The CHIME project – leveraging national registries and biobanks to develop AI-based solutions for cancer precision pathology

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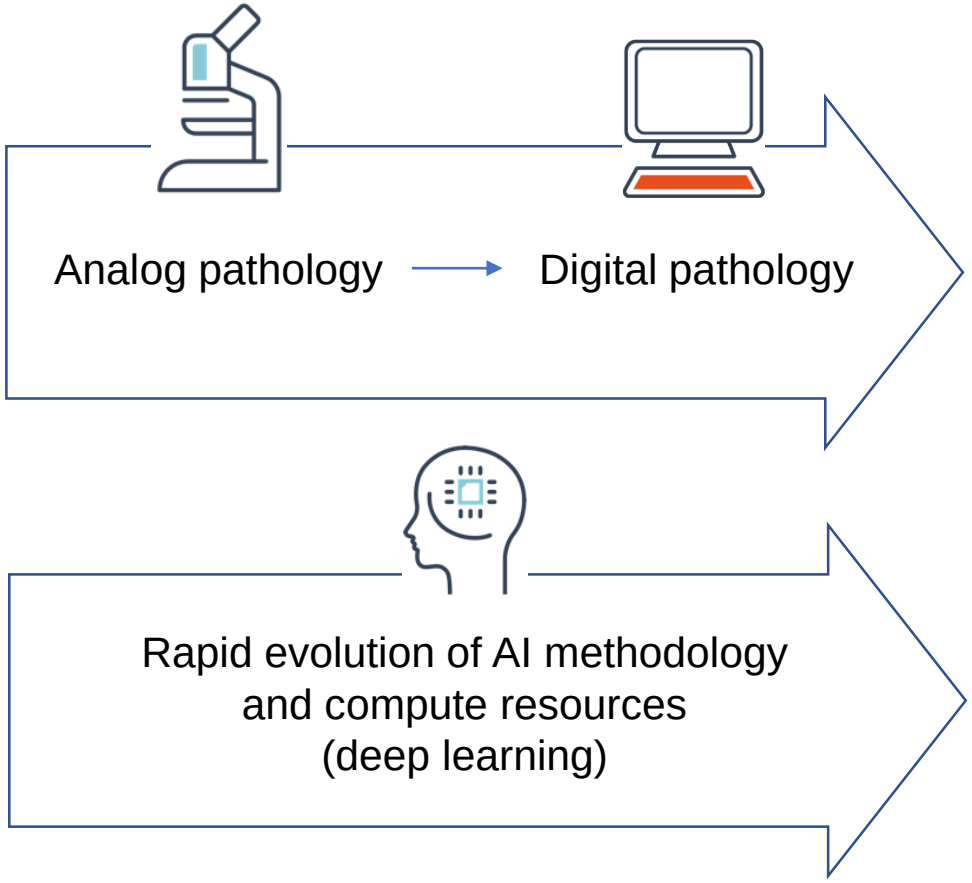
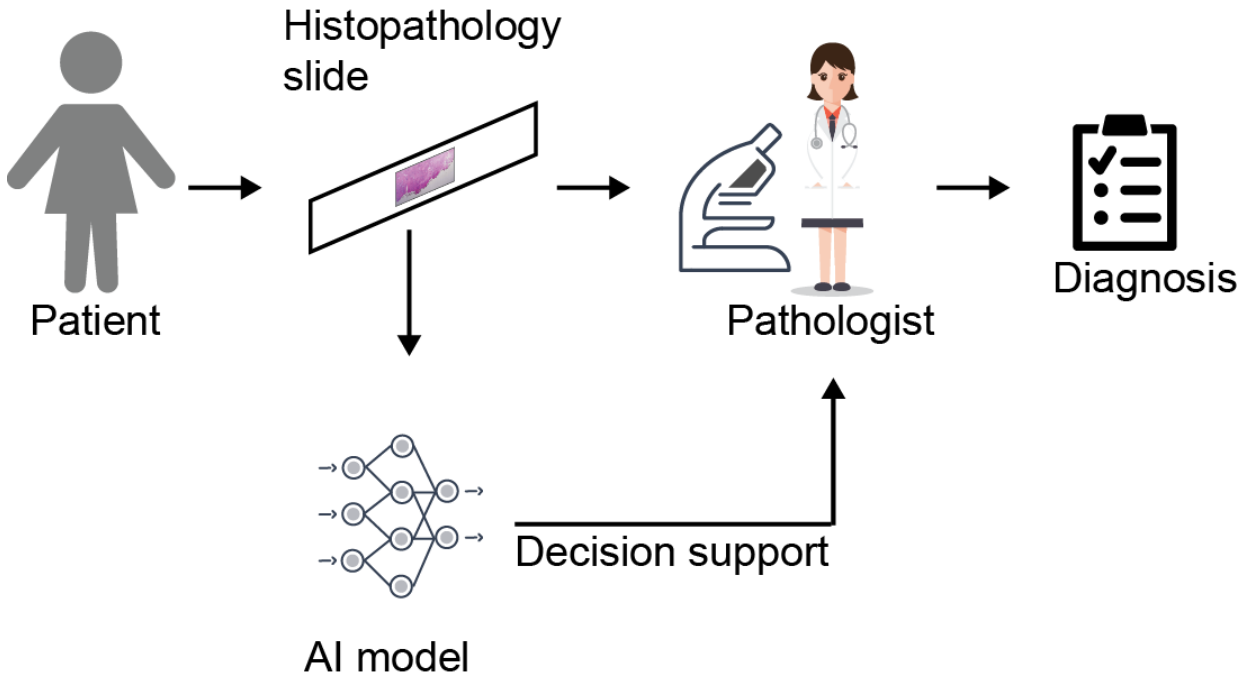
Nordic Biobank Conference, 8th of September 2022

Disclosures

Co-founder and shareholder: Stratipath AB

Pathology is central in routine cancer diagnostics – the digital transition enables AI-based phenotyping, stratification and decision support solutions





AI-based decision support applications are now possible in clinical routine:

1) Routine pathology applications (replicate human assessor)
2) Precision diagnostics (extract novel phenotype information from images)

CHIME the **C**ancer **H**istopathology **IM**age **E**pidemiology project

- Launched in 2018
  - Support from a range of national and international funding bodies
  - Project has dedicated infrastructure: secure compute resources & slide scanning facility
  - AI-based precision pathology research
- Large multi-site retrospective cohort studies
- Digital images generated from biobanked specimen (slide scanning)
- To date >200,000 gigapixel whole slide images digitized, >400TB data
- Diagnoses: breast, prostate, colorectal, skin and lung cancer
- Practical challenges:
  - Logistics
  - Access to biobanks (sometimes)
  - Maintaining an even flow of materials through our digitization facility

