetic changes can be used to predict the risk of developing prostate cancer.
  → 50,000 participants

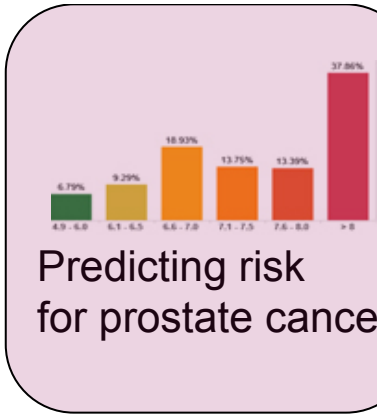
- Microsimulation was developed and used in Sthlm 2 for evaluating and planning screening strategies
  → Resulted in the design of Stockholm 3 study: Develop strategies to improve risk predictions

Stora prostata-cancerstudien:

STHLM 2


Molecular resources
Registers
Cohorts
Data integration
Bioinformatics
Image analysis
First stage analytical methods
Natural history modeling
Prediction
Microsimulation
Modeling and simulation
Trials
Policy

Sthlm 3 study: Predicting risk for prostate cancer based on PSA + biomarkers



- Constructed and validated Stockholm 3 model (S3M)
  - → Prediction algorithm for predicting a man's risk for having prostate cancer , which shows improved specificity (given constant sensitivity) over prostate specific antigen (PSA) testing alone in the population-based STHLM3 diagnostic trial
  - → 50 000 men in Study Q1 2015
  - → Thermo Fisher customized chip

- The developed microsimulation model will be used for health economics calculations

STHLM 3

Bättre diagnostik av prostatacancer

2015: eCPC sharpens the focus on translational medicine

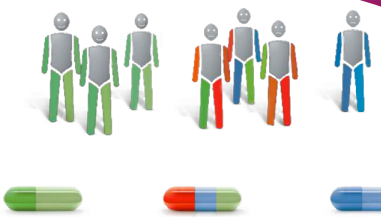
- Adding new prioritized field: **Clinical sequencing**
  → How can new high-throughput sequencing technologies aid cancer diagnostics and treatments?

