WGS based rare disease diagnostics in the Stockholm healthcare region – extension to national program

Berlin
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Technology driven opportunity to analyse the human genome

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>100,000 fold reduction in sequencing cost during last 15 years

- 2005

Human Genome Project
2.7 BUSD
Years / genome

2007

454 / Pyrosequencing
240 days / human genome

2018

NovaSeq
2 day / human genome
1000 USD / genome

Today genome sequencing is comprehensive, affordable and rapid

Next-generation sequencing is ready for clinical use in the routine healthcare

Clinical Genomics (Stockholm)

- **Infrastructure specifically established for processing samples from clinical routine**
- Personnel of approx. 25 FTE
  - 1/3 wetlab
  - 2/3 bioinformatics, SW development etc
- High level of automation in prep lab
  - 2 Agilent Bravo Option B
  - 2 in ongoing procurement
- High sequencing capacity
  - 3 NovaSeq™ 6000
  - 3 HiSeq™ 2500
- All in-house IT systems
  - HPC and associated Pb-scale storage
  - Browser-based clinical decision support
- ISO17025 accredited analyses

Ackred. nr 1926
ISO/IEC 17025

Karolinska University Hospital

- Largest university hospital in Sweden, covering population base of 2.3 M

- Key collaborating clinics
  - **Center for Inherited Metabolic diseases**
  - **Clinical Genetics**
  - **Clinical Immunology and Transfusion medicine**
  - Clinical Microbiology
  - Clinical Pathology

Genomic Medicine Center Karolinska

Technical expertise
Academic setting

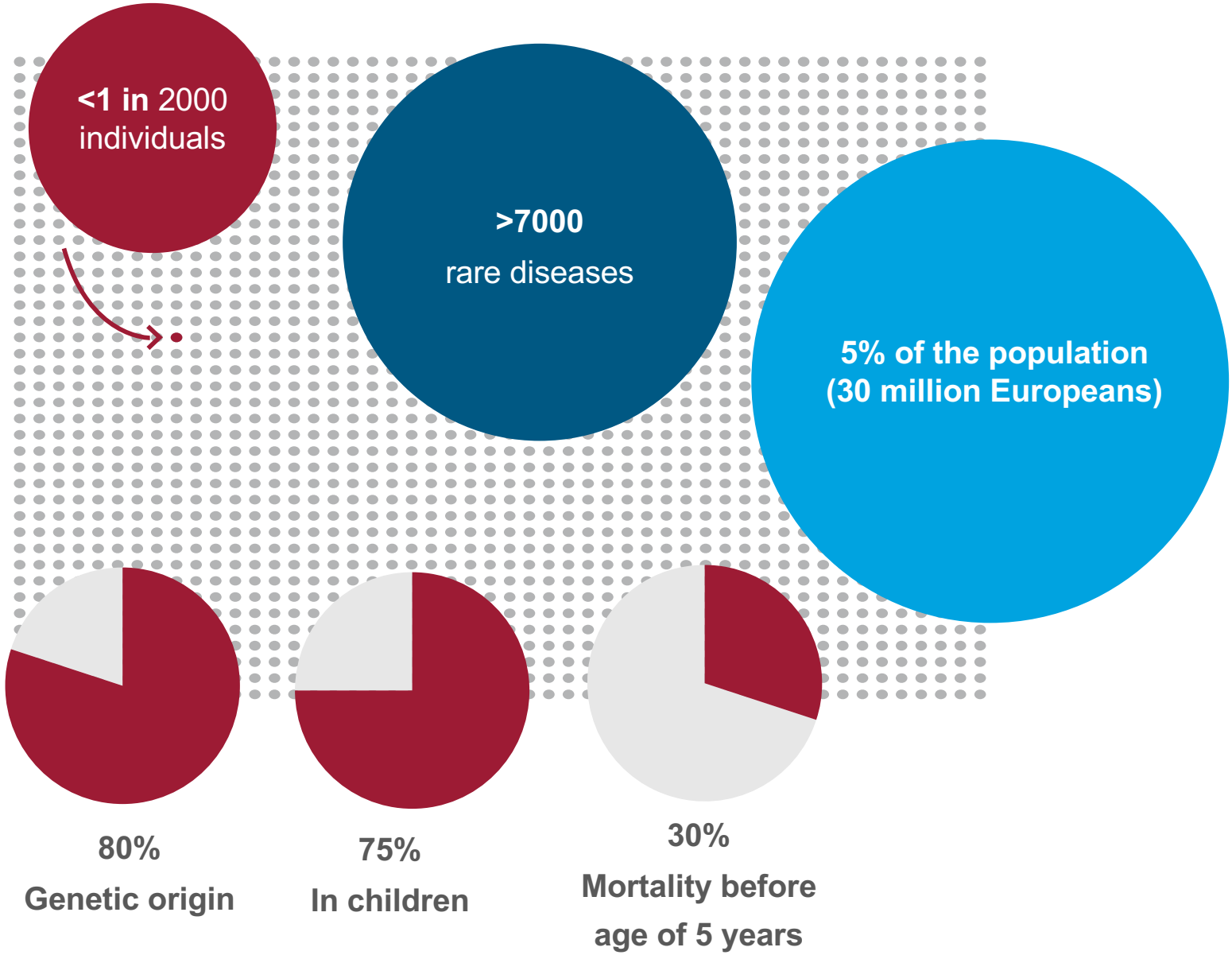
+

Medical expertise
Healthcare

Joint unit for introduction of genomics technologies into clinical routine.
Focus areas on rare diseases, cancer and microbiology

