Enhancing Molecular Pathology: Bridging the Gap between Genetics and Pathology

Nordic Pathology Meeting, 2025-05-19

Anders Edsjö, MD PhD
Clinical Genetics, Pathology and Molecular Diagnostics, Region Skåne, Sweden

Agenda

- Precision diagnostics for precision health
- Somatic & hereditary testing
- Overlaps & synergies
- Common challenges, solutions & opportunities
- Future directions

Precision Medicine – a straight forward concept

"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"

- President Obama, January 30, 2015

the WHITE HOUSE
PRESIDENT BARACK OBAMA

- **EU 2015:** Personalised medicine (ICPerMed International Consortium)

European Commission

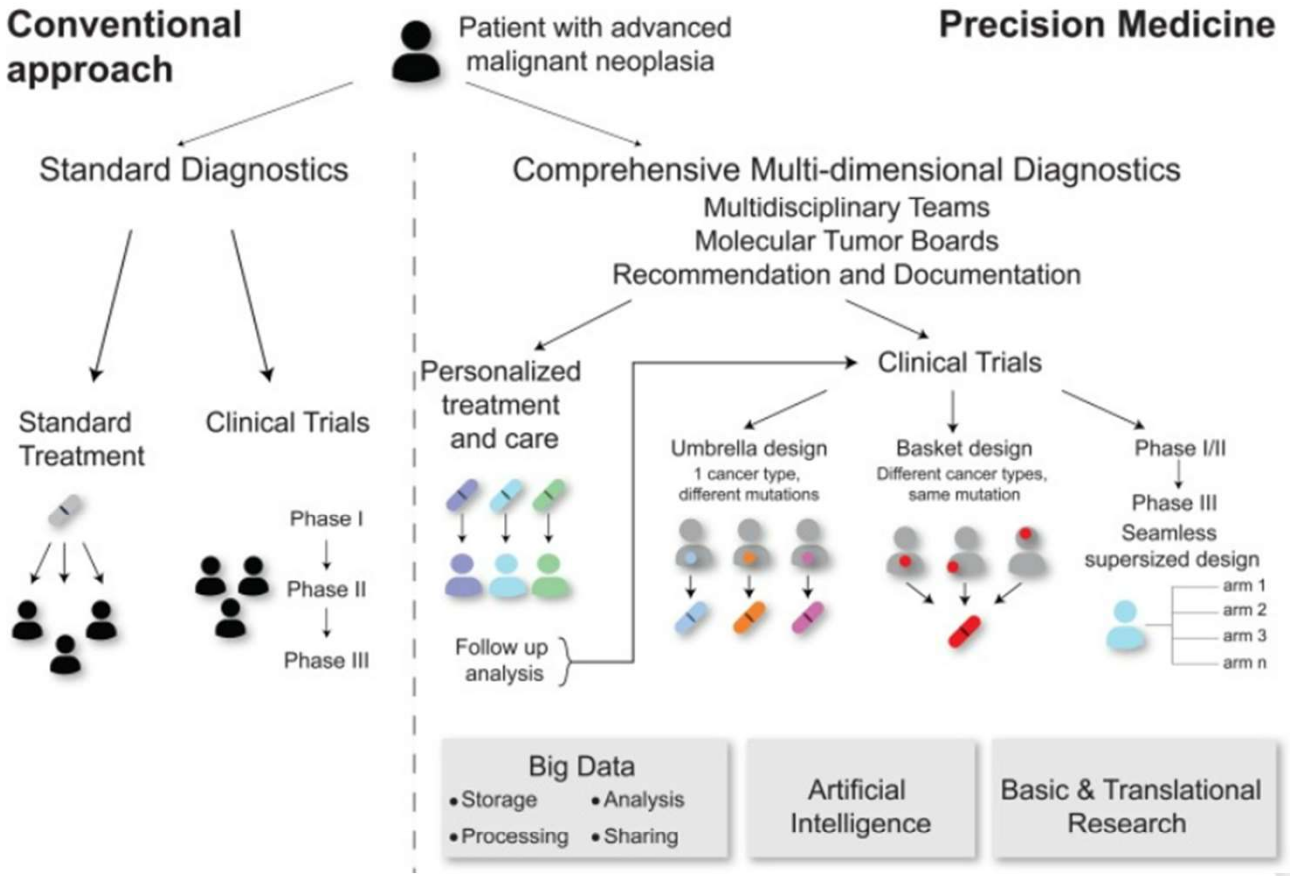
' a medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. '

REGION SKANE

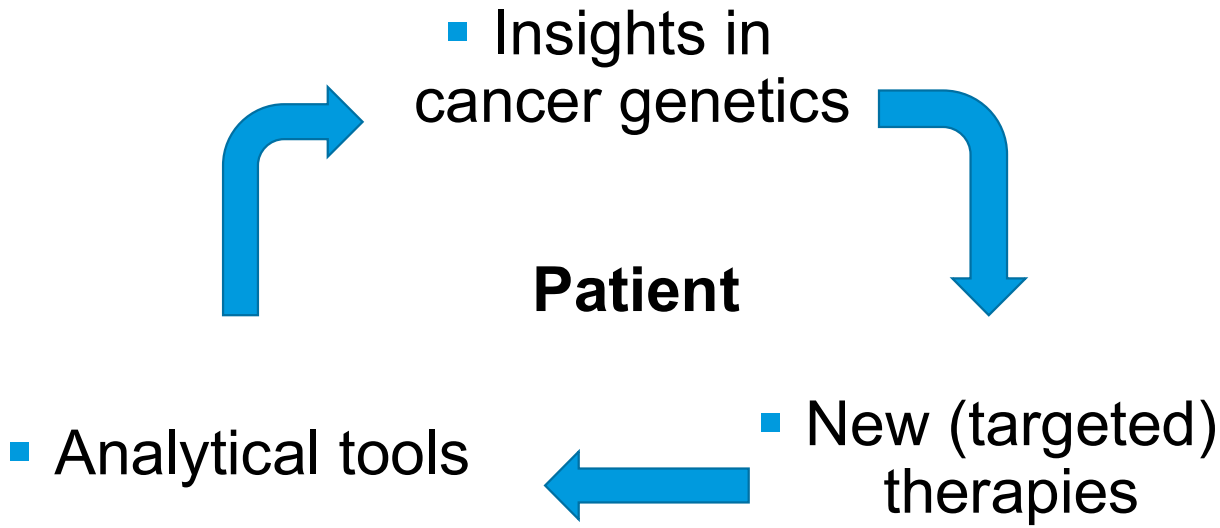
Precision Medicine - complex in clinical practice

