Digitalisation in Pathology

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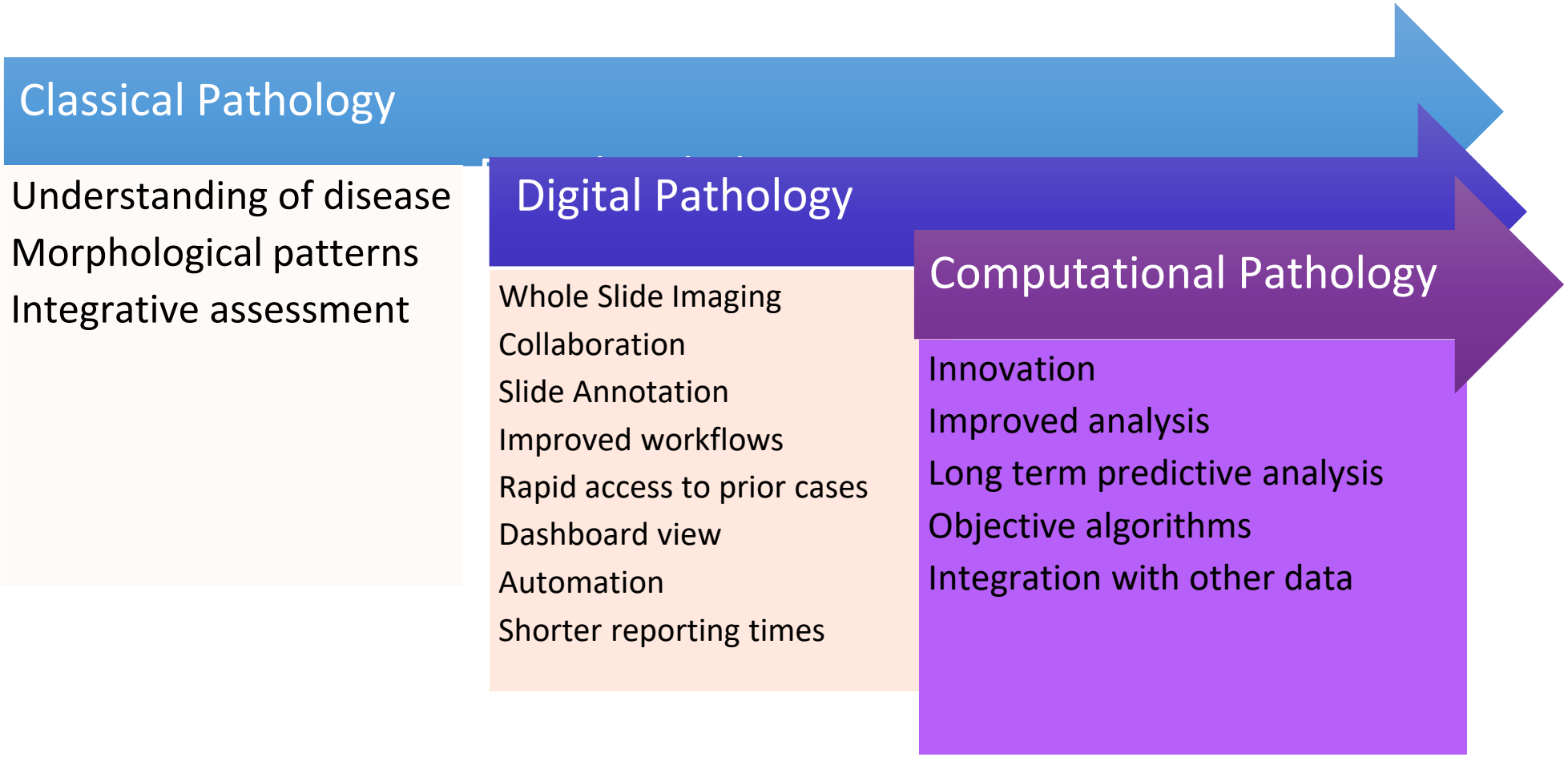
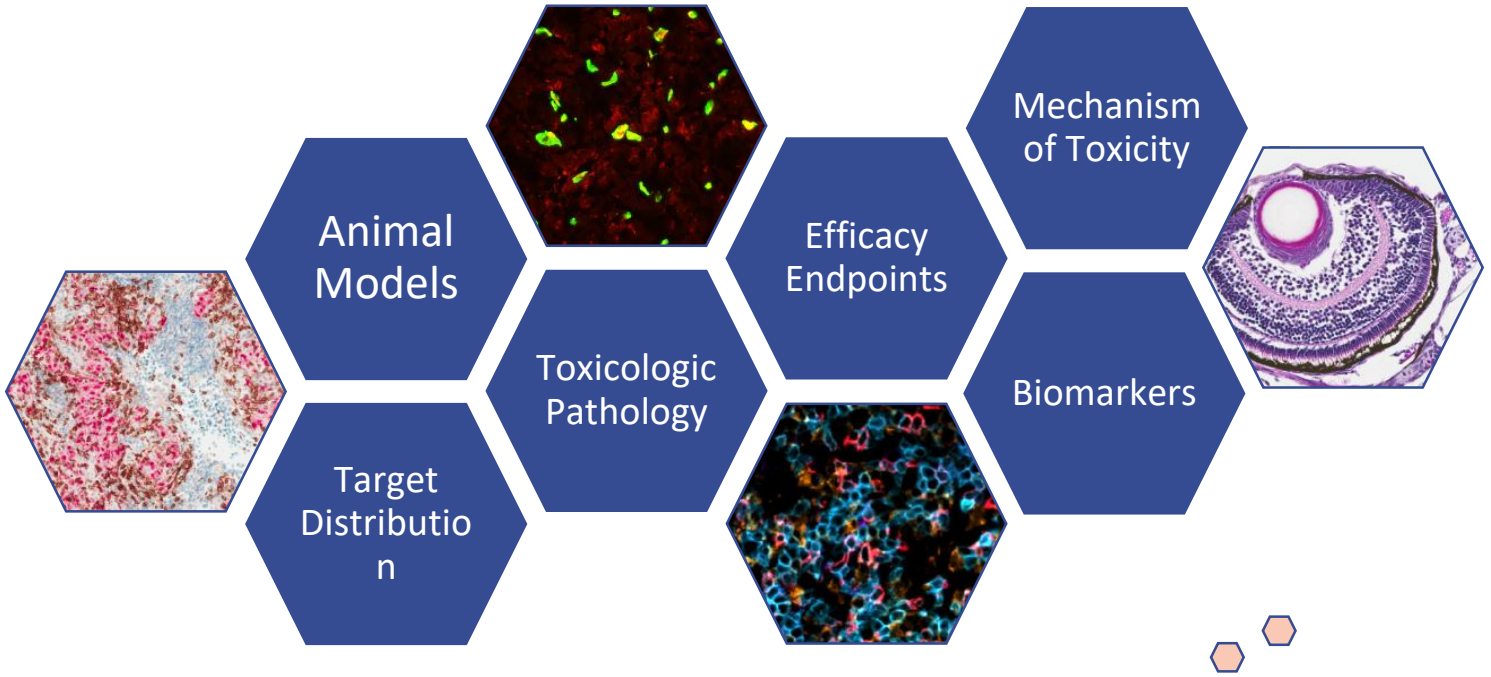
Digitalisation and Digital pathology in drug development