Joint unit established 2017 | Covers a population of approx. 2.3 million
Sweden's largest university healthcare region

Example of use of sequencing in diagnostics: Rare diseases

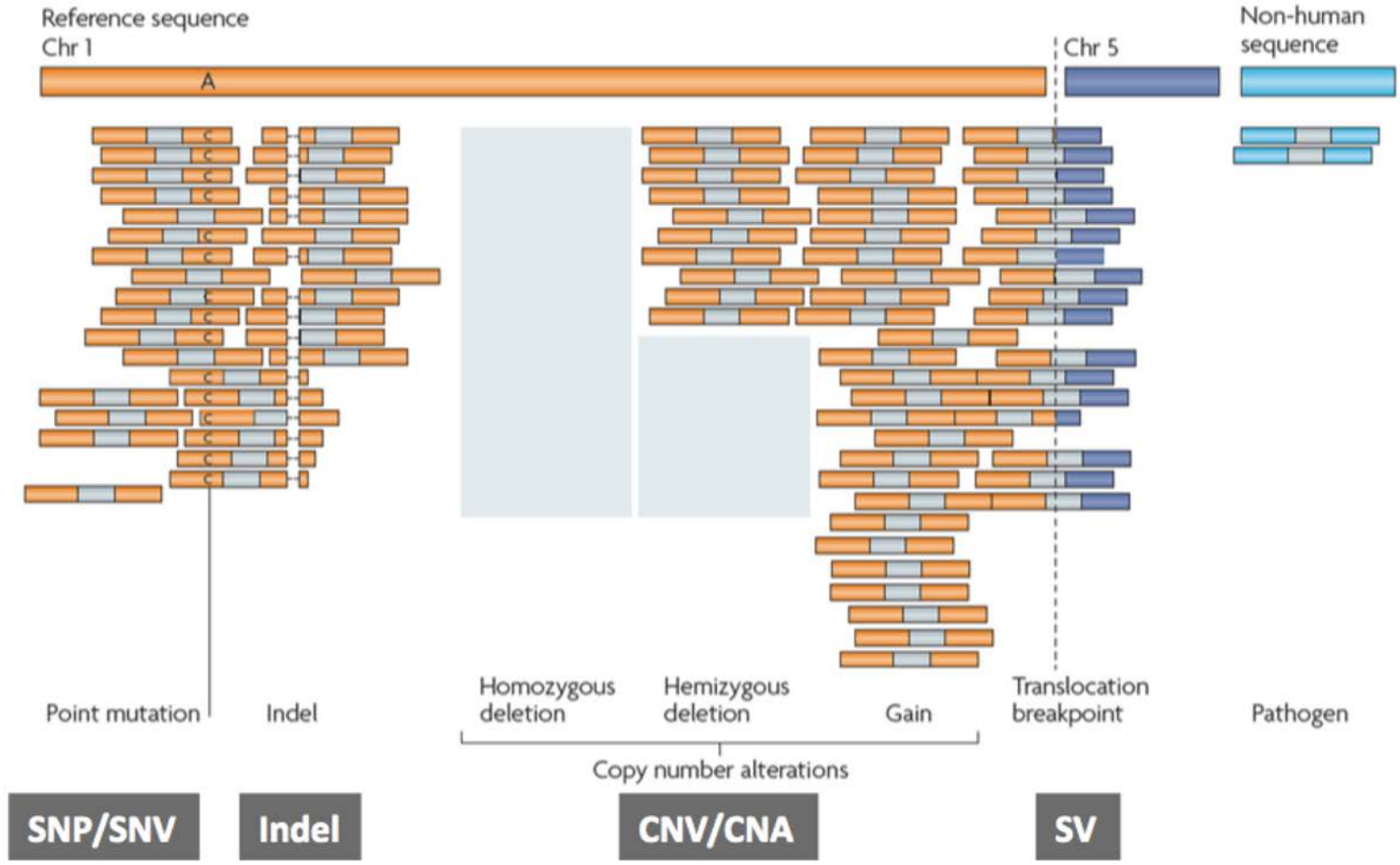


Typically caused by mutation(s) in 1 gene

Key challenge: How do we identify the disease causing mutation(s)?

Source: www.raredisease.org.uk

WGS allows for detection of several types of genetic aberrations



Source:
Broad Institute

Rare inherited diseases diagnostics using WGS

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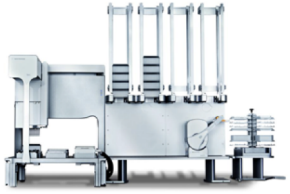
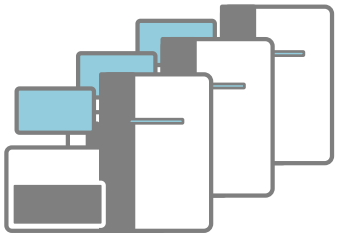
KAROLINSKA Universitetslaboratoriet

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 Universitetslaboratoriet

Clinical interpretation and reporting

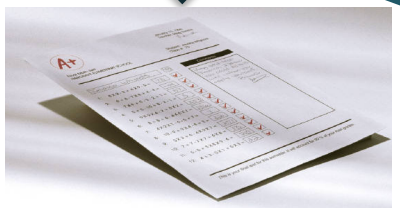
SWEDAC ACKREDITERING

Ackred. nr 1926
ISO/IEC 17025

> 15 patient categories ('national' coverage for some, regional for others)
>120 WGS analyses per month | >5000 samples since 2014
5-14 day turnaround time | Focus on custom developed informatics tools

Restricted to relevant information

Whole exome/genome seq



List of annotated and ranked variants

Known disease genes

Multidisciplinary team
Rapid evaluation

Diagnostic test

Discovery

Novel disease mechanism

Experimental validation
Informed consent

Custom developed tools for clinical implementation of WES and WGS

SciLifeLab

Mutation Identification Pipeline (MIP) and GENMOD

- Automated bioinformatics pipeline for processing raw data to annotated and ranked variants ready for clinical interpretation.