- Joint collaboration, SeRC and eSSENCE

PI: Juni Palmgren

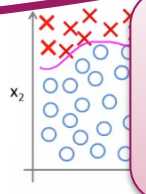
eCPC research on clinical sequencing

Applied e-Science research



Individualized diagnostics

e-Science methods development



Posters:
18 + 28

Prediction models,
machine learning

e-Infrastructure development

Posters:
41 + 46

Automation, Big Data

Clinical sequencing supported by eCPC

Stockholm: ClinSeq

- Short read technology
- Pan-cancer approach
- www.clinseq.se

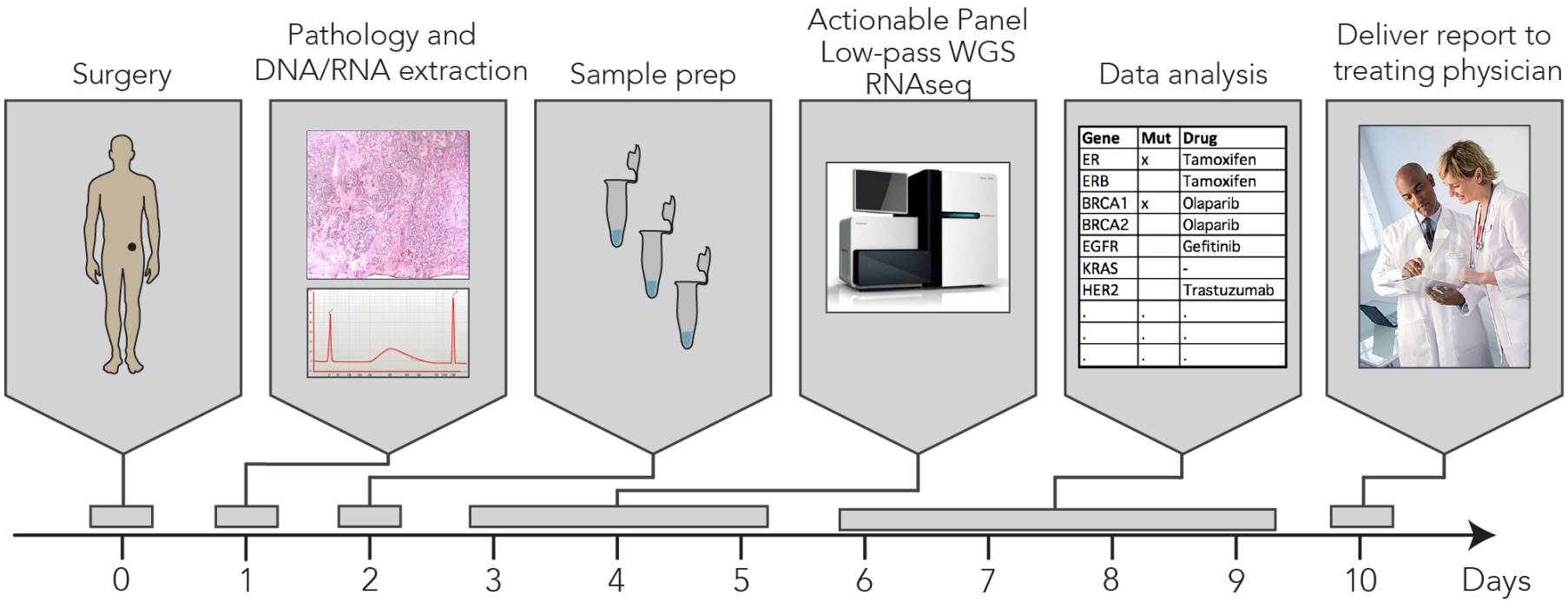
Uppsala

- Long read technology
- Targeted approaches

KAROLINSKA Universitetssjukhuset ↔ ecpc ↔ AKADEMISKA SJUKHUSET

ecpc ↕ SciLifeLab

ClinSeq pipeline



! Patient value

Research opportunities

Pan-cancer approach - the same pipeline for all cancers

E-science in ClinSeq

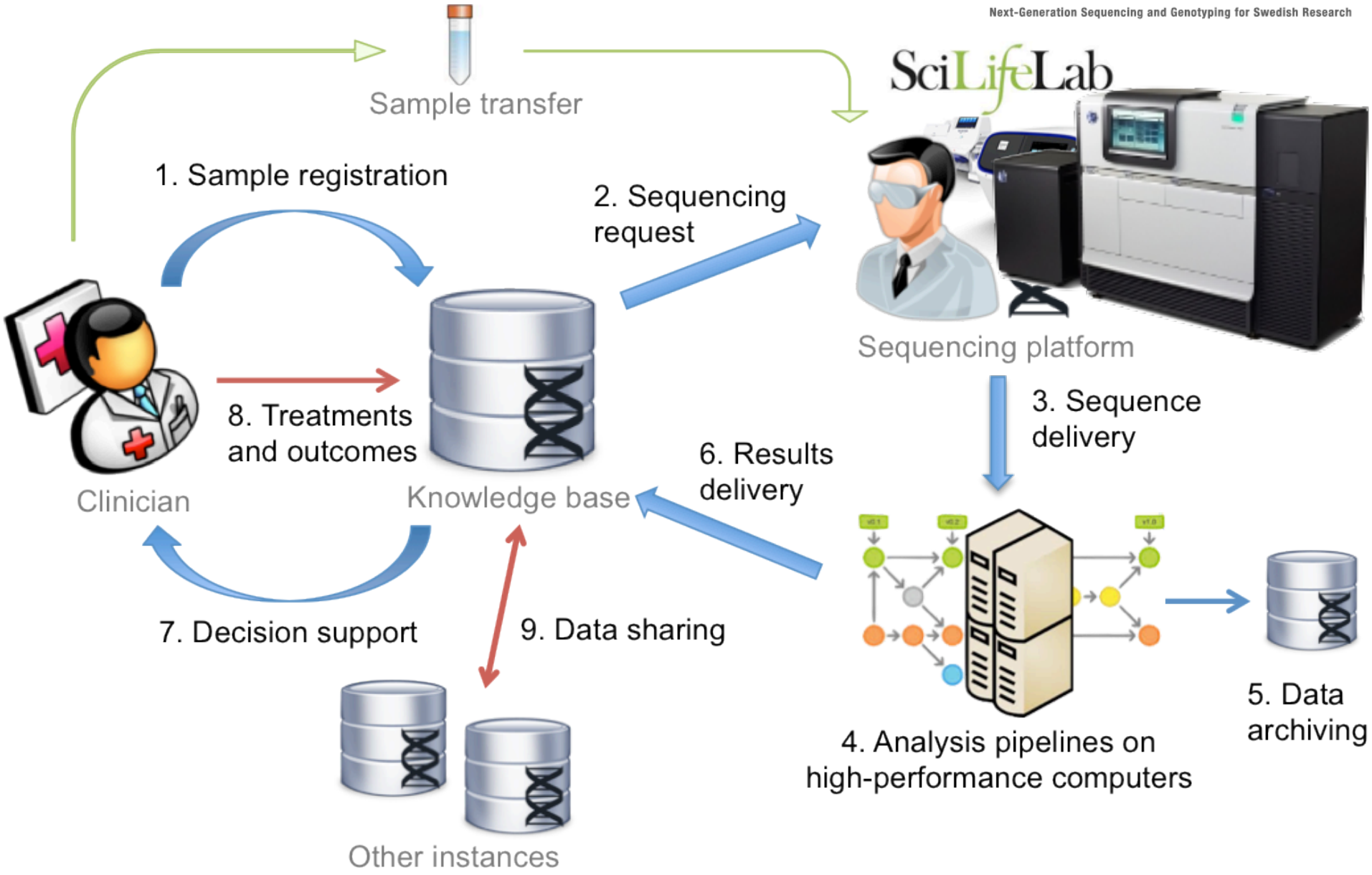
- **HPC / distributed computing**
  - → Bioinformatic pre-procesing in CLINSEQ: 15 Gb raw data per patient (~100 CPU hours / patient)
  - → Automated bioinformatic pipeline that run in cluster environment (e.g. UPPMAX)
- **Machine learning** and **computational statistics**: Methods development and application
  - → Supervised and unsupervised learning across multiple types of high-dimensional data
  - → Biomarker discovery (robust methods for variable selection): definition of robust sets of clinically relevant biomarkers
- Integration of in-house data with **public DBs and data sets**
  - → The Cancer Genome Atlas (TCGA), clinically relevant mutations (COSMIC, ClinVar)