Pathology Throughout Drug Discovery

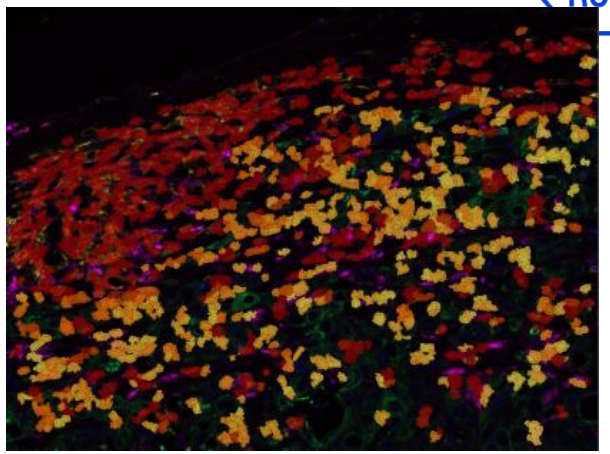
Entry into Portfolio | **Clinical Lead Selected** | **Entry Into Human** | **Filing**

Target Assessment to Lead Identification → Preclinical safety → Clinical Safety



Advantages of Digital Pathology

- **Collaboration**
  - Powerful tools to visualize, annotate, share and present data



- **Streamline** lab and data management
  - Sample management, data integration from other modalities
  - Archiving, workflow aspects

- **Image Analysis:**
  - **Quantification** of decision-making endpoints
  - ***in silico* multiplexing** of serial sections
  - **Standardization** and assessment of the whole slide
  - **Visualization** of data
  - **Artificial Intelligence** algorithms

- **Some things can only be done in digital:** *In silico* multiplexing, Volume analysis, 3D reconstruction of serial sections
- Annotation, Computer-assisted review, Spatial analysis , cell-cell interaction

Examples of Digital Images in Pathology

- Macroscopic Images
- Whole slide scans
- Digital microscopic images
- Electron micrographs
- 3-dimensional (3-D), cleared whole tissue sections

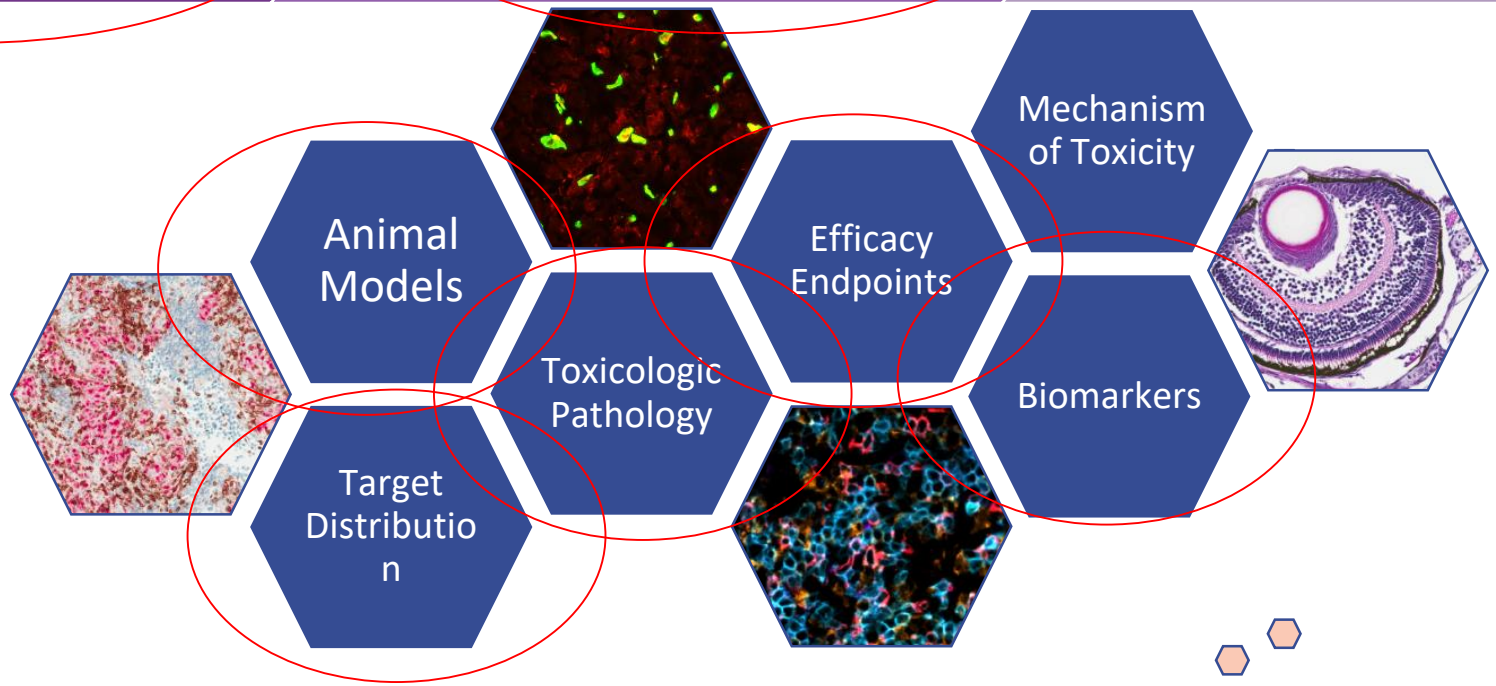
Application of Digital Images in Pathology