Challenges

- Medicine / biology
- Methodology / logistics
- Legality
- Funding
- Ethics
- …



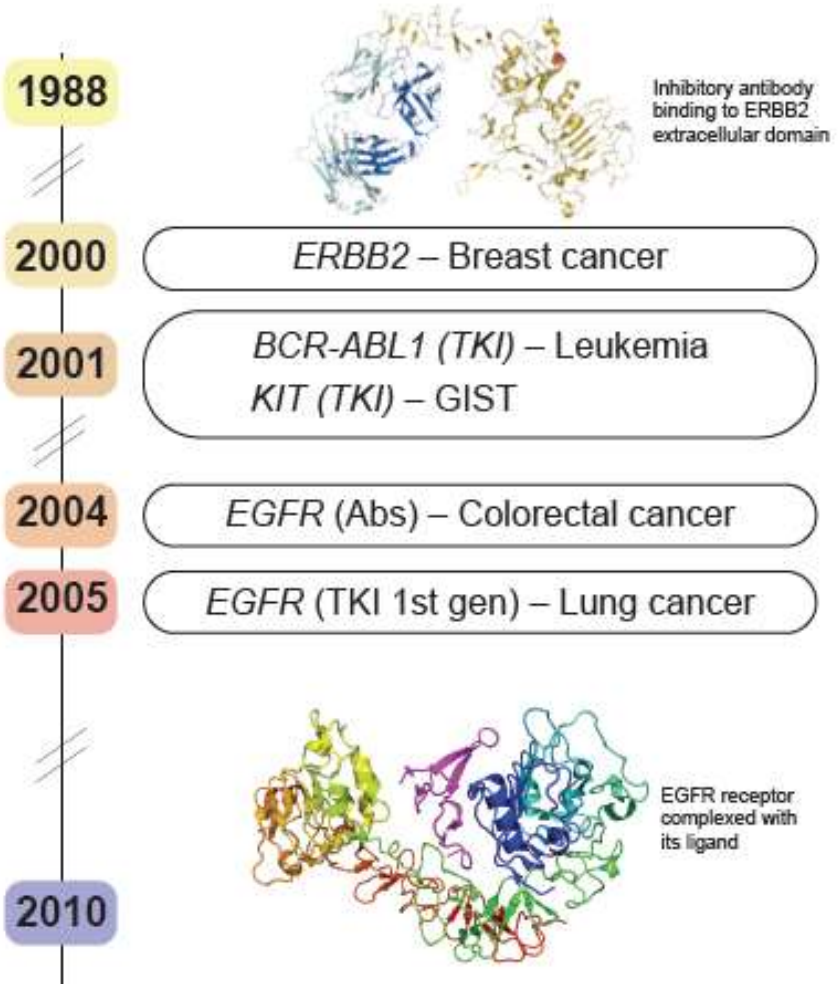
Driving forces molecular oncology



Insights in cancer genetics

- The human genome (HUGO)
- The molecular landscape of major cancer forms (e.g. TCGA)
- Exponential growth of generated data

New (targeted) therapies



Stenzinger et al. Semin Cancer Biol.2022

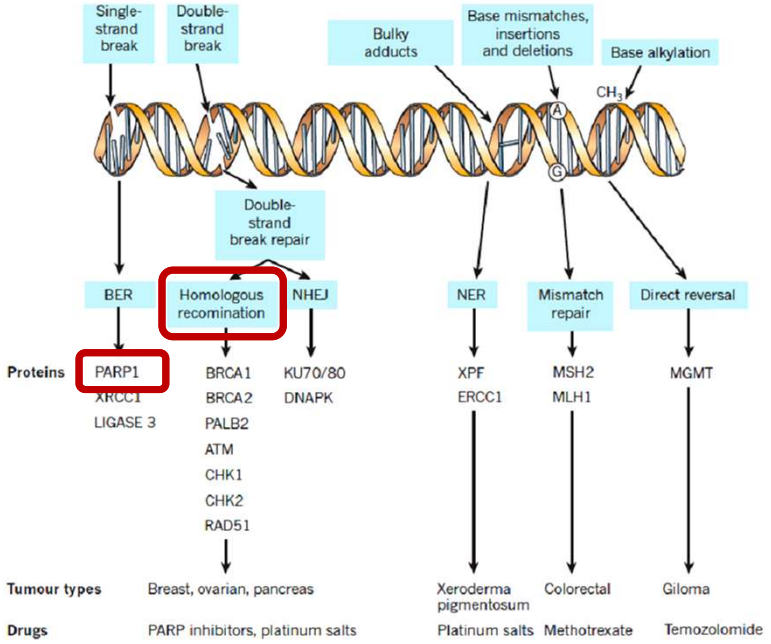
New (targeted) therapies

2012-

- Increasing speed
- New generations of tyrosine kinase inhibitors
- Immunotherapy
- Tumor agnostic therapies
- More complex biomarkers
- Beyond genomics…

Hereditary variants of relevance for treatment prediction - BRCA1/2 and homologous recombination

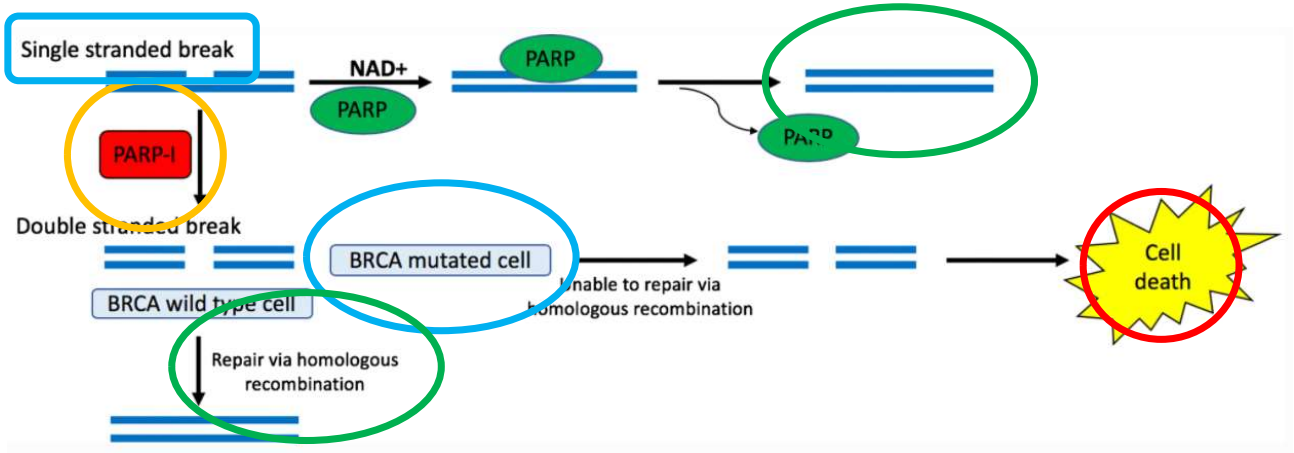
- Homologous remombination repair (**HRR**)
- Homologous recombination deficiency (**HRD**)
- Relevant for hereditary cancer but also for PARPI treatment prediction
- HRD status made up of BRCA1/2 status and genomic instability score