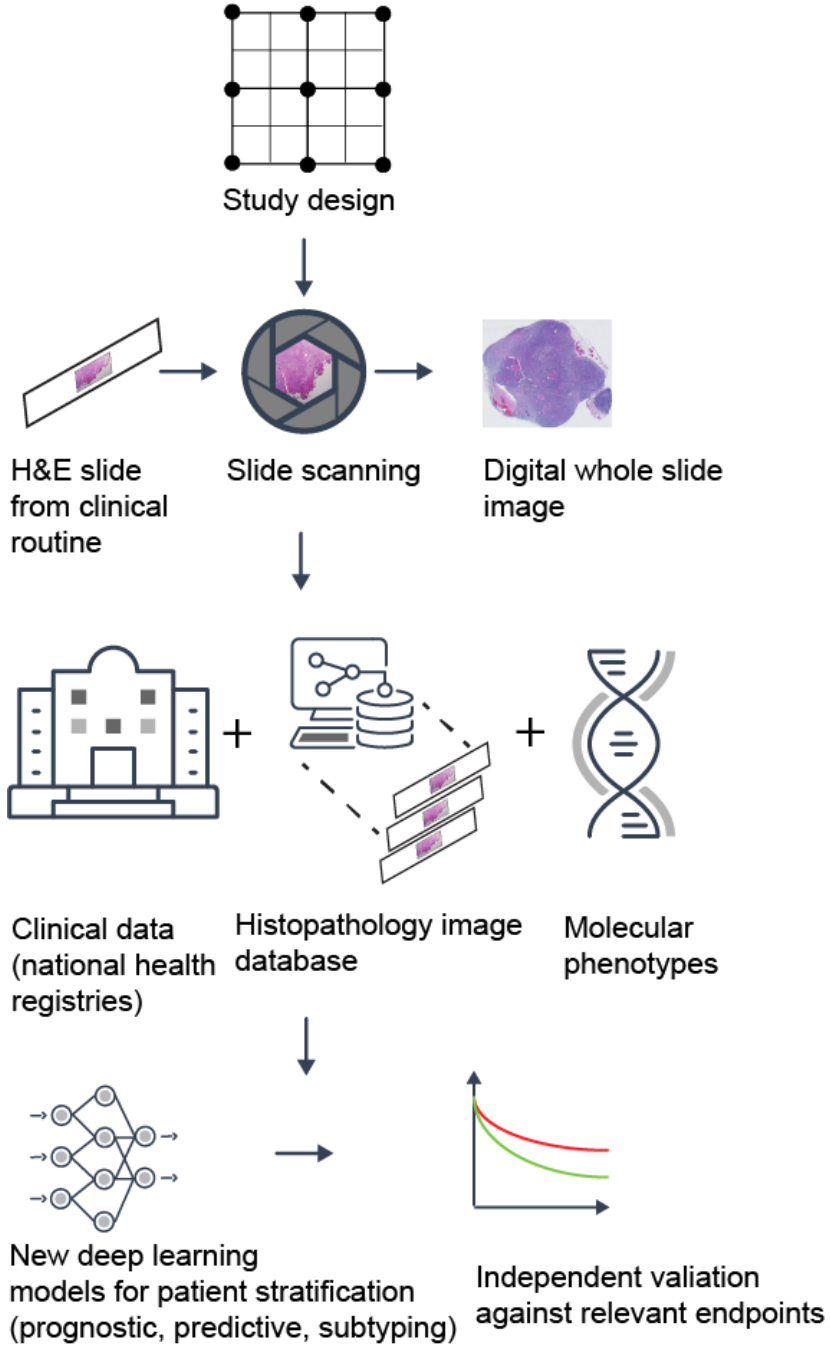
CHIME the **C**ancer **H**istopathology **IM**age **E**pidemiology project

1.Design of new studies

2. In-house slide digitization of biobank materials

3.Linking with registry-based clinical data & other phenotypes

4.Precision medicine & AI-based computational pathology research



- **Large population representative studies**
- In-house infrastructure and team that drive studies from start to finish
- Close collaboration with clinicians & industry

www.chimestudy.se

Our activities stretches from early stage research to clinical translation & implementation

CHIME the **C**ancer **H**istopathology **IM**age **E**pidemiology project

KI umbrella project: study design, infrastructure, AI-research

ABCAP **A**dvancing **B**reast **C**ancer histopathology towards **AI**-based **P**ersonalised medicine

ERA PerMed funded consortium with a focus on breast cancer precision pathology (four partners in the Nordic countries)

SWAIPP SWEDISH AI PRECISION PATHOLOGY

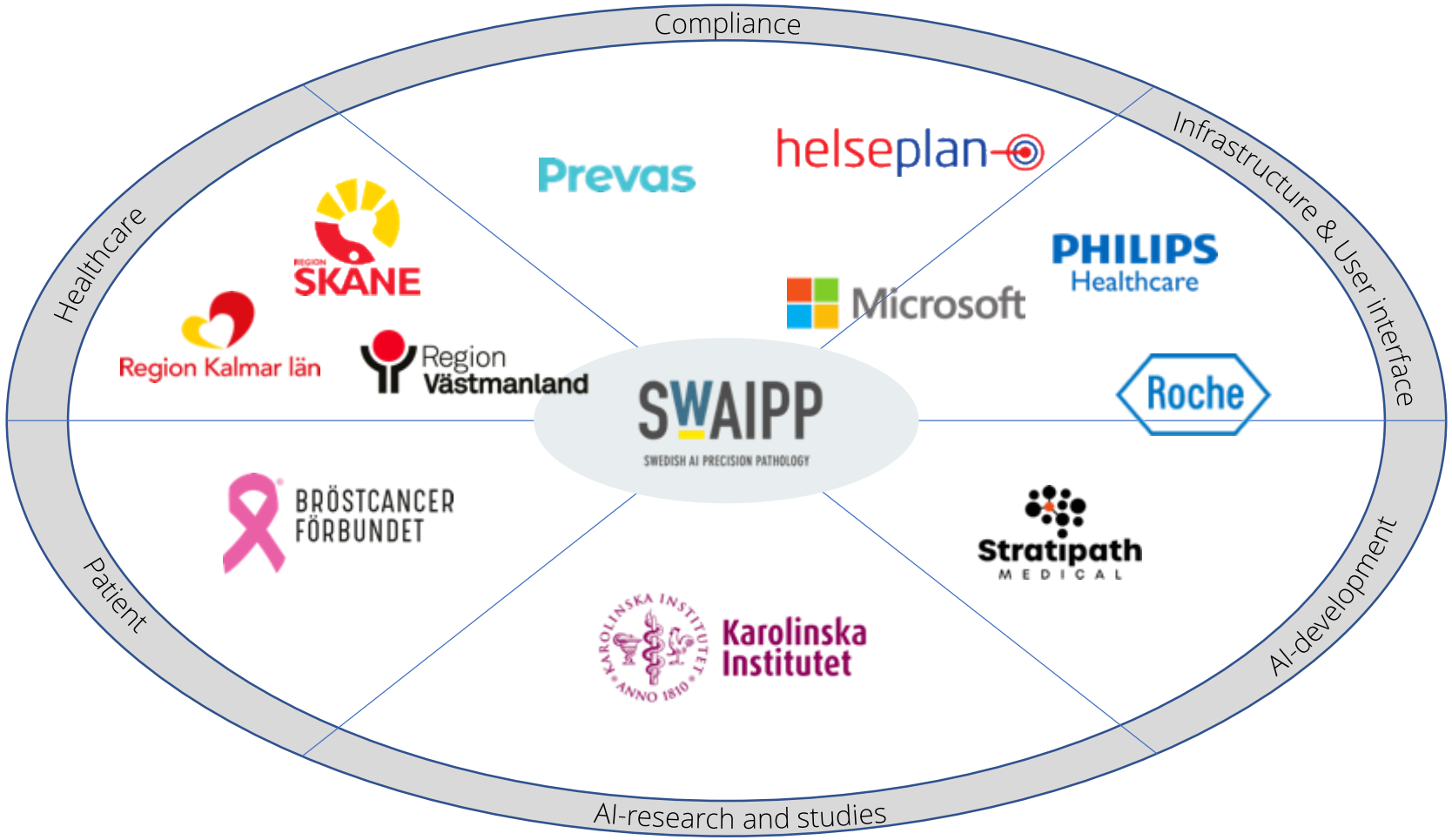
VINNOVA funded innovation environment for precision health; focus on translation and implementation (11 partners: healthcare, industry, academia and patients)

Discovery and early research

translation and implementation

SwAIPP - Swedish AI Precision Pathology

Routes to clinical implementation of AI-based precision pathology: from research to clinical translation of regulatory approved solutions, using breast cancer as a principal case.