ClinSeq in breast cancer

- Results suggests that routine clinical biomarkers could be replaced with DNA and RNA sequencing-based diagnostics
- The ClinSeq profile add value by providing more detailed diagnostic information (subtype, mutations, transcriptomic grade)
- Prospective validation study is planned (N=500)

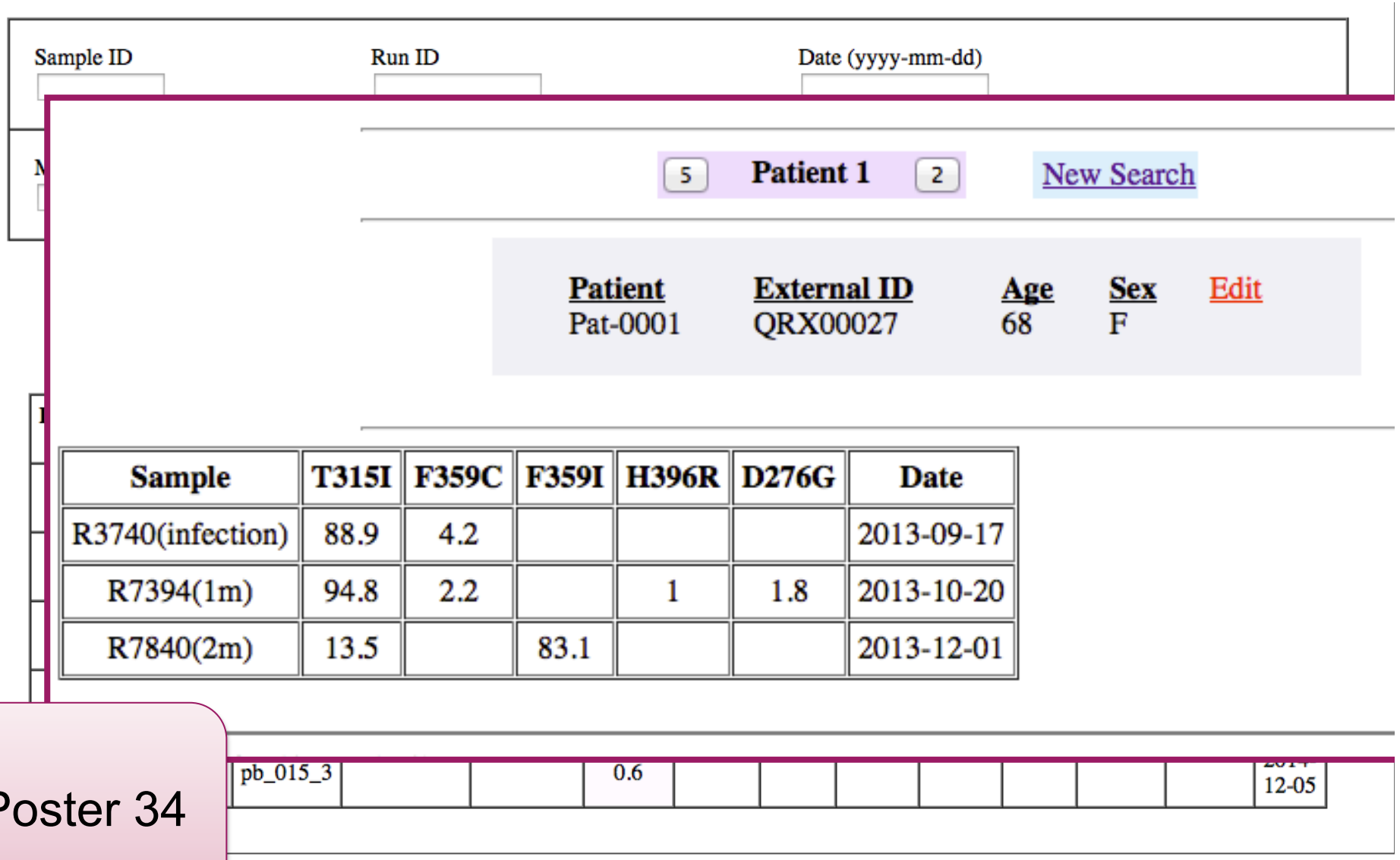
Supporting clinical sequencing at Uppsala Academic Hospital