Lord & Ashworth, *Nature* 2012

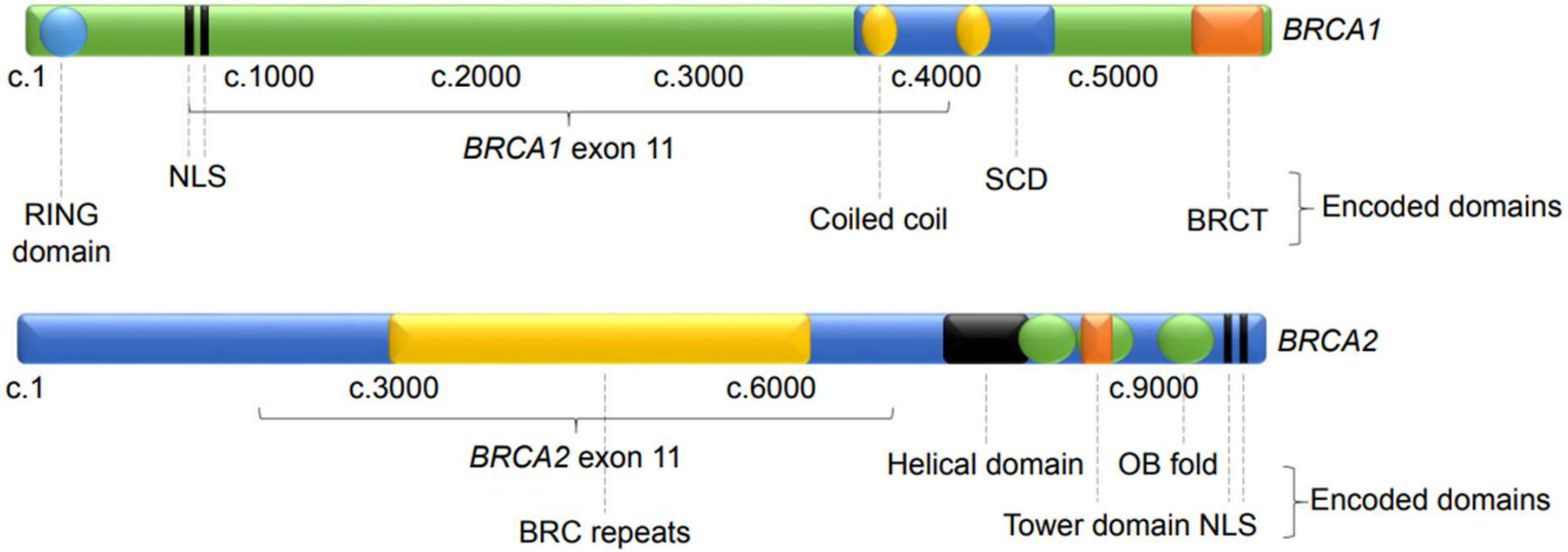
Synthetic Lethality & PARP inhibition

A combination of deficiencies in two or more genes lead to cell death



Sachdev, *Targeted Oncology,* 2019

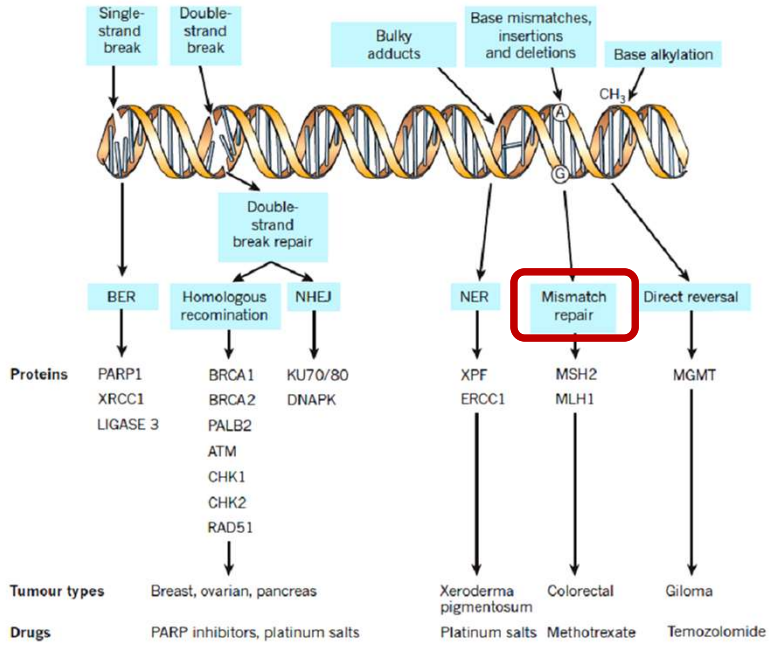
BRCA1/2



- The genes were cloned in the 1990ies – Mary-Claire King central
- Large genes (5,5 kb, 10,3 kb)
- Tumor suppressors -> loss-of-function mutations -> need to cover the entire genes

Molecular pathology in screening for heredtitary cancer - Lynch syndrome and mismatch repair

- Relevant for hereditary cancer but also for treatment prediction of e.g. checkpoint inhibitors
- Protein loss detected by IHC, PCR or NGS used for variant detection
- dMMR & MSI-H mismatch repair function is lost

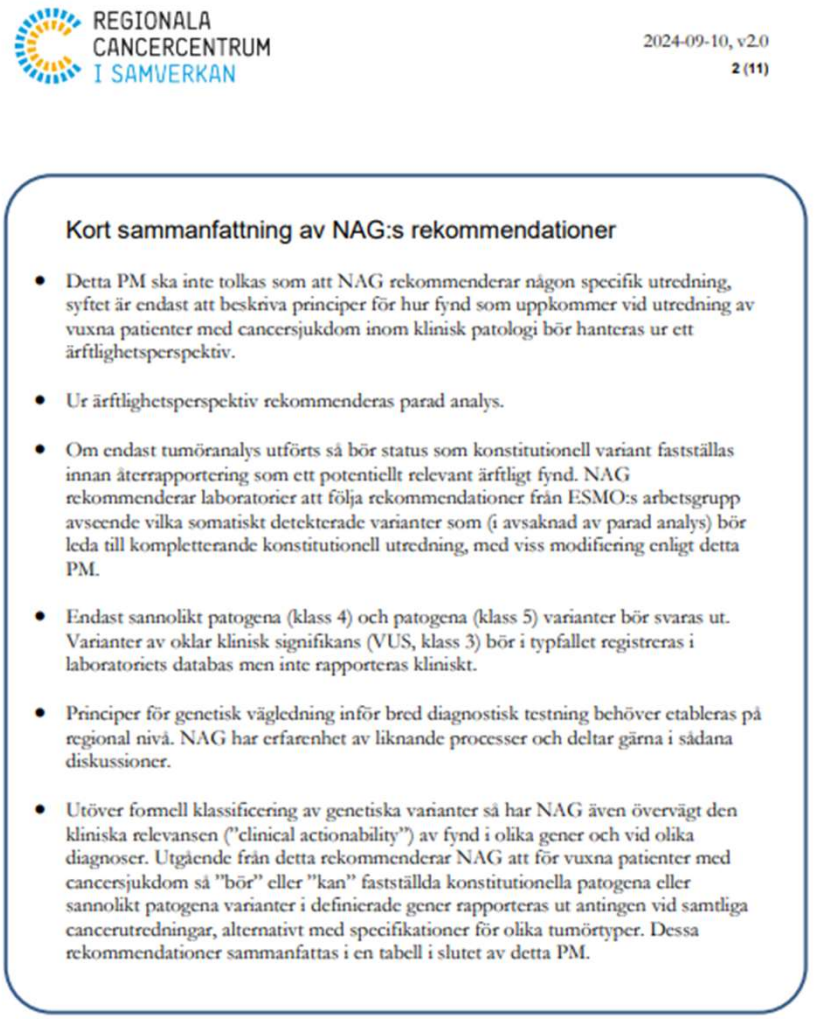


Increase in results relevant for hereditary cancer

- Larger panels detect added, potentially hereditary, variants
- Risk of results that might be difficult to handle and of added work load for the clinical genetic departments
- Normal blood samples more frequently used to filter out false positives in the somatic data
- The information can also be used to identify patients worth referring

National recommendations on reporting on constitutional variants

- Aligned with ESMO on variants to report
- A tumor only result should be verified before reported
- Class 4 or 5 to be reported, not VUSes



REGIONALA CANCERCENTRUM I SAMVERKAN

2024-09-10, v2.0
2 (11)

Kort sammanfattning av NAG:s rekommendationer

- Detta PM ska inte tolkas som att NAG rekommenderar någon specifik utredning, syftet är endast att beskriva principer för hur fynd som uppkommer vid utredning av vuxna patienter med cancersjukdom inom klinisk patologi bör hanteras ur ett ärftlighetsperspektiv.
- Ur ärftlighetsperspektiv rekommenderas parad analys.
- Om endast tumöranalys utförts så bör status som konstitutionell variant fastställas innan återrapportering som ett potentiellt relevant ärftligt fynd. NAG rekommenderar laboratorier att följa rekommendationer från ESMO:s arbetsgrupp avseende vilka somatiskt detekterade varianter som (i avsaknad av parad analys) bör leda till kompletterande konstitutionell utredning, med viss modifiering enligt detta PM.
- Endast sannolikt patogena (klass 4) och patogena (klass 5) varianter bör svaras ut. Varianter av oklar klinisk signifikans (VUS, klass 3) bör i typfallet registreras i laboratoriets databas men inte rapporteras kliniskt.
- Principer för genetisk vägledning inför bred diagnostisk testning behöver etableras på regional nivå. NAG har erfarenhet av liknande processer och deltar gärna i sådana diskussioner.
- Utöver formell klassificering av genetiska varianter så har NAG även övervägt den kliniska relevansen (”clinical actionability”) av fynd i olika gener och vid olika diagnoser. Utgående från detta rekommenderar NAG att för vuxna patienter med cancersjukdom så ”bör” eller ”kan” fastställda konstitutionella patogena eller sannolikt patogena varianter i definierade gener rapporteras ut antingen vid samtliga cancerutredningar, alternativt med specifikationer för olika tumörtyper. Dessa rekommendationer sammanfattas i en tabell i slutet av detta PM.