MIP
Mutation identification pipeline

genmod

Chanjo coverage assessment

- Sample specific quality report addressing coverage on gene and transcript level. Identifies regions with insufficient coverage.

Scout interactive clinical decision making support software

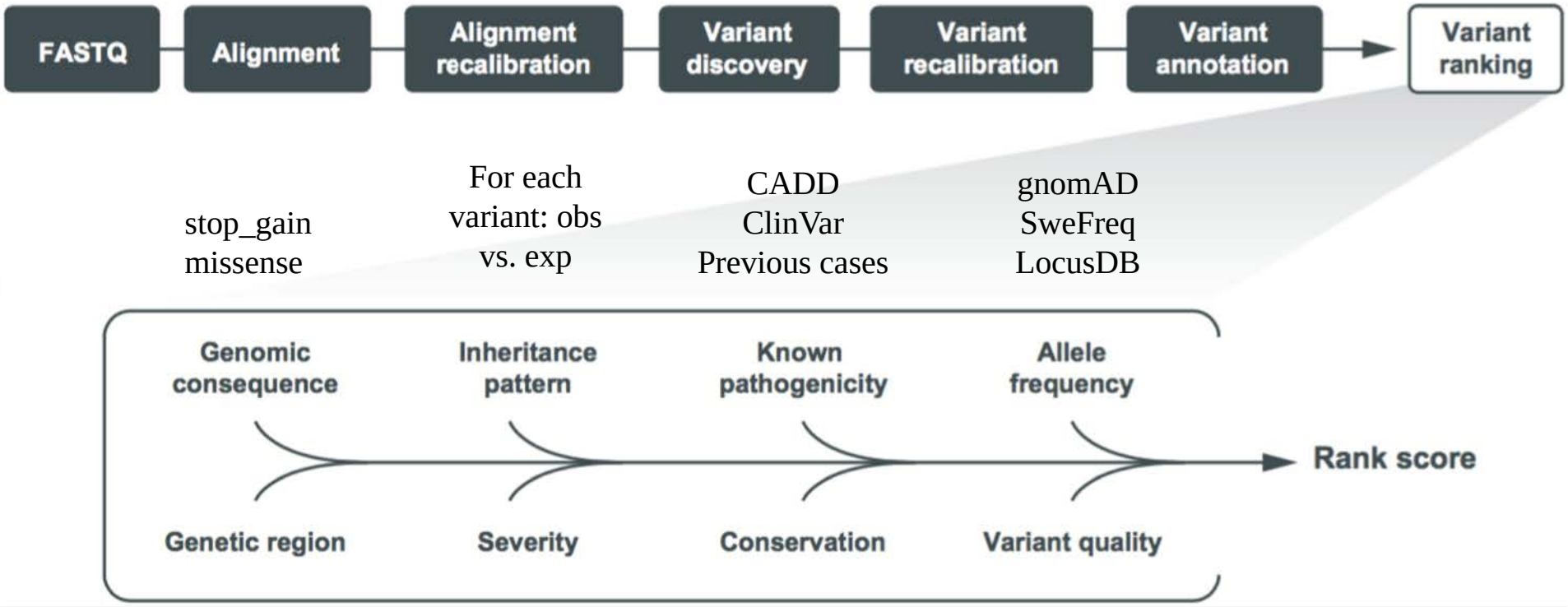
- Custom-developed, browser-based reporting tool enabling collaborating clinicians to view the ranked variants.

Scout

All code available at https://github.com/Clinical-Genomics

Variants evaluated on basis of calculated pathogenicity score (‘rank score’)

Contribution of each element (either positive or negative) added together to yield a final score. Supports disease specific models.

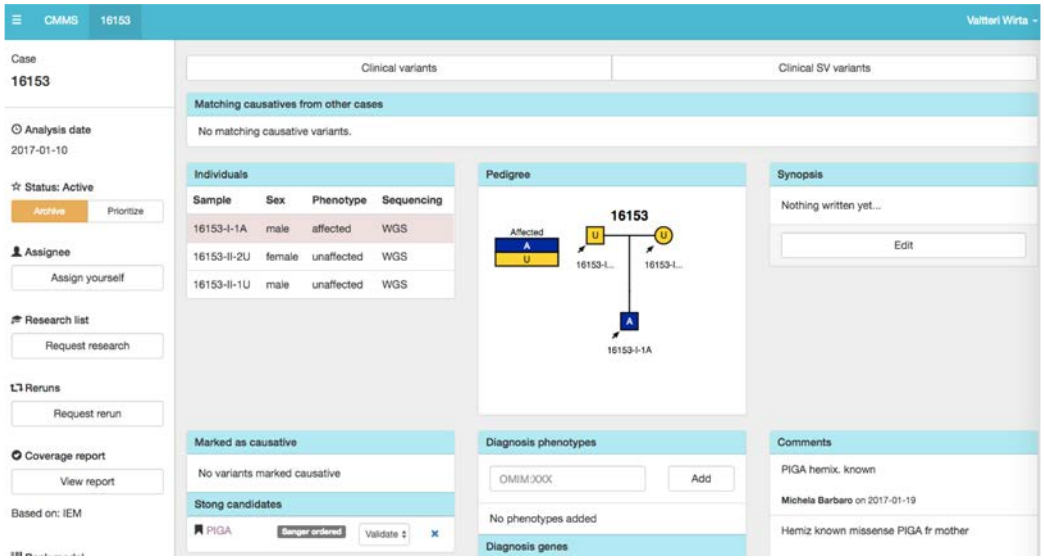


genmod

Scout – interface for interpretation

- Custom-developed, browser-based reporting tool enabling collaborating clinicians to view the ranked variants.
- All information required for interpretation is available within a few ‘clicks’
- Designed to address the major bottleneck – how to make the clinical interpretation easier?
- Developing to establish Scout as the central tool for interpretation