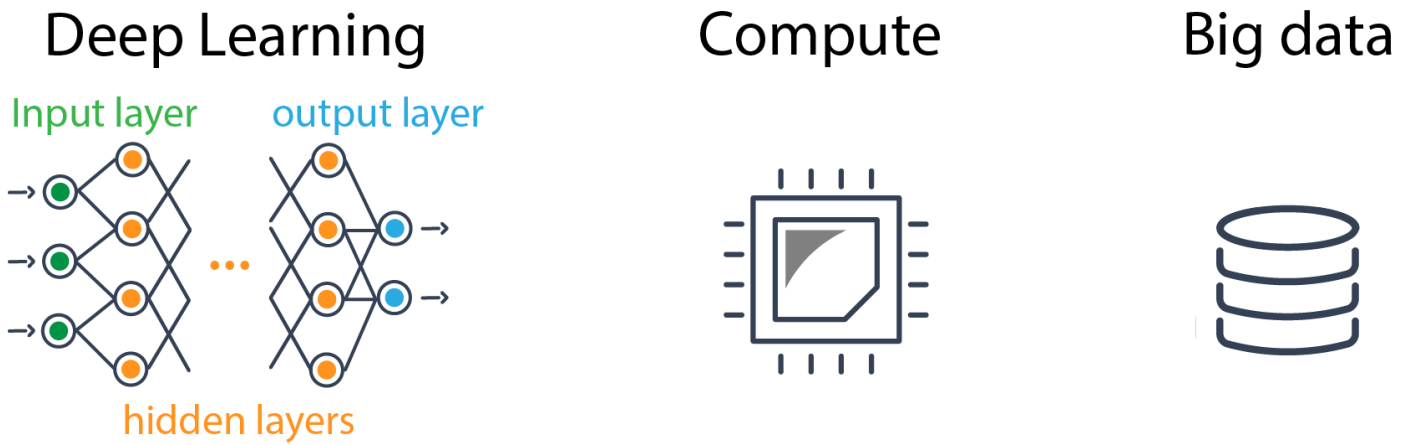
- *Vinnova/SweLIFE supported innovation environment*
- *20 MSEK from Vinnova/Swelife (total budget 38MSEK)*
- *Duration: 2,5 years*
- *Scope: R&D, Compliance, Clinical implementation, Clinical evidence and Dissemination*

“ ‘AI’ or ‘AI technologies’ describes **the use of digital technologies to create systems capable of performing tasks commonly thought to require human intelligence.** These can include algorithms using statistical techniques that find patterns in large amounts of data, or perform repetitive cognitive tasks using data, without the need for constant human oversight.”
Ref: Understanding healthcare workers’ confidence in AI; NHS AI Lab & Health Education England, Report, May 2022

“/../ we define it as an umbrella term for a range of algorithm-based technologies that **solve complex tasks by carrying out functions that previously required human thinking.** Decisions made using AI are either fully automated, or with a ‘human in the loop’.”

Ref: Leslie D. Explaining Decisions Made with AI. SSRN Electron J. 2022. doi:10.2139/ssrn.4033308

Enabling factors:

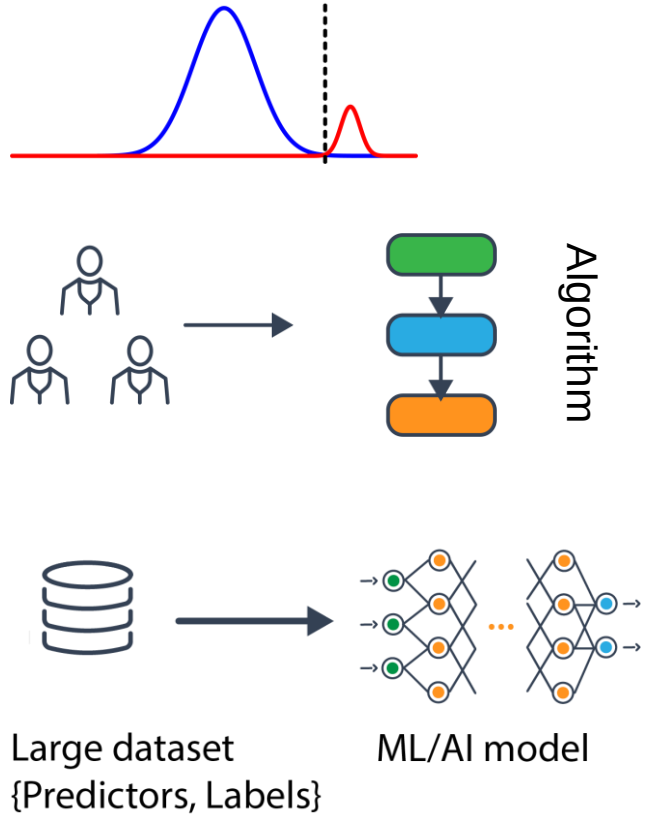


From simple decision rules - to handcrafted expert systems - to data driven machine learning and AI

- **Simple decision rules:** univariate decision rules derived from human domain experts and/or basic statistical analyses

- **Hand-crafted expert systems:** human domain specialists designed rules (strong hypotheses) + statistical analyses

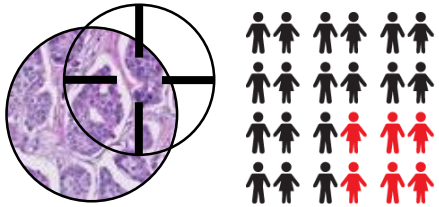
- **Data-driven ML/AI:** the use of information in data from large-scale studies to identify patterns and establish models with classification / prognostic / predictive capability



Our interests in AI precision pathology

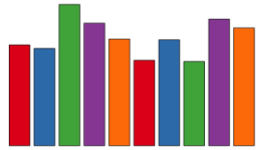
1. Improved routine pathology

- Decision support
- Reduction in inter-assessor and inter-lab variability
- Increase safety (automated 2nd reader)
- Efficiency gains



2. AI-based precision diagnostics

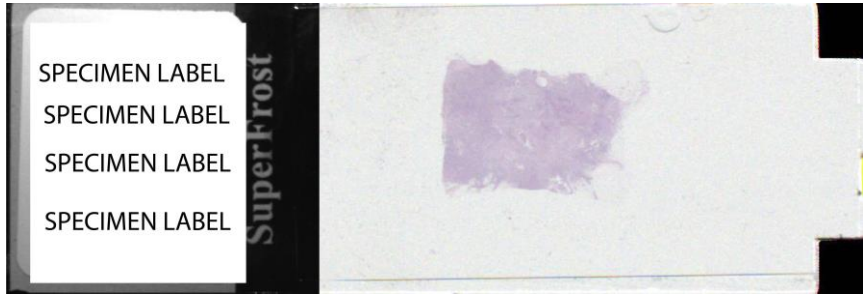
- Utilization of AI (deep learning) to ”see” information beyond the human eye
- Risk stratification / prognostic models
- Treatment predictive models