National working group on hereditiary cancer, Regional cancer centers in collaboration

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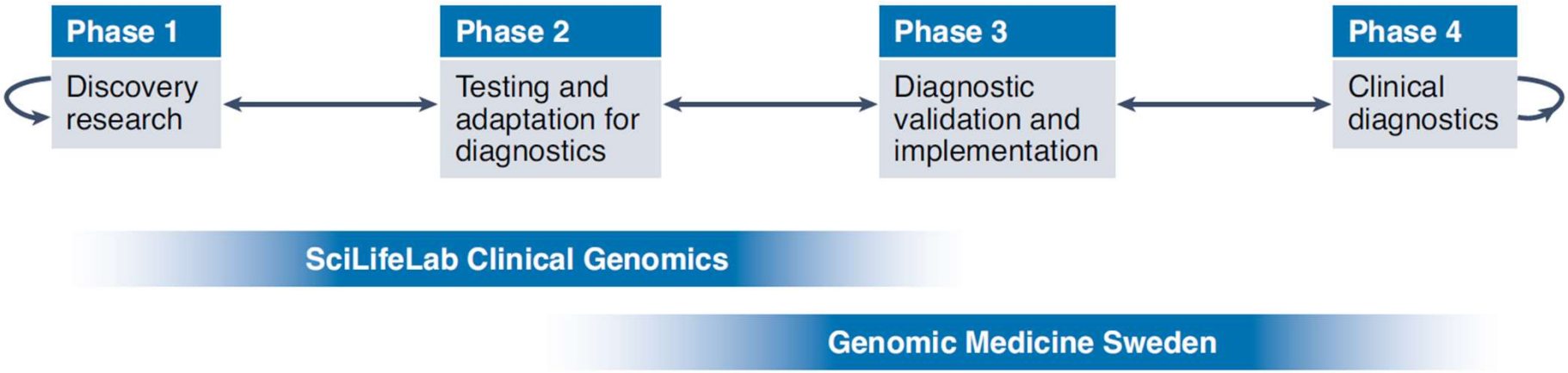
Shared competence and toolbox

- Staffing for data generation, bioinformatics and variant interpretation
- Shared need for upscaling testing and introducing new methods
- Possibility to lower costs and speed up diagnostics
- Long read sequencing latest example of field spearheaded by rare desease diagnostics

SciLifeLab CG & GMS – a Swedish Research Implementation Network



Fioretos, T., Wirta, V., Cavelier, L. *et al.* Implementing precision medicine in a regionally organized healthcare system in Sweden. *Nat Med* (2022)

Genomic Medicine Sweden – a national infrastructure for precision medicine

Health care

+

Academia

+

Patients

+

Industry

GENOMIC MEDICINE SWEDEN

2017
Pre study

2018
GMS formed with support of Vinnova

2019
GMCs established at all university hospitals

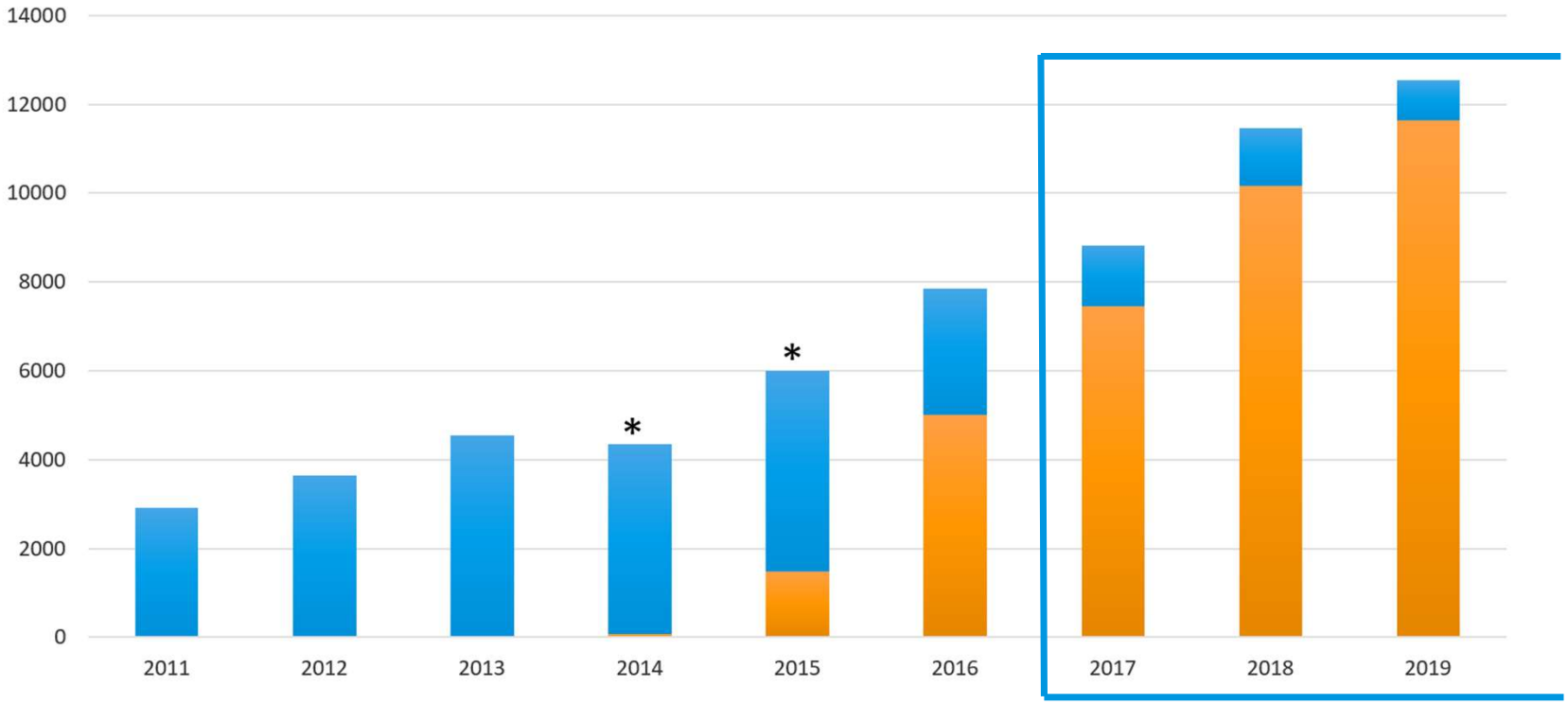
2020
Contiunued support from Vinnova and Department of Health