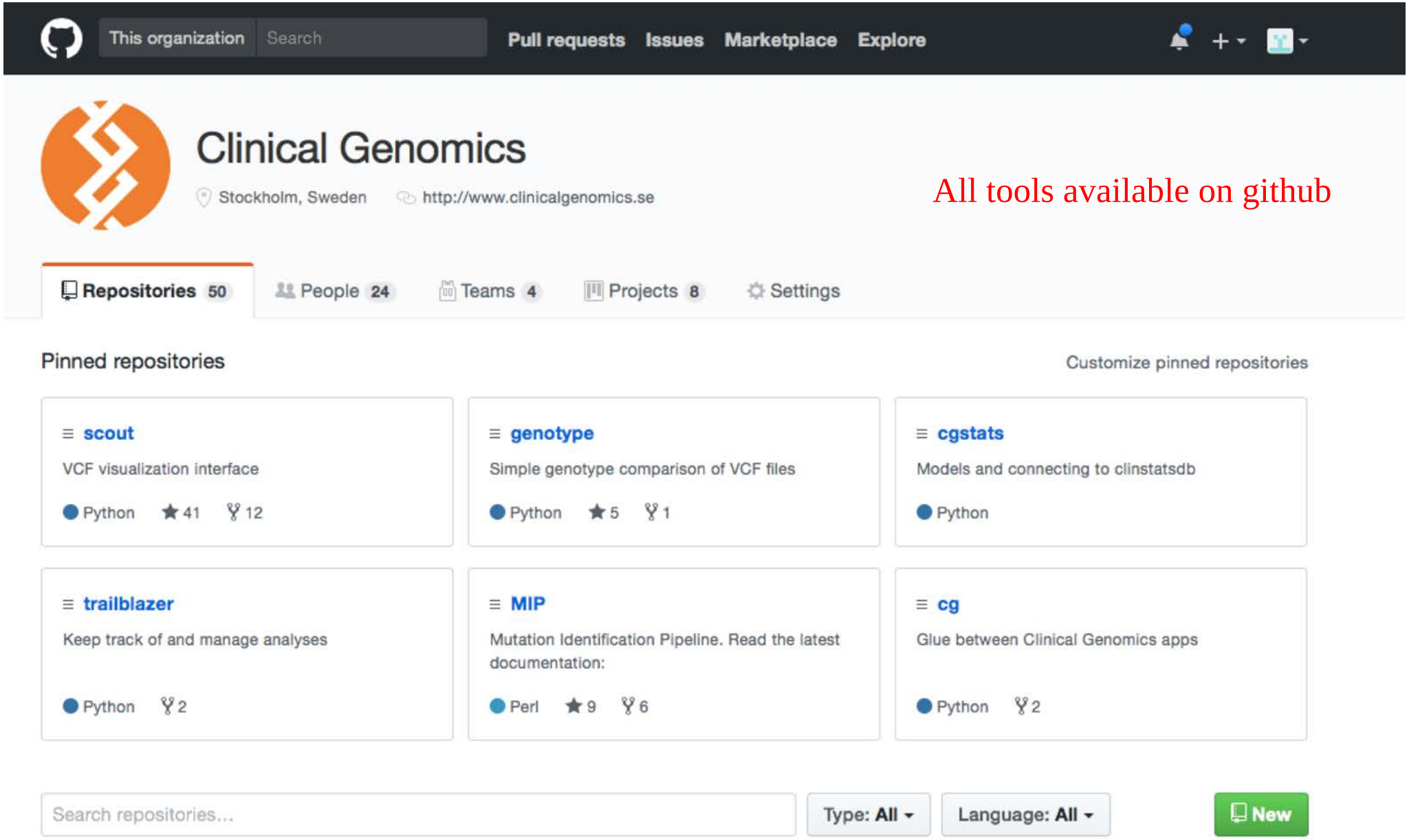
Scout



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

Github – code development

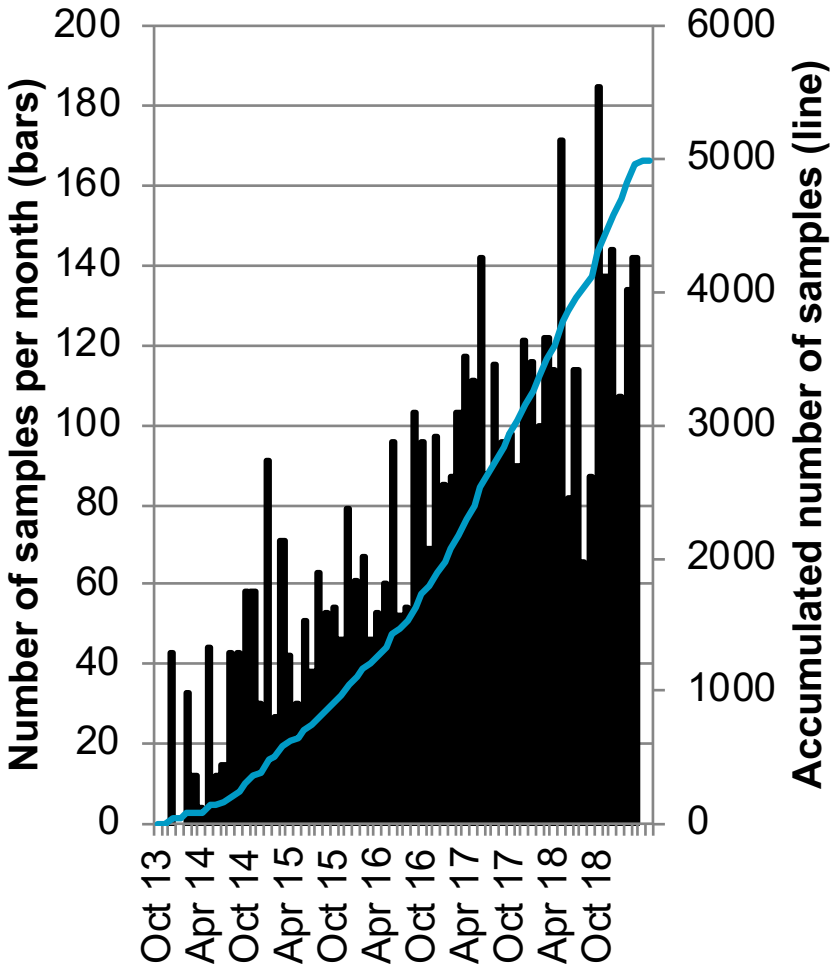
SciLifeLab



All tools available on github

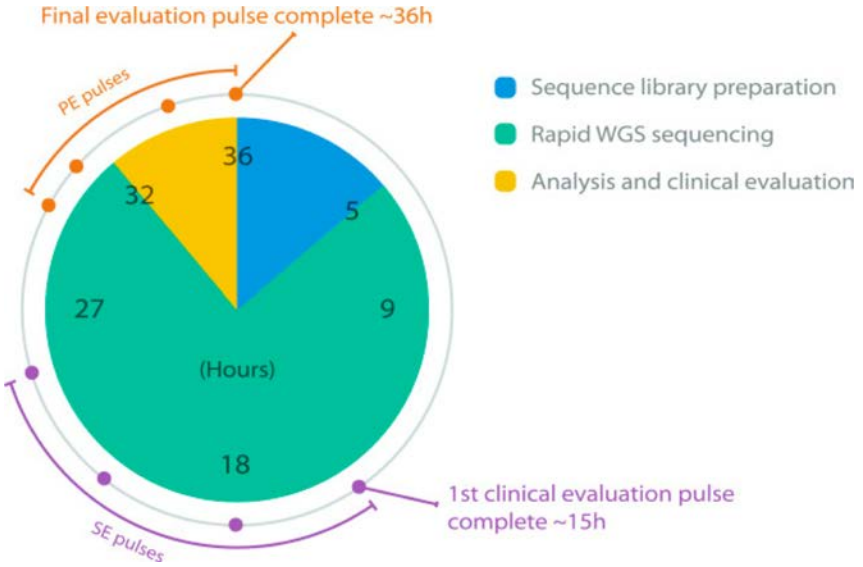
Rare diseases WES/WGS

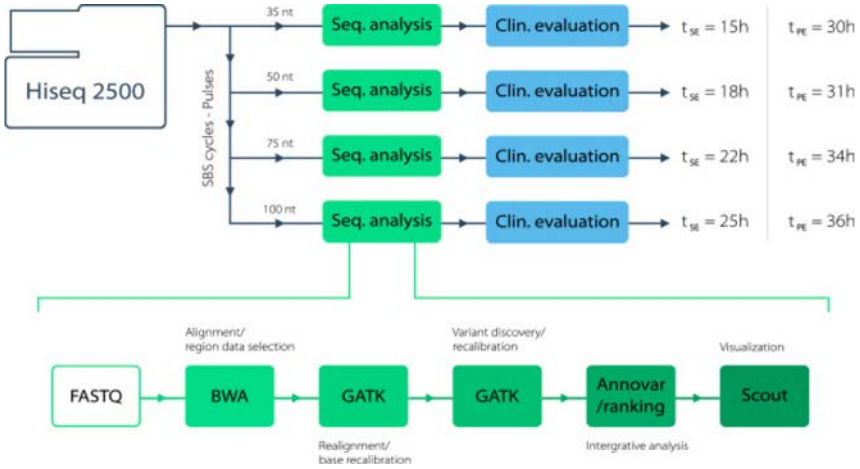
- On average 120 samples per month in 2018, covering an area of 2-3 M population base
- 20-75% receive a molecular diagnosis, approximately 35% average
- Dramatic impact for rare diseases!



WGS can be used as a rapid diagnostic tool for critically ill patients

- **1-2 week turnaround times are readily achievable with current technology**
- Technology can be pushed to deliver 1-2 day results, although at higher cost
- Rapid sequencing, rapid bioinformatic analysis
- Expert team interpretation

