Best Practice Example of Personalised Medicine Research & Implementation - From Basic Research to the Patient:

Genomic Medicine Sweden (GMS) - Acceleration of Implementation of Personalised Medicine for Rare Diseases and Cancer

Office for Life Sciences

2018-11-20

Jenni Nordborg, PhD
National Life Science Coordinator,
Government Offices of Sweden

Roadmap Life Sciences
- towards a national strategy

Illustration: Itziar Casany Ramirez

Government Offices of Sweden

Office for Life Sciences

Holistic and long-term perspective

- Systems transformation
- Knowledge and competence
- Patient / user co-creation
- Prevention – health focus
- International attractiveness
- Next-generation strengths

Illustration: Itziar Casany Ramirez

3 priority areas

Illustration: Itziar Casany Ramirez

Efficient use of **health data**

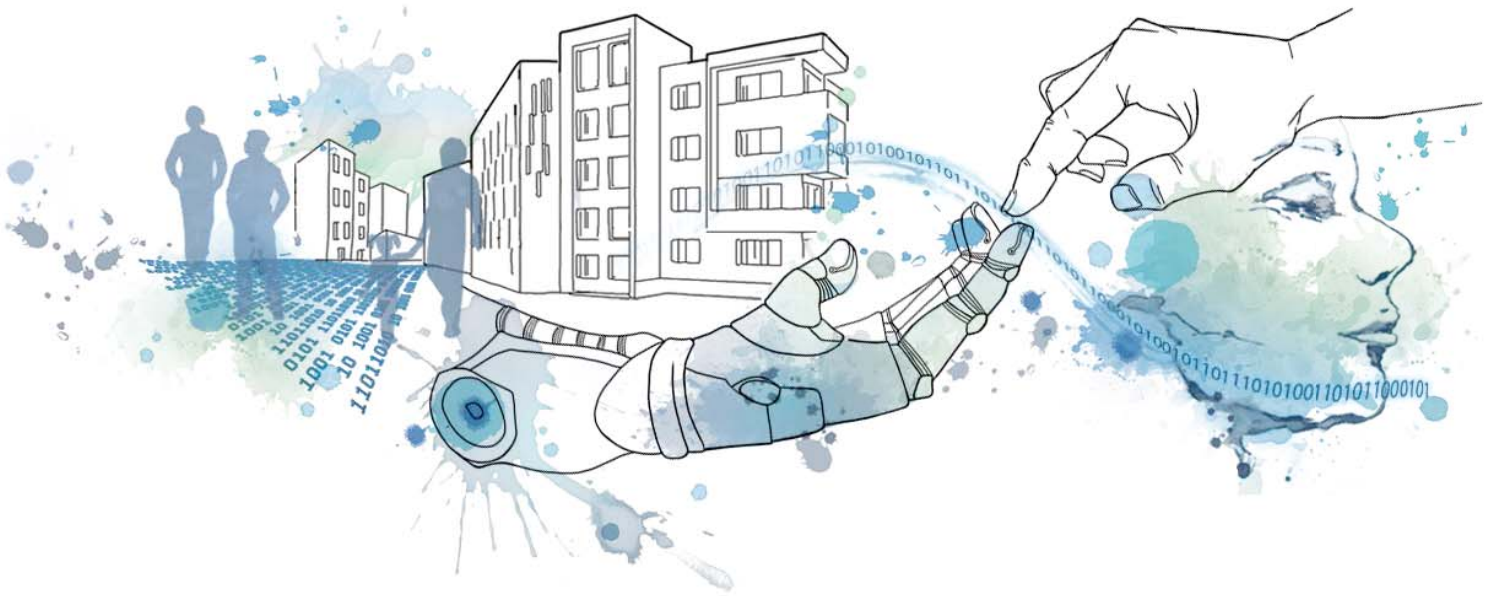


Illustration: Itziar Casany Ramirez

Precision medicine
future diagnostics, therapy and cure

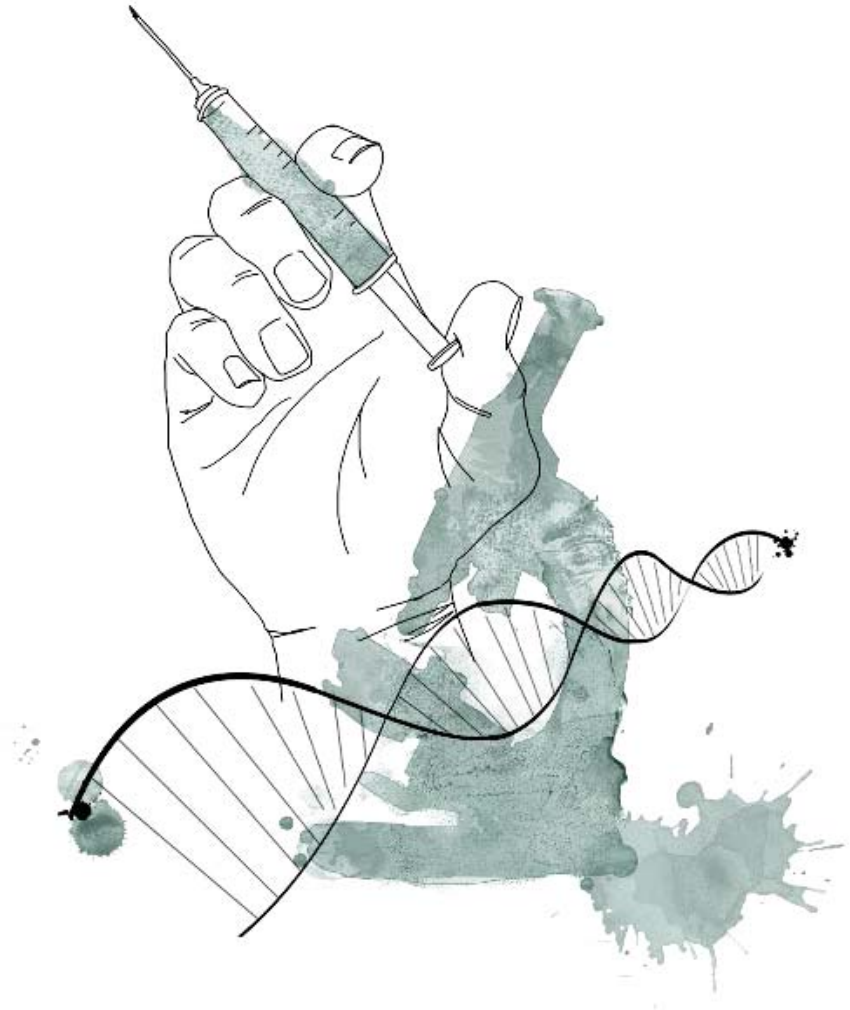


Illustration: Itziar Casany Ramirez

Future care improved integration of innovation and R&D

Illustration: Itziar Casany Ramirez

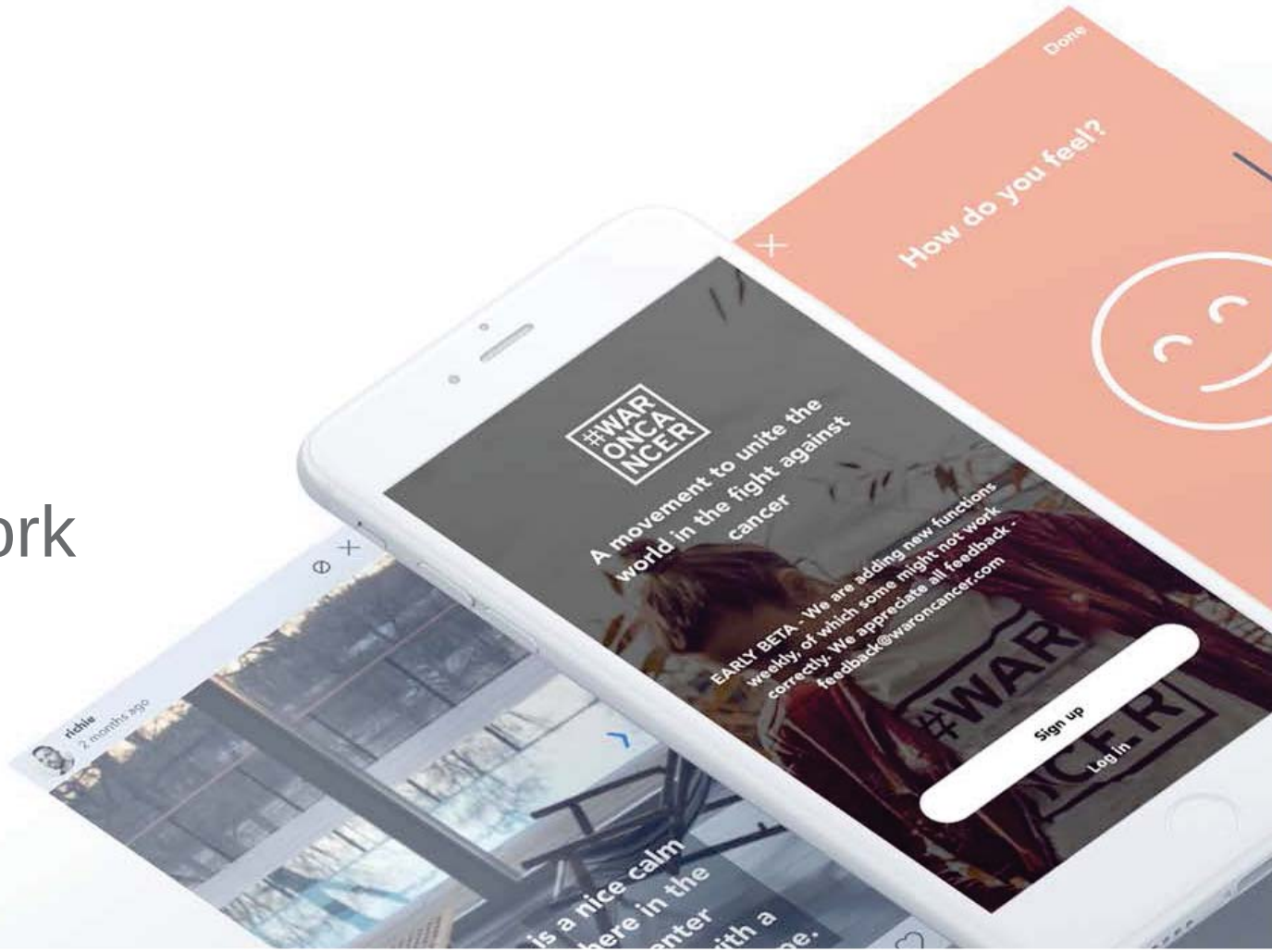
Thank you!