2021
Research and innovation bill 2021-2024

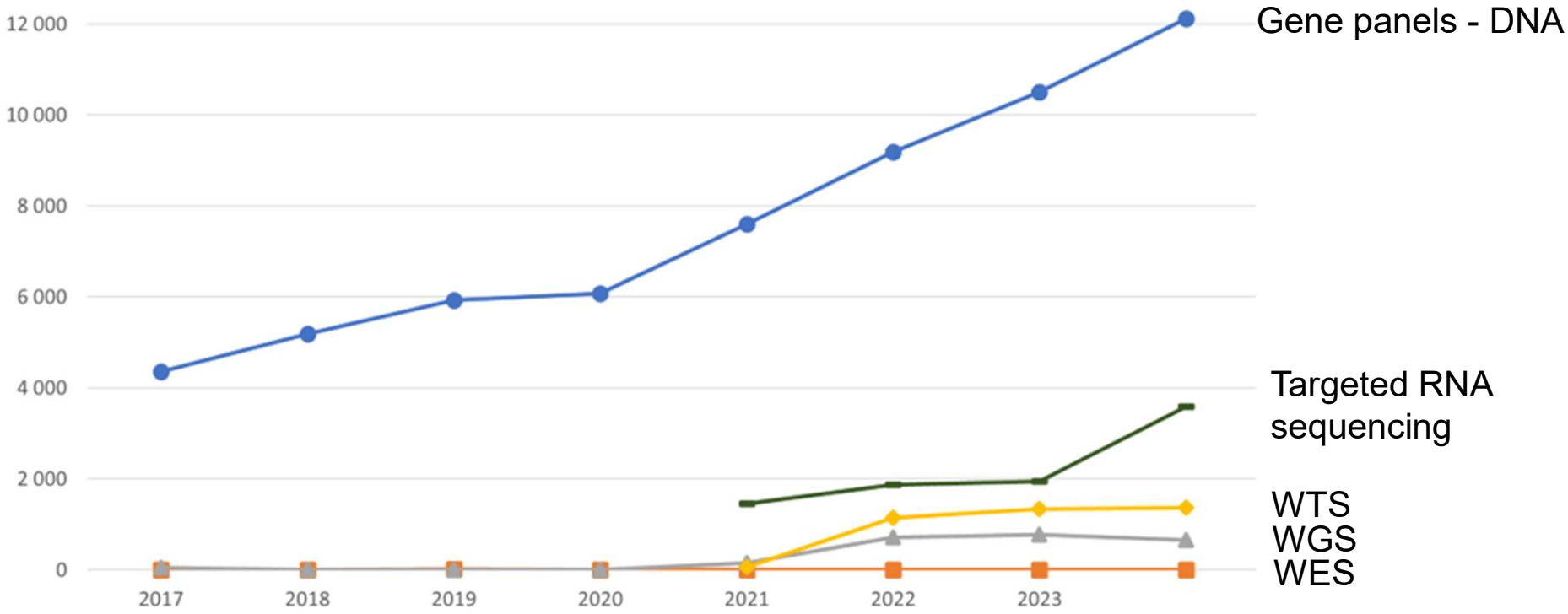
2025
Continued support precision health
(5 M EUR 2025, 10 M EUR 2026-30)

2030

Seqencing solid tumor – NGS a central tool

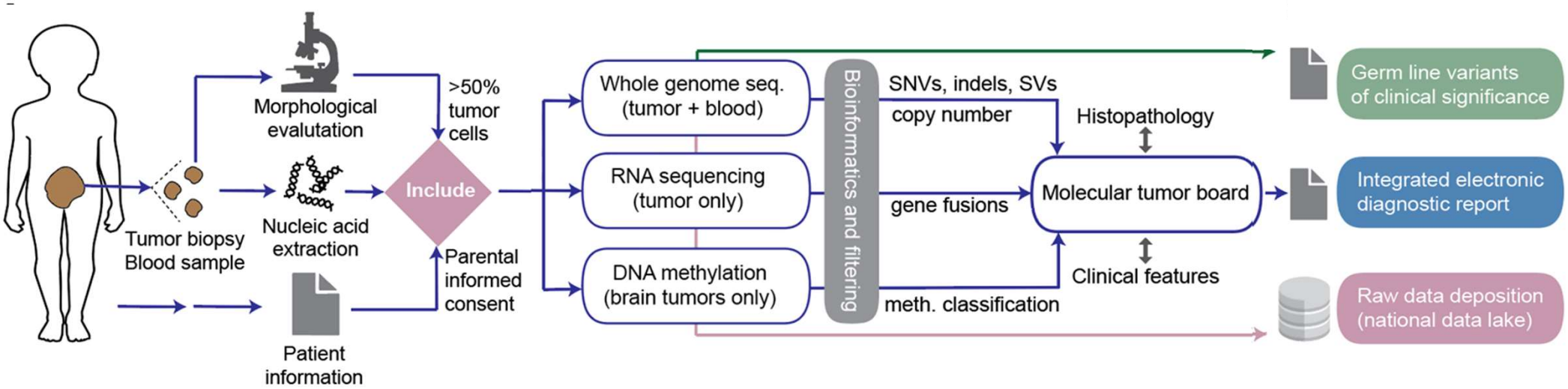


NGS solid tumors – GMS data



GMS Childhood cancer

David Gisselsson-Nord



Clinically relevant genetic alterations detected in 91%
Potential targeted therapy in 24% (Wadensten et al, JCP Precision Oncology 2023)

gms

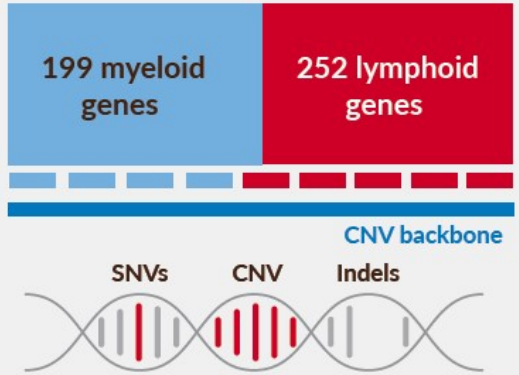
Barntumörbanken

BARNCANCER FONDEN

REGERINGSKANSLIET
Socialdepartementet

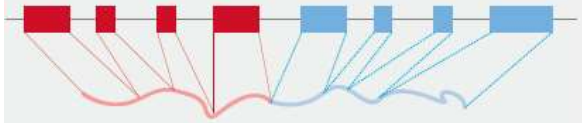
Strategy genomic profiling in hematological malignancies

National haematology panels



AML, MDS, MPN, CLL, Lymphoma

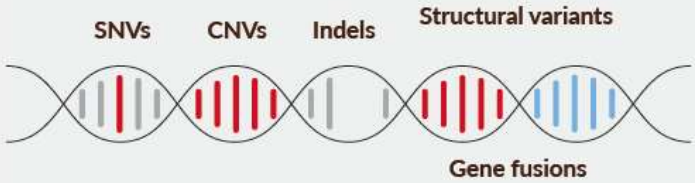
Transcriptome analysis



Fusion transcripts

Acute leukaemias

Whole-genome sequencing



Digital karyotyping

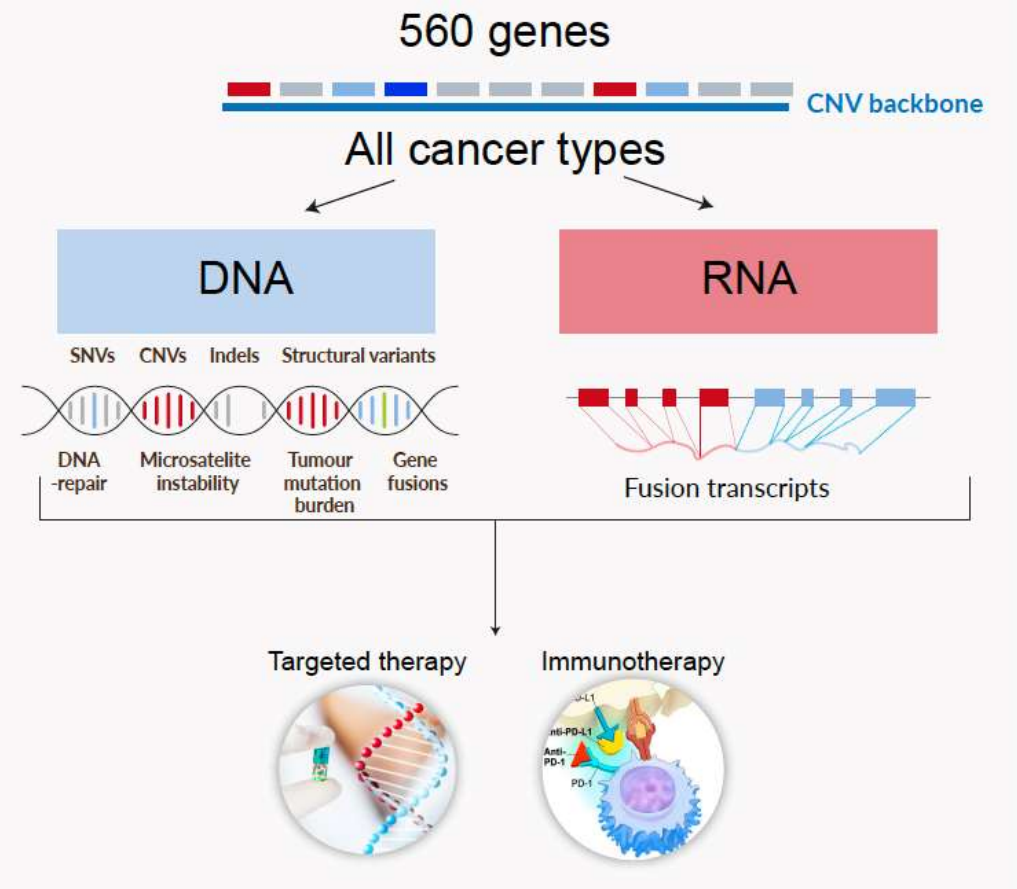
Acute leukaemias and germline predisposition