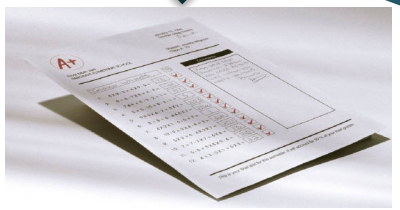




Stranneheim, 2014

Restricted to relevant information

Whole exome/genome seq



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Rapid evaluation

35%

Diagnostic test

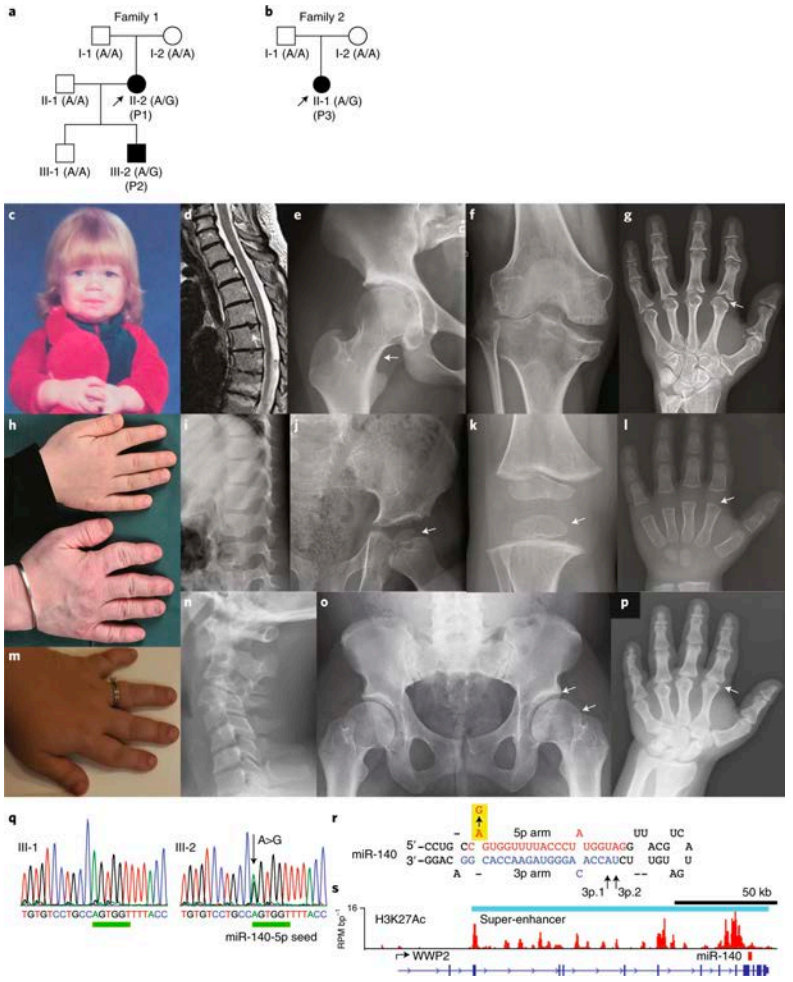
Discovery

Novel disease mechanism

Experimental validation
Informed consent

Discovery of new disease gene for skeletal dysplasia

- Patient with skeletal dysplasia
- WGS identified a previously uncharacteraised mutation in miRNA-140
- Autosominal dominant, de novo
- The first ever described example of pathogenic mutation causing both a loss-of-function and gain-of-function phenotypes



Grigelioniene, Nat Med, 2019

Data sharing in rare diseases

- Variant assessment is a truly global challenge due to rare / ‘private’ nature of variants
- Proposing to utilise data sharing solutions developed by **Global Alliance for Genomics and Health (GA4GH)**
- Classified variant submission to international resources such as ClinVar
- Could be retained in a national db, but not sufficient to advance the field
- **Policy proposal for all publicly funded healthcare**: submission to public data sharing repositories should be mandatory?

Status: Implemented support solution for ClinVar reporting, Beacon node using Elixir implementation and launching a MME node in Q3’19

Our key principles of clinical WGS

SciLifeLab

§1 Stringent and ethically acceptable

§2 Quality assurance in every step of the process

§3 Accurate medical interpretation, broad clinical expertise

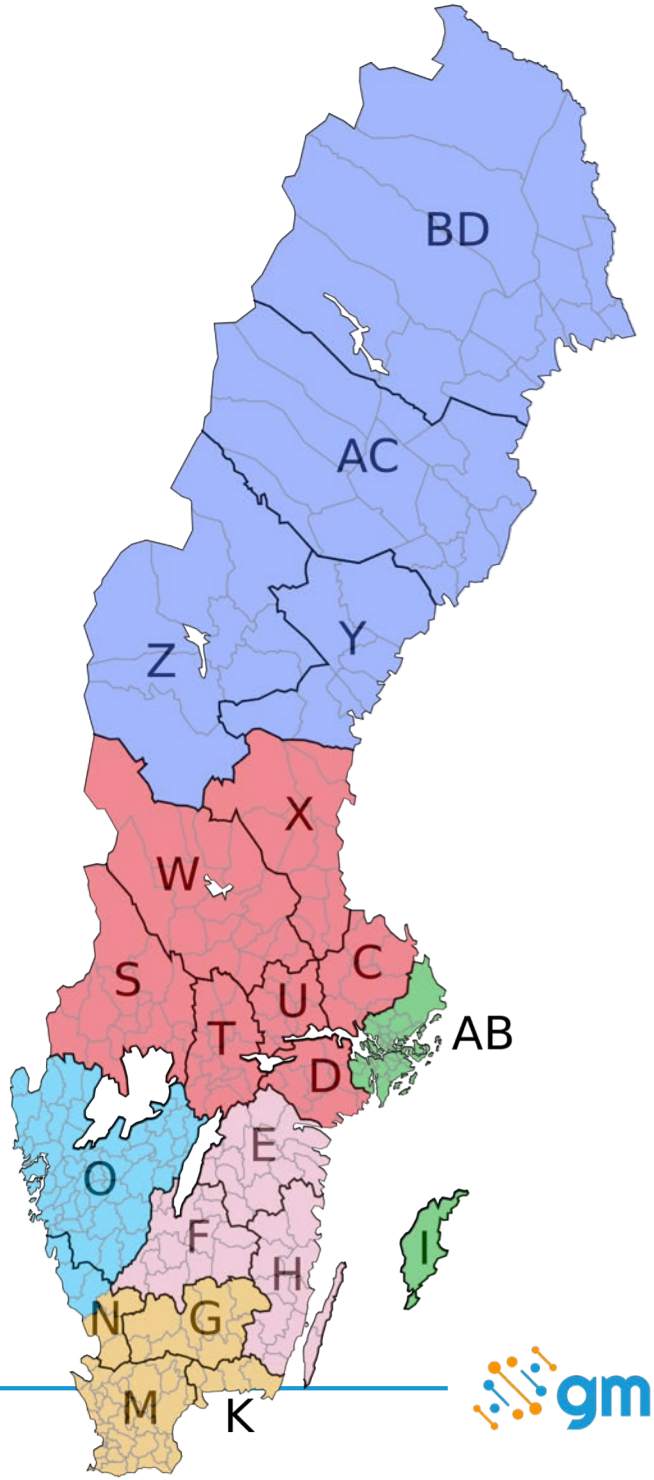
§4 Rapidly translated into clinical action

