Molecular Pathology Practice in Europe: Sweden

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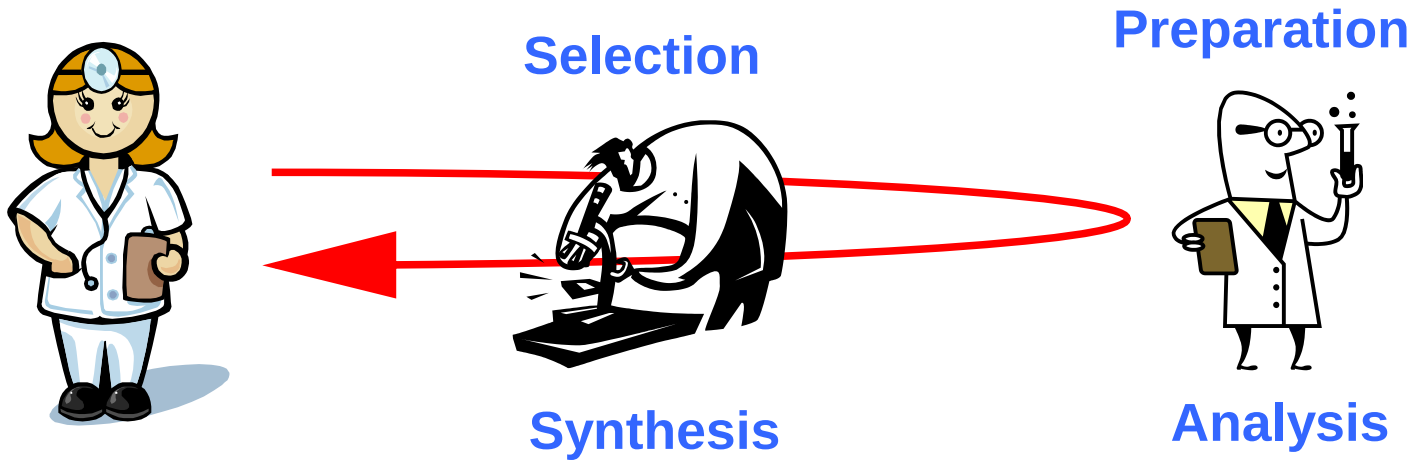
Swedish Molecular Pathology (MP) - outline

- Basic facts
- Future perspectives
- Structured to mirror the other presentations
- Summed up in handout

Who performs MP in Sweden?

- Typically a team made up of pathologists, molecular biologists and biomedical laboratory scientists
- Molecular characterization of hematological malignancies are often partly performed in other laboratory specialities like clinical genetics
- There is no legal authorization and no special qualification/diploma is required to perform MP



Swedish tests & testing strategies

- Treatment predictive testing in solid tumors largest volume (**Breast** – ERBB2; **NSCLC** – EGFR, ALK, ROS1 etc; **CRC** – RAS & RAF, **MM** – BRAF)
- Almost 10 000 NGS analyses and 15 000 “other” MP tests yearly
- Sequencing in gene panels – pricing roughly 1 000 euros
- Predicitive and diagnostic testing generally dependent on WHO recommendations and other consensus documents
- Malignant hematology, pediatric malignancies and bone- / soft tissue tumors most extensively characterized (up to WES + RNAseq)
- HPV screening set up within pathology in some regions

NSCLC in Sweden – alternate strategies

Common for all labs

- Morhphology + IHC for diagnosis
- PD-L1 IHC (might be centralized)
- DNA gene panel (centralized)

Differing strategies for fusion genes and Met exon skipping

- IHC+FISH (for ALK, ROS1 fusions)
- RNA panels (for fusions and skipping)
- Nanostring (for fusions and skipping)

Liquid biopsies

- In clinical routine only for NSCLC
- Mainly for detecting TKI resistance mutations
- Some analyses in a primary setting in which tissue/cytology is sufficient for diagnosis but not molecular characterization
- ddPCR and NGS main methodologies

Funding of MP in Sweden?

- MP paid for by the clinical department referring to testing
- Temporary regional funding for implementation
- No system for reimbursement
- A gene panel for treatment predictive purposes – 1 000 Euros

Involvement of pharma and dx companies?