- Macroscopic Images → Medical application (ex dermatology, remote necropsy…)
- Whole slide scans → Remote peer review
- Digital microscopic images → Direct slide comparison, slide matching, annotations/measurement…
- 3-dimensional (3-D), cleared whole tissue sections →
  - Refined visualization of anatomical structure
  - Target assessment at 3D level (IHC)

Where do we stand now? – Digital Pathology in Preclinical Drug Development

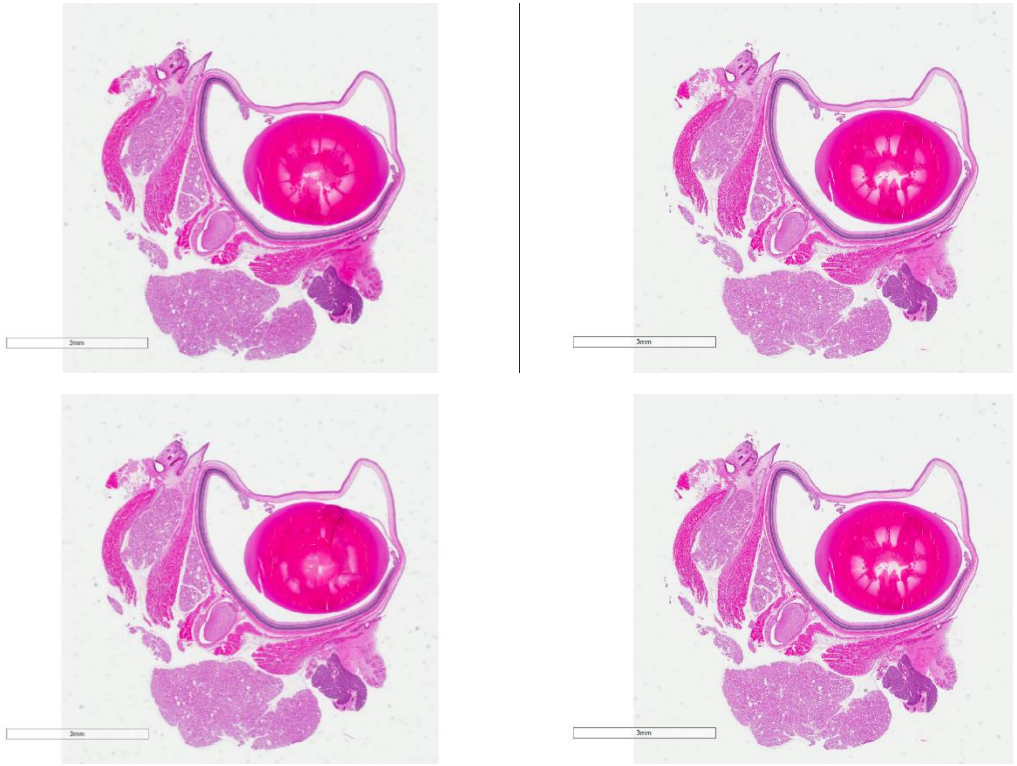
Entry into Portfolio | **Clinical Lead Selected** | **Entry Into Human** | **Filing**

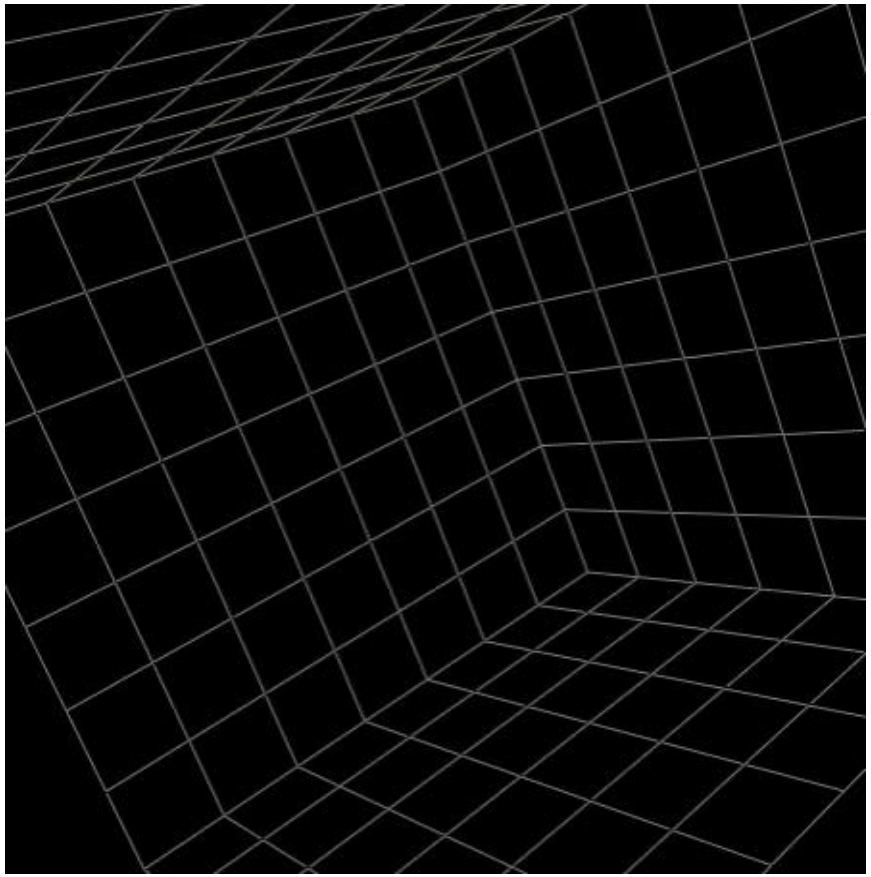
Target Assessment to Lead Identification → Preclinical safety → Clinical Safety



