Welcome!

Hearing / Dialogue

Regarding AI-decision support tools for automatic detection and segmentation of colorectal cancer (primary and lymph node metastases) in digital pathology images and the integrated diagnostic processes

2020-01-21

KAROLINSKA UNIVERSITY HOSPITAL

We are part of Stockholm County Council

Purpose of Hearing

- To present Karolinska and the Project
- To create interest and understanding of the project by Industry

  -> to participate in RFI

- Ultimatelly leading to Development an Implementation of AI-tools at Karolinska
- Creating values for all parties involved

Agenda

- Welcome
- Presentation Karolinska Universitetslaboratoriet Patologi Cytologi, incl clinical partner Semmelweis - 10 min
- Automatic detection and segmentation of colorectal cancer - 30 min
- IT infrastructure Digital pathology - 10 min
- Process forward est timeline, RFI document - 15 min
- Q&A

Environment for Research and Innovation

Attila Szakos
Clinical Pathology and Cytology
Site Huddinge

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Environment and organisation 1

- **Stockholm's County Council**
  - Responsible for the specialized and hospital health care
- **Karolinska University Hospital**
  - Responsible for highly specialized health care and 90 % of health care education in Stockholm (Karolinska Institute)
- **Function Karolinska University Laboratories**
  - Comprises all medical laboratory professions
  - The only non-private medical laboratory in Stockholm

Environment and organisation 2

- **Function Area Clinical Pathology and Cytology**

  - 4 sites, 5 Function Units
  - 430 employees, 300000 cases/year, 500 million SEK/year
  - Nationally accredited laboratory and 5 diagnostic areas
  - **Coordinated quality –** the workload or personnel can be redistributed between Function Units
  - **Digitalization in progress**
  - **3rd largest scientific activity at Karolinska**
  - **Involved in three major AI projects**

Environment and organisation 3

- **Function Unit Huddinge**

  - 190 coworkers/45 doctors in 5 (+1) units
  - 180 000 cases/year, continuously growing
  - Subspecialized in whole depth
  - Advanced immunohistochemistry
  - 15 diagnostic subspecialties (responsible for 9 over sites)
  - **4 innovative projects in digitalization**

Medical teams	Histology lab *	IHC *	Kidney lab	MOL *	FACS	EM	Cytology *	HPV	Secretary	Morgue +
Hemato	own staff				own staff					
Gastro *	own staff									
Hepato *	own staff									
Pancreatic *	own staff									
Renal/allograft			own staff							
Perinatal	own staff									own staff
Respiratory										
Gynecologic	own staff									
Urogenital *	own staff									
(Dermato)	(own staff)									
ENT & others (CUP)										
Cytopathology *										
Autopsy										own staff

Opportunities for Innovation at Different Levels 1

- **Karolinska University Hospital**
  - Own agency for innovation and development
- **Karolinska University Laboratories**
  - Financing internal developmental projects
  - Coordinative, operative and administrative support

Opportunities for Innovation at Different Levels 2

- **Clinical Pathology and Cytology including Function Unit Huddinge**
  - Own laboratory and administrative section for research
  - **Close relation and communication with the clinicians in all sub-specialties**
  - **Residents (partly centrally financed, obligatory developmental project** according to regulations**)**
  - **Representation in** most **national boards** within healthcare
  - **International collaborative partners** (Semmelweis University, Queen Mary Hospital, etc)

Semmelweis University Budapest, Hungary

- 1st and 2nd Department of Pathology
- Full/partial digitalization
- 1/3 of cases, personnel and infrastructural resources in a previous AI project
- Collaboration 20 years research
  10 years clinical

AI-decision support tools for automatic detection and segmentation of colorectal cancer (primary and lymph node metastases) in digital pathology images and the integrated diagnostic processes

Carlos Fernandez Moro

Pathologist, Karolinska University Laboratory

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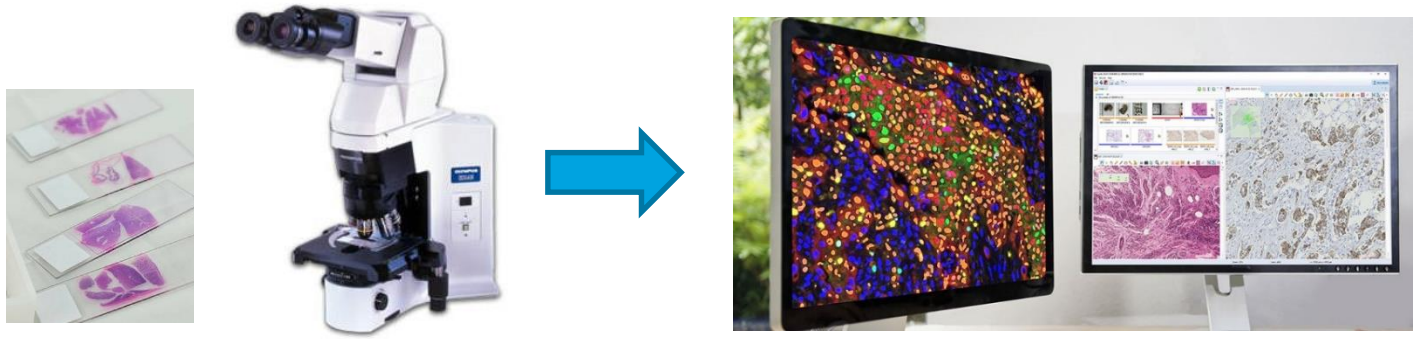
Clinical pathology

- Became decisive for oncological care.
- Sub-specialization (diagnostic areas), advanced diagnostic methods.
- Only partly automated - mostly on the laboratory side.
- The results must be reproducible and evidence based - quality assurance and standardization.
- Cancer registers must be supplied with accurate data – research and public health planning.

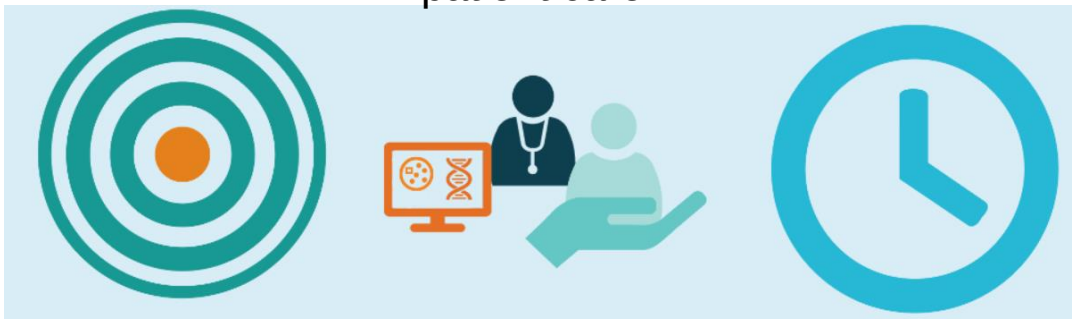
Clinical pathology goes digital & computational



Better diagnosis

Improved value-based patient care

Optimize laboratory processes



https://www.usa.philips.com/healthcare/resources/landing/what-is-computational-pathology

AI digital pathology diagnostic support tools

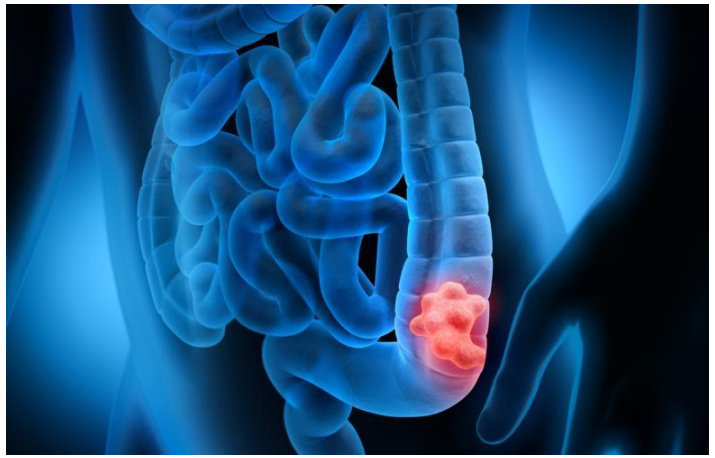
Cancer projections are growing → Increasing number of probes.

Surgical techniques and oncological treatments are improving (personalized medicine) → Increasing complexity and reporting requirements.

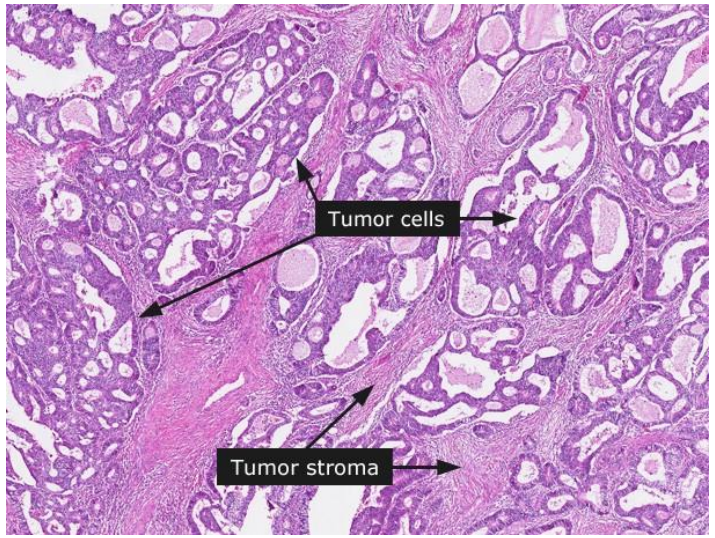
Shortage of pathologists worldwide → Digital diagnostic tools our best chance!