- No current funding of tests from pharmaceutical companies
- Facilitation of training and education
- Testing through commercial external testing currently not recommended within the publicly funded health care
- Roche has applied for approval for FoundationOneCDx
- Broader discussion with authorities initiated

Swedish MP instrumentation and methodology

- Focus on NGS with a trend towards upscaling and collaboration
- QPCR, MLPA, pyrosequencing etc for specific purposes
- Sanger no longer used for somatic testing.
- Fully automated devices rarely used but has been introduced for MSI testing in smaller labs

Swedish Molecular Pathology Map

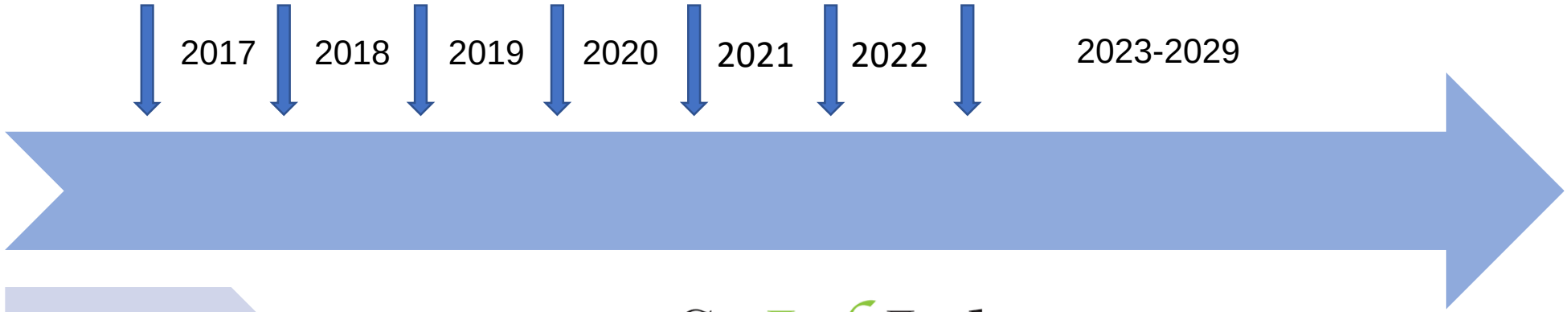
- 10 million inhabitants
- All covered by MP testing

- 21 regions are responsible for health care
- Nearly 30 pathology labs
- 7 nodes in a national precision medicine initiative

Swedish Molecular Pathology Map

- 7 nodes in a national precision medicine initiative
- 2 additional satellites performing NGS

Genomic Medicine Sweden – Time line



Formation — Bottom up initiative — SciLifeLab

Pre-study — Swelife – Vinnova (Aug 2017-July 2018) — SWElife

Start-up — Top down – new national steering board Vinnova (June-Oct 2018) — VINNOVA

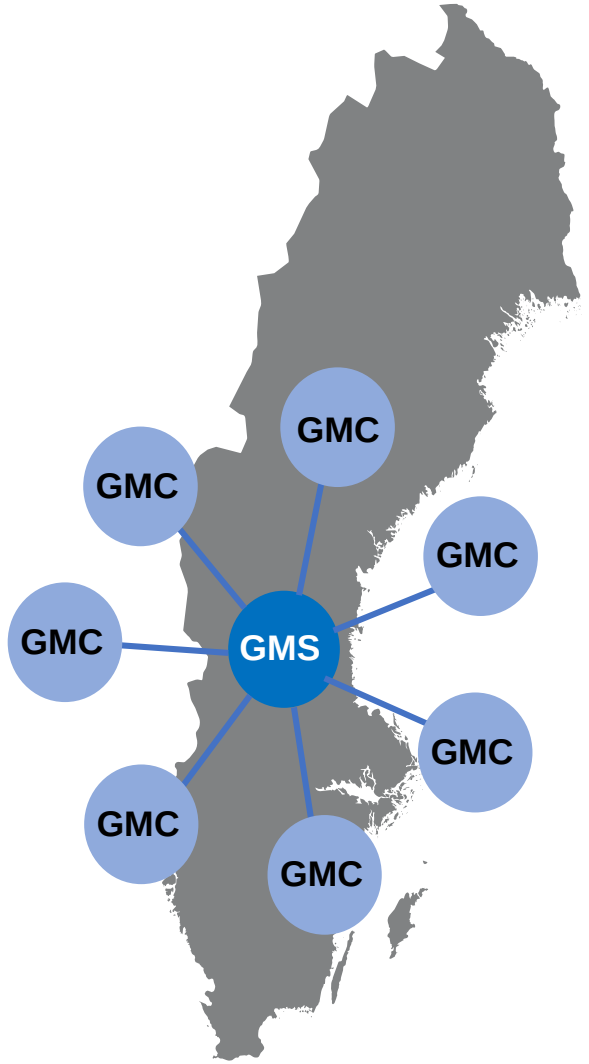
Implementation — Vinnova (Nov 2018 - Dec 2020)