The Value of Morphologic Pathology

in silico 3D Reconstruction



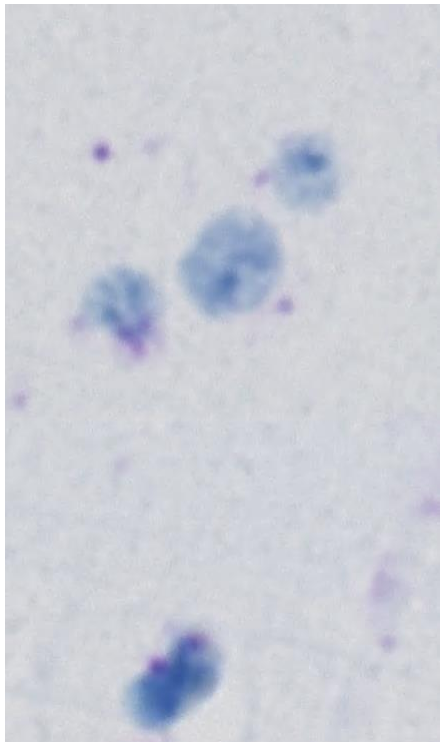


Quantification strategy in a PKPD preclinical study

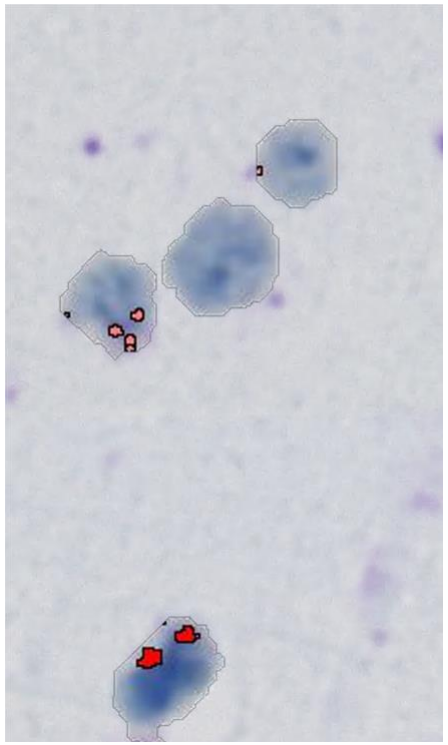
Target compound has been stained by ISH.
Probe detected: in the nuclei and in cytoplasm separately.