Colorectal cancer

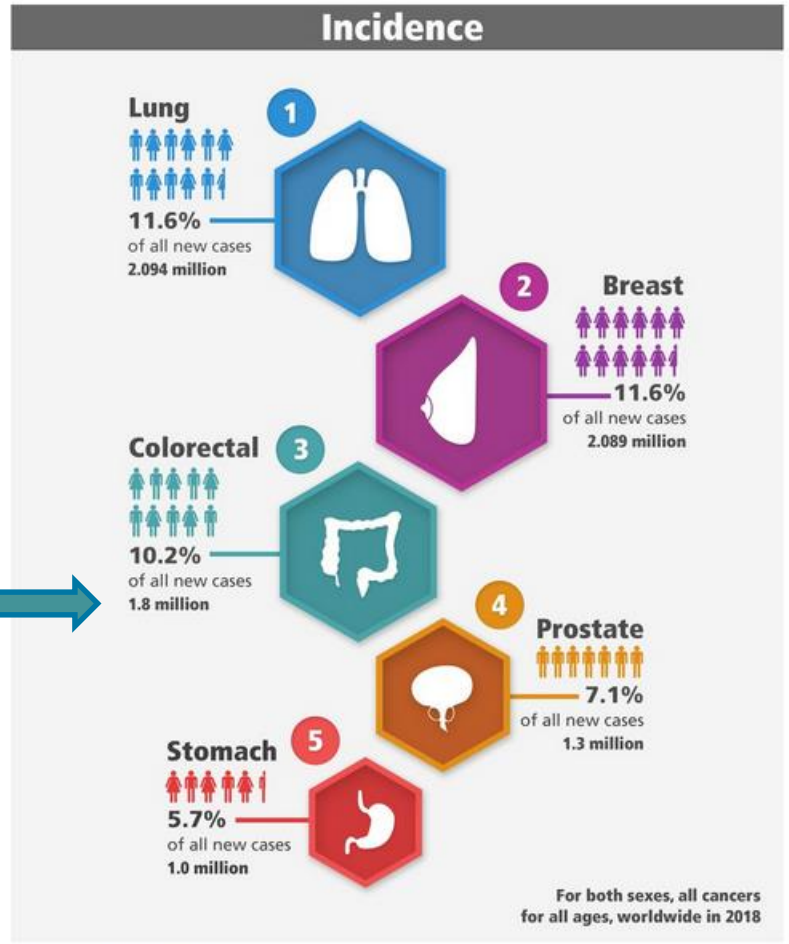
- Starts in the colon or the rectum.



- 96% adenocarcinoma (histological type)



New cancer cases worldwide 2018



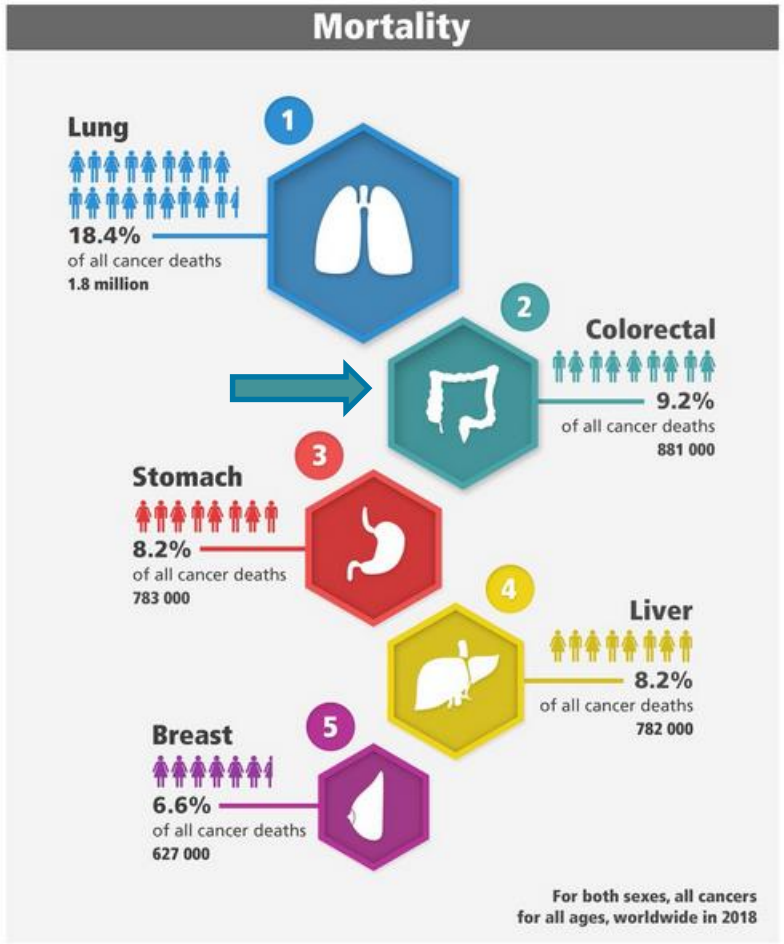
Data source: GLOBOCAN 2018
Available at Global Cancer Observatory (http://gco.iarc.fr/)

Colorectal cancer rates

Rank	Country	Age-standardised rate per 100,000
1	Hungary	51.2
2	South Korea	44.5
3	Slovakia	43.8
4	Norway	42.9
5	Slovenia	41.1
6	Denmark	41.0

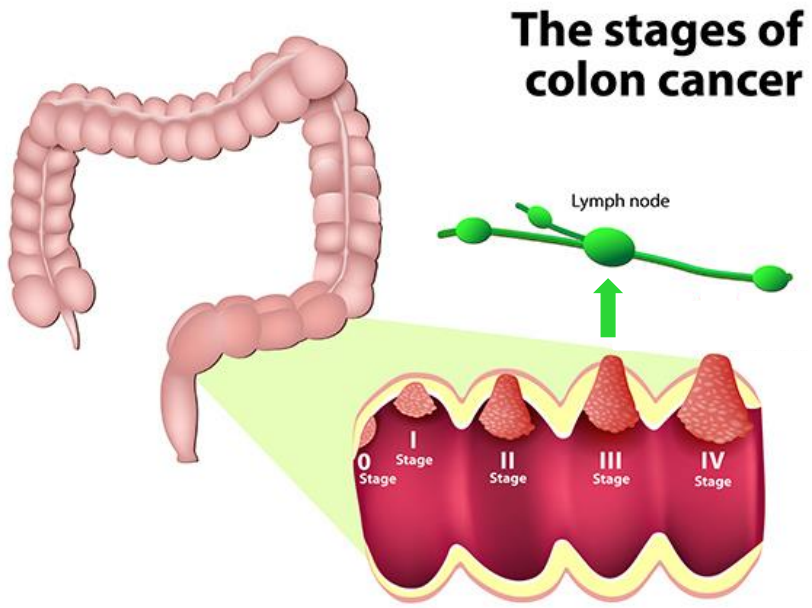
Sweden: 6721 newly diagnosed patients in 2016

Cancer deaths worldwide 2018



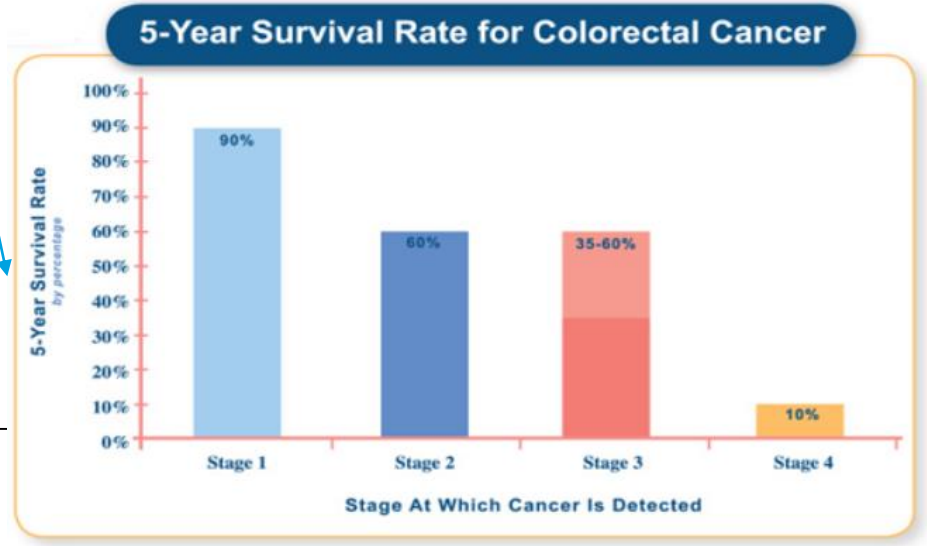
5-year survival (all stages included): 65 %

Tumor stage determines treatment and prognostic stratification



Treatment for colorectal cancer by stage

STAGE	SURGERY	CHEMOTHERAPY / BIOLOGICS	RADIATION	INTERVENTIONAL RADIOLOGY
Stage 0	Yes	No	No	No
Stage 1	Yes	No	No	No
Stage 2	Yes	Yes, for rectal and high risk colon cancers. FOLFOX (5-FU/Leucovorin/Oxaliplatin) or CapeOx (Capecitabine/ Oxaliplatin)	Yes, for rectal cancer. Given in tandem with 5-FU or Xeloda	No
Stage 3	Yes	FOLFOX or CapeOx	Yes, for rectal cancer. Given in tandem with 5-FU or Xeloda	No
Stage 4	Yes, if the tumor is obstructive or blocking the bowel. No, if the tumor is not blocking the bowel	FOLFOX, FOLFIRI, FOLFIRINOX, Irinotecan, Avastin, Erbitux, Vectibix, Zaltrap, Stivarga, Lonsurf, Cyramza	Yes, for rectal cancer and in certain other cases	Possibly. Options could be Radio Frequency Ablation (RFA), Stereotactic Body Radiation Therapy (SBRT), or chemoembolization