How to extend to national level and ensure coordinated action across the healthcare?

Genomic Medicine Sweden

Swedish healthcare system

- Population of 10 million
- Publicly funded healthcare, provided by 21 independent healthcare regions
- 7 university health care regions
  - University hospital
  - University with medical faculty
- Vision / expectation of ‘equal healthcare’
- Strong tradition of lab developed tests in university healthcare settings
- No direct governmental decision making on regional issues



Genomic Medicine Sweden

- National program for coordinating the implementation of genomics into the Swedish healthcare
- Contribute towards equal access across the regions
- Contribute to precision medicine – the right treatment to right patient at the right time
- National databases for diagnostics and research
- Innovation and industry cooperation
- Initial focus areas
  - Rare diseases (5,000 per year)
  - Cancer (50,000 per year)

Initial funding through Swedish Innovation Agency (until 2020)

VINNOVA

Nyheter | Bilder & Videor | Kontaktpersoner | Dokument

Nationell satsning på precisionsmedicin ska ge fler patienter rätt behandling i rätt tid

Pressmeddelande · Nov 20, 2018 11:01 CET

Nu växlar Sverige upp arbetet med precisionsmedicin inom hälso- och sjukvården och den kliniska forskningen. Satsningen innebär att fler patienter kan få rätt behandling i rätt tid och skapar ökade möjligheter för Sverige som ett attraktivt land för innovation och klinisk forskning.

Partners

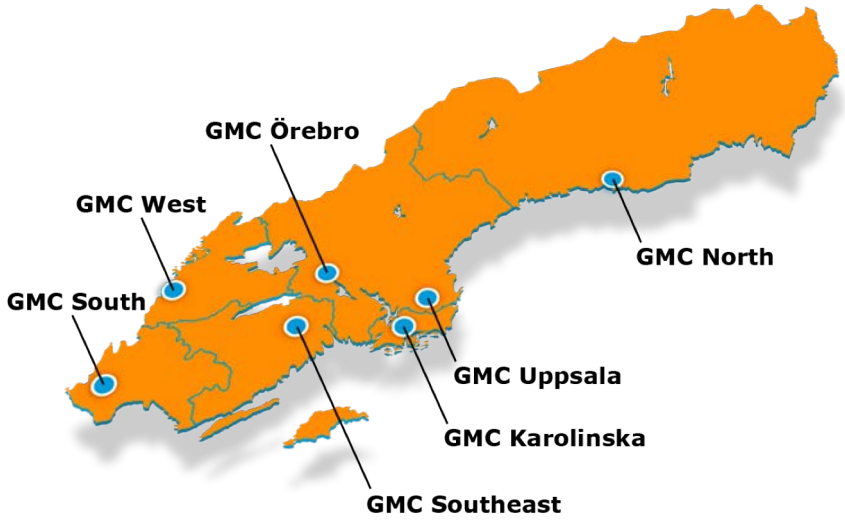
Karolinska Institutet
Uppsala Universitet
Lund University
University of Gothenburg
Linköping University
Umeå Universitet
Örebro University
Region Skåne
Region Örebro län
Region Uppsala
Västerbottens läns landsting
Region Stockholm
Region Västra Götaland
Region Östergötland