Extention phase (5-10 year perspective)

gms

Genomic Medicine Sweden - aims

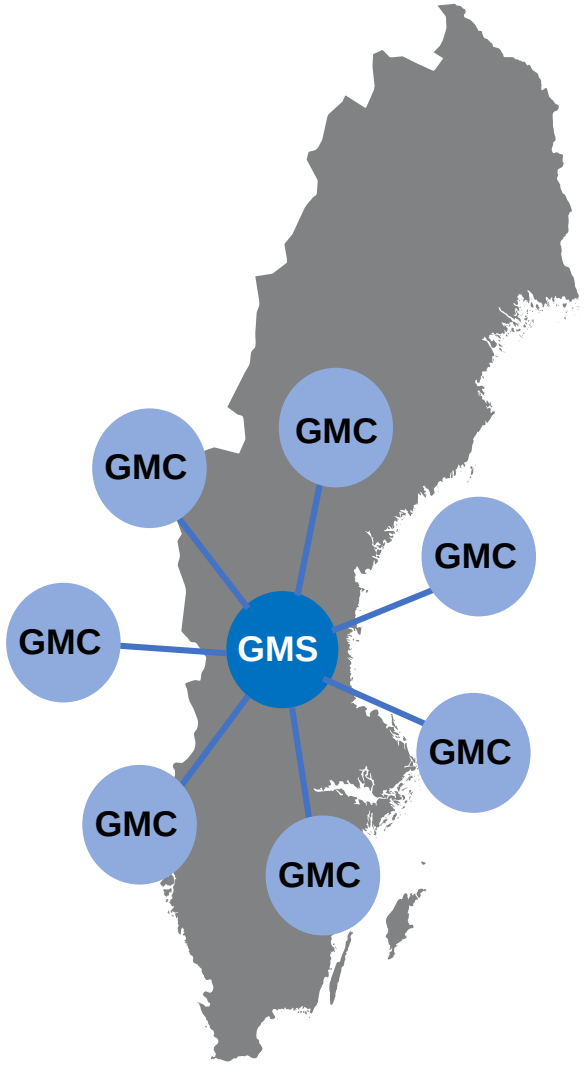
- Cutting edge diagnostics – initial focus on next generation sequencing technologies
- Precision medicine – the right treatment to the right patient and the right time
- Through a nationwide collaborative effort offer all patients equal care regardless of healthcare region
- A unique national research database
- Innovation and industry cooperation



Genomic Medicine Sweden – central functions

- Harmonized informatics and cost effective data storage
- Pooled resources and coordinated efforts on assay development, validation and implementation
- Work packages to solve key issues

Genomic Medicine Centers



- Relies on the national infrastructure and supports national collaborative efforts
- Governed by the university hospitals and their corresponding medical faculties
- Represents the healthcare regions and supports highly specialized medical care
- Access to advanced molecular diagnostics and decision support
- Hub for inclusion in clinical trials