NATIONAL GENOMICS INFRASTRUCTURE
Next-Generation Sequencing and Genotyping for Swedish Research



Chronic Myeloid Leukemia (CML)

SciLifeLab AKADEMISKA SJUKHUSET



Sample	T315I	F359C	F359I	H396R	D276G	Date
R3740(infection)	88.9	4.2				2013-09-17
R7394(1m)	94.8	2.2		1	1.8	2013-10-20
R7840(2m)	13.5		83.1			2013-12-01

pb_015_3			0.6								12-05

Poster 34

e-Science in eCPC clinical sequencing in Uppsala

- Construct and automate pipelines on HPC and Cloud
- Transfer results into database system
  → Structured data (variants, tables, visualizations, data files etc.)
  → Inside hospital domain with clinical phenotypes (future)
- Security – sensitive personal information
- Encrypt and archive raw data
- Build up knowledge base for future predictive modeling

- *Now*: In pilot production at UAH
- *Future*: Extend to other cancers and genomic regions

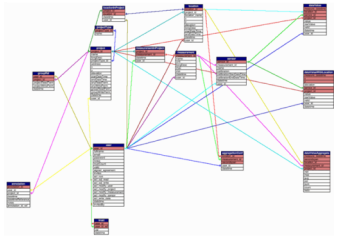
eCPC involvements

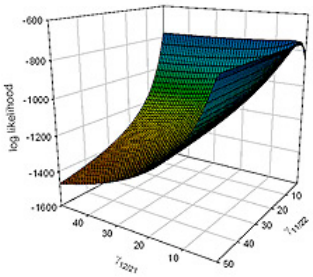
- NIASC – The Nordic Information for Action e-Science Center of Excellence (http://nordicehealth.se/, 2014-1018)
  - → Integrated Nordic research in population-based cancer screening
  - → generic eScience infrastructure
  - → eScience-based predictive algorithm within a national screening program

- PhenoMeNal H2020 project (start Sept. 1st 2015)
  - → clinical metabolomics

Sweden and Nordic countries

Enormous potential for eScience in medical research





Reliable demographics and healthcare registers

Clinical and population cohorts

National biobanks

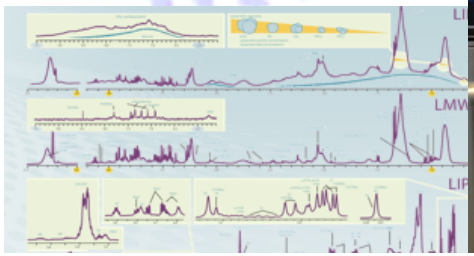
Biotechnology and Information technology

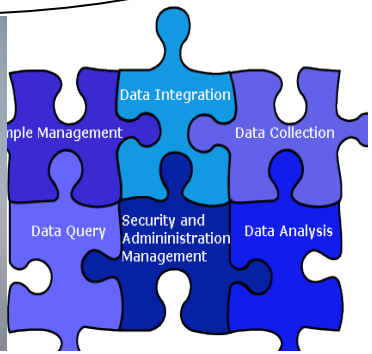
High quality epidemiology and clinical research

Bioinformatics, computational biology, biostatistics

illumina

Applied Biosystems





- Thank you -

www.ecpc.e-science.se