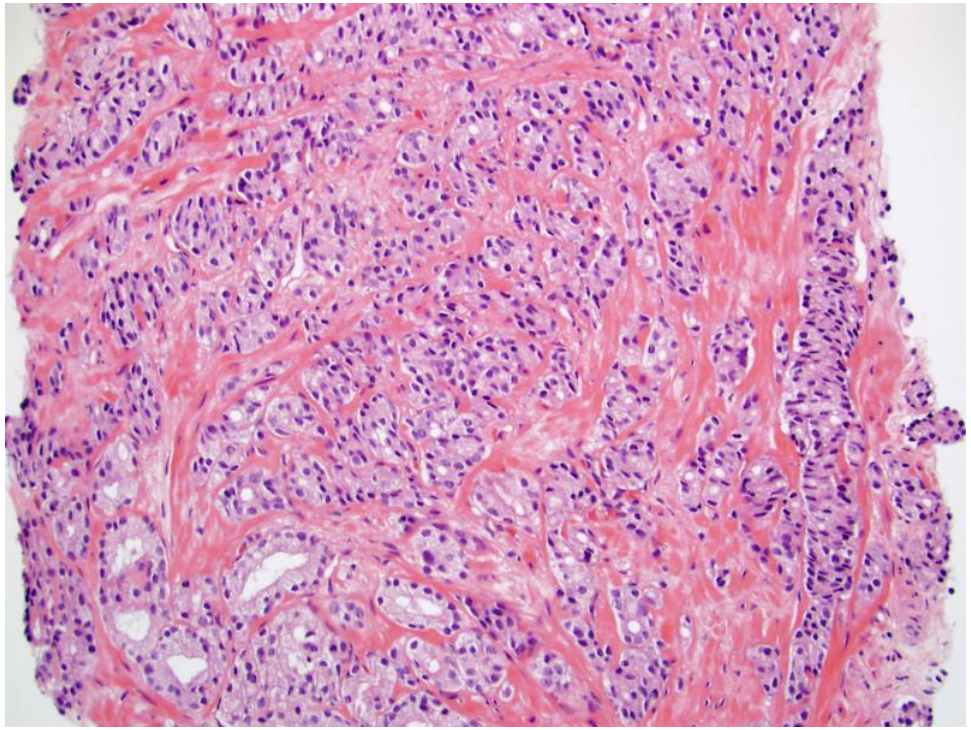


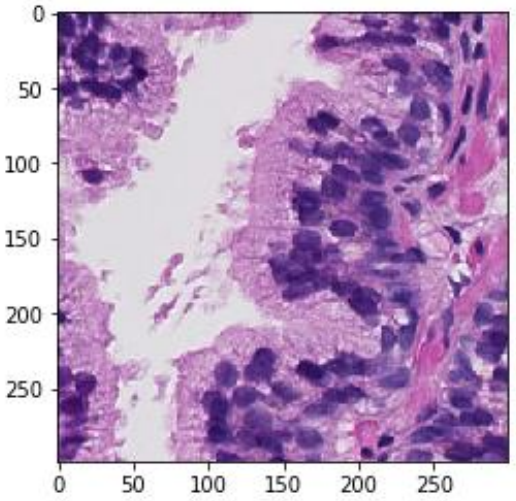
3. AI-based phenotyping for subtyping and subgroup analyses

- Standardized morphological phenotypes (deep learning representations of multiple types)
- Complementary & shared information with molecular phenotyping
- Intra-tumour heterogeneity information for free
- Cost effective and scalable

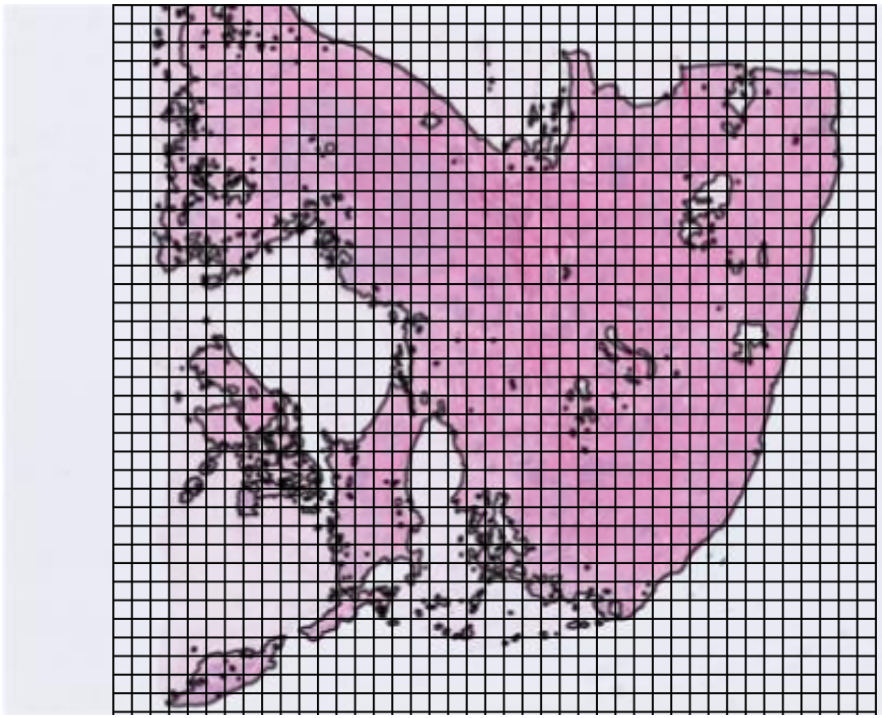
Digital whole slide images







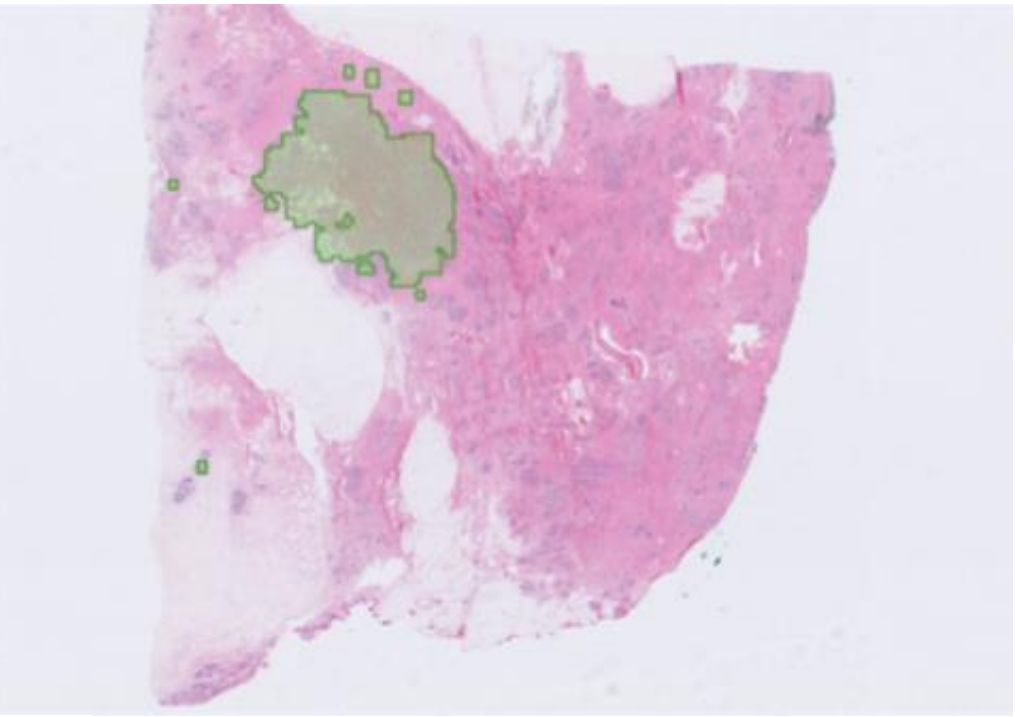
Tissue mask & tiles



Gigapixel WSI is split in to small image pieces (tiles).