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

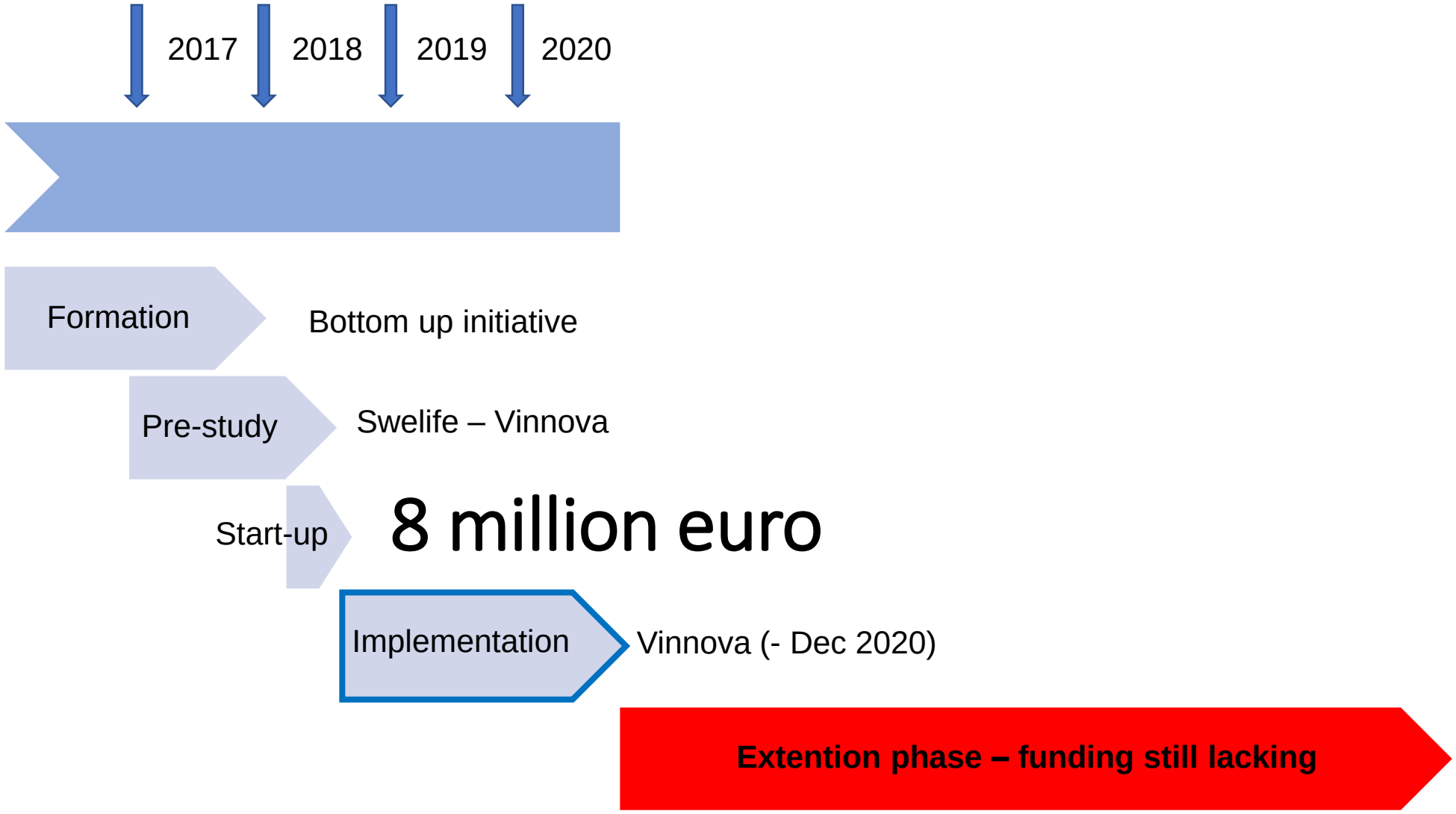
Health economy

Education & communication

Regional infrastructure

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

Genomic Medicine Sweden – Funding



Genomic Medicine Sweden – examples of current projects

- National gene panels for hematological malignancies ordered and solid tumors panels in late design stage
- WGS + RNAseq for all pediatric maligncies in collaboration with BTB (the national pediatric tumor biobank)
- WGS pilots in hematological malignancies and rare disease
- Pilots for a national computational and storage solution (raw and variant data with added meta data)