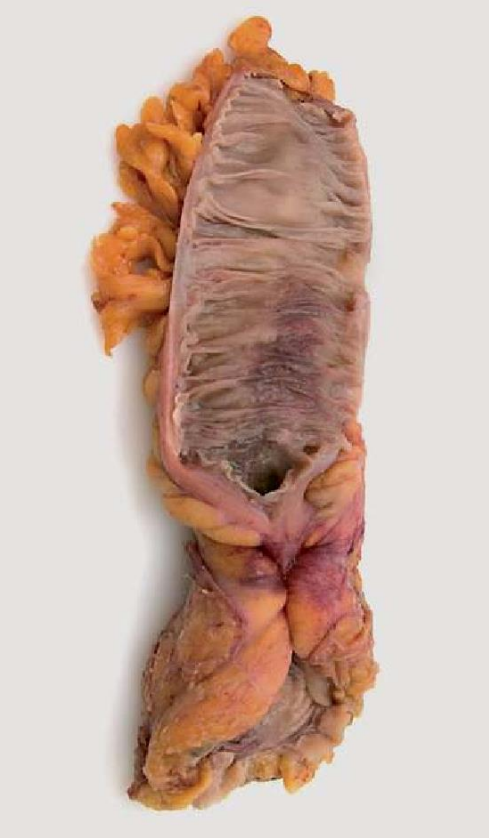


Pathological diagnosis in colorectal cancer

- Precise **tumor staging**.
- Further **management of the patient**:
  - **Lymph node metastasis** is a crucial factor to decide the use of **adjuvant chemotherapy** after surgical resection.
- **Multidiscipinary team conference** - feedback information & quality assurance of:
  - Preoperative radiological diagnosis.
  - Quality of the surgical procedure.
  - Result of preoperative oncological treatment.

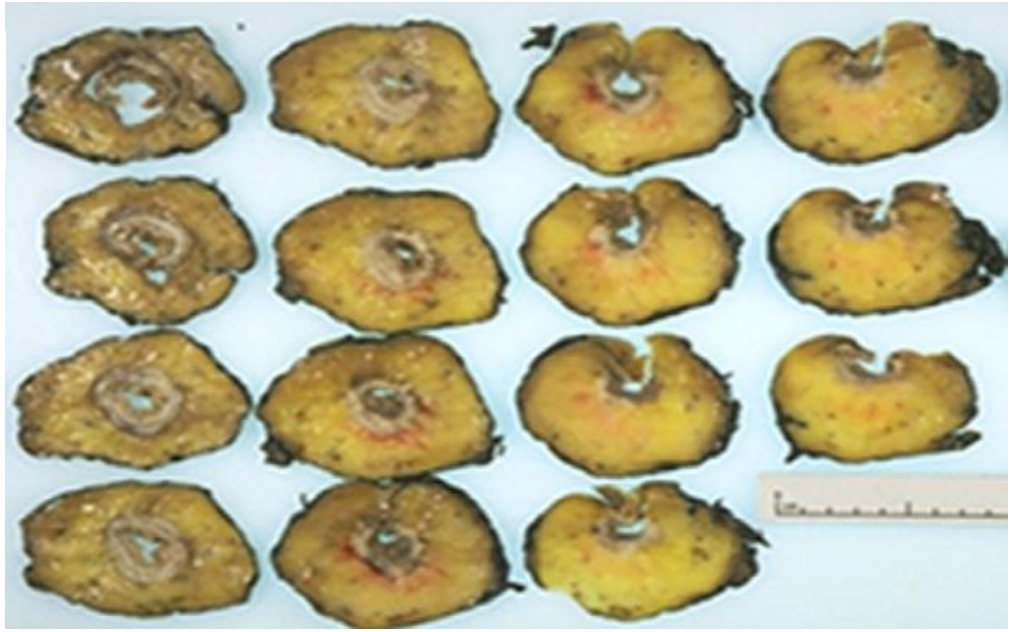
Pathological diagnosis – Macroscopic assessment and grossing

Colorectal surgical specimen

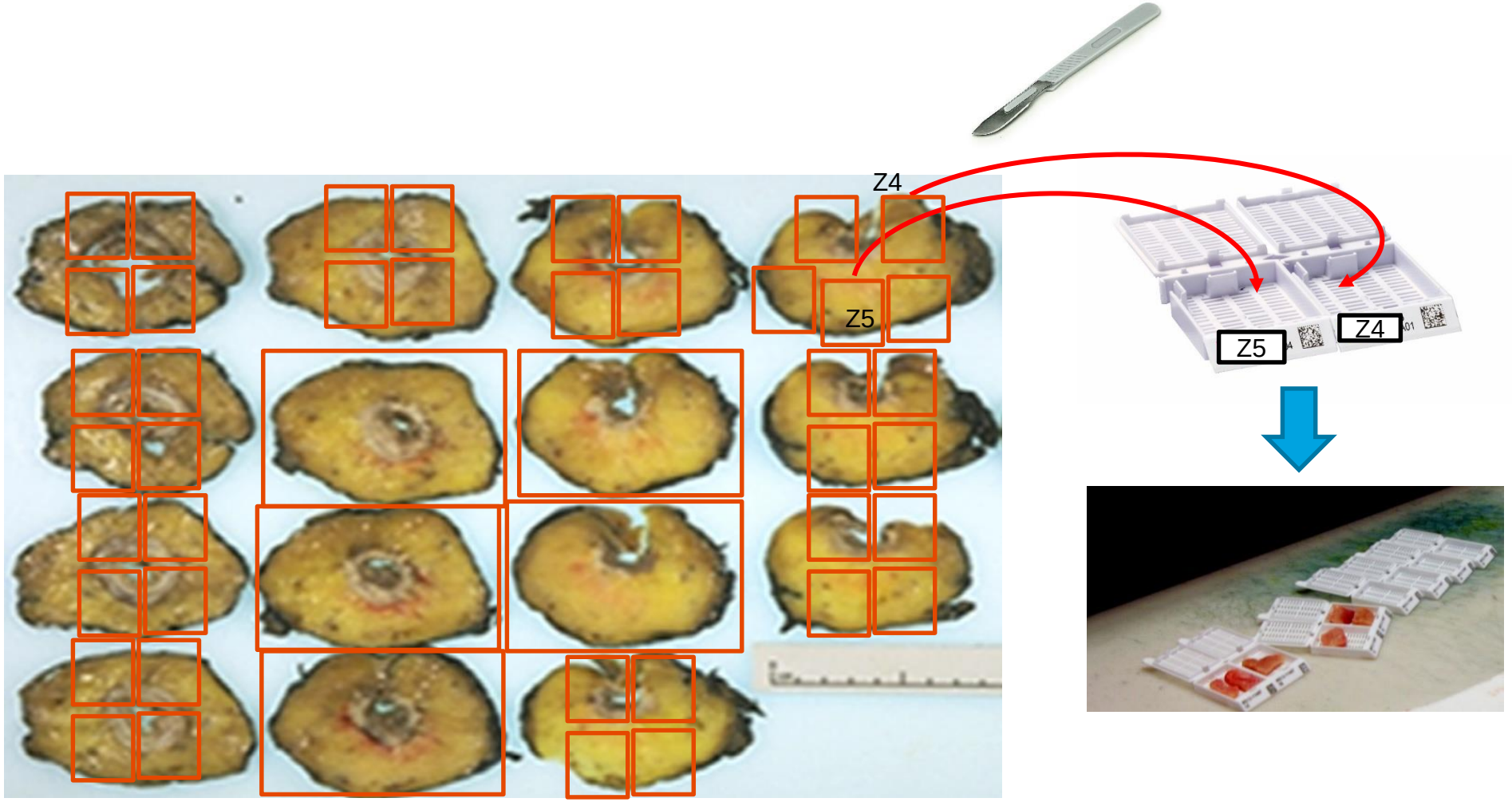


The specimen is cut serially into 3-5 mm thick tissue slices, placed in order in a tray and photo documented.

Colorectal tissue slices



Pathological diagnosis – Tissue sampling for histology



Pathological diagnosis – Examination of histological slides (H&E, 40 – 100+ per case)

Clinical requirements

- Precise **tumor staging**
- Further **management of the patient**
- **Multidisciplinary team conference**

Pathological diagnosis in colorectal cancer – Minimal dataset

Tumörstadium – operationsfynd och PAD

Adenocarcinom	☐ Nej ☐ Ja
Ange om tumören är ett adenocarcinom eller ej. Enbart adenocarcinom skall rapporteras till registret.	
Bedömningen gjord på storsnitt	☐ Nej ☐ Ja
Standardiserad svarsmall använd	☐ Nej ☐ Ja
Gradering av den mesorektala fascian – OBS ifylls endast för TME-rektalpreparat	☐ A=Komplett/mesorektal ☐ B=Nästan komplett/intramesorektal ☐ C=Inkomplett/i muskelplanet ☐ D=Ej bedömbar
Bedömningen utförd på	☐ Färskt preparat ☐ Fixerat preparat

T-stadium	**N-stadium**
☐ TX	☐ NX
☐ T0	☐ N0 Om inga positiva lymfkörtlar finns och TD=Ja blir N-stadium N1
☐ T1 → ☐ T1sm1 ☐ T1sm2 ☐ T1sm3	☐ N1 ☐ N2
☐ T2	
☐ T3 → ☐ T3A ☐ T3B ☐ T3C ☐ T3D	Avstånd till fri serosayta ....., ... mm
☐ T4 → Serosagenomväxt	☐ Nej ☐ Ja
Överväxt till annat organ	☐ Nej ☐ Ja
Antal undersökta körtlar:.....	Antal positiva körtlar.....