jenni.nordborg@gov.se

INTRODUCING

#WAR ONCA NCER

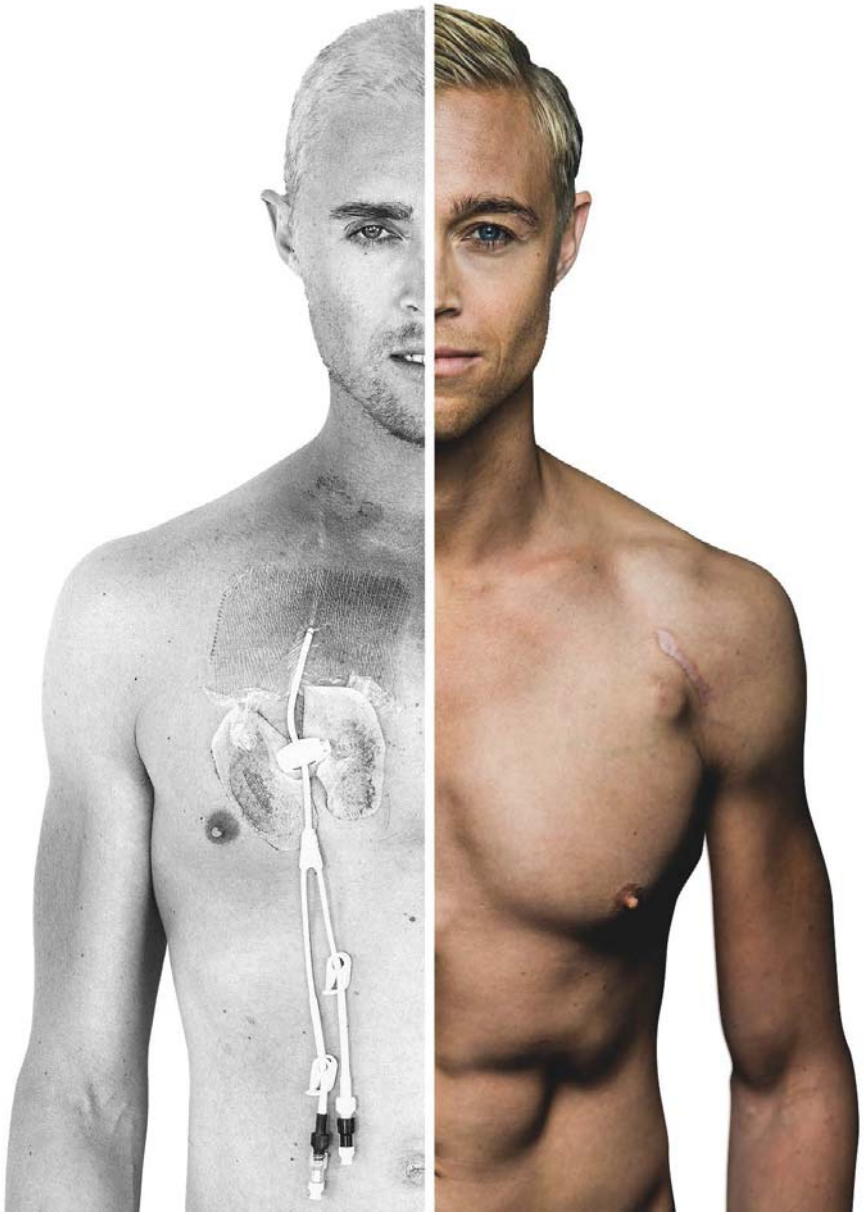
The social network for cancer

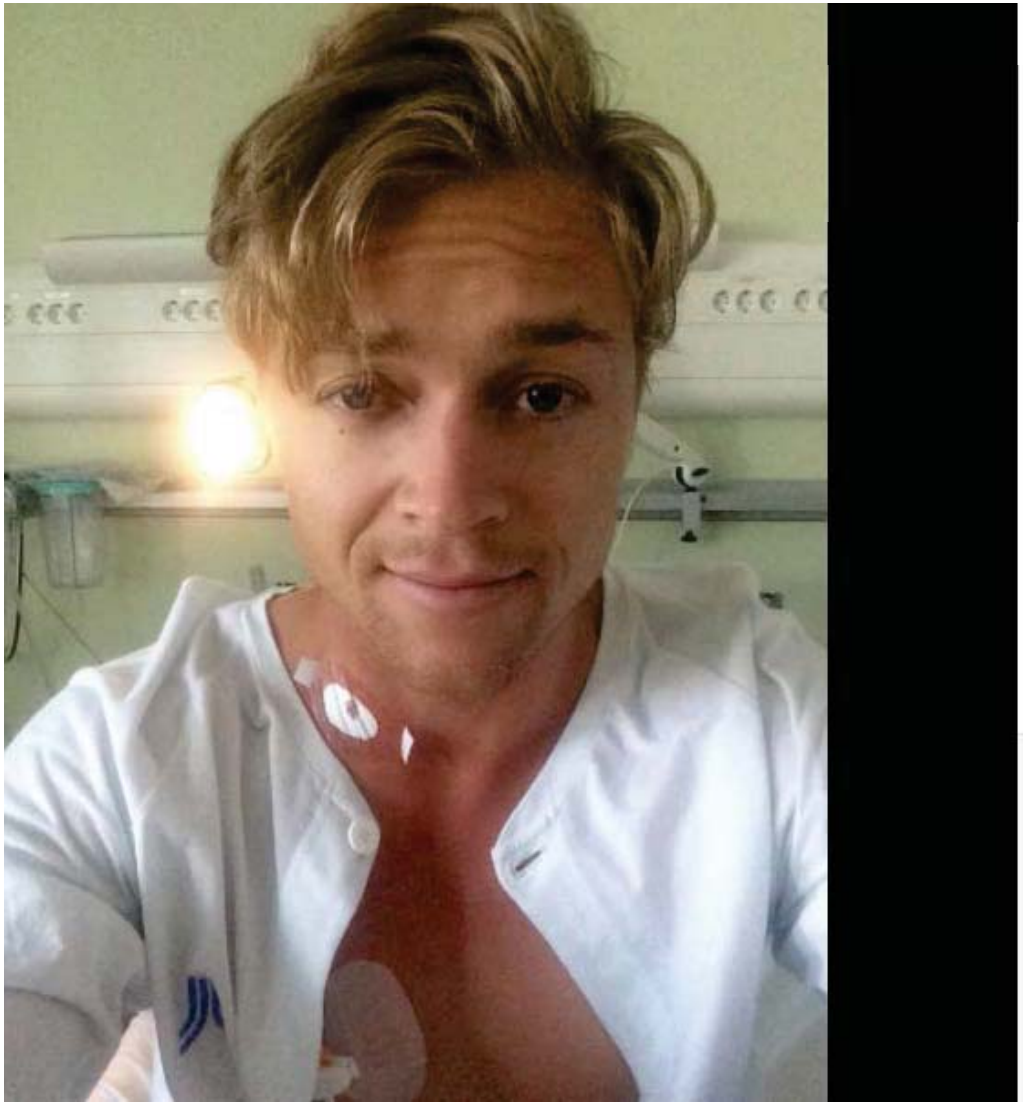


Fabian Bolin

CEO & Co-founder,
WarOnCancer

@fabianbolin @waroncanceruntd





Fabian Bolin
Published by Fabian Bolin [?]
Like This Page · July 5, 2015 · Edited ·

Hello my friends, family and followers,

On the 2nd of July I was diagnosed with leukemia. For those of you who are not familiar with this term, it's blood cancer.

I apologize in advance for the lengthiness of this letter.... See More — feeling broken with Fabian Bolin at Karolinska Institutet.

Tag Photo | Edit

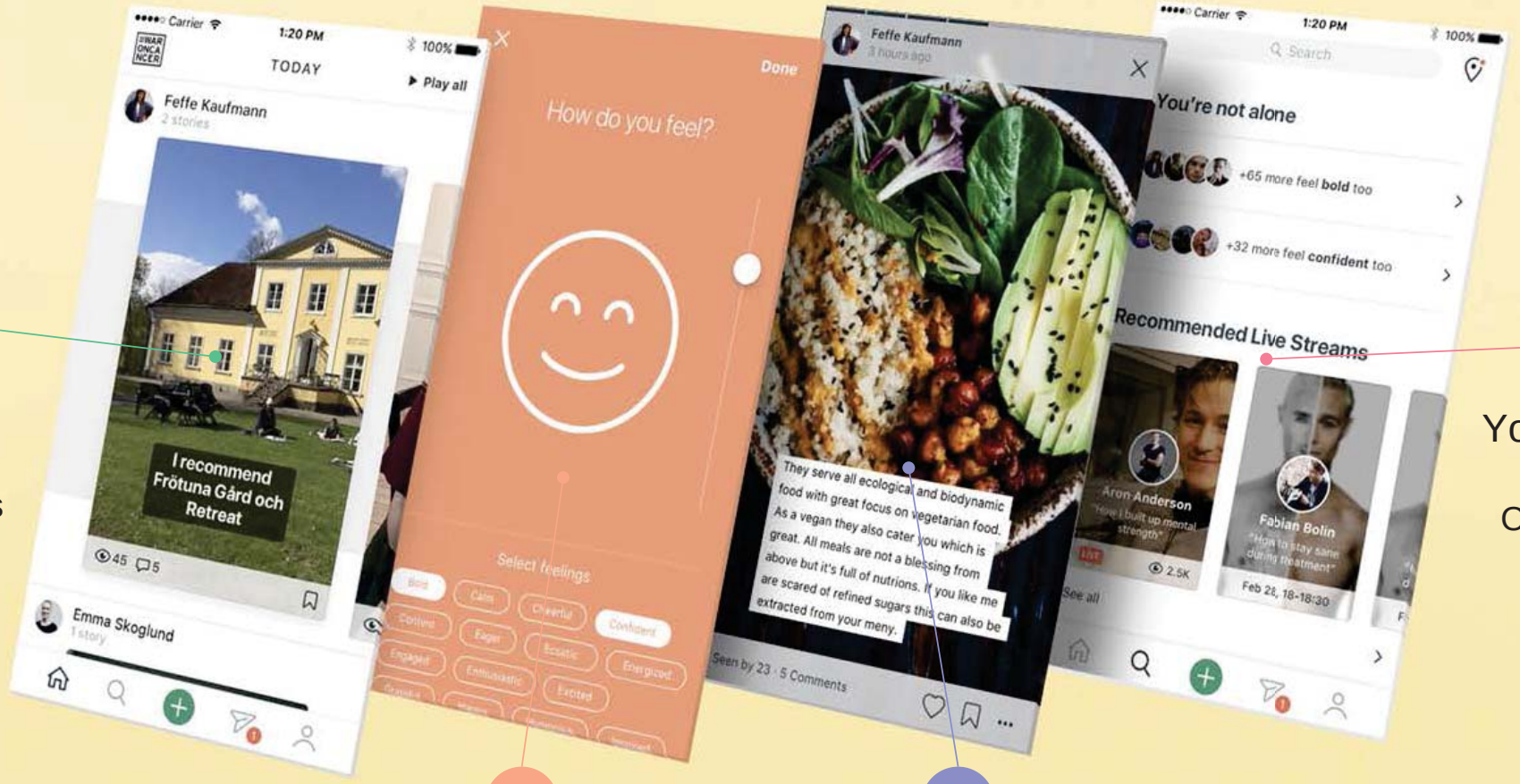
Love | Comment | Share

27K | Top Comments

12,727 Shares | 2.1K Comments

Henrik Lindell Alla ni som ser detta: det finns något ni kan göra. Ni kan anmäla er till Tobias-registret. Det är ett register man anmäler sig till om man vill vara donator av benmärg. Om man har

Write a comment...



1

Share your journey

Follow others

2

Share your health data

Track your impact

3

Share knowledge

Learn from others

4

You are not alone

Others feel like you

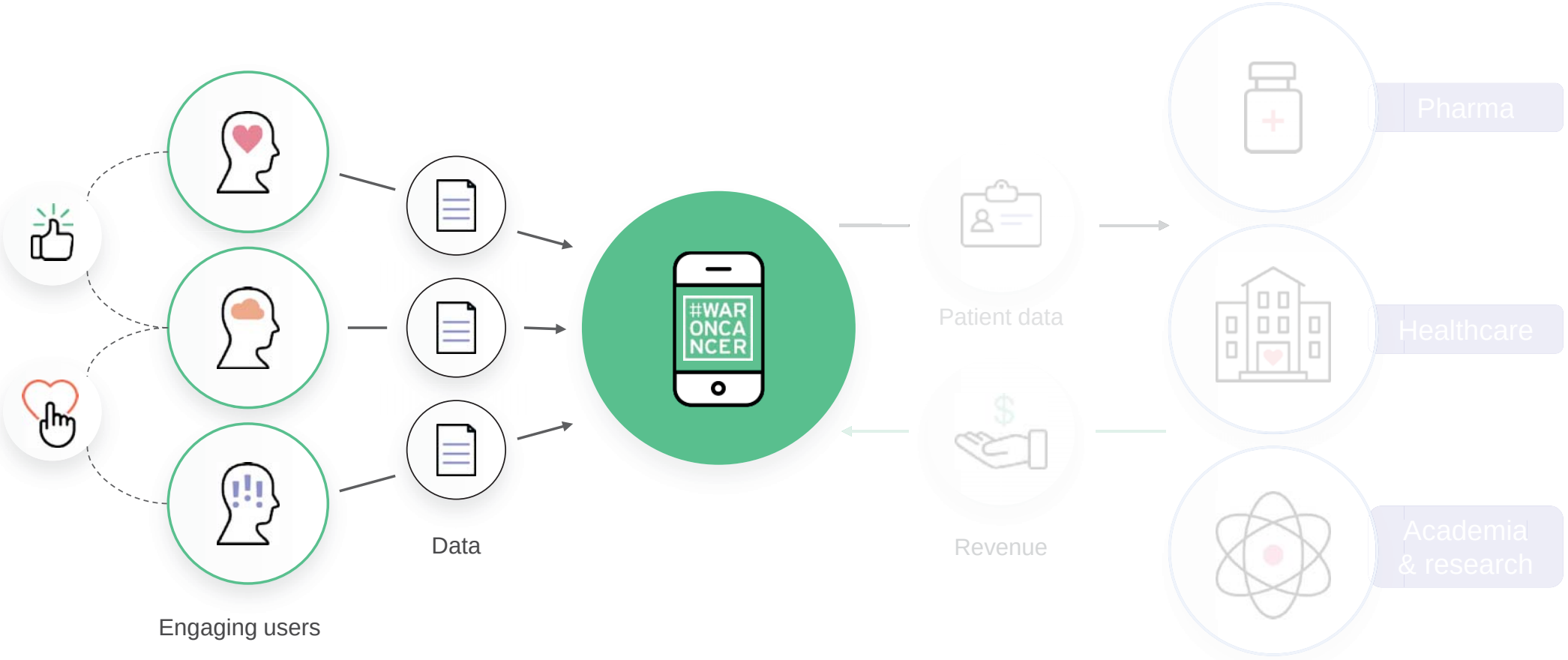
Sebastian Hermelin

COO & Co-founder,
WarOnCancer

@sebhermelin @waroncanceruntd

OPPORTUNITY

Social Network...