Nuclear probe detection

Staining: nuclei / Probe

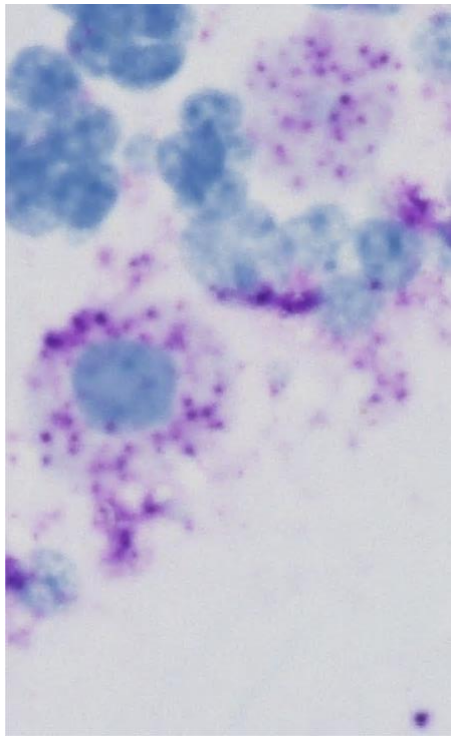


probe detection

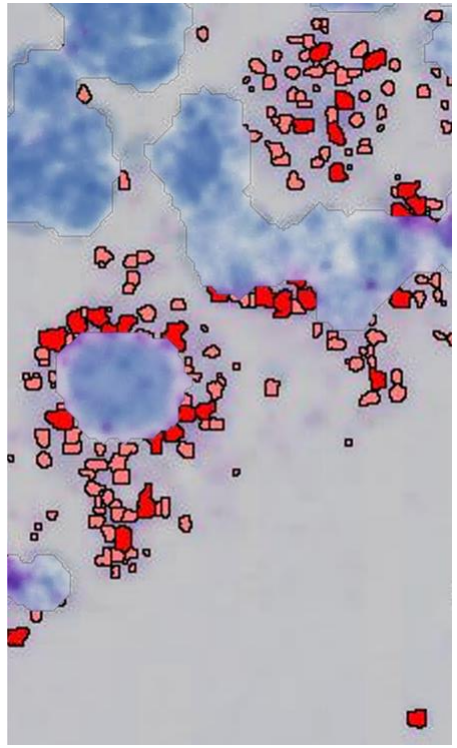


Cytoplasmic probe detection

Staining: nuclei / probe



ATXN2 LNA probe detection

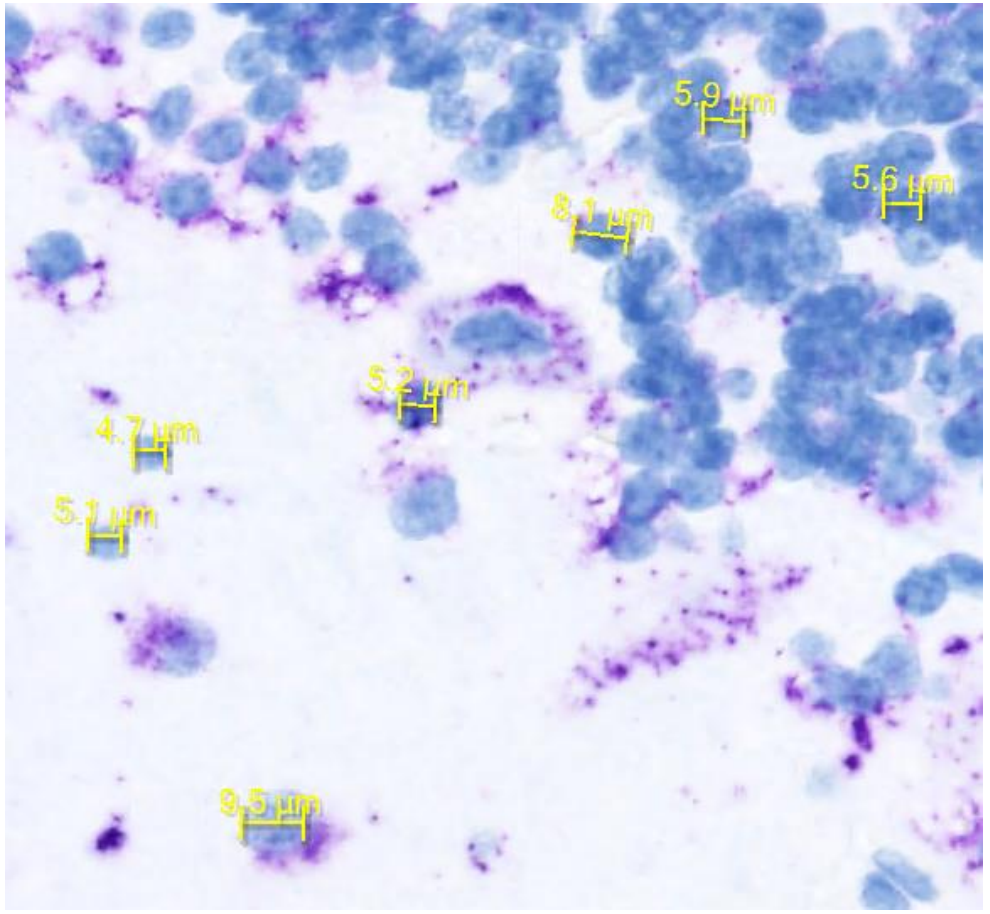


Shanon Seger, Daniela Calini and Gabrielle Branellec

Normalization by cell number

Cell number has been calculated based on:
- Hematoxylin stained area
- Average nuclei area by brain regions (min 50 nuclei analyzed)

	average Nuclei area
CBL	25.14471139
RTH	38.81016221
PFC	58.36883297
ANC	30.38132953



- Dose dependent tissue exposure of target compound in Cerebellum, Anterior Commissure and pre-frontal Cortex and Thalamus.
- Higher number of probes detected in nuclei versus cytoplasm

➢ Pathology expertise critical to guide the method of analysis (tissue/cell morphology, analysis per cell number/ area)

Shanon Seger, Daniela Calini and Gabrielle Branellec

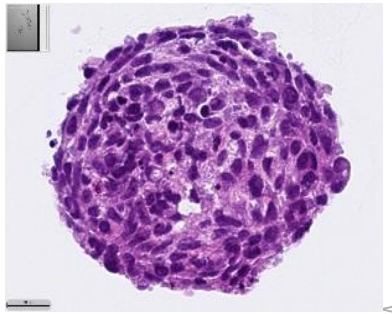
AI algorithm for morphologic killing readout of organoids

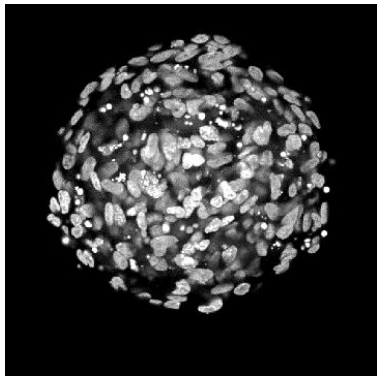
AI guided 40x high resolution morphologic readout was established for the blood-brain barrier organoid model

– upscaling (efficacy/toxicity & different models) is currently under evaluation -

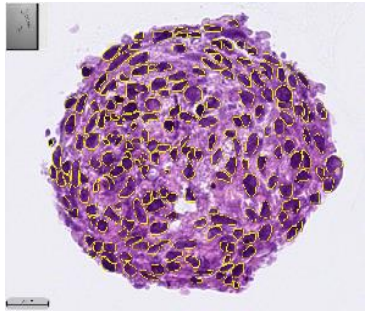
A 2D high resolution scan (light microscope)

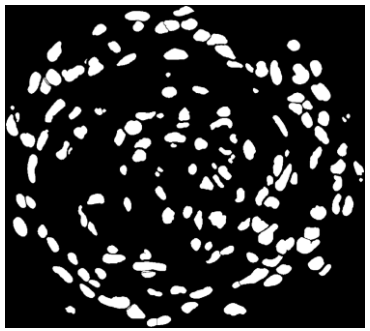
B 3D high resolution scan (confocal)