(100s – 10000s tiles /WSI)

Model-based segmentation of invasive cancer region



Only the tiles in the cancer area (green) are used for downstream analyses

Pre-processing and QC (automated)

Manually annotated data

Tissue segmentation

Tiling and Quality Control

Color normalization

Tumor Detector CNN

Unannotated data

Annotation extraction

Predict tumor tiles

Tissue segmentation

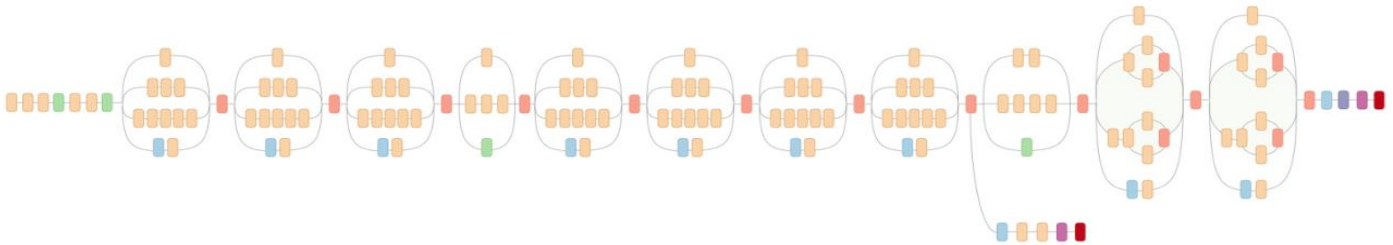
Tiling, quality control and color normalization

Tumor probability

Tumor segmentation

Used for analysis

Model development



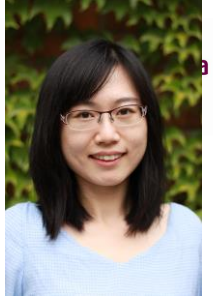
Deep CNN model (millions of parameters)

Development and optimisation of deep learning models for patient stratification

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE



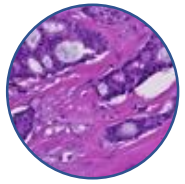
Yinxi Wang

Improved breast cancer histological grading using deep learning

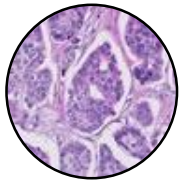
Y. Wang[1], B. Acs[2,3], S. Robertson[2,3], B. Liu[1], L. Solorzano[4], C. Wählby[4], J. Hartman[2,3,5†] & M. Rantalainen[1,5*†]

Departments of [1]Medical Epidemiology and Biostatistics; [2]Oncology-Pathology, Karolinska Institutet, Stockholm; [3]Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm; [4]Department of Information Technology and SciLifeLab, Uppsala University, Uppsala; [5]MedTechLabs, BioClinicum, Karolinska University Hospital, Solna, Sweden

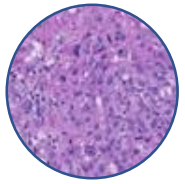
NHG 2 tumours account for up 50% of the cases, but carries no information relevant for clinical decision making (adjuvant chemotherapy; ER+/HER2- patients)



Grade 1

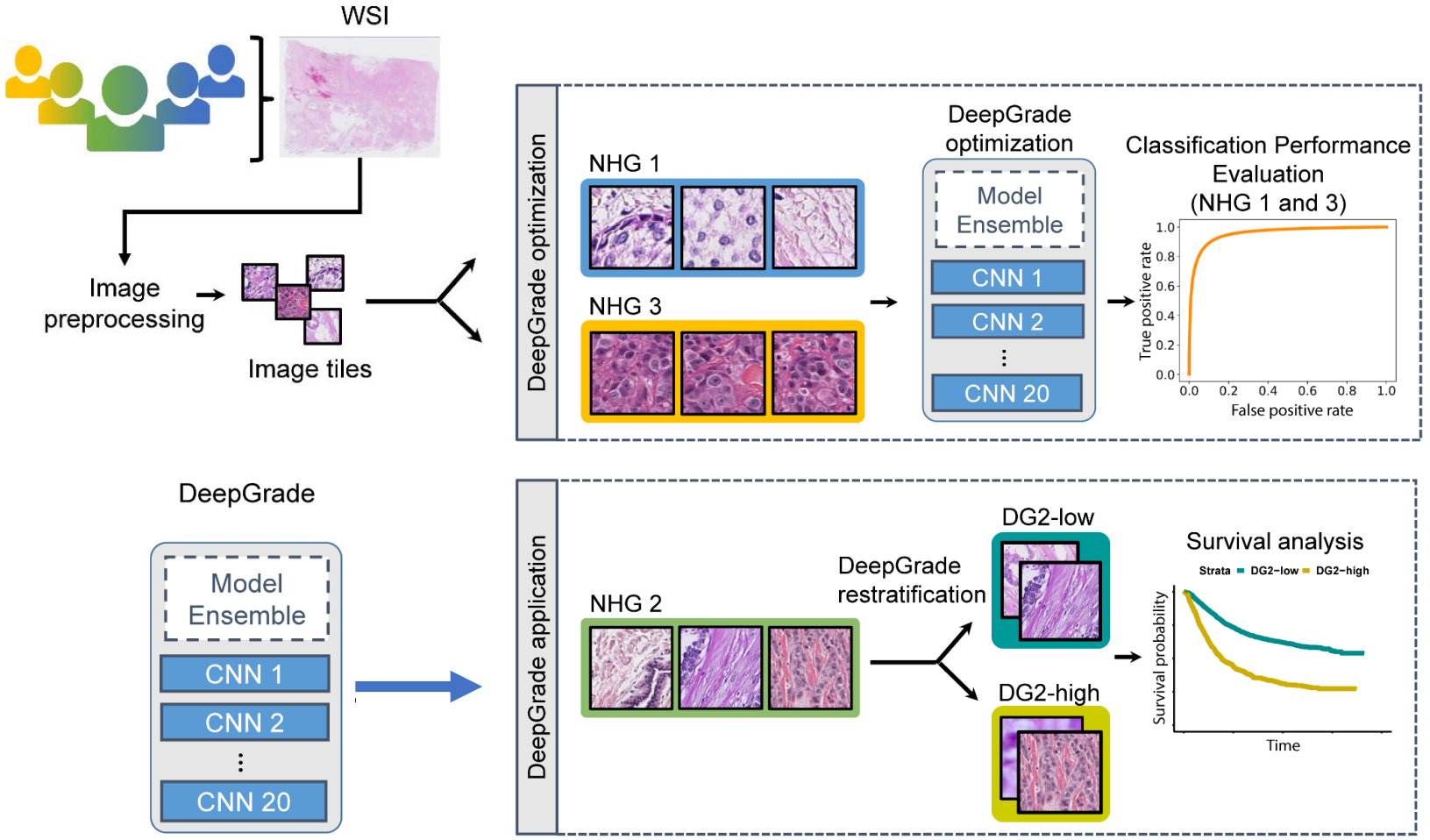


Grade 2

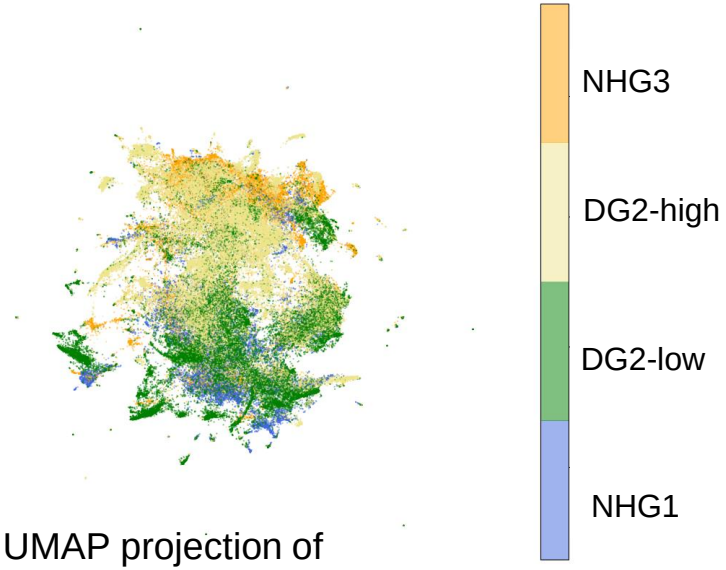


Grade 3

Aim: Improved risk stratification of breast cancer NHG 2 cases (intermediate risk) using deep CNN models