Mucinös cancer	☐ Nej ☐ Ja
TD (diskreta fria tumörhärdar utan lymfkörtel- eller kärlrest)	☐ Nej ☐ Ja, antal .....
Perineural växt påvisad	☐ Nej ☐ Ja
Kärlinväxt påvisad	☐ Nej ☐ Ja → Föreligger extramural veninväxt (EMVI)? ☐ Nej ☐ Ja
Differentieringsgrad	☐ Högt/medelhögt = Low grade ☐ Lågt/odiff = High grade
Minsta cirkumferentiella resektionsmarginal ..... ,..... mm (anges i mm eller del av mm)	
Minsta longitudinella resektionsmarginal....., ... mm (avstånd i mm el del av mm till närmaste resektionsrand i tarmväggen)	
Mikroskopiskt tumörfri resektionsrand	☐ Nej ☐ Ja ☐ Ej bedömbart
Tumörregression enligt AJCC (Anges endast för neoadjuvant behandlade tumörer)	☐ Inga viabla cancerceller ☐ Enstaka små grupper av cancerceller ☐ Kvarvarande cancer överskuggas av fibros ☐ Minimal eller ingen påverkan på tumören

Immunhistokemiska färgningar för MMR-proteiner (endast då kliniker begärt detta)

☐ Ej utfört ☐ Utfört:

Utfall av immunhistokemiska färgningar för MMR-proteiner

MLH1	☐ (+) Bevarad	☐ (–) Förlust	☐ Svag/heterogen	☐ Ej bedömbar
PMS2	☐ (+) Bevarad	☐ (–) Förlust	☐ Svag/heterogen	☐ Ej bedömbar
MSH2	☐ (+) Bevarad	☐ (–) Förlust	☐ Svag/heterogen	☐ Ej bedömbar
MSH6	☐ (+) Bevarad	☐ (–) Förlust	☐ Svag/heterogen	☐ Ej bedömbar

Sammanfattande bedömning av MMR-funktion:

☐ Normal ☐ Defekt ☐ Oklar/obestämbar


HOUSTON. . .

Current challenges in the pathological diagnosis of colorectal cancer

- Time and resource **intensive work-loads**:
  - The pathologist has to examine a high number (40 to 100+) of slides for each colorectal cancer probe including the accompanying lymph nodes, which takes several hours.

- A **high diagnostic accuracy** is mandatory to treat patients correctly.
  - Overlooking regions of cancer cells may lead to under-staging and under-treatment of patients.

Current challenges in the pathological diagnosis of colorectal cancer

- **Short turnaround times**:
  - The multidisciplinary team conference needs to take decision on further treatment soon after the operation.

- **Shortage of pathologists** subspecialized in gastrointestinal pathology:
  - Special, dedicated training is required.
  - Medical students and trainees in pathology may opt for other specialties and diagnostic areas with better work-life balance and time for research.

How can AI-based automatic tumor detection enhance pathologists?

- **Optimizing the work-loads**:
  - The pathologist dedicates a major amount of time and energy screening and eye-balling the numerous slides searching for cancer cells.
  - This repetitive, time- and resource-consuming task can be significantly streamlined by the AI.

- **Securing the diagnostic accuracy**:
  - By graphically signaling to regions of high cancer cell probability.

How can AI-based automatic tumor detection enhance pathologists?

- **Shortening turnaround times**:
  - The use of automatic tumor detection can reduce significantly the pathologist time needed for case review (screening, eye-balling).

- **More subspecialized gastrointestinal pathologists**:
  - By AI supported work-loads and improved working conditions.

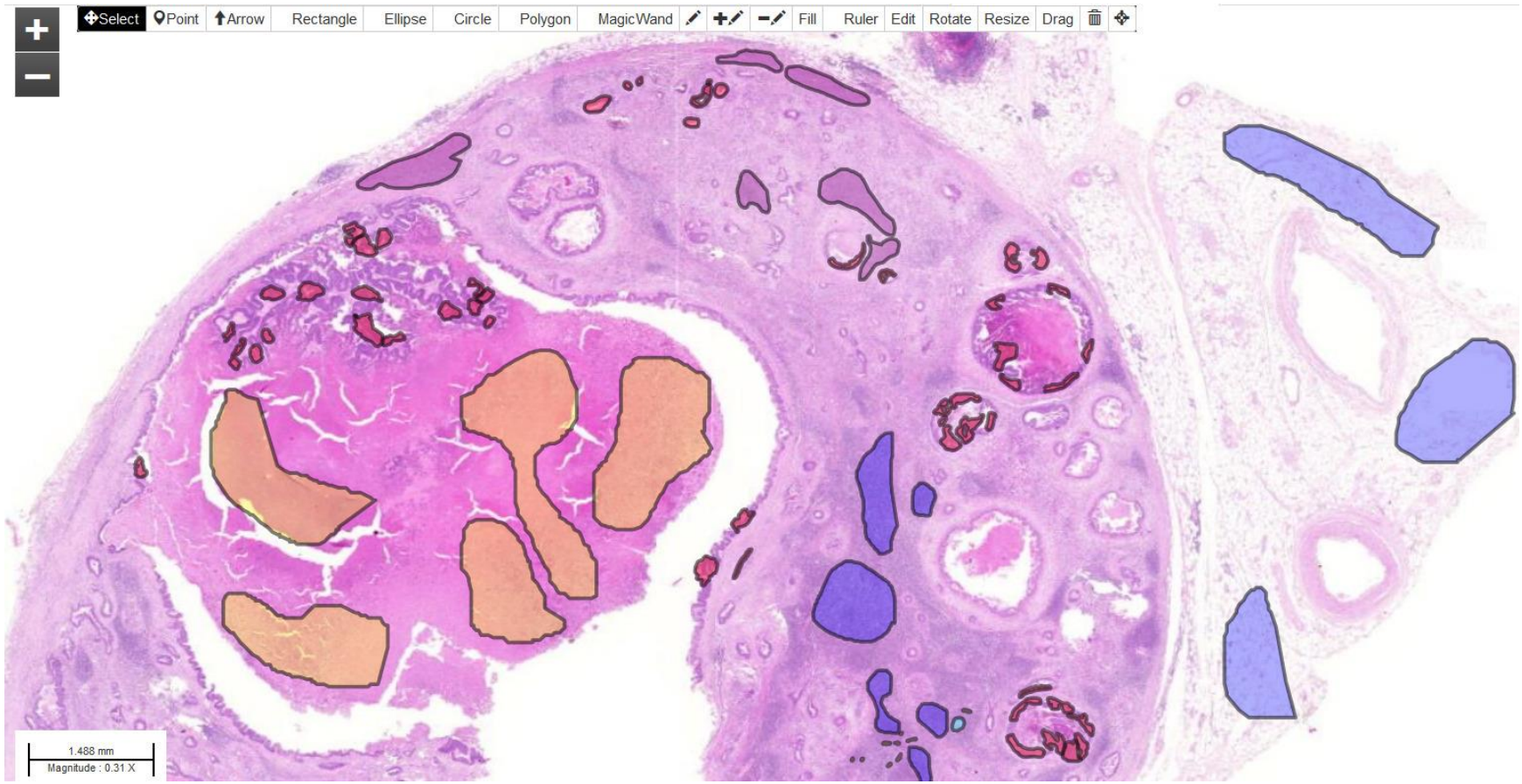
R&D Feasibility Study - AI for automatic tumor detection - colorectal cancer (2015-2018)

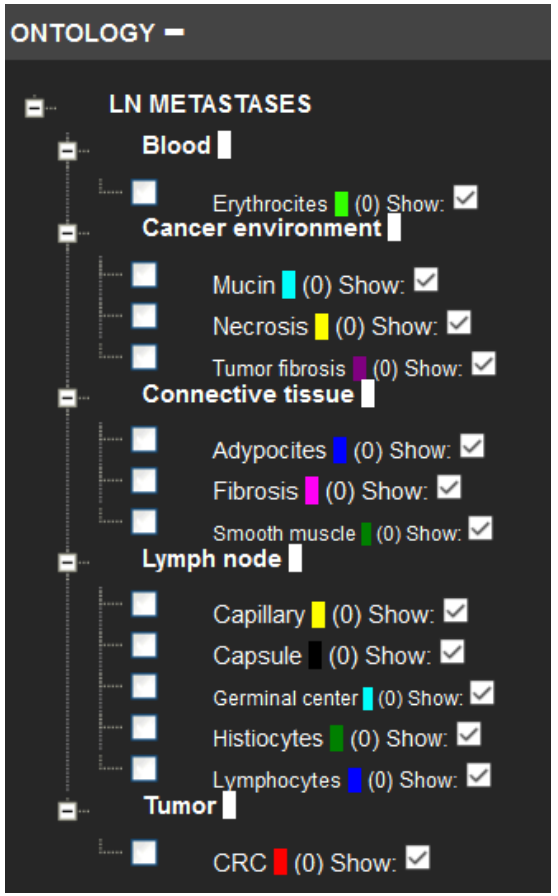
- Creation of a large multi-class **repository** of pathology annotations (ground truth).
- Training of AI models
  - Sensitivity much more important than specificity at this stage
- Evaluation of AI models for tumor detection.