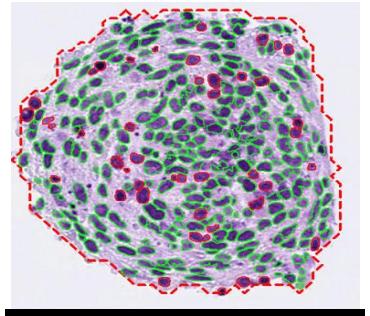


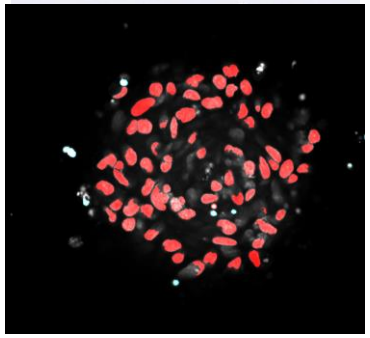
Nuclear segmentation

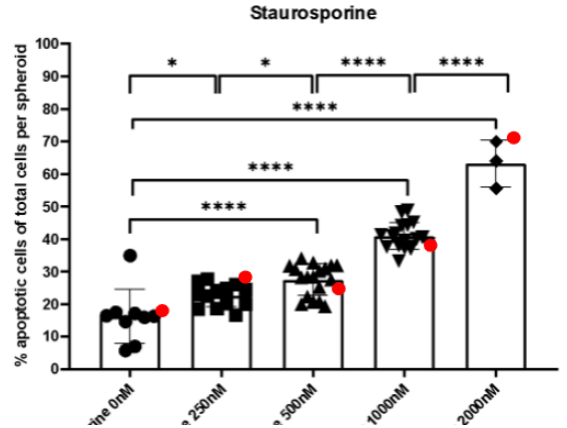




Identify necrosis/apoptosis







readout:

→ unlabelled detection of apoptosis/necrosis
→ % of cells affected
→ which cell type
→ at what dose
→ at which time point

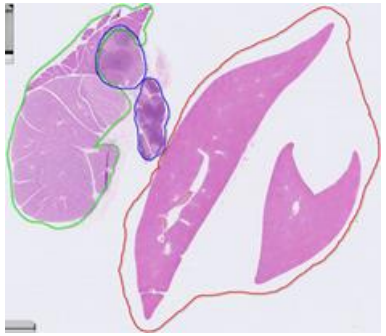
★ Single cell resolution possible for in vitro efficacy (toxicity) quantitative readout
★ Image analysis: Easy, fast, reproducible workflow in 2D HE (no special stain needed to identify necrotic cells)
★ 3D reconstruction of confocal images allows in depth visualization, but lacks scalability and automation as of now

OneD project team: Luisa Bell, Elena Kassianidou, Alessio Tovaglieri, Diederik den Hartog, Benjamin Gutierrez Becker, Tom Albrecht, Roberto Villaseñor & Nadine Stokar

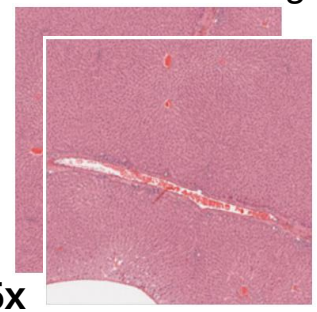
Organ identification with AI

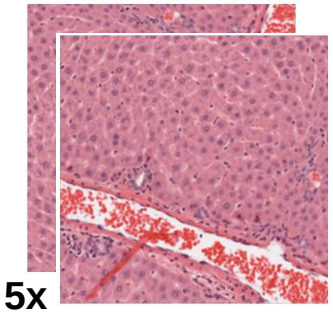
Training:

Annotations



Tile generation:



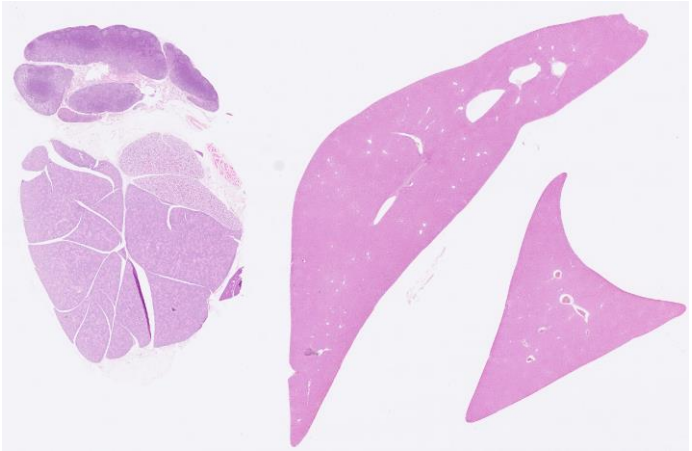


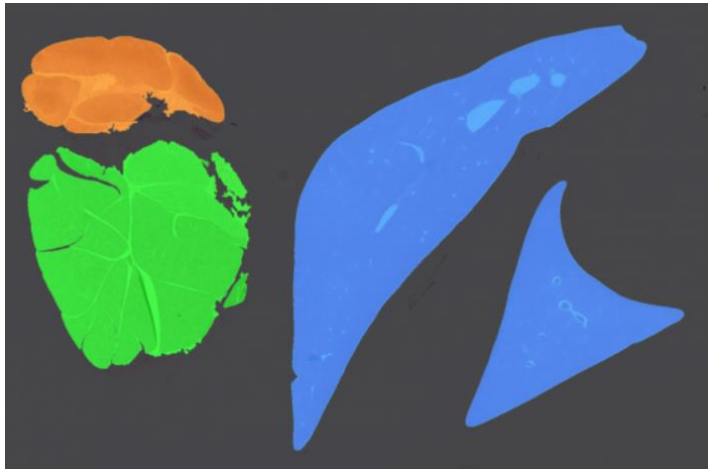
Training:

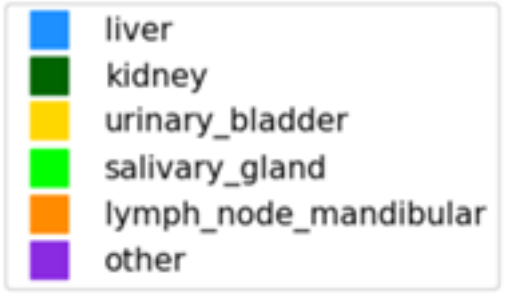
CNN

DenseNet-121

Test:

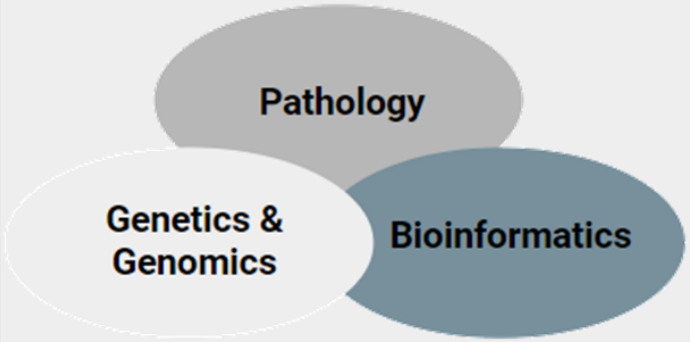




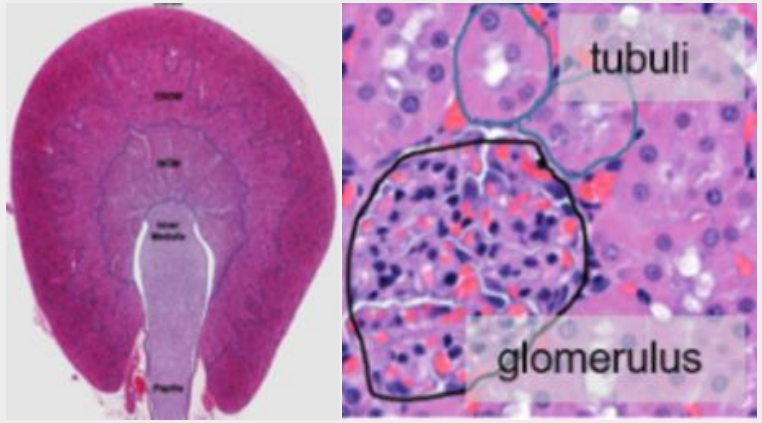


Fernando Romero-Palomo, Citlalli Gámez Serna, Filippo Arcadu

Spatial transcriptomics and artificial intelligence towards next generation toxicology workflows



Morphological features

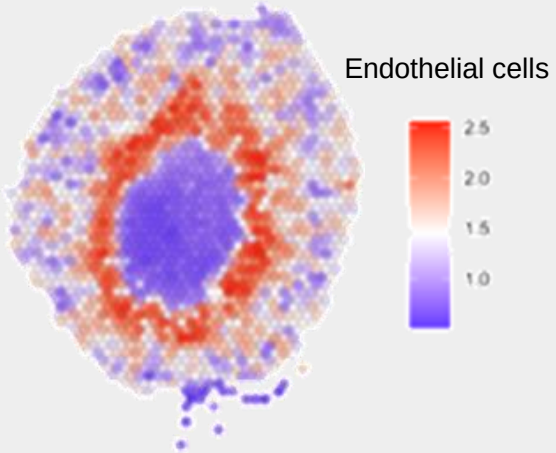


Roche PS- Spatial Omics Squad
Schwalie P, Valdeolivas A, Hahn K

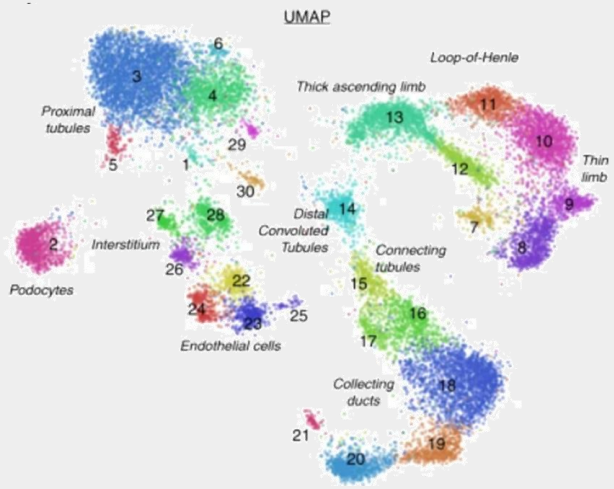
University of Heidelberg:
Prof. Julio Saez-Rodriguez