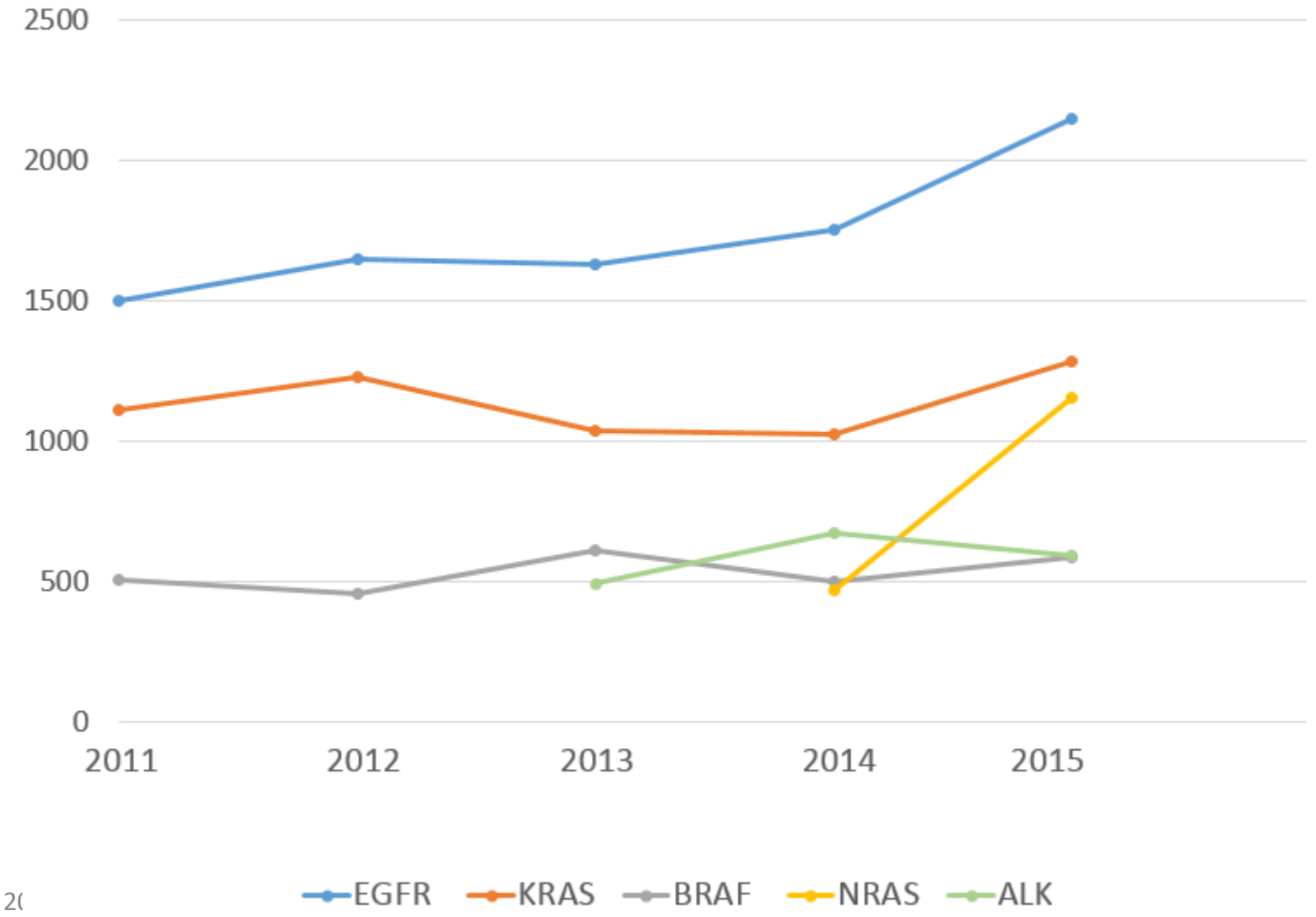
Accreditation

- ISO 15189 is the ISO standard used for MP (and histomorphological diagnostic work)
- Accreditation is not mandatory to perform diagnostic work
- There are sites that have specific assays accredited but none has an accreditation for the complete MP work flow
- Most sites plan to apply for a complete accreditation