WARONCANCER

Gamification of Altruism

Track your impact

San Francisco Uni.
Research study on
diet and cancer

Stockholm
Hospital
Patient-reported outcome report

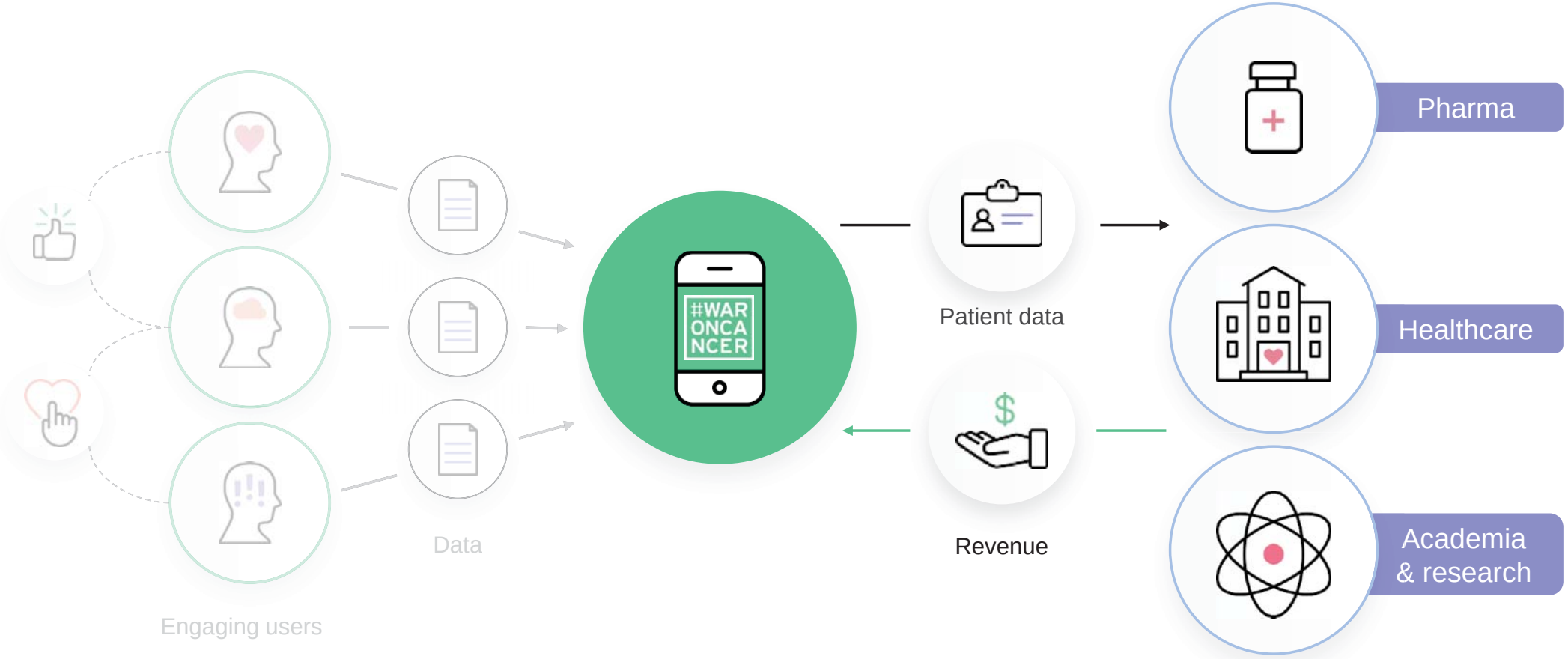
Rio de Janeiro
Pharmaceutical company,
Drug development: Liver
Cancer

Sydney
Pharmaceutical company
Clinical trial match-making

Bristol-Myers Squibb · Celgene · MSD · janssen · AMGEN · BAYER

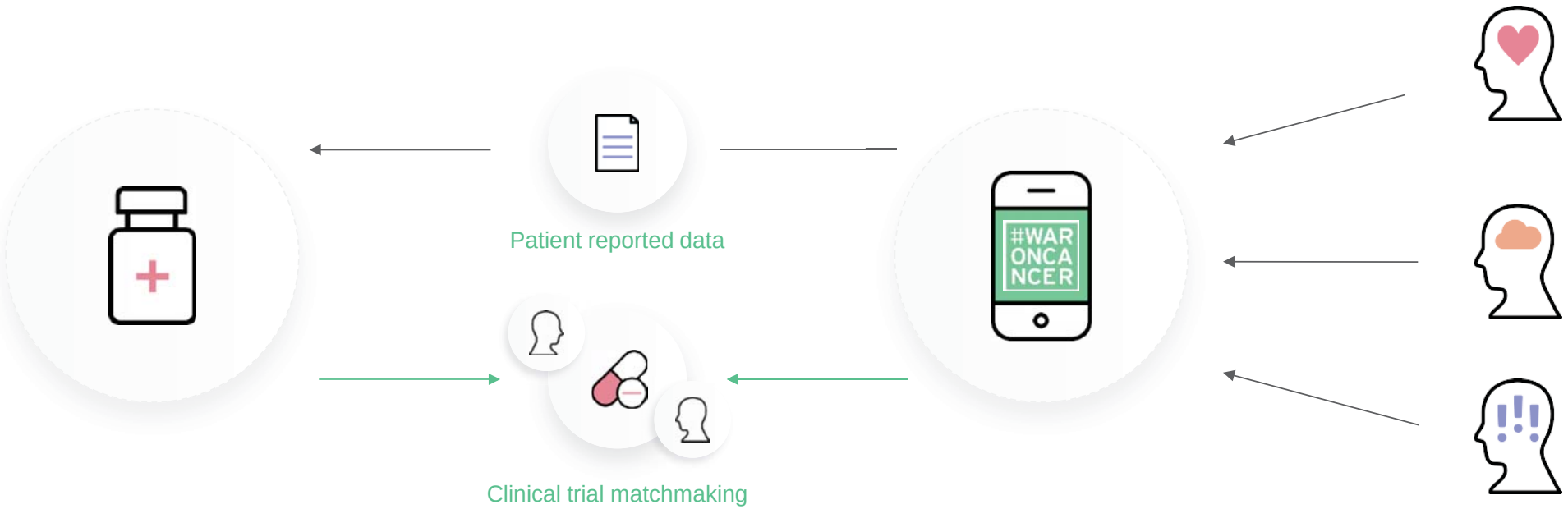
OPPORTUNITY

...meets Patient-reported data



WARONCANCER

Biopharma partnership



Partners:

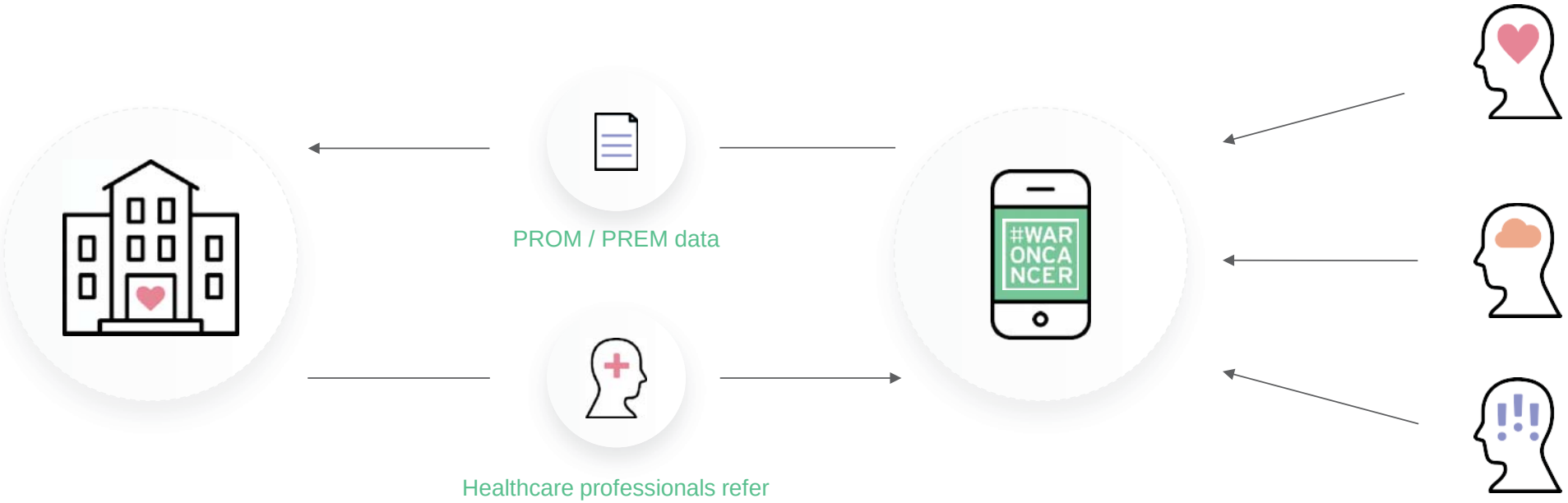
Bristol-Myers Squibb · Celgene · MSD · janssen · AMGEN · BAYER

Impact through:

- Targeted Surveys
- Insights/Reports
- Clinical trials matching
- Real Word Evidence

WARONCANCER

Healthcare partnership



PROM / PREM data

Healthcare professionals refer patients to WarOnCancer as a tool for mental recovery

In talks with

VÄSTRA GÖTALANDSREGIONEN · Capio · KAROLINSKA UNIVERSITY HOSPITAL · sas · Karolinska Institutet

Impact through:

- Targeted Surveys
- Insights/Reports
- WarOnCancer prescription
- Link PRO- and clinical data