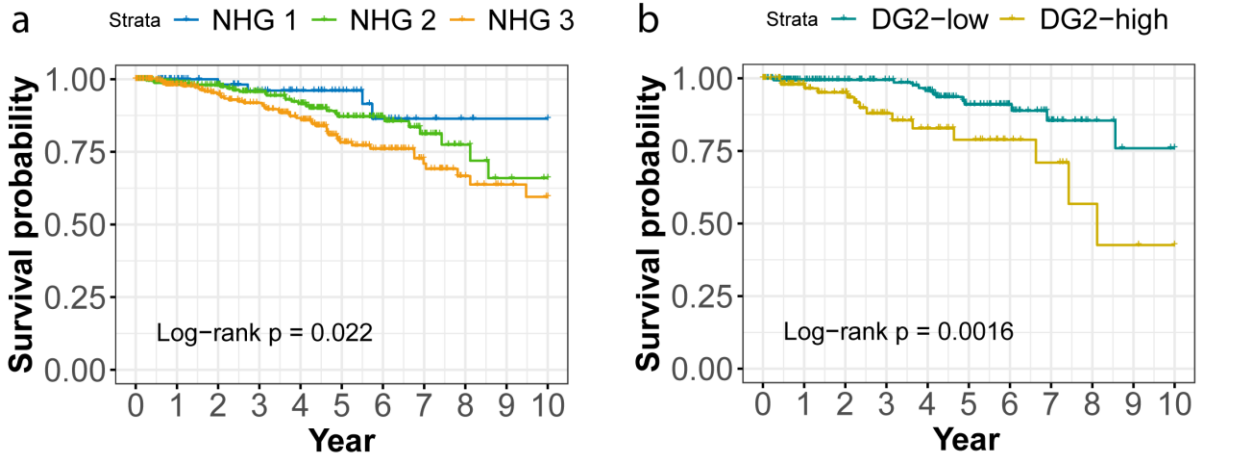
The study includes >2,800 patients in total, of which 1,200 patients in a fully independent validation cohort



UMAP projection of DeepGrade CNN feature representations (scatter of image tiles)

Wang Y, Acs B, Robertson S, Liu B, Solorzano L, Wählby C, Hartman J, Rantalainen M. Improved breast cancer histological grading using deep learning, *Annals of Oncology.* 2022

DeepGrade provides independent prognostic information for stratification of NHG 2 breast cancer cases (time-to-event (RFS))



a

Variable	Level	N	HR (95% CI)	p
Age		670	1.04 (1.01, 1.06)	0.001
Tumor size	<20 mm	253	Reference	
	>=20 mm	417	1.93 (1.01, 3.68)	0.047
Lymph node	Negative	422	Reference	
	Positive	248	2.10 (1.27, 3.49)	0.004
ER status	Negative	135	Reference	
	Positive	535	0.83 (0.46, 1.49)	0.536
HER2 status	Negative	574	Reference	
	Positive	96	0.88 (0.47, 1.66)	0.695
Grade	NHG 1	81	Reference	
	NHG 2	305	2.15 (0.64, 7.18)	0.214
	NHG 3	284	3.74 (1.12, 12.55)	0.033

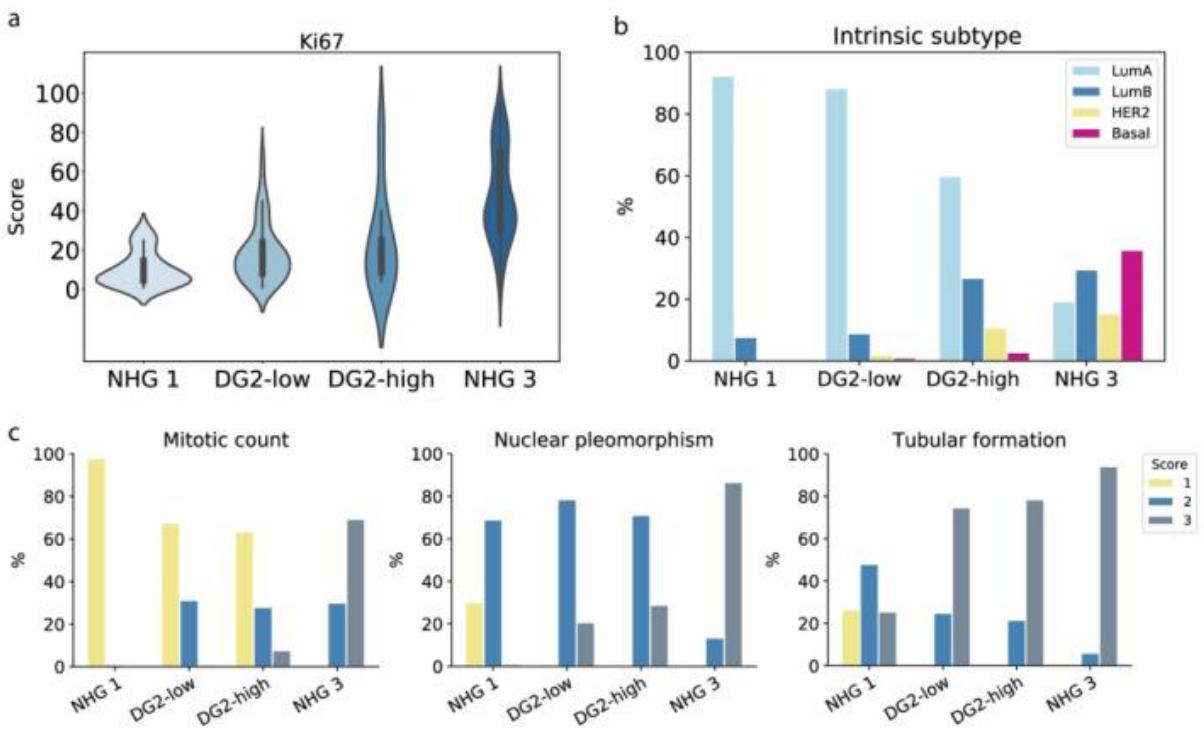
0.5 1 2 5 10

b

Variable	Level	N	HR (95% CI)	p
Age		305	1.05 (1.01, 1.09)	0.019
Tumor size	<20 mm	123	Reference	
	>=20 mm	182	1.10 (0.38, 3.19)	0.863
Lymph node	Negative	193	Reference	
	Positive	112	3.22 (1.26, 8.24)	0.014
ER status	Negative	18	Reference	
	Positive	287	0.67 (0.13, 3.61)	0.644
HER2 status	Negative	275	Reference	
	Positive	30	0.91 (0.17, 4.84)	0.912
DeepGrade	DG2−low	198	Reference	
	DG2−high	107	2.94 (1.24, 6.97)	0.015

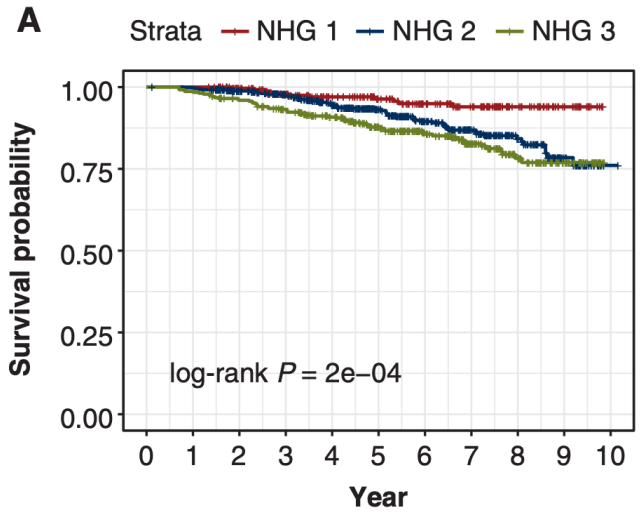
0.2 0.5 1 2 5

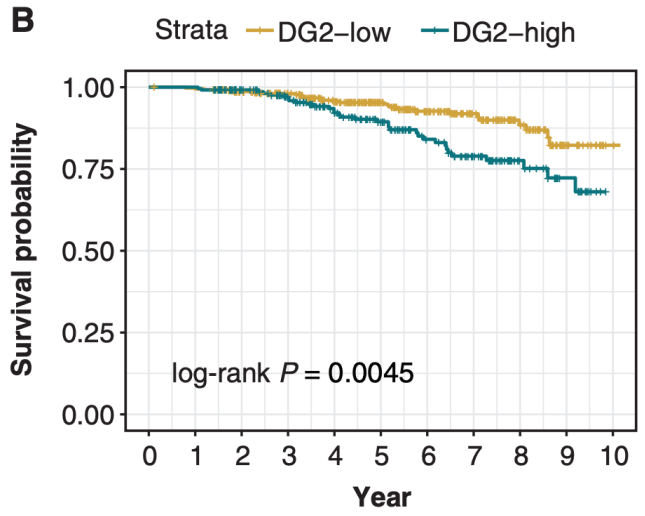
Prognostic stratification has similar performance as currently available molecular assays (gene expression profiling)



Ki67 (routine proliferation marker) do not provide information that can substitute DeepGrade. Molecular subtypes are consistent with DeepGrade stratification of NHG2.