Project leader
Richard Rosenquist Brandell , MD PhD

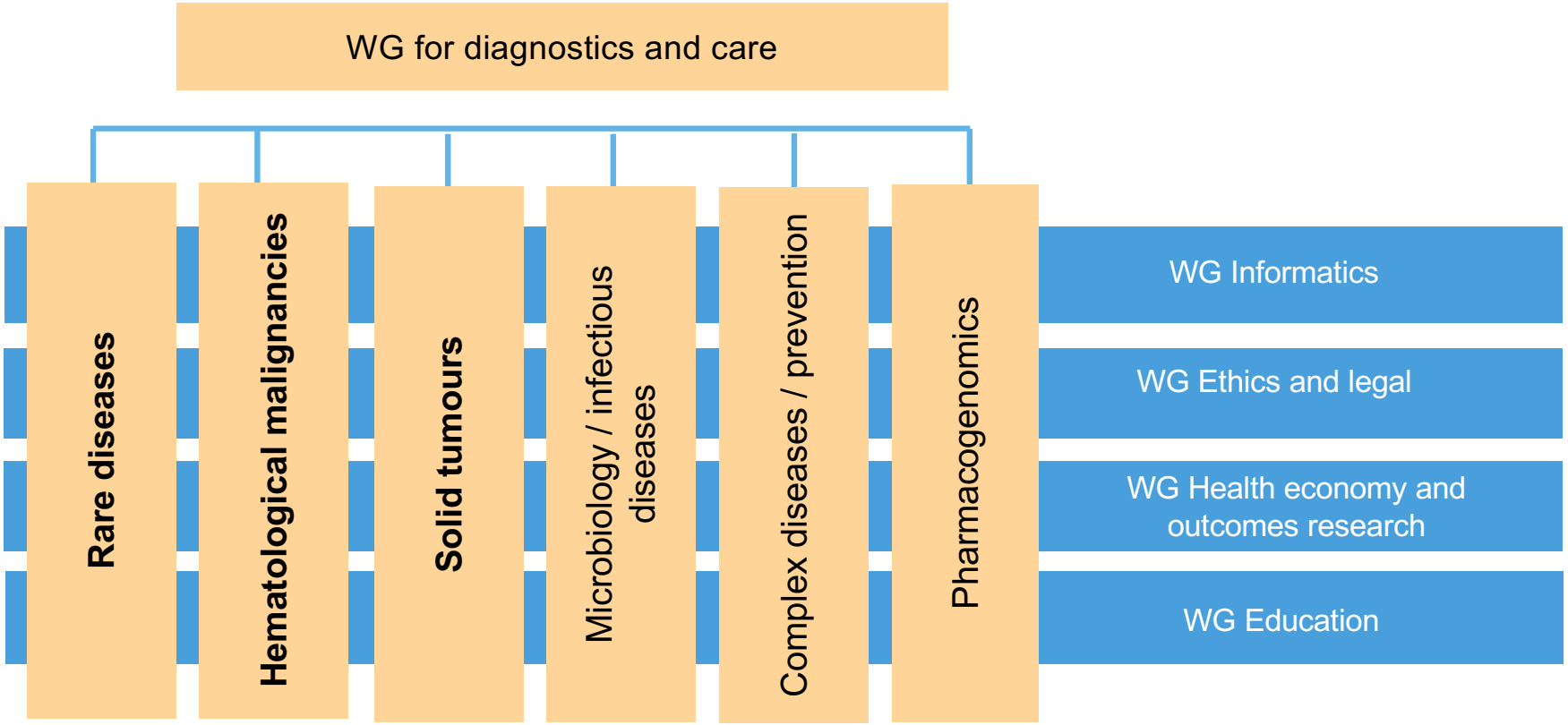
gms

Regional Genomic Medicine Centres are the engines of the system

- University hospitals in collaboration with the University
- **Build on regional expertise and interests → not identical**
- A broad competence in advanced molecular diagnostics
- Build expert PM teams



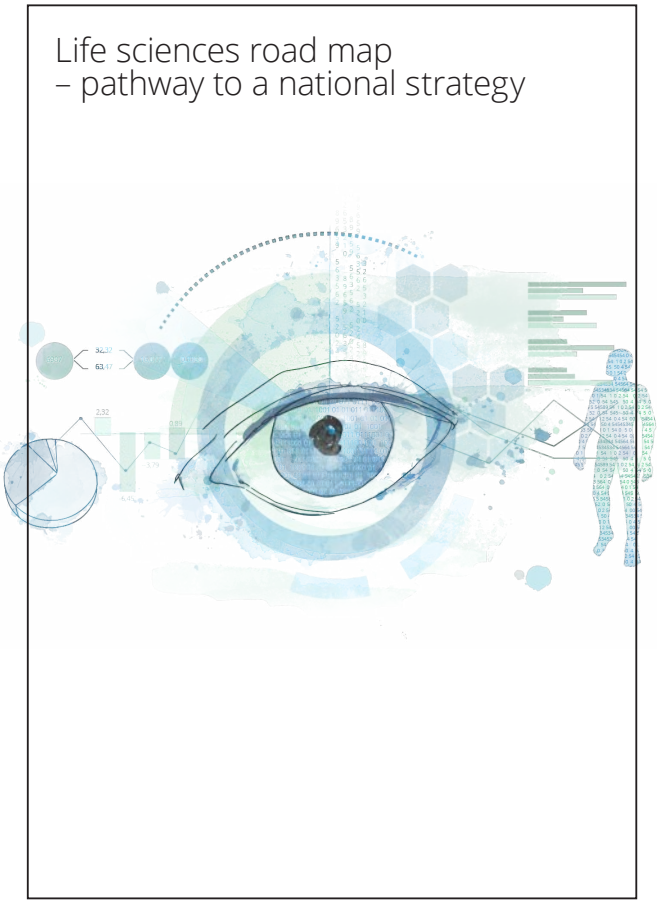
Focus areas


WG for diagnostics and care
Rare diseases
Hematological malignancies
Solid tumours
Microbiology / infectious diseases
Complex diseases / prevention
Pharmacogenomics
WG Informatics
WG Ethics and legal
WG Health economy and outcomes research
WG Education

Life science road map - pathway to a national strategy

- In 2018, Swedish government identified three prioritized areas to develop healthcare:
  - Utilization of digital health and health care data
  - Precision medicine – tomorrow´s diagnostics, treatment and cure **(Genomic Medicine Sweden)**
  - Tomorrow's health and social care – integration of research and innovation

- Life science and precision medicine strategy expected by YE'19



Collaborative effort

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Funders

Clinical Genomics team, annual planning retreat

Contact, links

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Links

https://clinical.scilifelab.se/
https://genomicmedicine.se/