WarOnCancerUnited

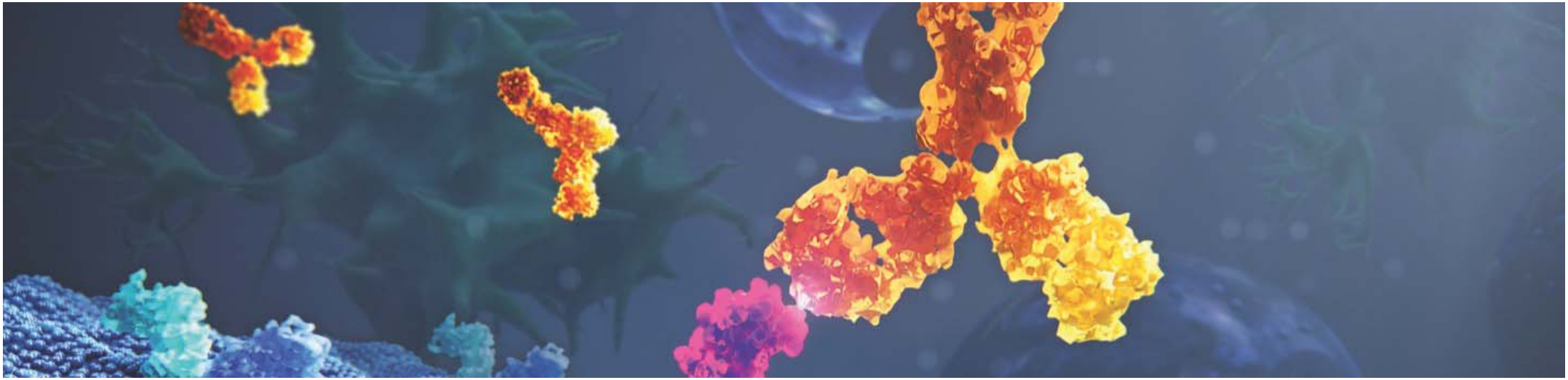
WarOnCancerUntd

WarOnCancer AB

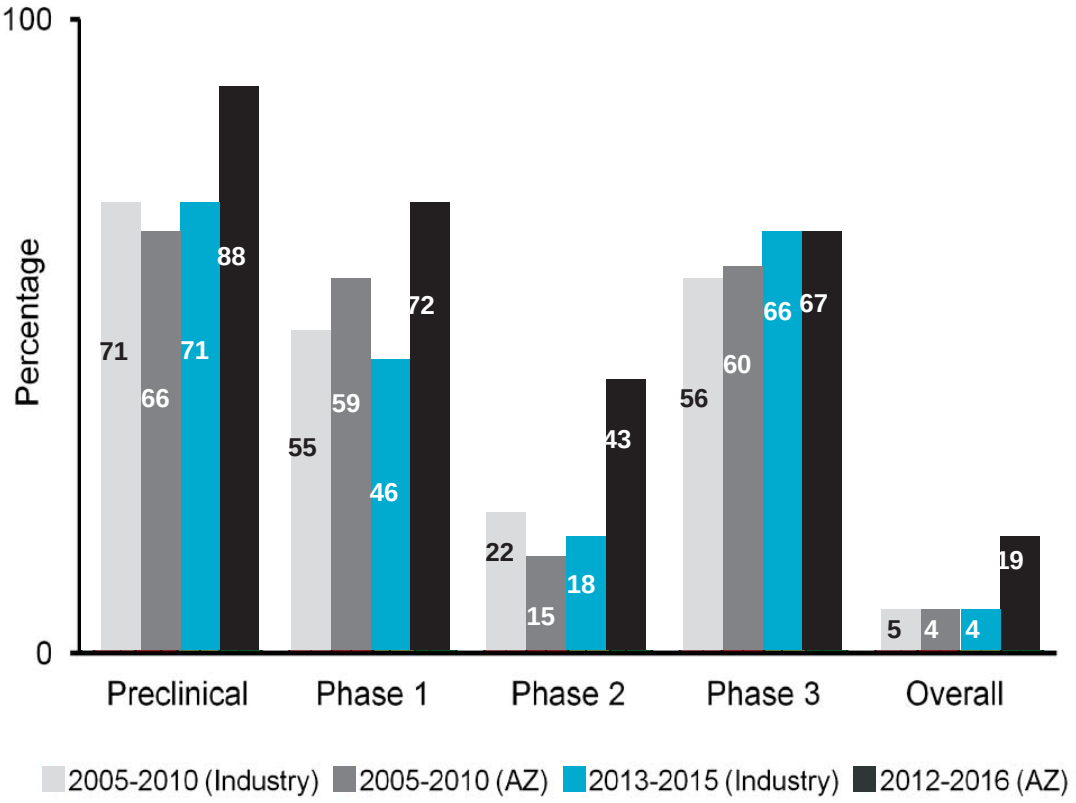
Personalised Medicine Research & Implementation - From Basic Research to the Patient

Joachim Reischl,
Precision Medicine & Genomics

November 2018



Focus on science is driving innovation and quality: 4 fold improvement in success rates since 2012



nature REVIEWS DRUG DISCOVERY

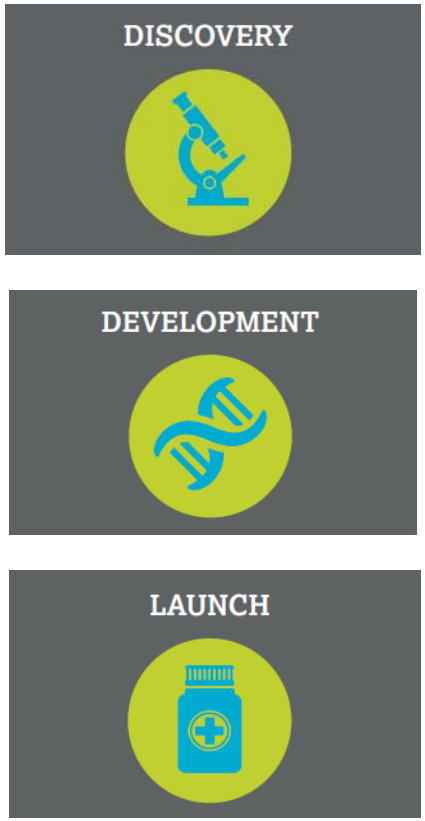
OUTLOOK

Impact of a five-dimensional framework on R&D productivity at AstraZeneca

Paul Morgan, Dean G. Brown, Simon Lennard, Mark Anderton, J. Carl Barrett, Ulf Eriksson, Mark Fidock, Bengt Hamrén, Anthony Johnson, Ruth E. March, James Matcham, Jay Mettetal, David J. Nicholls, Stefan Platz, Steve Rees, Michael A. Snowden and Menelas N. Pangalos

Abstract | In 2011, AstraZeneca embarked on a major revision of its research and development (R&D) strategy with the aim of improving R&D productivity, which was below industry averages in 2005–2010. A cornerstone of the revised strategy was to focus decision-making on five technical determinants (the right target, right tissue, right safety, right patient and right commercial potential). In this article, we describe the progress made using this '5R framework' in the hope that our experience could be useful to other companies tackling R&D productivity issues. We focus on the evolution of our approach to target validation, hit and lead optimization, pharmacokinetic/pharmacodynamic modelling and drug safety testing, which have helped improve the quality of candidate drug nomination, as well as the development of the right culture, where 'truth seeking' is encouraged by more rigorous and quantitative decision-making. We also discuss where the approach has failed and the lessons learned. Overall, the continued evolution and application of the 5R framework are beginning to have an impact, with success rates from candidate drug nomination to phase III completion improving from 4% in 2005–2010 to 19% in 2012–2016.

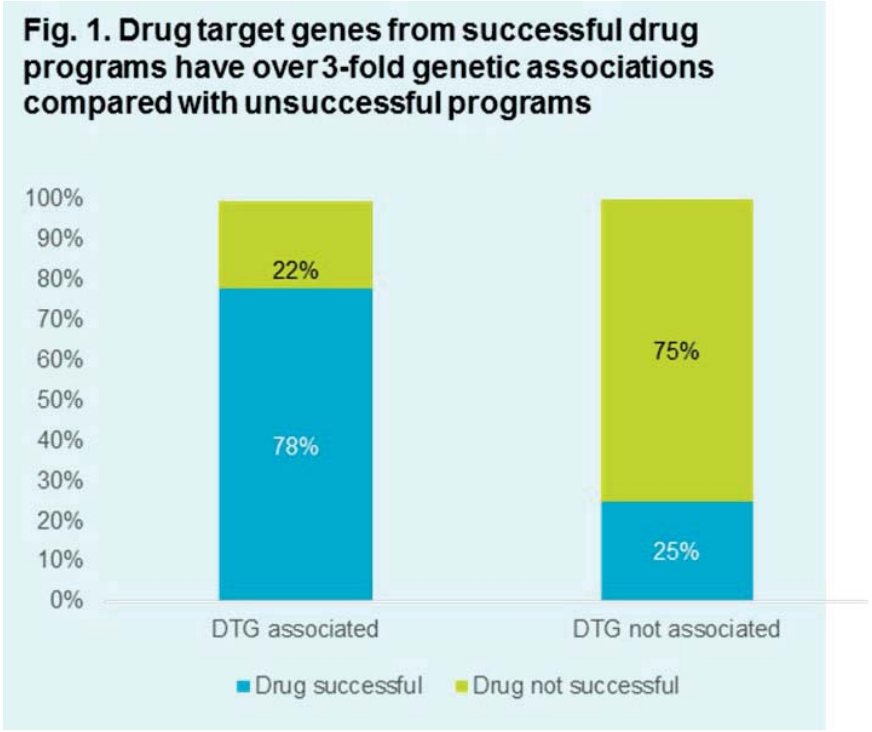
Integrating genomics across the portfolio can transform discovery and development



Innovative drug targets linked to molecular mechanisms: discover new biology and new targets

The right clinical trials: new patient populations matched to causative treatment

Delivering better medicines, faster: launching new, more effective medicines for the right patients



ASHG2017
ORLANDO • OCTOBER 17-21, 2017
SHARING DISCOVERIES. SHAPING OUR FUTURE.

AstraZeneca & MedImmune Genomics Initiative

We are harnessing the power of genomics through our integrated Genomics Initiative

2 million

We have the bold ambition to analyse up to two million genomes by 2026

500,000

Up to 500,000 genomes will be sequenced from genomic samples collected from AstraZeneca and MedImmune clinical trials

The power of genomics

- Understand more about the biology of disease
- Identify new targets for medicines
- Support selection of patients for clinical trials
- Allow patients to be matched with treatments more likely to benefit them

Approximately 90% of our NME clinical pipeline follows a Precision Medicine approach

~ 90% of our clinical pipeline follows a Precision Medicine approach, compared with 10% in 2009

Figure from 2017 AZ IMED Annual Report

This has enabled 26 Diagnostic test approvals to date

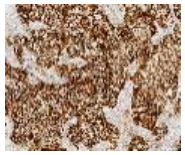
- AstraZeneca has achieved **26 diagnostic test approvals since 2014**, in **three major global markets** (US, EU and Japan).

- These innovative diagnostics are linked to **five therapies**, including **four AstraZeneca precision medicines.**

Diagnostics linked to four AZ medicines to guide therapy

Durvalumab
PD-L1 monoclonal antibody

PD-L1 complementary Dx (for Bladder – US), CE IVD (for NSCLC – EU)



Partner: Ventana

VENTANA
A Member of the Roche Group

Gefitinib
EGFR inhibitor

***EGFR* tissue (US) & plasma (EU)**
1st plasma CDx CE-IVD for solid tumour
Partner: Qiagen

QIAGEN

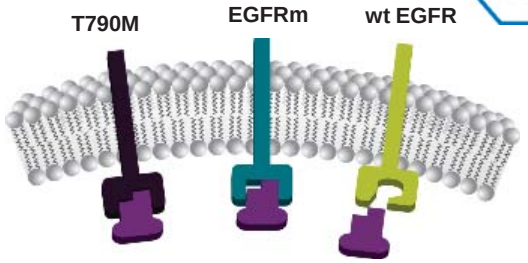
***EGFR* tissue & plasma (US)** *Partner: RMS*

Roche

Osimertinib
Mutant-selective EGFR inhibitor

***EGFR T790M* tissue & plasma (US, EU, JPN)**
AZ's first FDA approved ctDNA test
***EGFRm* tissue & plasma (US, JPN)**
1st concurrent CDx tissue & plasma
Partner: RMS

Roche



***EGFR T790M* tissue NGS panel (US)**
Partner: FMI

FOUNDATION MEDICINE

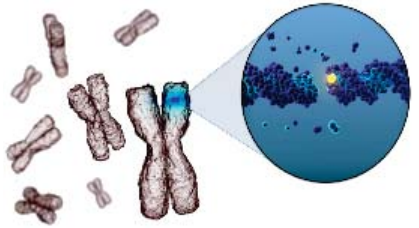
Olaparib
PARP inhibitor

Germline *BRCA* (US, EU, JPN)
Partner: Myriad
1st BRCA LTD CDx

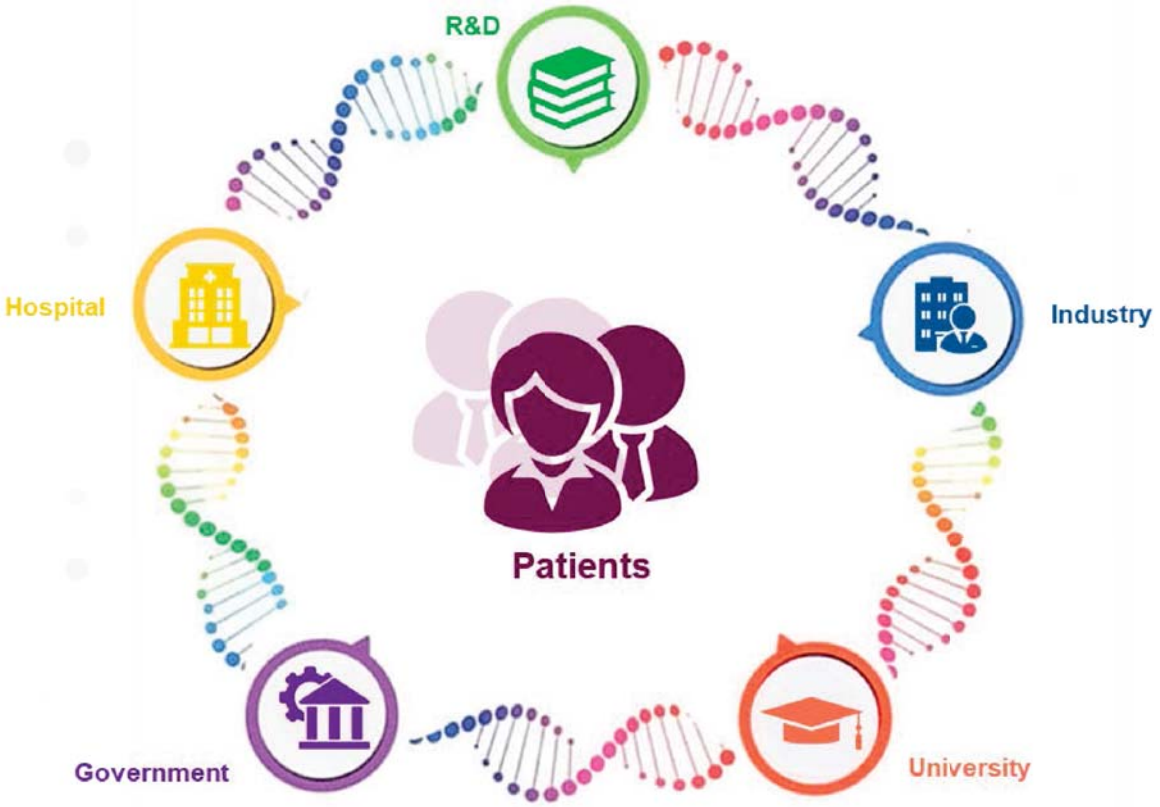
MYRIAD

Tumour *BRCA* CE IVD (EU)
Partners: Myriad, Multiplicom, Qiagen

MYRIAD QIAGEN Multiplicom
A part of Agilent Technologies



Build a patient-centric cross-sector ecosystem to bring innovation to patients fast



What is needed?