Stratification of NHG2 in the external validation cohort





Validated in an external cohort (N=1262).

A

Variable	Level	N	HR (95% CI)	P
Age		1191	1.05 (1.03-1.07)	<0.001
Tumour size	<20 mm	835	Reference	
	≥20 mm	356	1.83 (1.24-2.71)	0.002
Lymph node	Negative	858	Reference	
	Positive	333	1.08 (0.73-1.60)	0.695
ER status	Negative	122	Reference	
	Positive	1069	0.36 (0.22-0.58)	<0.001
HER2 status	Negative	1094	Reference	
	Positive	97	0.95 (0.50-1.81)	0.866
Grade	NHG 1	265	Reference	
	NHG 2	583	1.63 (0.84-3.15)	0.149
	NHG 3	343	1.59 (0.78-3.24)	0.201

0.5 1 2

B

Variable	Level	N	HR (95% CI)	P
Age		583	1.05 (1.02-1.08)	<0.001
Tumour size	<20 mm	397	Reference	
	≥20 mm	186	1.15 (0.65-2.06)	0.633
Lymph node	Negative	416	Reference	
	Positive	167	0.77 (0.41-1.44)	0.415
HER2 status	Negative	555	Reference	
	Positive	28	0.73 (0.18-3.05)	0.669
ER status	Negative	21	Reference	
	Positive	562	0.39 (0.15-0.99)	0.048
DeepGrade	DG2-low	362	Reference	
	DG2-high	221	1.91 (1.11-3.29)	0.019

0.2 0.5 1 2

Conclusions (DeepGrade)

- DeepGrade enables risk-stratification of intermediate-risk breast cancer patients based on routine H&E slides
- **Example of what we refer to as precision pathology** – i.e. a model that goes beyond the ability of routine pathology and the capability of human assessors
- DeepGrade was evaluated in the context of prognostic performance (but not optimised against outcome)
- Additional validation studies are on-going
- Regulatory approved product was released in June 2022

CANCER RESEARCH

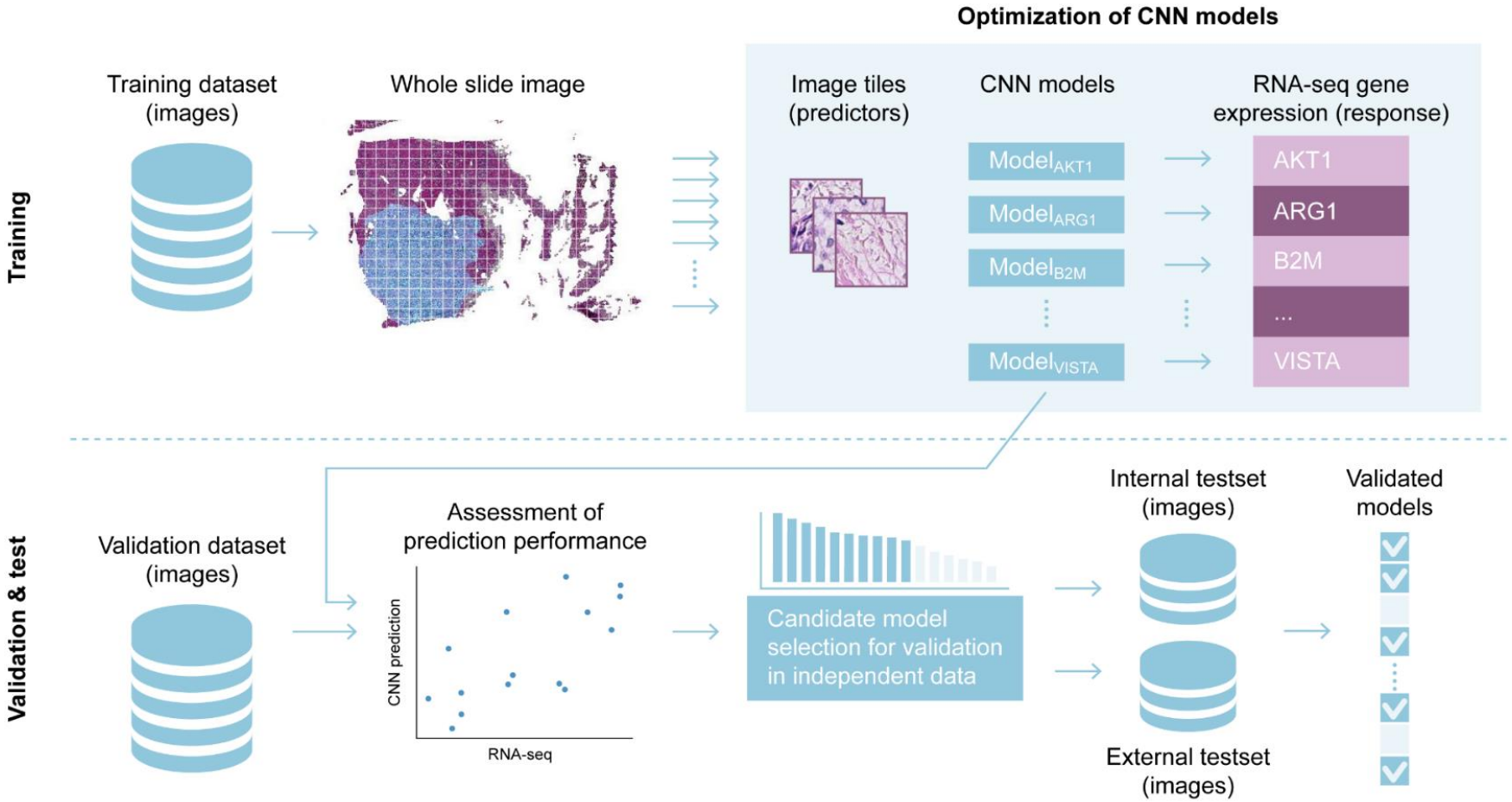
Convergence and Technologies

Predicting Molecular Phenotypes from Histopathology Images: A Transcriptome-Wide Expression–Morphology Analysis in Breast Cancer

Yinxi Wang, Kimmo Kartasalo, Philippe Weitz, Balázs Ács, Masi Valkonen, Christer Larsson, Pekka Ruusuvuori, Johan Hartman, and Mattias Rantalainen

DOI: 10.1158/0008-5472.CAN-21-0482 Published October 2021

Aim: Prediction of mRNA expression in breast tumours from H&E WSIs - can molecular phenotypes be predicted from histopathology images using deep learning?