Implemented at 5 GMCs
(>4 200 panels in 2022)

Thoas Fioretos

Lucia Cavelier

Comprehensive genomic profiling in solid tumors



Ongoing implementation of gene panel testing at all 7 GMCs

Ongoing developmental work on liquid biopsies

Pilots on WGWTS

Anders Edsjö

Johan Botling

Pharmacogenomics

- Initial focus on treatment prediction in cancer
- Design for exon sequencing integrated in national cancer gene panels
- Information logistics and access to EHRs a challenge

DPYD
–5-fluorouracil
–kapecitabin

TPMT och NUDT15
–merkaptopurin
–azatioprin
–tioguanin

+ CYP2D6, CYP2C19, UGT1A1

gms-pgx CPIC Clinical Pharmacogenetics Implementation Consortium KNMP Apothekersorganisatie

gms

Gene panel analyses:
Validation, implementation, development

Government Offices of Sweden
Ministry of Health and Social Affairs

- **Design, Development and Clinical validation**

  Federated national effort

  Structured analysis to decide on content for clinical routine and research purposes

  Treatment prediction, clinical study inclusion, and tumor biology relevant targets

  Regulatory aspects added

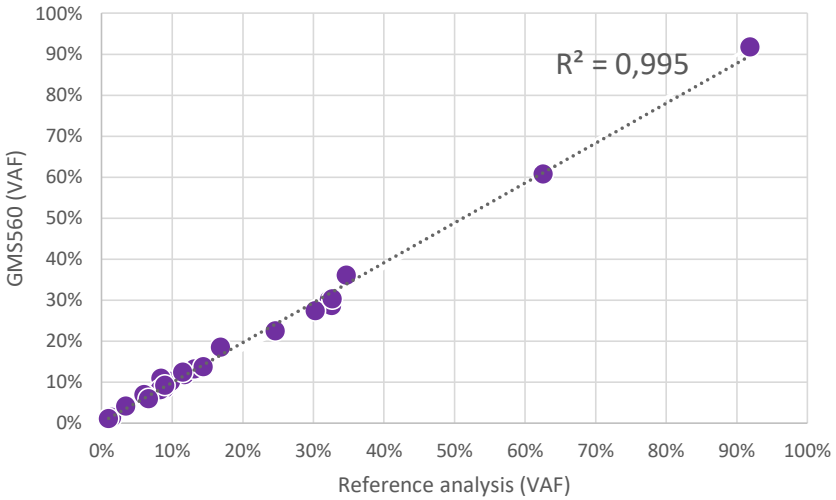
- **Pilots in precision medicine**
  Ministry of Health and Social affairs, 2021-
  Pediatric cancers (focus on WGS, WTS, methylation arrays with added gene panel effort)
  Breast cancer (stage 4 disease, initial focus on treatable variants)
  Ovarian cancer (HRD 2021, oncogenetics 2022)
  Lung cancer (Added 2022, tissue and liquid biopsies)

- **2025: 1.8 M EUR** ”Tissue testing, liquid biopsies for solid tumours”

Current work solid tumours – pilots under discussion

- **Redesign of gene panel for tissue testing**
  Update for study inclusion
  Addition of diagnostic content (especially on the RNA side)
  Merging of design with KI gene panel
- **Pilots for global analyses**
  German WGS FFPE ring trial
  WGSTS for select cases
- **Liquid biopsies**
  Comprehensive genomic profiling + smaller panel for actionable targets
- **Support for upscaling – possible link poor prognosis cancers**

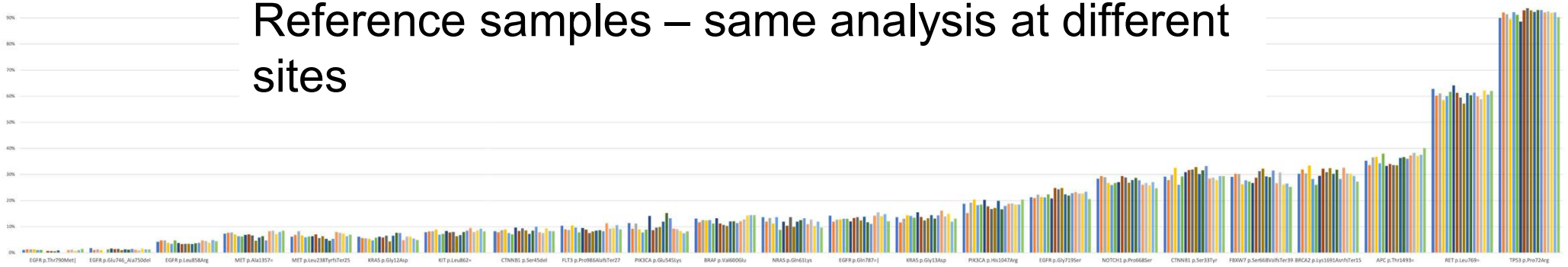
GMS560 *vs* reference
(VAF known mutations)



National validation - comparison of results

- Competence building
- Joint continued development
- Follow-up of comparable results

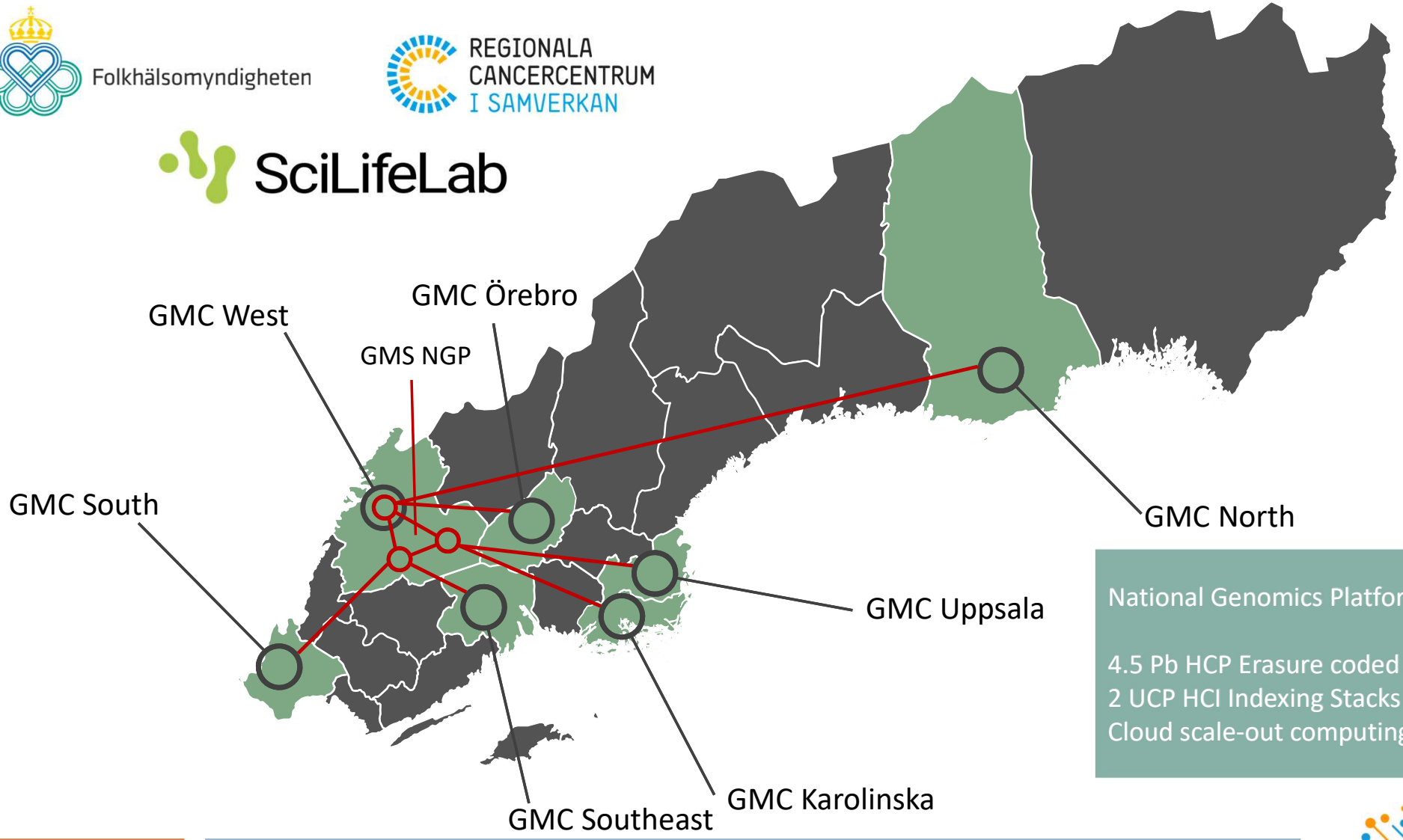
Reference samples – same analysis at different sites