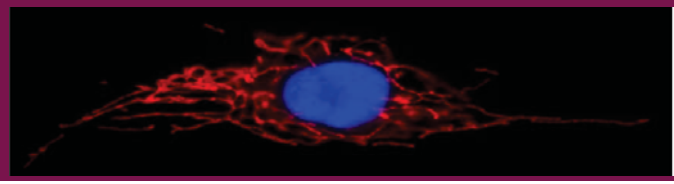
- Ensure **access to high quality testing**
- Move **testing to earlier stages of disease**, linked to treatment decisions
- Build national and international **databases with large patient cohorts**, linking genomic and clinical data
- Harness the **power of data for research and clinical decision making** – apply AI / machine learning

Confidentiality Notice

Clinical Implementation of Whole Genome Sequencing

Anna Wedell, MD, PhD, Professor

Head, Centre for Inherited Metabolic Diseases



SciLifeLab

Karolinska Institutet

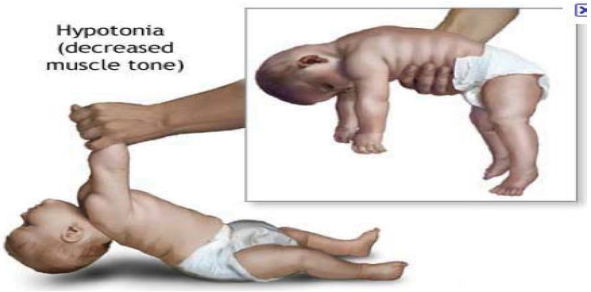
KAROLINSKA Universitetssjukhuset

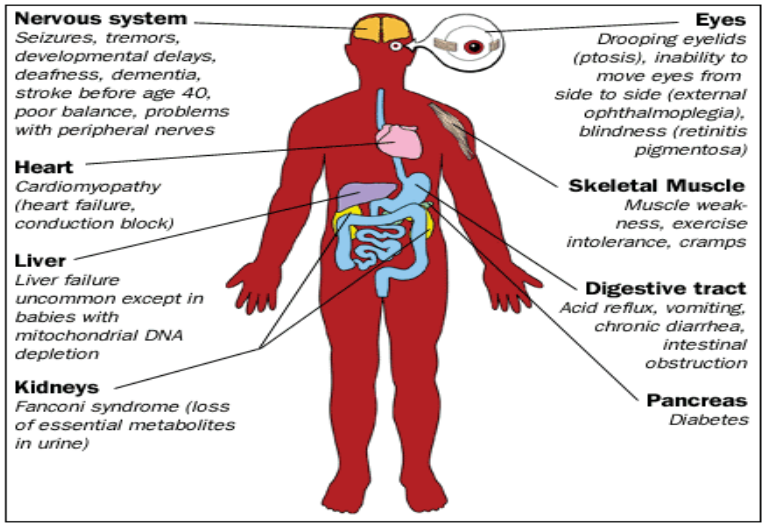
Inborn Errors of Metabolism (IEM): around 1 000 rare diseases

Affect all clinical disciplines. Often treatable.

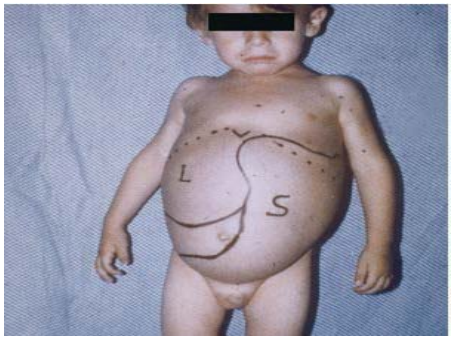
Adult

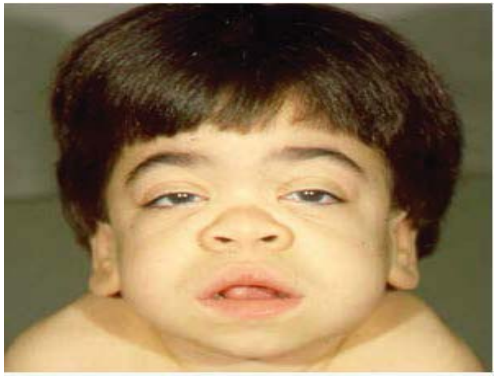
Acute, neonatal

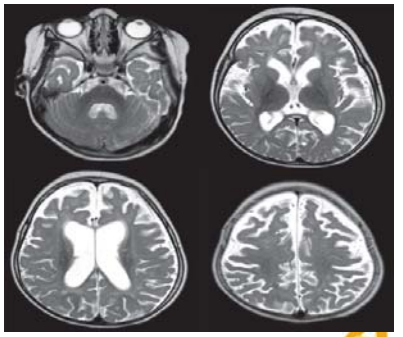




Gradual, progressive







KAROLINSKA
Universitetssjukhuset

Centre for Inherited Metabolic Diseases, CMMS

Cross-disciplinary organisation

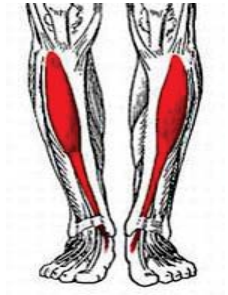
Laboratory medicine: clinical genetics, clinical chemistry

Clinical medicine: pediatrics, neurology, endocrinology

Biochemical + genetic investigations + treatment controls

Mitochondrial investigations: Muscle biopsy

ATP synthesis, ativities of enzyme complexes, morphology, RC assembly



PKU laboratory

National neonatal screening program

115 000 Swedish newborns/year

24 diseases as of Nov, 2010

National registry for patient follow-up

Registret för Medfödda Metabola Sjukdomar

KI – Max Planck lab for molecular metabolism

Karolinska Institutet

MAX PLANCK INSTITUTE FOR BIOLOGY OF AGEING

SciLifeLab

A national center for high-throughput bioscience

Focus on genomics, protein profiling, bioimaging and bioinformatics with relevance for environment and health

Clinical whole genome sequencing

- Stringent and ethically acceptable
- Quality assured
- Restricted to relevant information
- Accurate medical interpretation
- Rapid translation into clinical action

SciLifeLab *Clinical Genomics*

KAROLINSKA *Universitetslaboratoriet*

Clinical Grade Analysis

Filter

Whole genome sequencing

Known disease genes

dbCMMS: ≈900 genes

HPO

Multidisciplinary team

List of variants

Discovery

Novel disease mechanisms

Experimental validation

Custom data processing strategy

MIP
Mutation identification pipeline

genmod

- Automated bioinformatics pipeline for processing raw data to annotated and ranked variants ready for clinical interpretation.
- Enables individualized analysis based on patient phenotypes (HPO)
- Exomes 2-3 hours, WGS 24 hours.
- Developed by *Henrik Stranneheim* (CMMS) and *Måns Magnusson* (CMMS, Clinical Genomics)

Henrik Stranneheim

- Sample specific quality report addressing coverage on gene and transcript level. Identifies regions with insufficient coverage.
- Developed by *Robin Andeer* (Clinical Genomics)

Robin Andeer

- Custom-developed, browser-based reporting tool enabling clinicians to view the ranked variants
- Enables data sharing between teams
- Developed by *Robin Andeer, Måns Magnusson*, and *Henrik Stranneheim*.

Scout

- https://github.com/Clinical-Genomics/scout

Måns Magnusson

Collaboration SciLifeLab Clinical Genomics – Karolinska

KAROLINSKA

SciLifeLab

Delivery to SciLifeLab

Manual or Automated library preparations

Rapid sequencing

Automated, secure data processing and QC

Dedicated HPC cluster for data processing

MIP

Mutation identification pipeline

Alignment, variant call, functional annotation

Sample specific quality measurement

Scout

Browser-based data presentation for collaborating physicians

KAROLINSKA

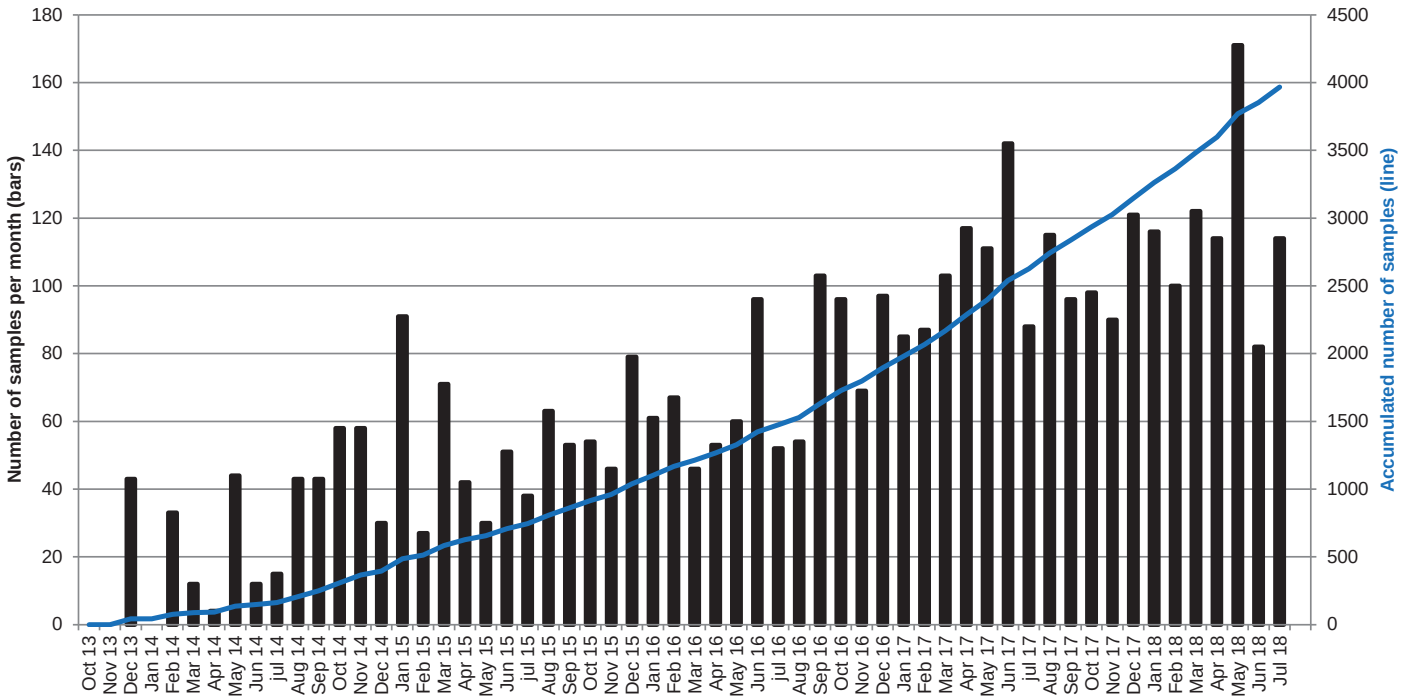
Clinical interpretation and reporting

SWEDAC ACKREDITERING

Ackred. nr 1926
ISO/IEC 17025

- Building complementary teams, ”Rare disease community”
- Data sharing
- Genomic Medicine Center Karolinska, GMCK

Clinical WGS, > 4000 Rare Disease samples processed



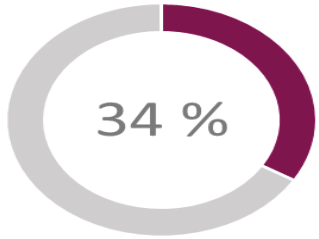
Turnaround time approximately 10-12 days on average (5 – 21 days)

Results, Clinical IEM track (known genes)

790 patients with suspected IEM

266 solved

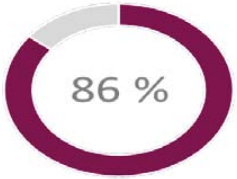
180 different genes. Extreme heterogeneity!