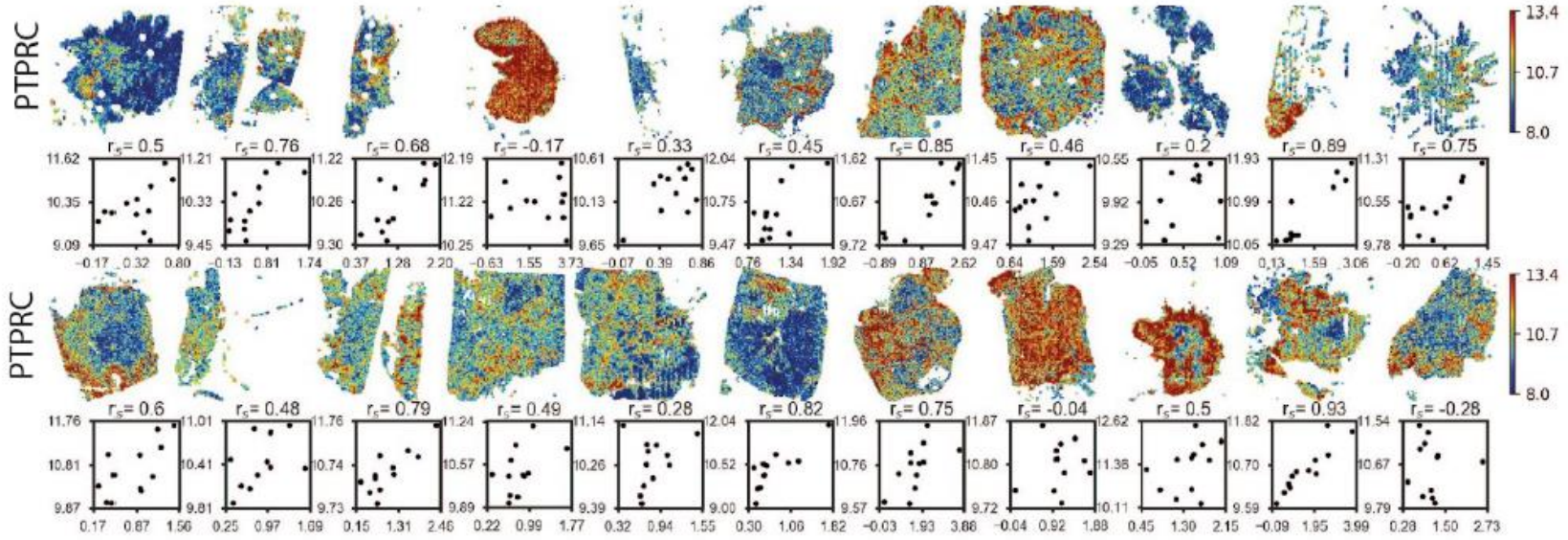


- Paired WSI – RNAseq
- First transcriptome-wide study with gene-specific deep CNN models
- Validation in fully external cohort (bulk RNAseq)
- Further validation by spatial transcriptomics
- >300k GPU hours on supercomputer
- 991 WSIs for training and internal validation
- 350 WSI in external test set

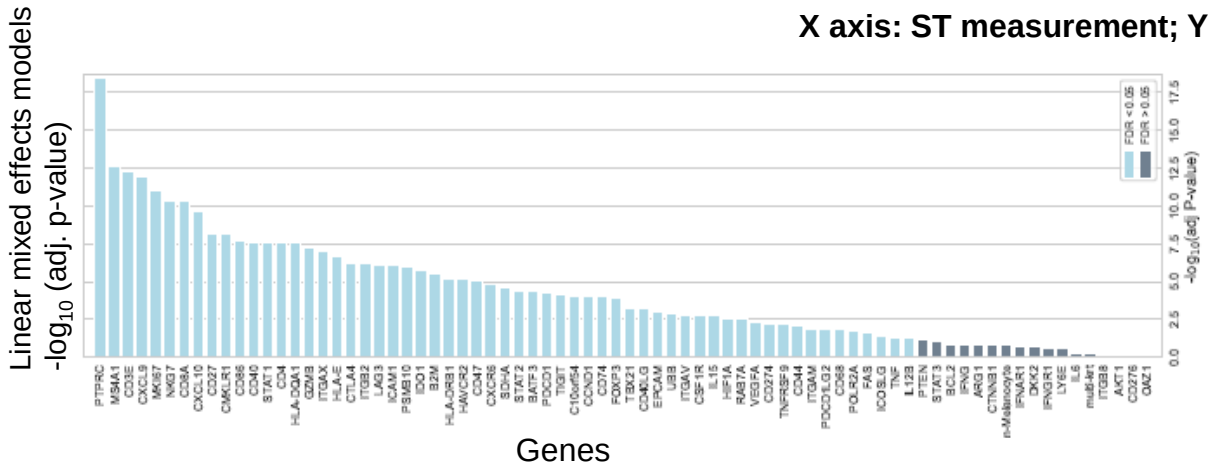
- **9,334/17,695 (52.75%) genes successfully predicted by CNNs** (FDR adj p-value <0.05, Spearman rank correlation between RNAseq estimates or mRNA expression and CNN predictions).
- **1,011 genes brought forward for validation**: 876 (87%, internal testset) and 908 (90%, external testset) successfully validated

EMO models enable prediction of spatial expression and quantification of intra-tumour heterogeneity

Predicted spatial expression as heatmaps together with validation results from spatial mRNA expression profiling (example mRNA: PTPRC*)



X axis: ST measurement; Y axis: EMO prediction



- Panel of 76 genes in the ST experiment
- 12 ROIs x 22 slides (264 ROIs in total)
- Linear mixed effects model (LR test)

- **59 (77.6%) of genes had a significant association between predictions and ST expression** (FDR adjusted p-value<0.05)

Validation of spatial expression predictions were performed using spatial transcriptomics (Nanostring GeoMx)

**Protein Tyrosine Phosphatase Receptor Type C*

Conclusions

- Biobanks together with health registries are a unique resource and enable leading AI-based precision diagnostic research
- Research in the space demands *very* large studies and dedicated infrastructure
- Clinical implementation as (mainly) decision support systems
  - Possibility to reduce errors and improve efficiencies
  - More exciting: precision diagnostics (i.e. going beyond what humans can extract from medical data)
- These solutions are potentially cost-effect: increased patient access and equality in healthcare

Rantalainen group @MEB, KI: AI & ML-based data-driven cancer precision medicine

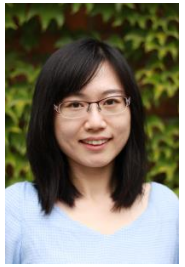
Kajsa Ledesma Eriksson

Bojing Liu

Philippe Weitz

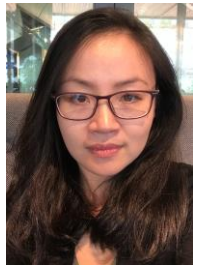
Sandy Kang Lövgren

Leslie Solorzano Vargas

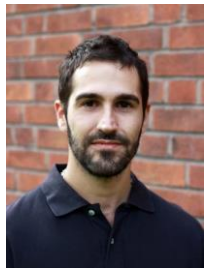


Yinxi Wang

Abhinav Sharma



Duong Tran



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CHIME the Cancer Histopathology IMage Epidemiology project

MedTechLabs

ABCAP

Vetenskapsrådet

VINNOVA

SWElife

CANCERFONDEN

ERAPerMed

Cancer Research KI

SeRC Swedish e-Science Research Centre

SWAIPP SWEDISH AI PRECISION PATHOLOGY

Key collaborators

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- Dr. Leena Latonen
- Prof Anne-Vibeke Laenkholm
- Prof. Anna Martling
- Prof Åke Borg
- Dr. Johan Vallon-Christersson
- Dr. Johan Staaf
- Dr. Anna Ehinger
- Dr. Johan Lindberg
- Stephanie Robertson
- Balasz Acs
- Anders Edsjö
- Helena Olofsson
- Ute Krüger
- … and more!