Folkhälsomyndigheten

REGIONALA CANCERCENTRUM I SAMVERKAN

SciLifeLab



National Genomics Platform (NGP)

4.5 Pb HCP Erasure coded storage
2 UCP HCI Indexing Stacks
Cloud scale-out computing

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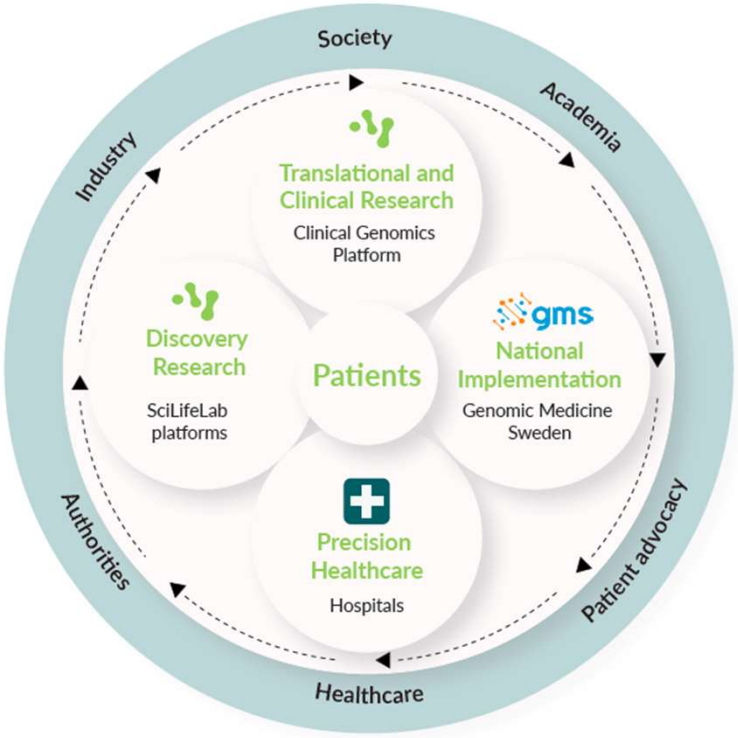
A web of interactions



FRANCE MÉDECINE GÉNOMIQUE 2025
aviesan

ZPM

NATIONALT GENOM CENTER
DANISH NATIONAL GENOME CENTER

1+MG

European Genomic Data Infrastructure

PCM4EU
Personalised Cancer Medicine for all EU Citizens

PRIME-ROSE
Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trials

EUnetCCC
JA PCM
…

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Swedish National Precision Cancer Medicine Study

- Multi-stakeholder effort – coordination from Testbed Sweden PHC
- A DRUP-like study to allow for data sharing and collaboration with other similar studies
- Engine for upscaling comprehensive genomic profiling and implementing a national molecular tumour board
- Interactions within the PCM4EU/PRIME-ROSE consortium crucial
- CTIS application May 2025

FOCU·SE
The Swedish Precision Cancer Medicine Trial

Molecular Tumor Board Portal

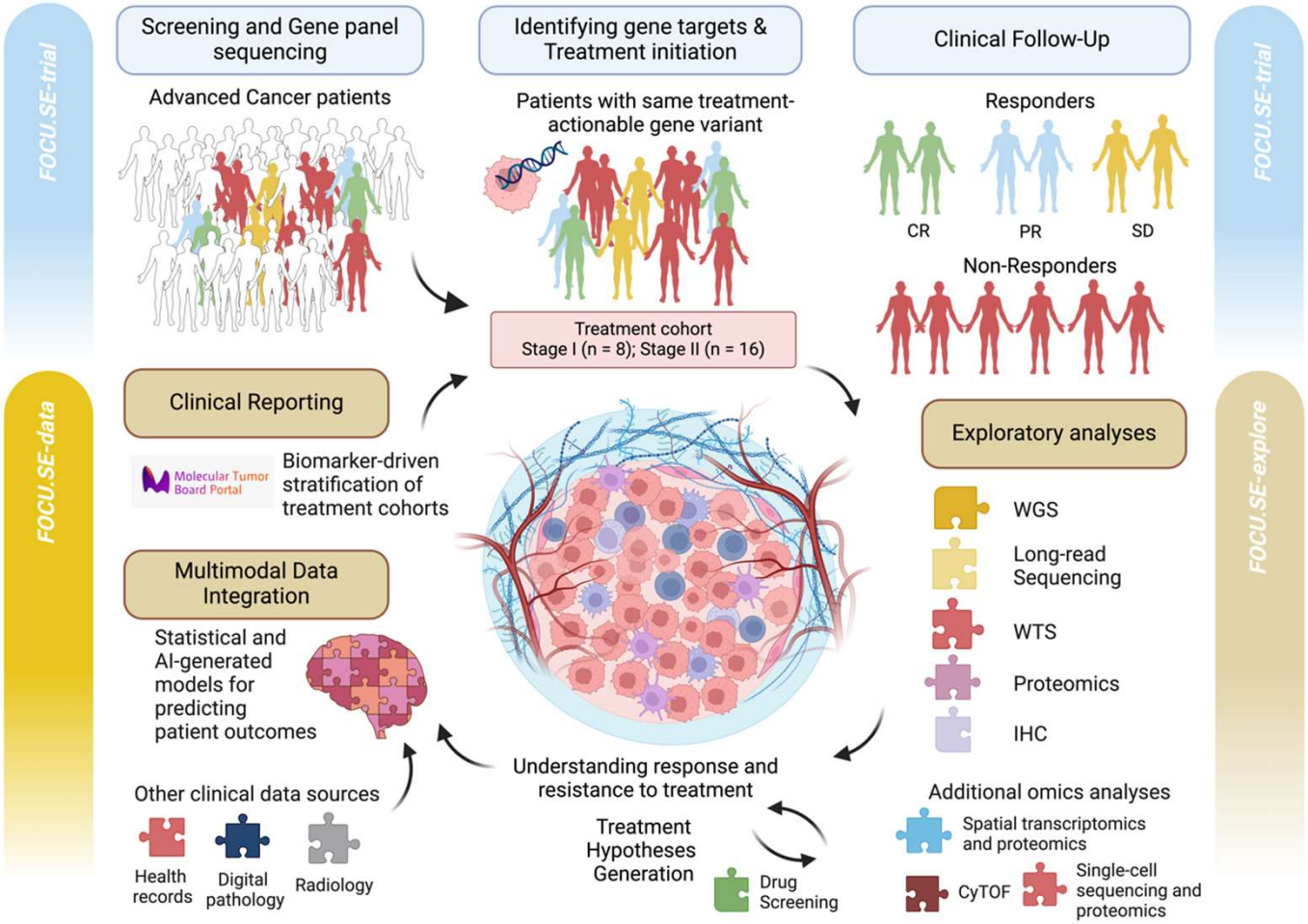
TESTBED SWEDEN
Precision Health Cancer
Innovation hub initiated by Vision Zero Cancer, Genomic Medicine Sweden & SciLifeLab