- Hospital partner: Semmelweis University Hospital, Budapest

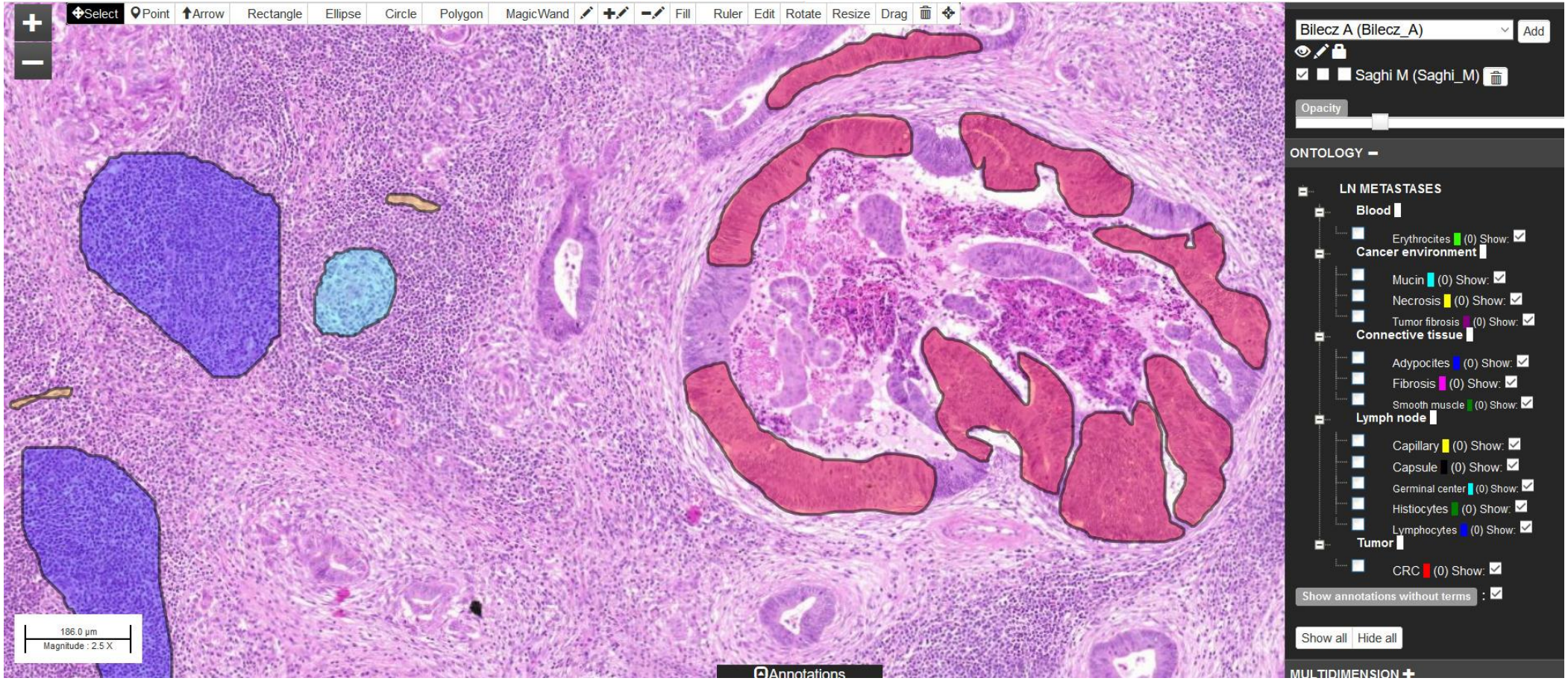
- R&D Collaboration with Saab (industry) and Queen Mary University of London (academy).