21 newborn screening positive

18 solved cases

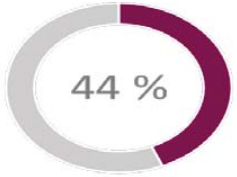
15 different genes



119 abnormal mitochondrial biochemistry

52 solved cases

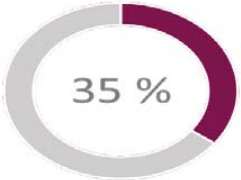
46 different genes



270 epileptic encephalopathies

95 solved cases

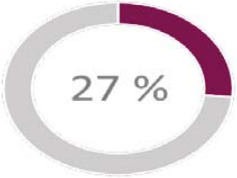
54 different genes



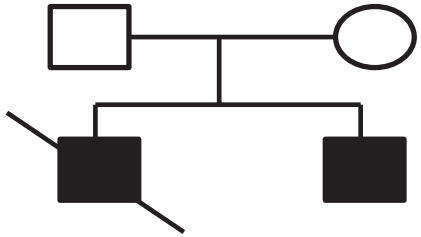
380 other

101 solved cases (of 380)

65 different genes



Case Clinical track (*dbCMMS*):



- Boy born healthy, at 5 weeks lethargy and lack of appetite
- Seizures 2 days later
- Develops severe brain damage (MRI)
- Dies at 2 months

- Younger brother born healthy 1.5 years later
- Lethargy at 5 weeks
- MRI: first signs of similar brain damage

- Clinical WGS in 4 days, mutations in *SLC19A3*
- Diagnosis: Biotin-responsive basal ganglia disease
- Treatment: High dose thiamine & biotin

Newly discovered diseases & metabolic pathways:

Wibom R et al: ***AGC1*** *deficiency associated with global cerebral hypomyelination.*
N Engl J Med (2009): 361:489-495

Bjursell MK et al: ***ADK*** *deficiency disrupts the methionine cycle and causes hypermethioninemia, encephalopathy and abnormal liver function.*
Am J Hum Genet. (2011) 89:507-515

Freyer C et al: Rescue of primary ubiquinone deficiency due to a novel ***COQ7*** *defect using 2,4-dihydrobensoic acid.*
J Med Genet (2015) 52:779-783

Kishita Y et al: Intra-mitochondrial methylation deficiency due to mutations in ***SLC25A26*** *(****SAMC****)*
Am J Hum Genet. (2015) 97:761-768

Stödberg T et al: Mutations in ***SLC12A5*** in epilepsy of infancy with migrating focal seizures
Nature Commun. (2015) 6:8038

Haack TB et al: Absence of the Autophagy Adaptor ***SQSTM1/p62*** Causes Childhood-Onset Multisystem Neurodegeneration with Ataxia
Am J Hum Genet. (2016) 97:761-768

Clinical genome sequencing in rare diseases

- Dramatic clinical impact!
- A new landscape of monogenic diseases is emerging
- Early identification of treatable disorders
- Identification of pathways relevant for human pathology
- Discovery of novel disorders and disease mechanisms
- Discovery of biomarkers and drug targets / treatment
- Relevance for common disorders

Integration &
Data sharing
between teams

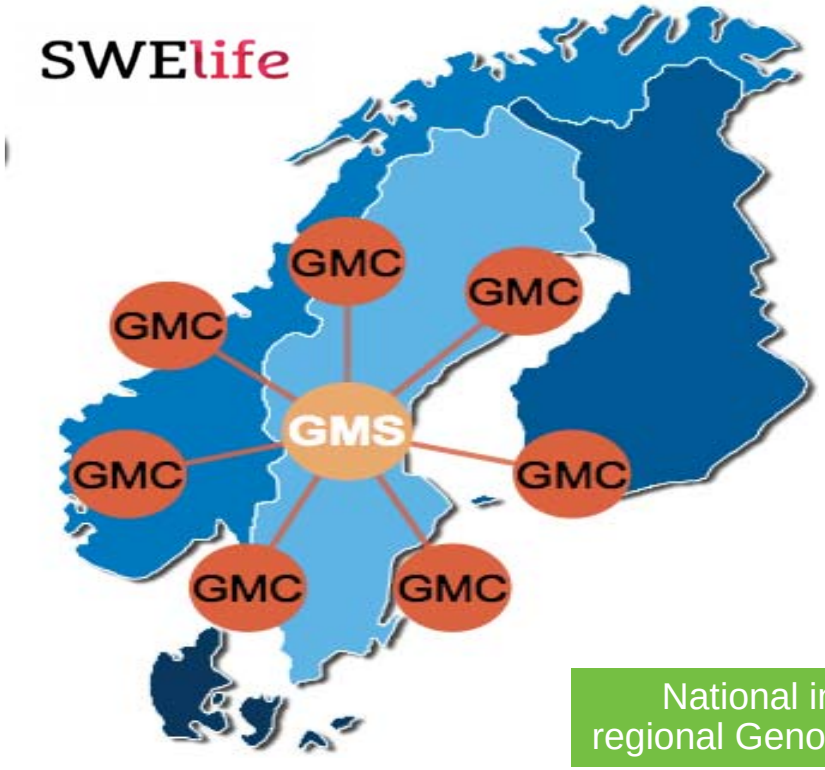
Laboratory medicine
Clinical medicine
High-throughput technology
Basic experimental science

KAROLINSKA Universitetssjukhuset
Karolinska Institutet
SciLifeLab
MAX PLANCK INSTITUTE FOR BIOLOGY OF AGEING

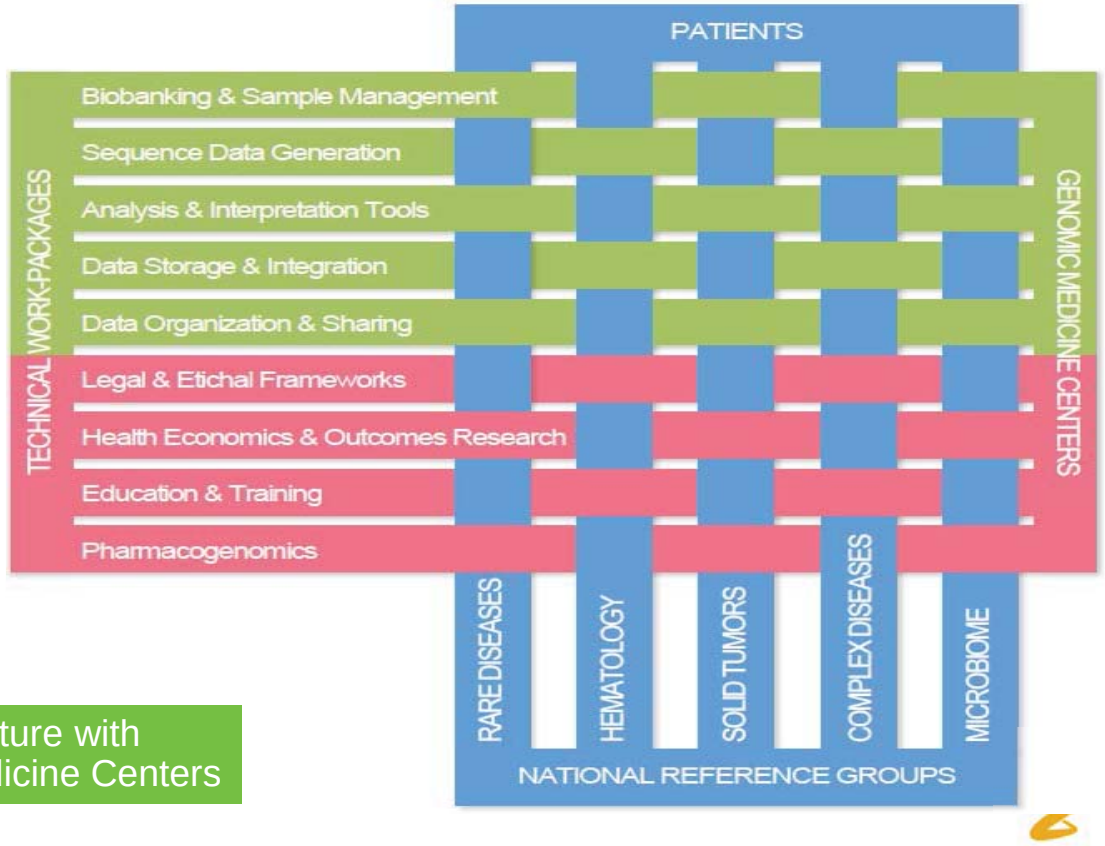
Genomic Medicine Center Karolinska (GMCK)

a part of

Genomic Medicine Sweden (GMS)



National infrastructure with
regional Genomic Medicine Centers



KAROLINSKA Universitetssjukhuset

Karolinska Institutet

SciLifeLab

CMMS

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Vetenskapsrådet

Hjärnfonden 1994-2014

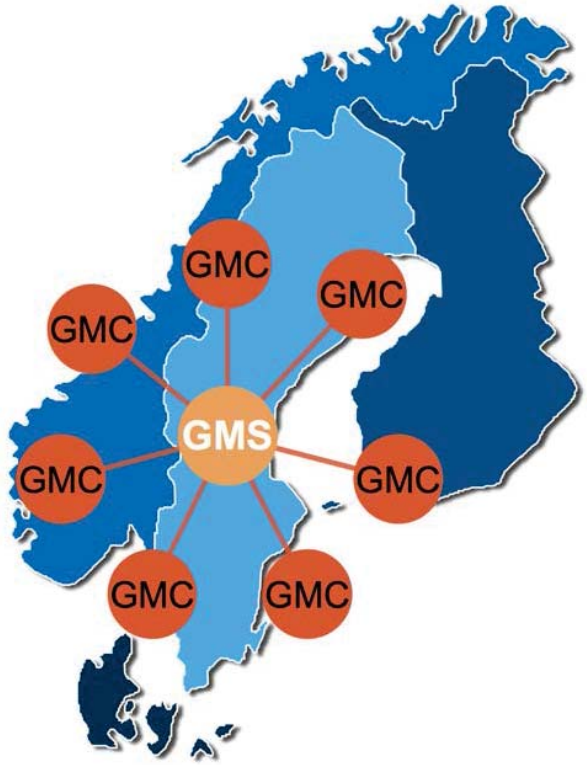
erc

Max Planck Institute

MAX PLANCK INSTITUTE FOR BIOLOGY OF AGEING

Genomic Medicine Sweden

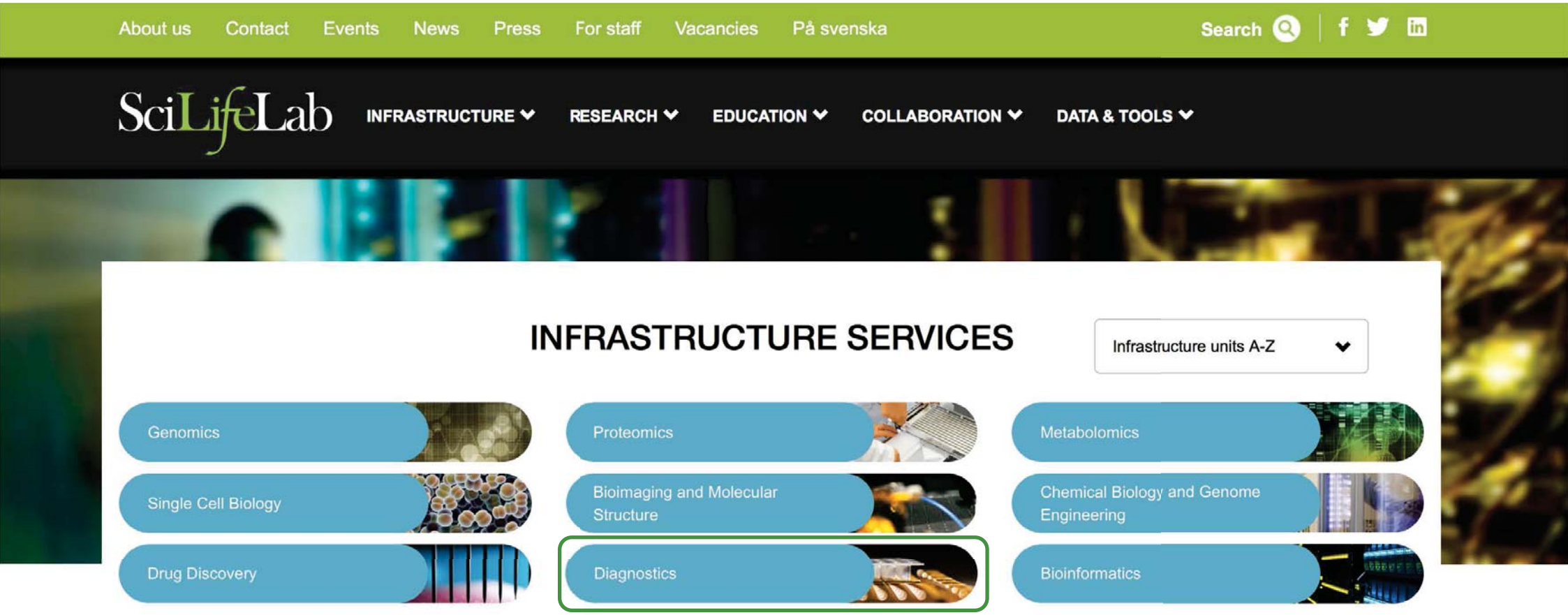
Richard Rosenquist Brandell
Karolinska Institutet &
Karolinska University Hospital