Quality assessment & quality assurance

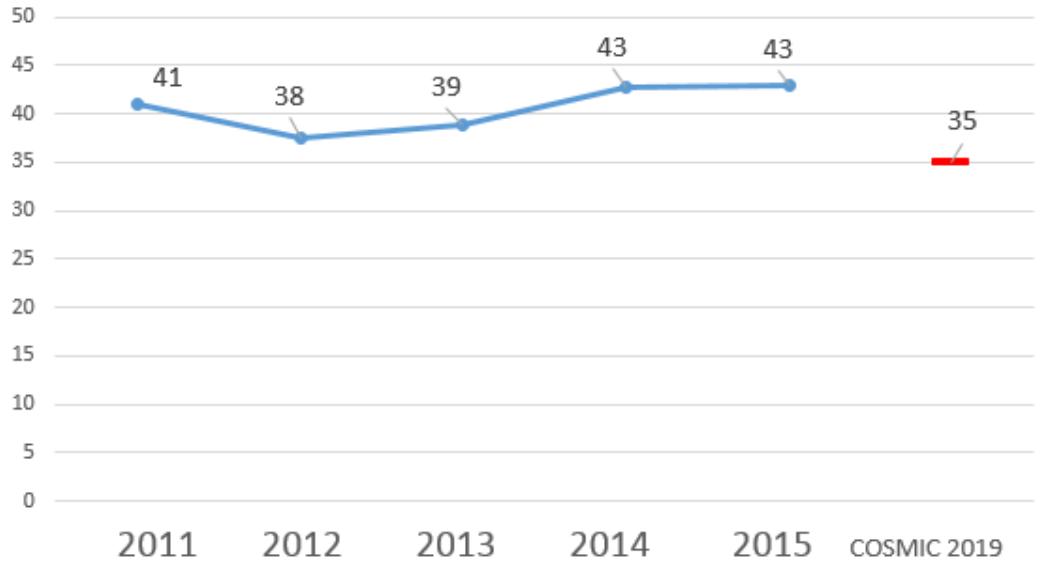
- National EQA schemes starting with KRAS in CRC (2008, 2008, 2009)
- Joined European efforts in 2009 (ESP, IQN-)
- Additional national schemes in select areas (e.g. BRAF in MM, HER2/ERBB2 in gastric cancer)
- Decision to rely on European EQA work
- Volumes and aggregated data on variants from all labs 2011-2015
- A variant database linked quality registries to couple variants with treatment outcome as part of Genomic Medicine Sweden’s

Analyses 2011-2015 (NSCLC, CRC, MM)

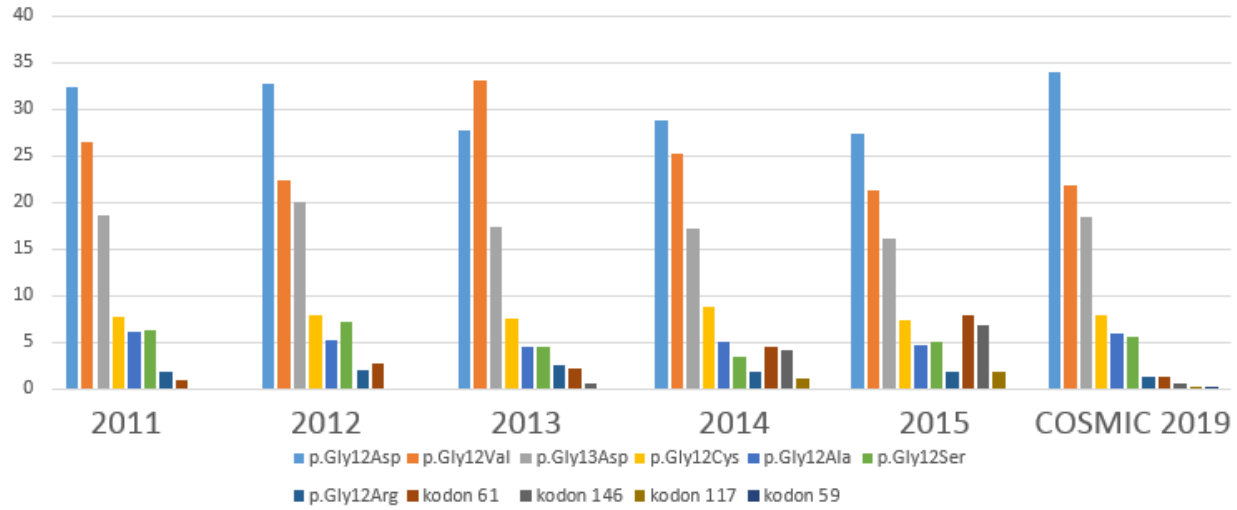


KRAS: Activating mutations 2011-2015 (%)

All activating mutations (%)



Individual mutations (%)