Available: Multi-class annotation of whole slide images – Lymph node metastases

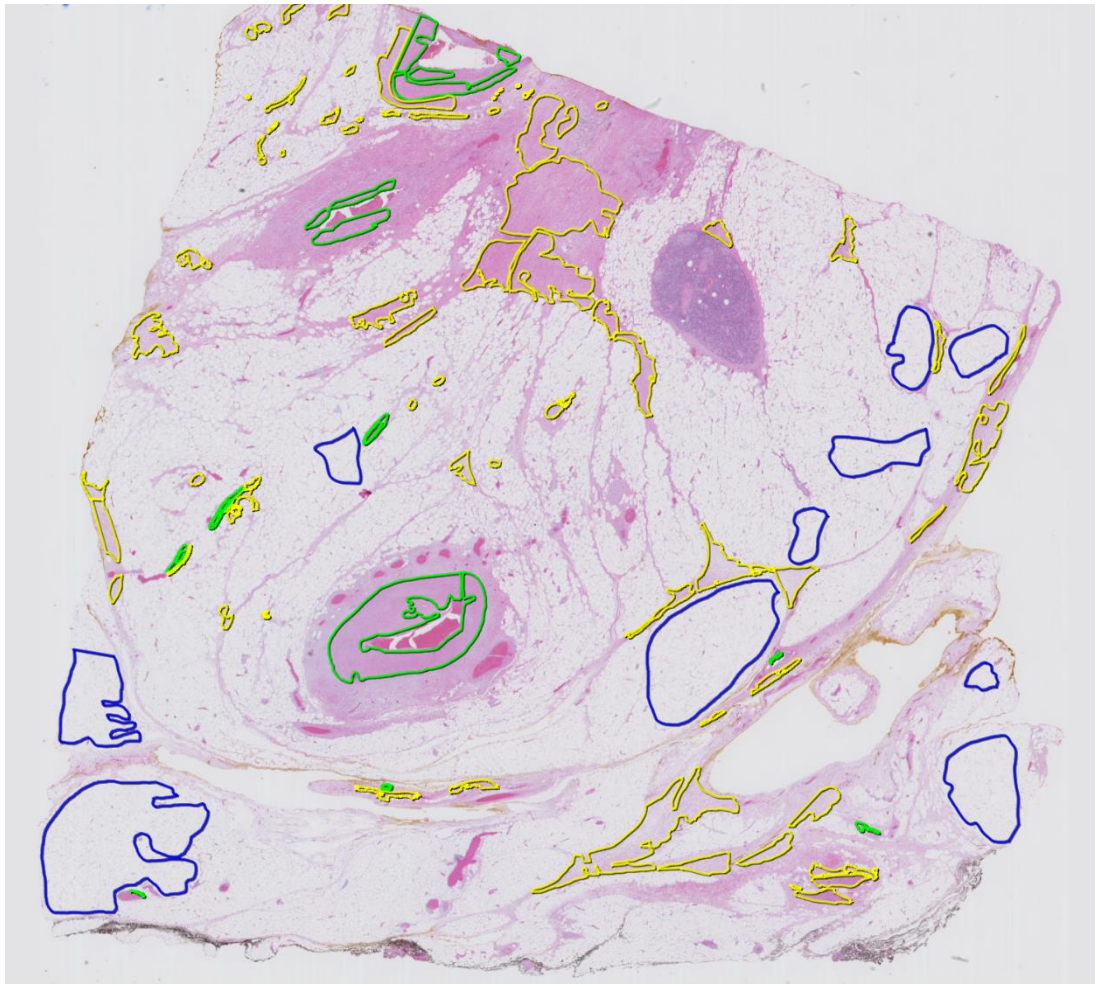


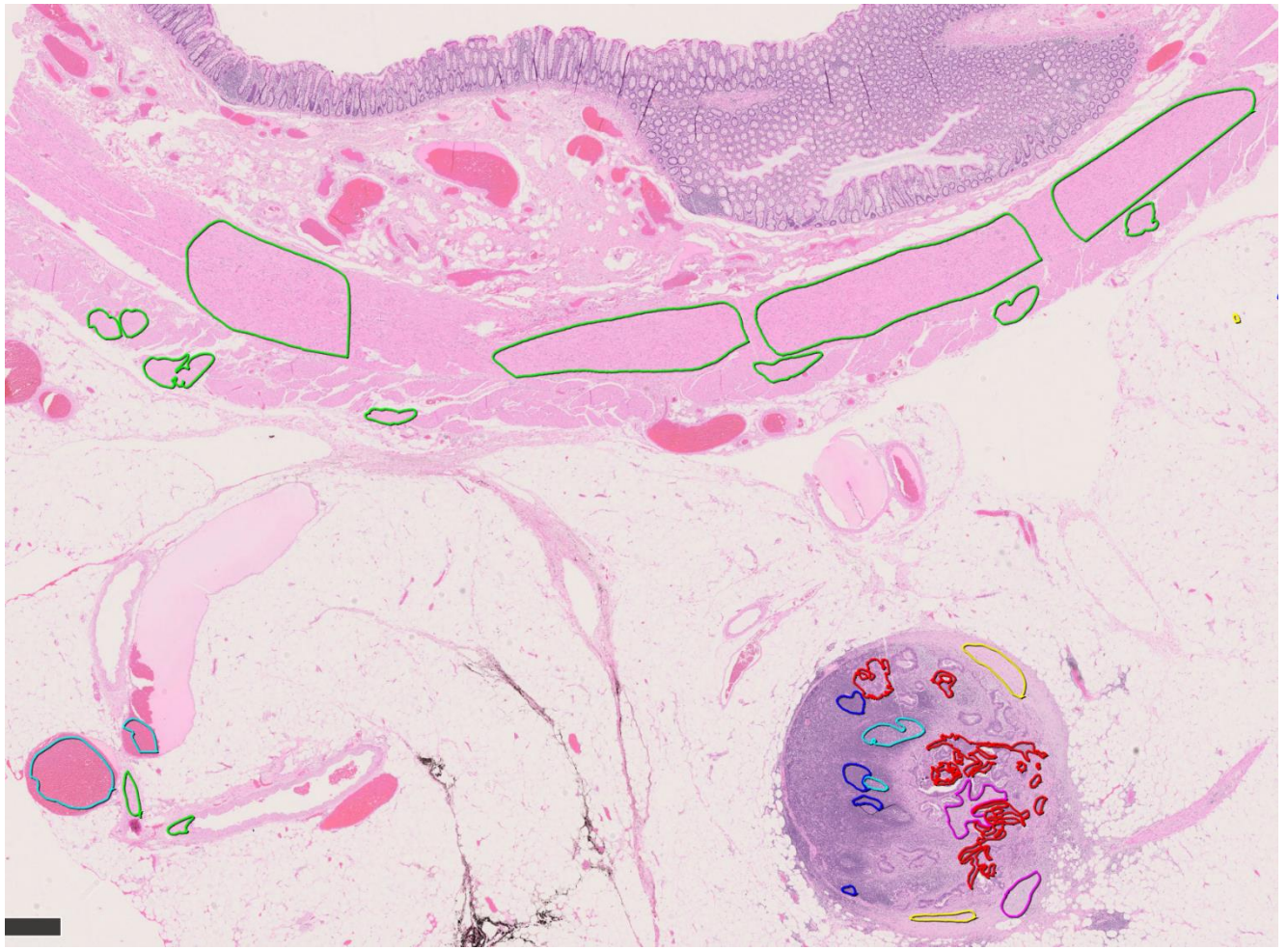


Available: Multi-class annotation of whole slide images – Lymph node metastases



Available: Multi-class annotation of whole slide images – Soft tissue components





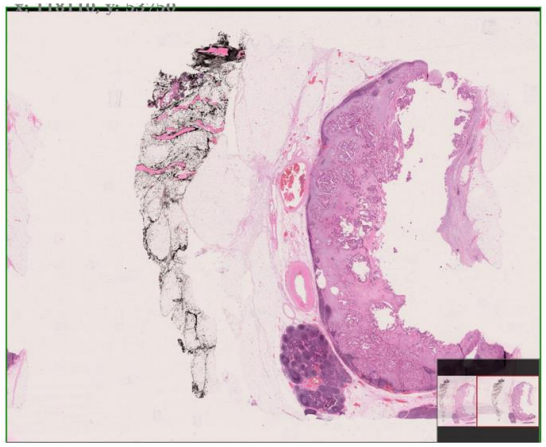
Available: Large repository of high-quality pathology annotations of CRC lymph node metastases

- The dataset: 646 WSIs, +70 000 annotations
- Number of pathology annotations by class:

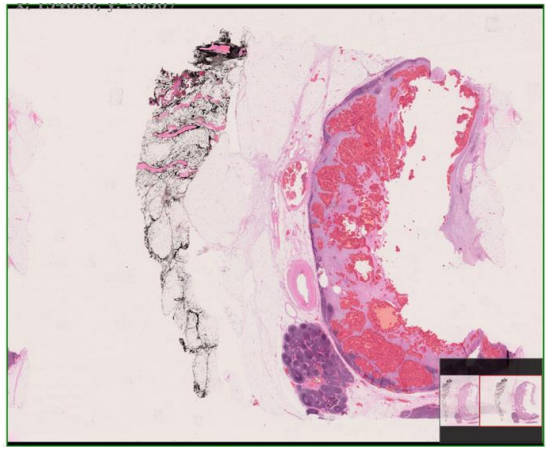
Colorectal cancer cells	40453
Necrosis	4774
Mucin	1492
Tumor fibrosis	2280
Lymphocytes	4169
Germinal centre	2930
Capsule	1687
Histiocytes	768
Capillary	1937
Blood	1584
Adipocytes	2544
Smooth muscle	1206
Fibrosis	917
Nerve	1342

R&D Feasibility Study - AI for automatic tumor detection - colorectal cancer

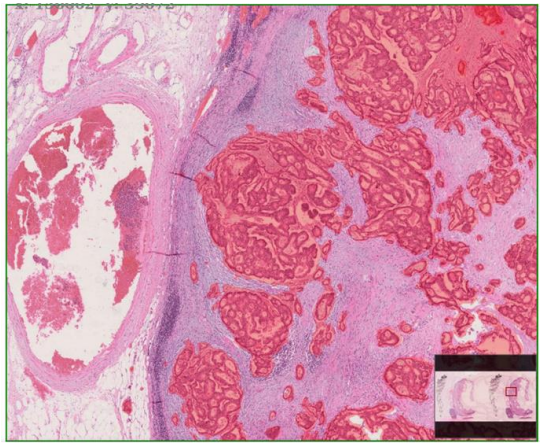
Original (hematoxylin&eosin)



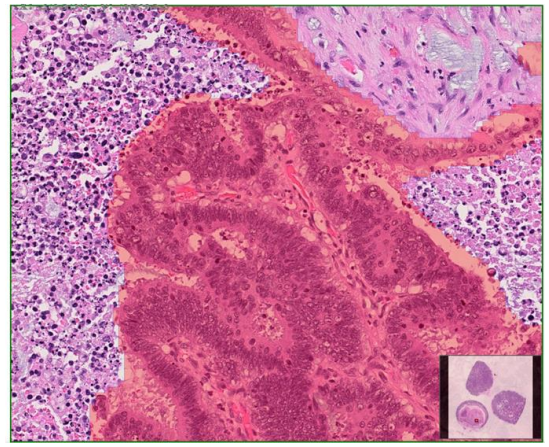
Model prediction



Original (hematoxylin&eosin)



Model prediction



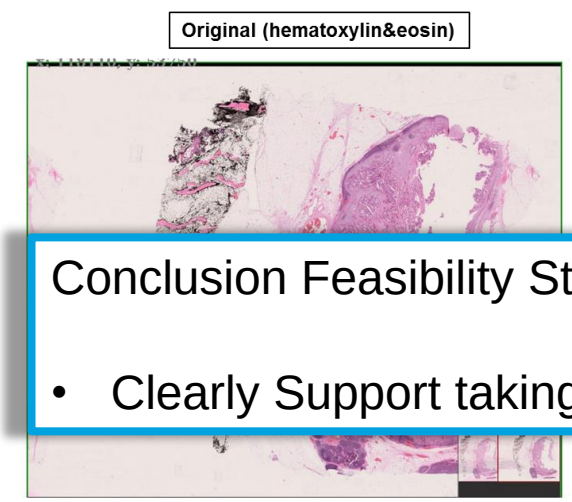
Grouped positive/negative classes confusion matrix:

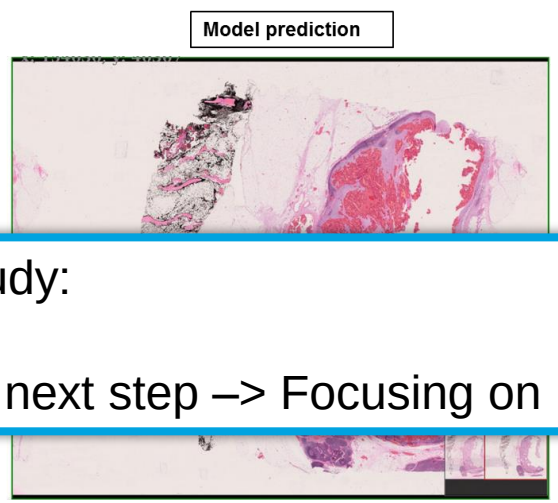
	T	N	M	L	TF	GC	C	H	B	CP	BG	AD	SM	F	NV	GG	D	FC	SRoutsi
T																			
N																			
M			99.4																0.6
L																			
TF-FT																			
GC																			
C																			
H																			
B																			
CP																			
BG																			
AD																			
SM																			
F																			
NV																			
D																			
FC																			
SR			0.2																99.8

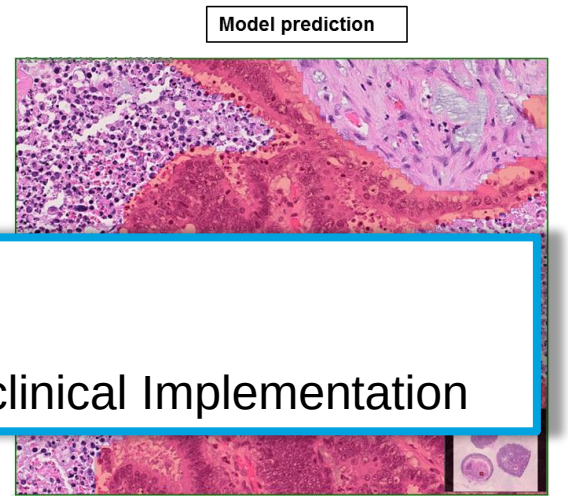
Sensitivity (found share of positives in annotated positives):
99.4 %
Specificity (found share of negatives in annotated negatives):
99.8 %
Precision (share of true positives in found positives):
97.0 %

R&D collaboration with SAAB and Queen Mary University of London

R&D Feasibility Study - AI for automatic tumor detection - colorectal cancer







Conclusion Feasibility Study:

- Clearly Support taking next step –> Focusing on Product co-development and clinical Implementation

Grouped positive/negative classes confusion matrix:

	T	N	M	L	TF	GC	C	H	B	CP	BG	AD	SM	F	NV	GG	D	FC	SRoutsi
T																			
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NV																			
D																			
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Sensitivity (found share of positives in annotated positives):
99.4 %
Specificity (found share of negatives in annotated negatives):
99.8 %
Precision (share of true positives in found positives):
97.0 %

R&D collaboration with SAAB and Queen Mary University of London

Ambition going forward:

- Identify and Select Optimal Industry Partner (/consortium) – through procurement
- **Co-development** of an advanced **AI-based** diagnostic support tool for **automatic tumor detection** in hematoxylin-eosin stained slides of colorectal cancer.
- Clinical validation of AI-tool
- CE-marking for clinical use of AI-tool - by Industry partner
- Implement and integrate AI-tool within the digital clinical diagnostic work-flow
- Improve/upgrade AI-tool through continuous feedback-loop from pathologists
  - Misclassified regions, new tissue morphologies, etc.
- Commercialize AI-tool to benefit pathology departments worldwide - by industry partner

Why Pathology @ Karolinska?