New tool box for diagnostics & research

Whole-genome	Exome	Gene panels
		
3 000 000 000 bp	21 000 genes	100 genes

Whole-genome sequencing, exome sequencing and targeted sequencing are now offered as clinical tests

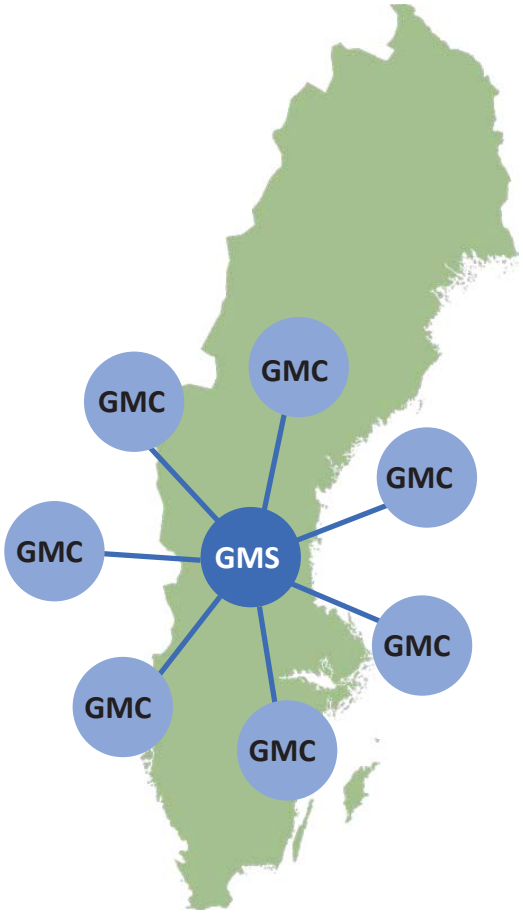


Developed NGS-based tests for healthcare since 2013 (WGS, WES, gene panels)
Collaborative effort between healthcare, universities & SciLifeLab (at 4 sites)
Initiated Genomic Medicine Sweden

What Genomic Medicine Sweden aims to accomplish?

Through a nation-wide collaborative effort offer all patients equal care regardless of healthcare region

- Front edge diagnostics– e.g. with next-generation sequencing technologies
- Precision medicine – the right treatment to the right patient and the right time
- A national research database
- Innovation and industry cooperation



How do we create a leading PM infrastructure?

Building on existing national resources:

- Science for Life Laboratory (SciLifeLab)
- Biobank Sweden
- Swedish National Quality Registries
- Regional Cancer Centres
- Centres for Rare Diseases
- Clinical studies in Sweden (trial alliancies)

SciLifeLab

NATIONELLA BIOBANKSRÅDET

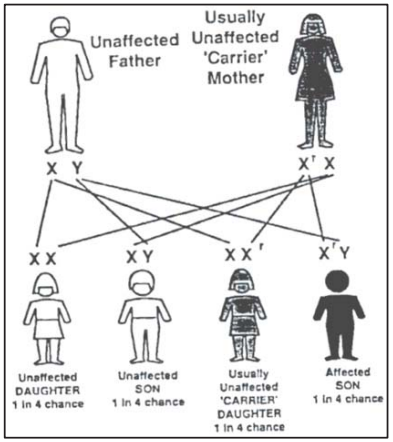
REGIONALA CANCERCENTRUM I SAMVERKAN

NFSD
NATIONELLA FUNKTIONEN SÄLLSYNTA DIAGNOSER

NATIONELLA KVALITETSREGISTER
Kunskap för bättre vård och omsorg

Kliniska Studier Sverige

GMS focus areas



Rare Diseases:

- Whole-genome sequencing
- Samples per year in routine diagnostics:
  - Today: <2,000 samples/year
  - In 5 years: 5,000 samples/year

Cancer:

- Solid tumors and leukemia:
  - Gene panels
  - RNA-sequencing/WGS
- Samples per year in routine diagnostics:
  - Today: >5,000 samples/year
  - In 5 years: 45,000 samples/year

Genomic Medicine Sweden – Time line

Basic concepts - organisation

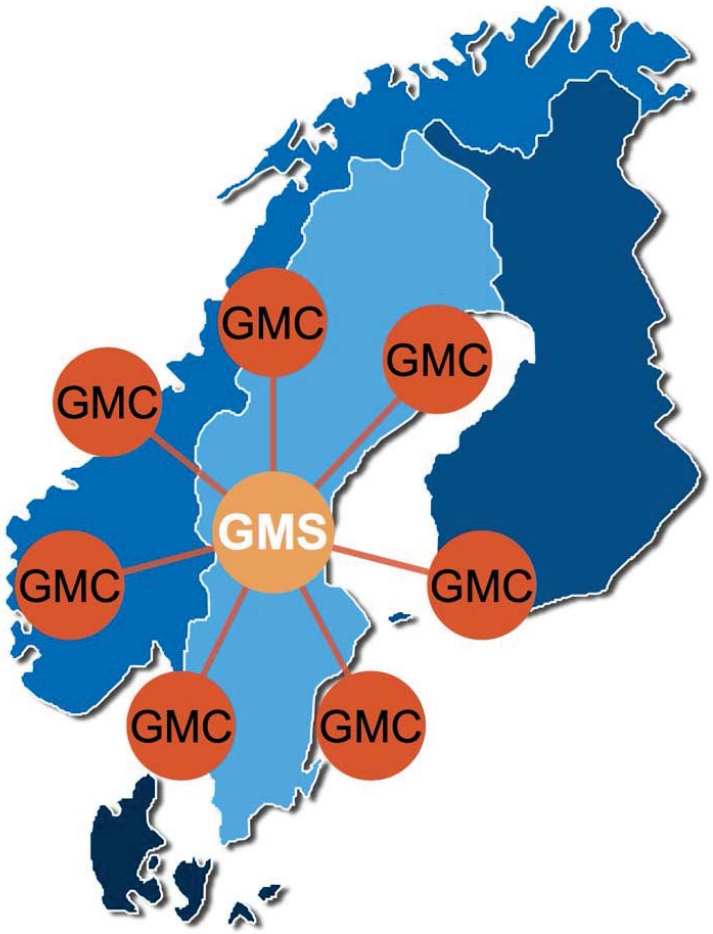
National infrastructure

- National reference groups
  - Rare Diseases
  - Hematology
  - Solid tumors
  - Micro-biology
  - Complex diseases
  - Pharmaco-genomics
- Informatics
  - Data processing
  - Decision support
  - Data sharing
  - Data storage
- Ethical and legal aspectcs
- Health economy
- Education & communication

Regional infrastructure

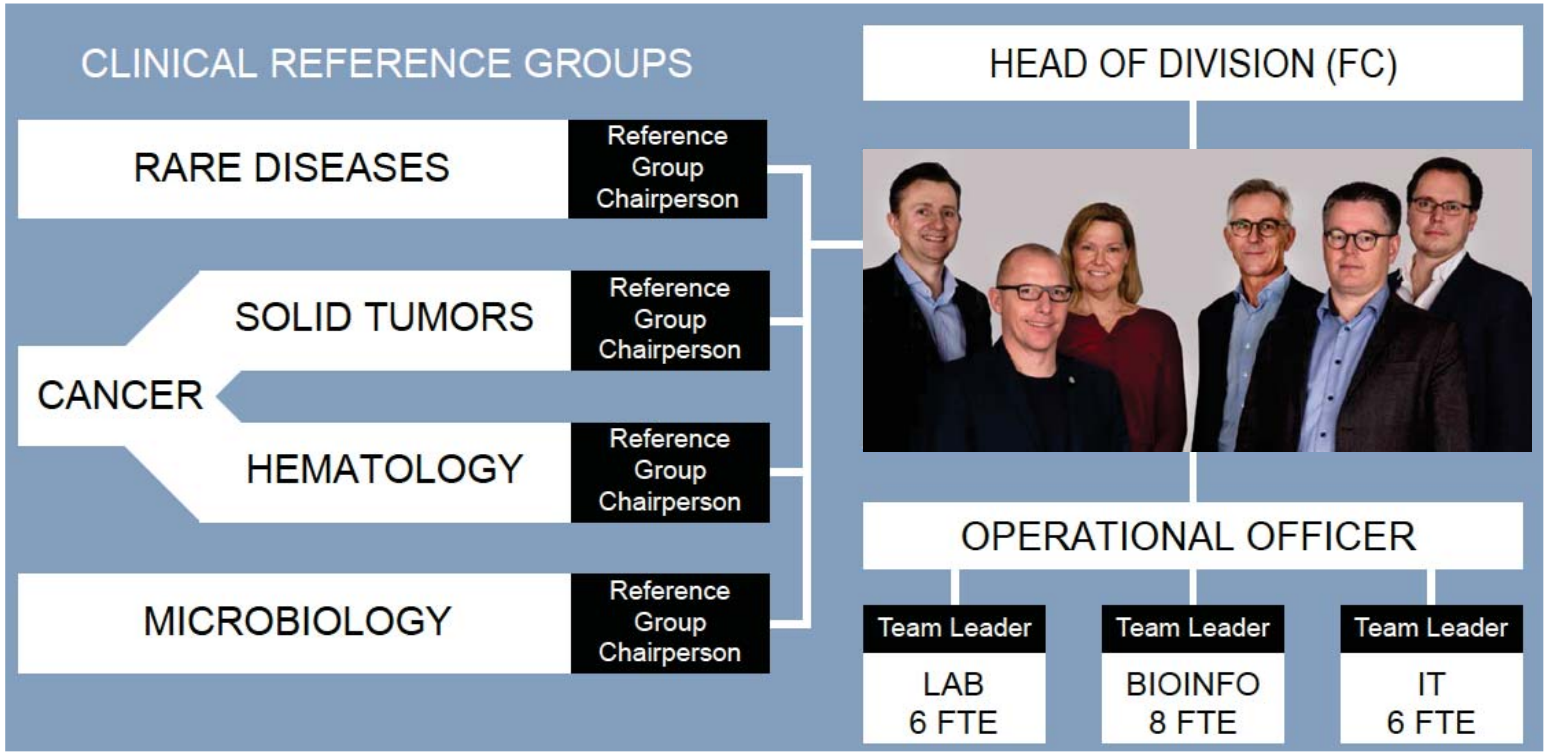
- GMC Uppsala
- GMC Norr
- GMC Örebro
- GMC Karolinska
- GMC Västra
- GMC Sydöstra
- GMC Syd