FOCU·SE
The Swedish Precision Cancer Medicine Trial

FOCU·SE-trial

FOCU·SE-explore

FOCU·SE-data



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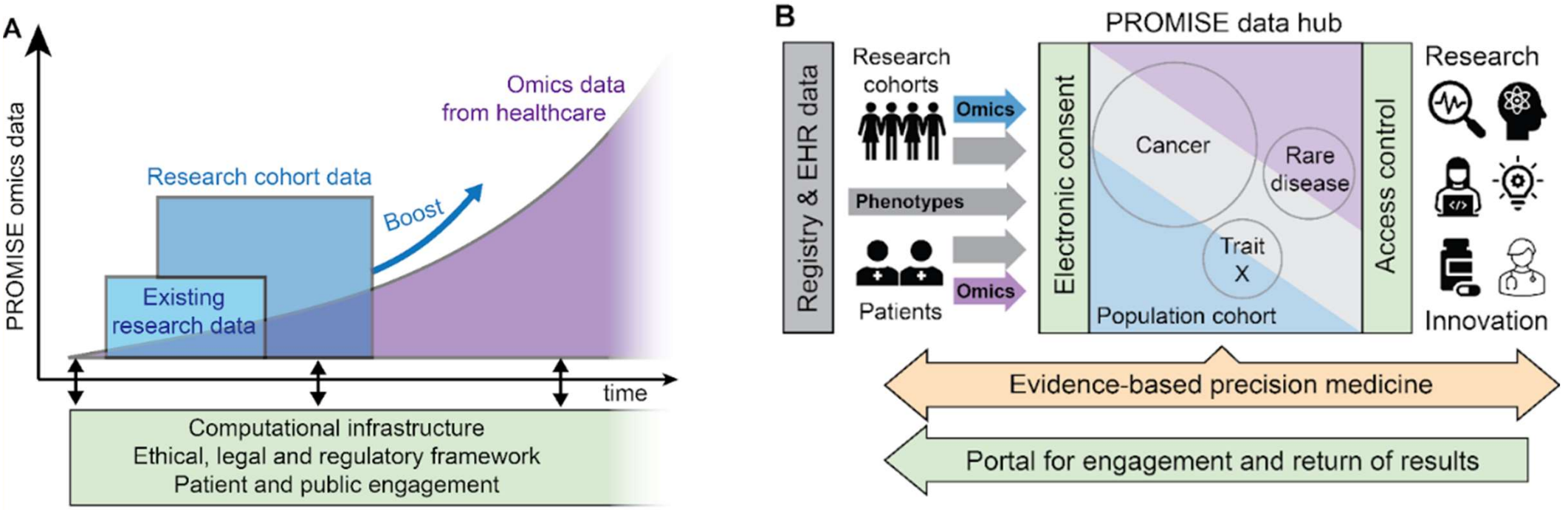
Genomic Medicine Sweden

TESTBED SWEDEN
Precision Health Cancer
Innovation hub initiated by Vision Zero Cancer, Genomic Medicine Sweden & SciLifeLab

Precision Omics Initiative Sweden - PROMISE



Nat Med 2025 Apr 4.doi: 10.1038/s41591-025-03631-9. Online ahead of print.

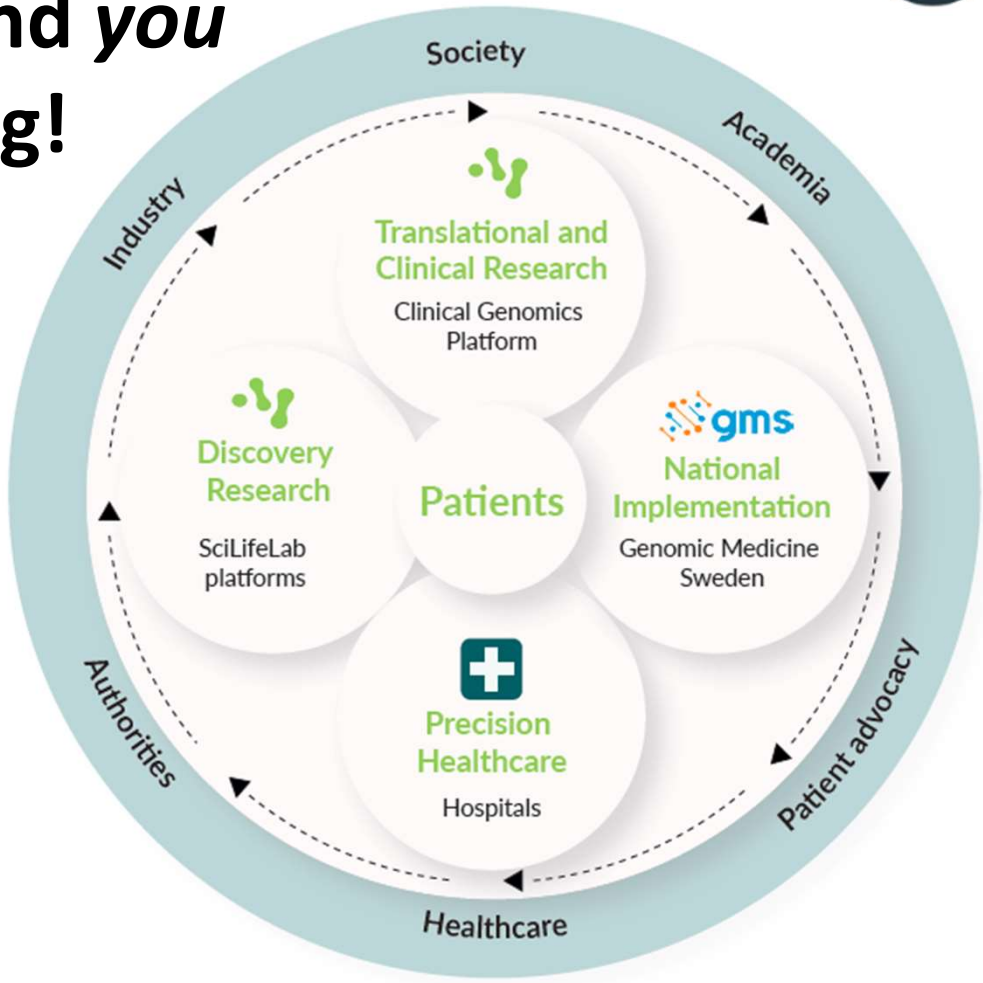
Challenges & possibities

- Fragmented health care decision making
- Lack of coordination on a national level
- Legal support for data sharing insufficient
- Long term support announced – regional planning initiated
- National laws planned and EHDS implementation under preparation
- Implementation and upscaling of GMS analyses in health care lagging
- 5 year support for cancer testing likely
- Competence from all diagnostic fields integrated at each node

Future perspectives

- Additional variants & more complex biomarkers
- New sample types
- Treatment response, resistance (, and early detection)
- Omics beyond genomics
- Diagnostics & integration with hereditary disease
- Competence supply, education and long term funding key issues
- **Collaboration crucial!**

Thanks to *all* involved and *you* for listening!



Research-Implementation cycle

SVENSK FÖRENING FÖR PATOLOGI
SWEDISH SOCIETY OF PATHOLOGY

VINNOVA

SWElife

SciLifeLab

BARNCANCER FONDEN

Government Offices of Sweden
Ministry of Health and Social Affairs

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