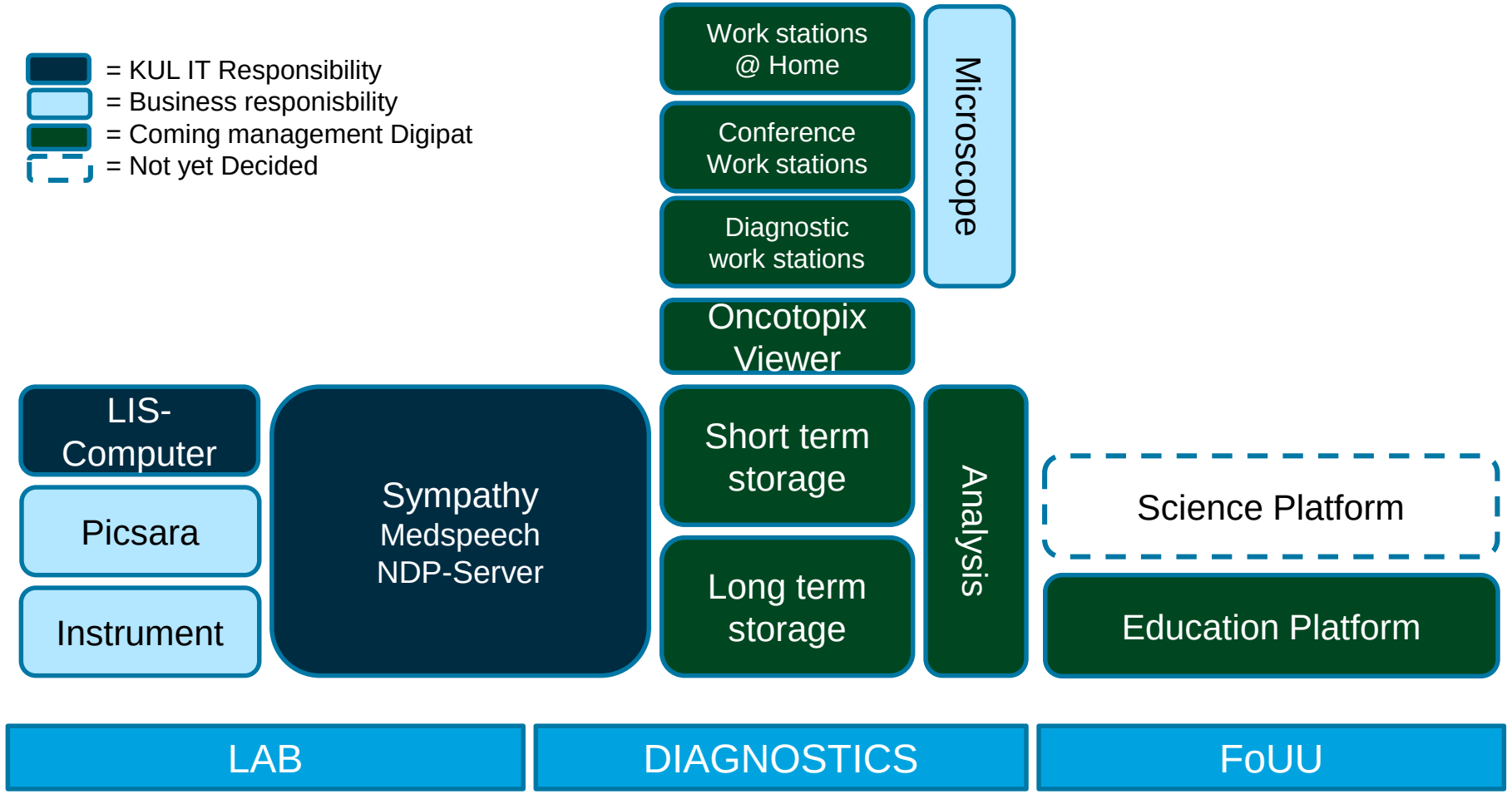
- Outstanding expertise in diagnostic pathology.

- Extensive, world-class repository of annotated whole slide images (ground truth) from two major European university hospitals (Karolinska Stockholm and Semmelweis Budapest):
  - Precise, high-quality annotations of both cancer cells and surrounding benign tissues performed and curated by pathologists.
  - Comprehensive, flexible, organ- and tumor-type agnostic, multiclass annotation schema, designed to be able to generalize, with additional training data, to further organs and tumor types, like gastric, liver, pancreatic, breast and prostatic cancer, etc.

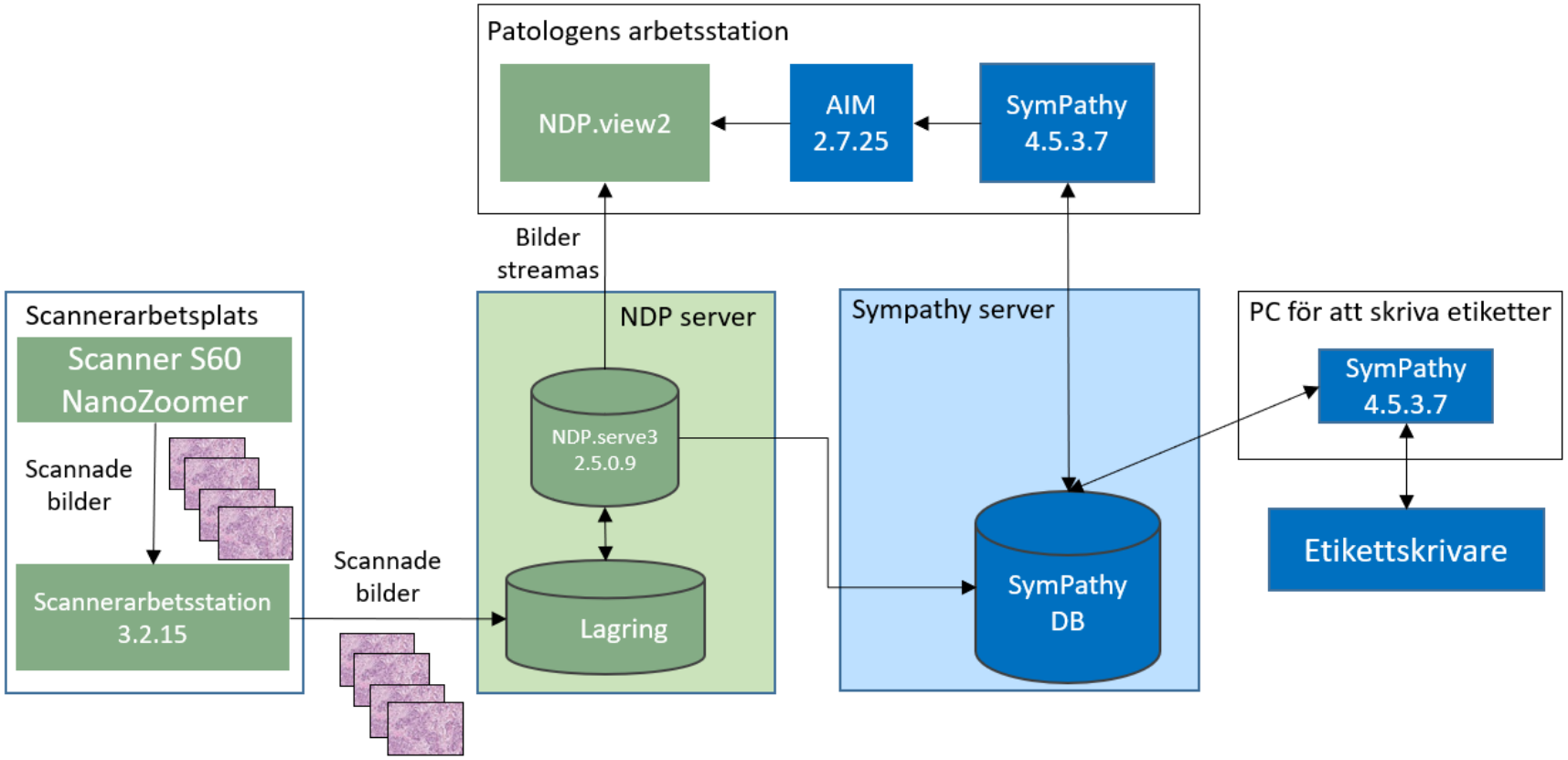
Why Pathology @ Karolinska?

- Engagement of our teams of expert clinical pathologists in the processes for AI development, test, validation and continuous improvement (feedback-loop).
- Extensive experience in digital pathology AI research, knowledge transfer and interaction with AI/CS/IT teams.
- Commitment to excellence in healthcare provision, education, innovation, research and long-term collaboration with our hospital, academic and industry partners.
- Extensive archive of pathology slides and new prospective probes comprising all organ systems and tumor types, both hematoxylin&eosin and immunohistochemistry, and its potential connection with the associated, high-quality clinical data.