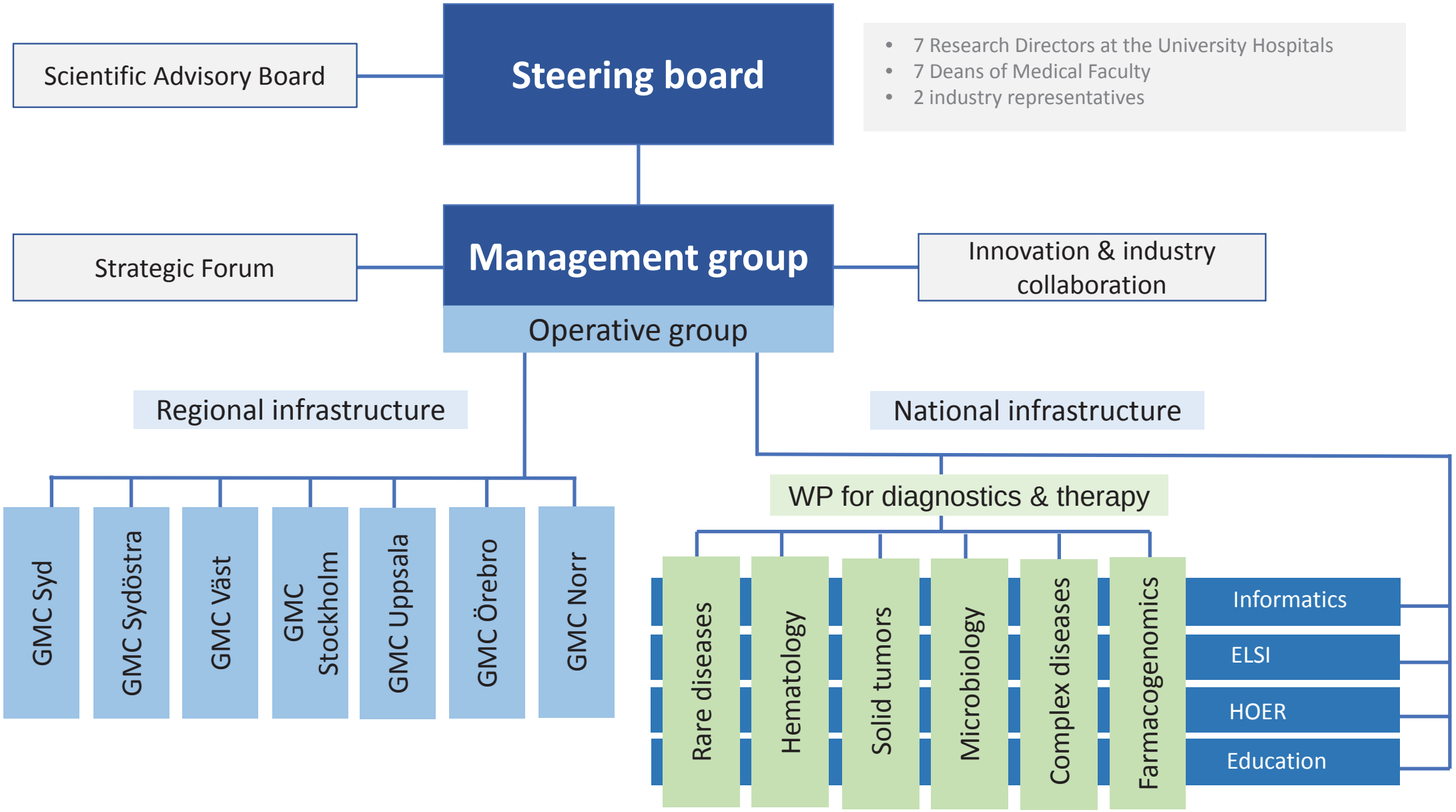
Genomic Medicine Centers



- At the university hospital in collaboration with the university
- Build on regional expertise and investments
- Broad competence in advanced molecular diagnostics
- Build expert PM teams
- Node for inclusion in clinical trials
- Promote coordination at national level

Genomic Medicine Center Karolinska




Scientific Advisory Board
Steering board
7 Research Directors at the University Hospitals
7 Deans of Medical Faculty
2 industry representatives
Strategic Forum
Management group
Innovation & industry collaboration
Operative group
Regional infrastructure
National infrastructure
GMC Syd
GMC Sydöstra
GMC Väst
GMC Stockholm
GMC Uppsala
GMC Örebro
GMC Norr
WP for diagnostics & therapy
Rare diseases
Hematology
Solid tumors
Microbiology
Complex diseases
Farmacogenomics
Informatics
ELSI
HOER
Education

Clinical Diagnostics

Genomic analysis

Variant list

Filter

Known
disease genes

Multidisciplinary conferences

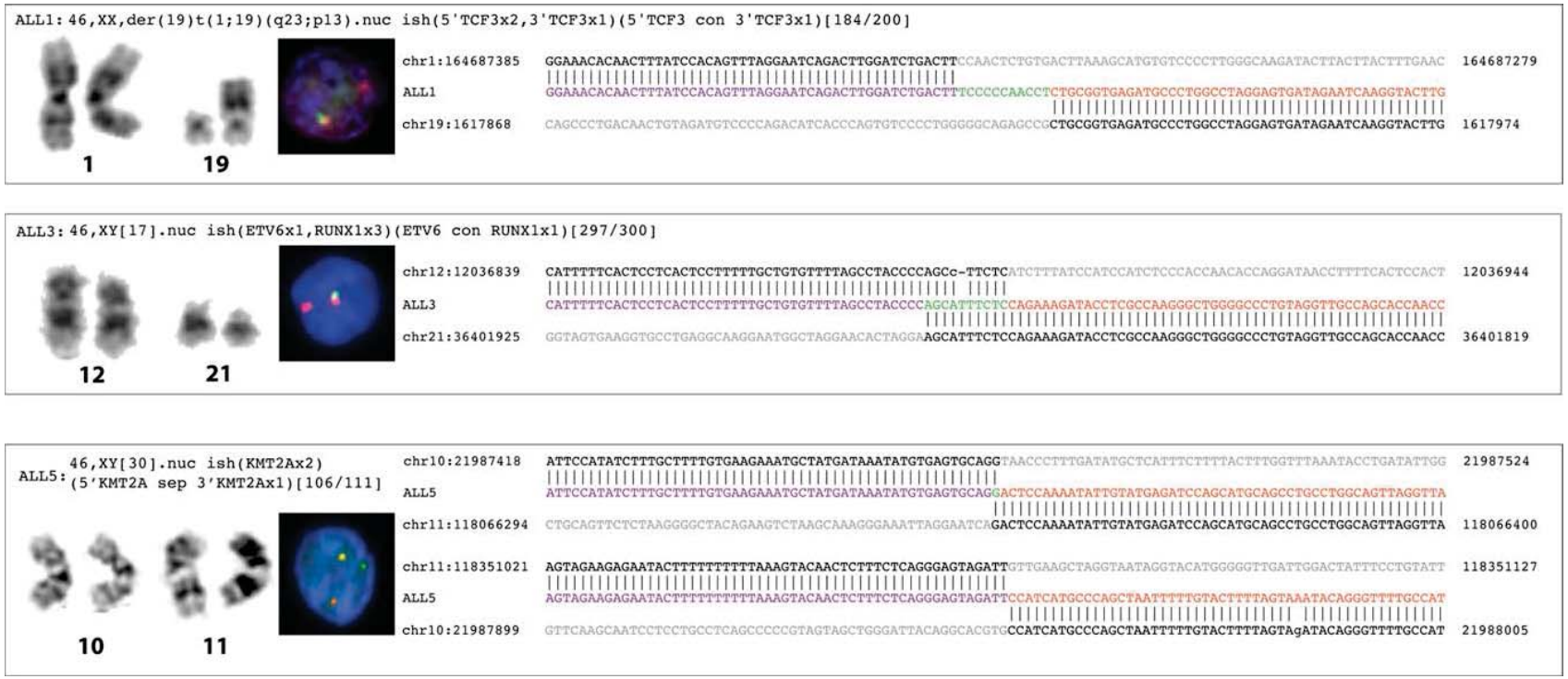
Filter

New biomarkars

Cancer sequencing – future challenges

- ✓ 1st generation gene panels (5-50 genes)
- ❑ 2nd generation gene panels (500 genes)
  All treatable targets, all forms of cancer
- ❑ 3rd generation - global sequencing
  WES, WGS, RNA-Seq

Implementing WGS in acute leukemia

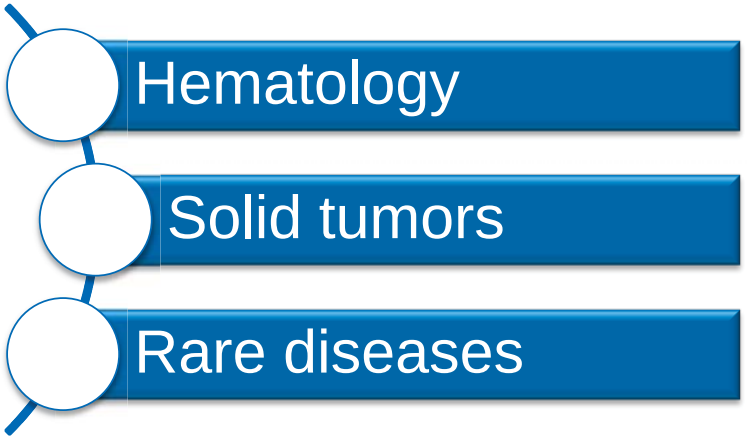


Tran et al, PLOS ONE 2018

PLOS ONE

GMS – Pediatric Cancer

- National collaborative effort:
  - Swedish Childhood Tumor Biobank
  - Pediatric hematology and oncology
  - Genomic Medicine Sweden
  - Swedish Childhood Cancer Society

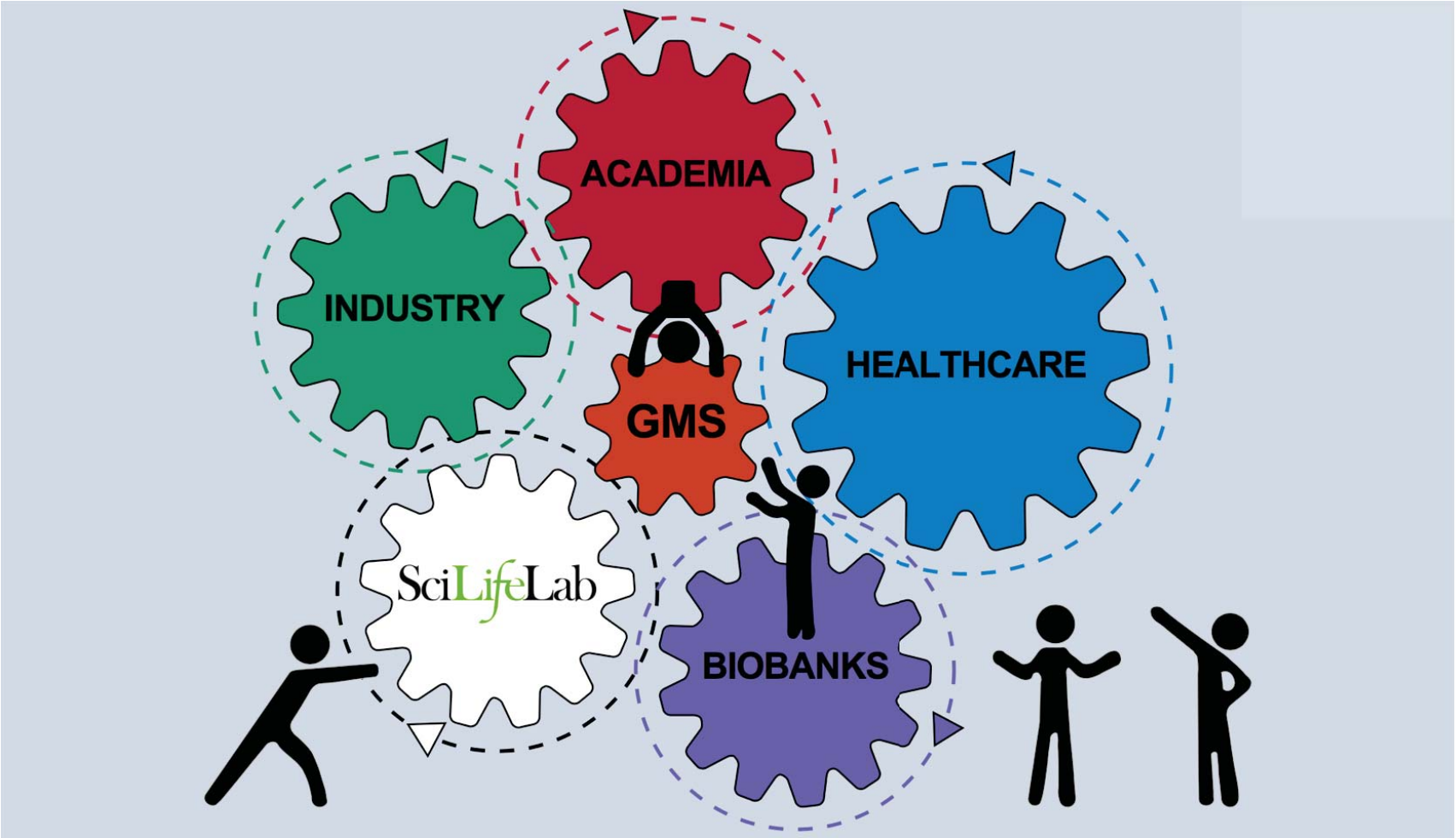


- WGS on 350 children per year

Barntumörbanken

BARNCANCER FONDEN

Thank you for listening!



A common IT infrastructure where all Swedish registries are linked with biobank registries and genomic data.

The first step is to listen to what those needs might be

Support for our cross-disciplinary approach, allowing deep integration of laboratory medicine, clinical medicine, and basic science

Access to high quality tests for patients early in the disease journey

A more straight forward way for healthcare to adopt patient-led innovation and for entrepreneurs to get an understanding of this process

Joint union between industry, healthcare and acedemia to strengthen PM.