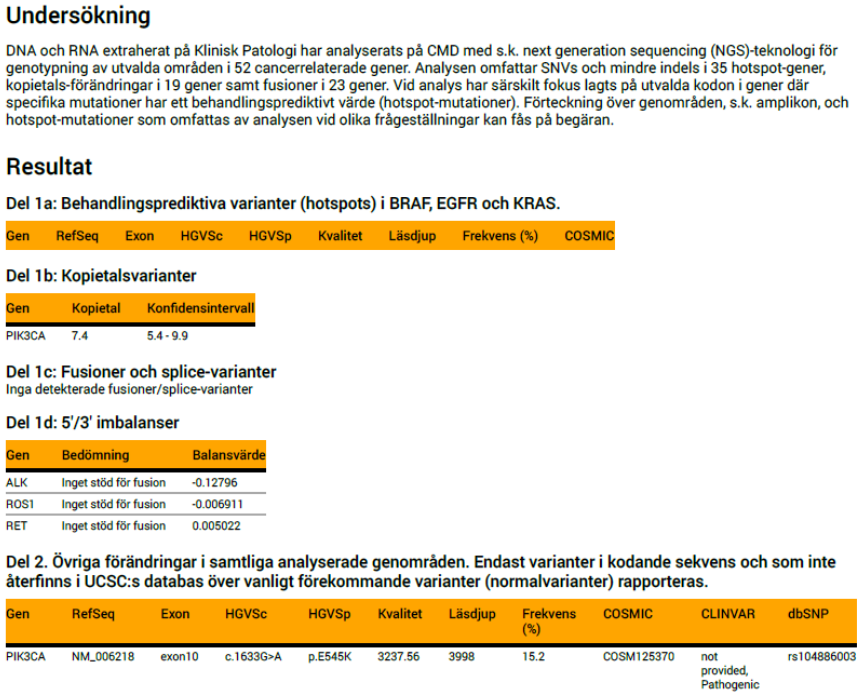


Training

- MP in curriculum for residents but no mandatory training for specialists
- Yearly national short course but no in-depth educational modules
- No structured add on for molecular biologists

Inclusion of MP results in pathology reports ?

- Recommended nationally and an aim in all institutions
- Degree of integration varies between disease areas and health care regions
- Layout and content dependent on the needs and background of involved clinicians
- Harmonization ongoing



Undersökning

DNA och RNA extraherat på Klinisk Patologi har analyserats på CMD med s.k. next generation sequencing (NGS)-teknologi för genotypning av utvalda områden i 52 cancerrelaterade gener. Analysen omfattar SNVs och mindre indels i 35 hotspot-gener, kopietals-förändringar i 19 gener samt fusioner i 23 gener. Vid analys har särskilt fokus lagts på utvalda kodon i gener där specifika mutationer har ett behandlingsprediktivt värde (hotspot-mutationer). Förteckning över genområden, s.k. amplikon, och hotspot-mutationer som omfattas av analysen vid olika frågeställningar kan fås på begäran.

Resultat

Del 1a: Behandlingsprediktiva varianter (hotspots) i BRAF, EGFR och KRAS.

Gen	RefSeq	Exon	HGVSc	HGVSp	Kvalitet	Läsdjup	Frekvens (%)	COSMIC

Del 1b: Kopietalsvarianter

Gen	Kopietal	Konfidensintervall
PIK3CA	7.4	5.4 - 9.9

Del 1c: Fusioner och splice-varianter

Inga detekterade fusioner/splice-varianter

Del 1d: 5'/3' imbalanser

Gen	Bedömning	Balansvärde
ALK	Inget stöd för fusion	-0.12796
ROS1	Inget stöd för fusion	-0.006911
RET	Inget stöd för fusion	0.005022

Del 2. Övriga förändringar i samtliga analyserade genområden. Endast varianter i kodande sekvens och som inte återfinns i UCSC:s databas över vanligt förekommande varianter (normalvarianter) rapporteras.

Gen	RefSeq	Exon	HGVSc	HGVSp	Kvalitet	Läsdjup	Frekvens (%)	COSMIC	CLINVAR	dbSNP
PIK3CA	NM_006218	exon10	c.1633G>A	p.E545K	3237.56	3998	15.2	COSM125370	not provided, Pathogenic	rs104886003

Conclusions - Sweden

- All MP testing needed for indicated diagnostics and treatment prediction performed
- Hope to upscale MP to general, comprehensive up front testing through the national Genomic Medicine Sweden effort but financing still unclear
- Training of pathologists (and other health care professionals) an important challenge