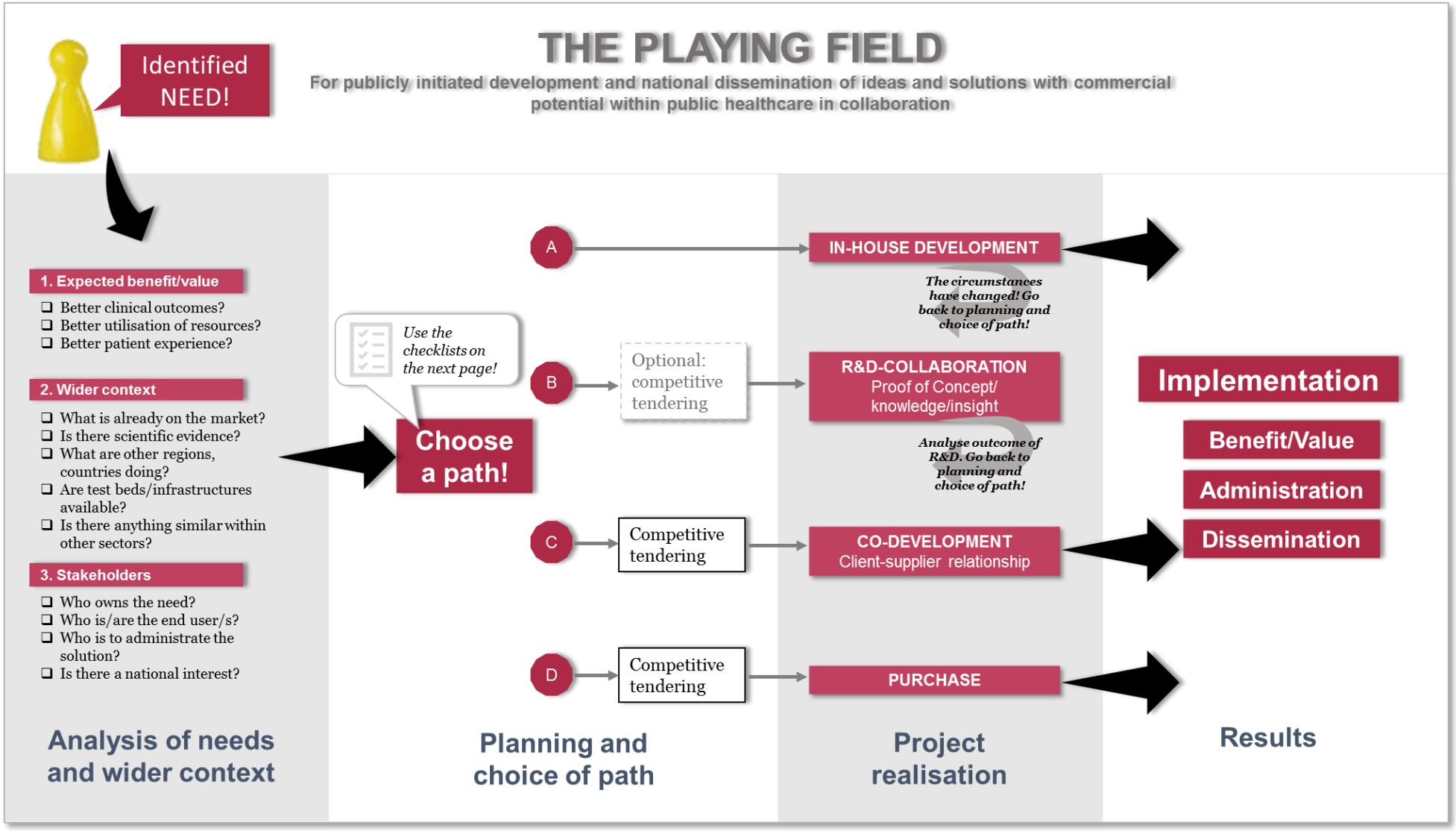
The system management objects



Technical environment



Context and Process Forward


THE PLAYING FIELD
For publicly initiated development and national dissemination of ideas and solutions with commercial potential within public healthcare in collaboration
Identified NEED!
1. Expected benefit/value
❑ Better clinical outcomes?
❑ Better utilisation of resources?
❑ Better patient experience?
2. Wider context
❑ What is already on the market?
❑ Is there scientific evidence?
❑ What are other regions, countries doing?
❑ Are test beds/infrastructures available?
❑ Is there anything similar within other sectors?
3. Stakeholders
❑ Who owns the need?
❑ Who is/are the end user/s?
❑ Who is to administrate the solution?
❑ Is there a national interest?
Use the checklists on the next page!
Choose a path!
A
IN-HOUSE DEVELOPMENT
The circumstances have changed! Go back to planning and choice of path!
B
Optional: competitive tendering
R&D-COLLABORATION
Proof of Concept/ knowledge/insight
Analyse outcome of R&D. Go back to planning and choice of path!
C
Competitive tendering
CO-DEVELOPMENT
Client-supplier relationship
D
Competitive tendering
PURCHASE
Implementation
Benefit/Value
Administration
Dissemination
Analysis of needs and wider context
Planning and choice of path
Project realisation
Results

General concept and direction of co-development process and business agreement:

Healthcare
Clinical need
Clinical resources
Data
Clinical infrastructure
Clinical validation

Industry
AI-expertise
Product dev
CE-marking

Each party carries its own costs

Co-development and Clinical Implementation Project

Royalty free license to product
Patient outcome improvement
Organization efficiency

Academia
Scientific expertise
Research Qs
Scientific validation

Product (IPR)
Ref customer
Business op

Scientific progress
Publications

Process forward – Estimated timeline

1. Hearing/dialogue
2. Dead-line RFI - 31st of January
3. 1-to-1 dialogues - during february
4. K-analysis and strategy – STOP/GO
5. External referral + dialogue - *during March*
6. K-analysis – STOP/GO
7. Publication of RFP – *1st of May*
8. Deadline RFP – *1st of June*
9. K-analysis Tender - STOP/GO
10. Anouncement – *1st of July*
11. Feedback/dialogue
12. Agreement signing - *August*

Official procurement documents and contracts will be in SWEDISH

RFI Questions

Q1: Short description of company

Q2: Current status of developments of digital pathology AI decision support tools (product)?

- Q2.1 Currently available CE-marked product(s)?
- Q2.2 Scope/functionalities of product(s) under development and estimated time to market?

Q3: Experiences from co-development of AI-products and working with diagnostic processes and related clinical IT-environment?

Q4: What are your company's thoughts on below described 'General concept and direction of co-development process and business agreement'?

Q5: What are your company's thoughts on, and potential experiences from, cross- European collaboration, also with regards to Q4?

Q6: Would your company want Karolinska to publish your company name and engagement in this RFI on our homepage, to potentially facilitate potential B2B collaborations?

Q and As from the Hearing:

Q: What is the estimated timeline for the project?

A: Difficult to say at this stage, will likely depend on what stage and maturity of potential on-going development at Industry partner, RFI will hopefully give better understanding of this.

Q: Will it be possible to use cloud for handling Images/data?

A: Anonymized images/data will be possible to transfer and process in the cloud.

Q: What is the Scope of the project, is it algorithm development only?, including a viewer? Including hardware?

A: The high-level scope is a software product including the AI-algorithm and to be specified functionalities that will be integrated in relevant Karolinska target IT-infrastructure and work-flows, to be further discussed during RFI.

Q: What is the format of the data of existing image repository?

A: Part of the dataset is composed of Hamamatsu WSIs and annotations (Hamamatsu viewer), the other is made of 3DHistech WSIs and their annotations are stored in Cytomine.

Q: Would it be possible to obtain examples of slides?

A: Maybe later in the process.

Q: Is there associated clinical data available for the slides in the repository?

A: Current images in the repository are currently disconnected from other clinical data. An amendment has been sent to Etikprovningsmyndigheten (Ethical board) to be able to work with pseudonymized images, opening a path to future connections with clinical data.

Q: The algorithms developed in the previous R&D feasibility study with SAAB and Queen Mary, will it be available for further development in this project?

A: The R&D algorithm belongs to SAAB. Karolinska (and its clinical partner Semmelweis) are the sole owner of the annotated image repository.

Q: Does Karolinska have more clinical partners and sites to test the developed algorithms on?

A: Currently Semmelweis, but potentially more in the future

Q: Will additional data be annotated?

A: Yes

Q: What reagent platforms do you use for staining?

A: Roche, DACO, etc, multiple vendors.

Q: Are you demanding a royalty free license for Semmelweis as well?

A: will be discussed during the RFI, general direction is that the partners providing resources and expert knowledge should gain accordingly from the project.

Q: How are the annotated images stored and is it possible to use cloud services?

A: Currently stored at Karolinska, cloud storage depend on anonymization of data and local Policy, will need to be discussed further.

Q: Does Karolinska have compute power (GPUs)?

A: No, industry partner is expected to handle the necessary computing power for algorithm development.

Q: How will transfer of data be handled?

A: Legaly the data will belong to Karolinska, and a specific agreement will be signed (Swedish: Personuppgiftbiträdes-avtal, PUB-avtal), which regulate the use of the data for the specific purpose. How data will technically be transferred will need to be discussed specifically in due time, there are multiple options.

Q: New regulation will demand storage and access to data for the CE-marked product, how will that work?

A: Data for algorithm development will be stored at Karolinska for the demanded time-frame (for research data), and we will need to further look into how this works for the Industry partner.

Q: How experienced are Karolinska w r t clinical validation?

A: Strong experience from all kinds of clinical validation, accredited lab etc etc

Q: How burning is this problem that you intend to solve with the AI-image analysis tool?

A: Work-flow is major issue, very time-consuming work, availability of current and future senior pathologists is a concern, pathology report key for staging and treatment decision.

Q: How has the annotation been performed?

A: A team of pathologists from Karolinska and a team of pathologists from Semmelweis performed the annotations, each pathologist working on different images. For many images, after annotation, a second pathologist expert in gastrointestinal pathology reviewed and curated the annotations.

Q: How do you see the potential to apply algorithms to other tumor/cancer forms?

A: Great potential to scale to other tumors/cancers with additional ground truth (annotations).

Q: What are the specific functional requirements?

A: To pre-analyze each case after scanning so when the pathologist opens it for review the regions of cancer cells are graphically indicated (automated tumor detection), minimizing the time needed to screen/eye-ball searching for the tumor regions in the slide. A very, very high sensitivity is crucial for the pathologist to safely be able to save time in the negative regions and slides.

Q: What is the volume of data to be analyzed / week? How many slides/patient?

A: Each pathology case for a colorectal surgical specimen typically has 40 to over 100 H&E slides including the lymph nodes.

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Pinboard / Anslagstavla:

Industry looking for partners