CHUV, Lausanne
Dr. Andrew Janowczyk

Spatial transcriptomics



Single cell/ nucleus sequencing

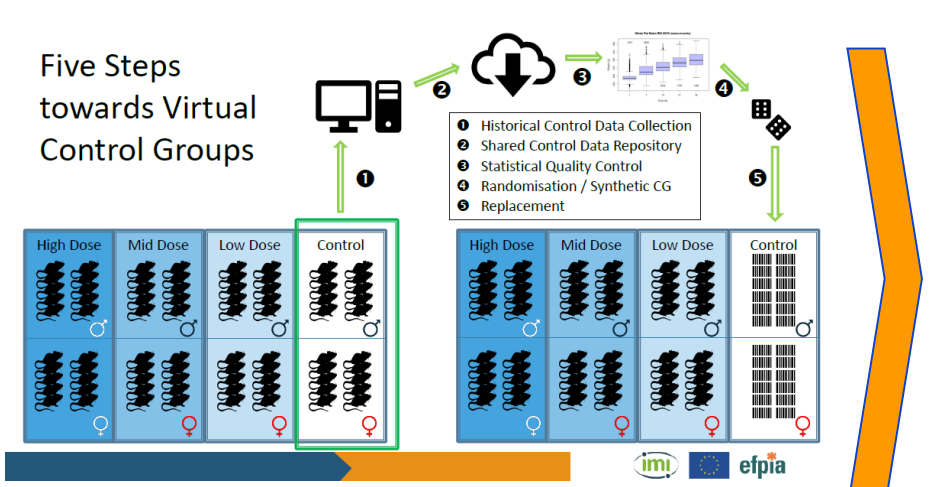


Virtual Control Group Project - PoC in Rat studies

AIM

Assess feasibility of
* using **historical control data** of non-clinical in-vivo safety studies to **build virtual control groups** and **reduce** control animals and
* **sharing** control animals data **amongst pharmaceutical companies** (eTRANSAFE consortium)

Method & Results

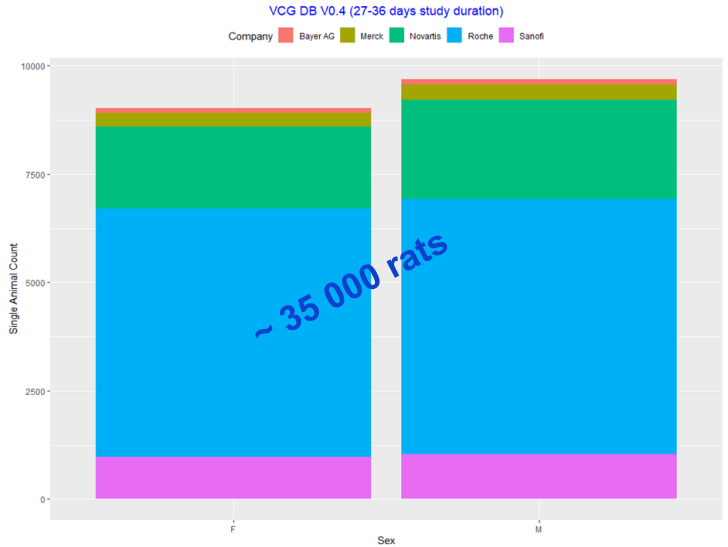


Expected IMPACT

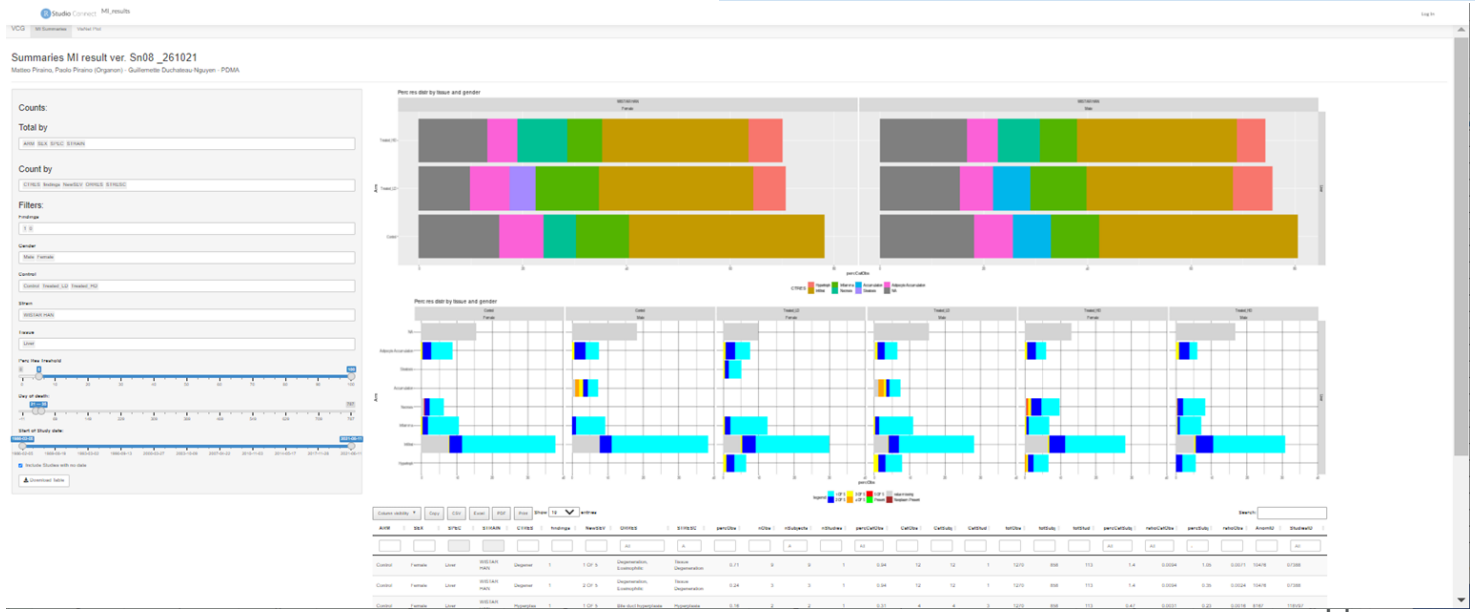
Understanding of sources of variability in animals and opportunity to put **unexpected/unusual project findings** into **historical context**.

Reduce 4-weeks GLP Tox control groups **by 30-60%**, cost reduction by ~10-15%

Access to several harmonized Pharma data repositories & new exploration tools (shiny apps)



VCG DB (4 weeks studies from 5 pharma available@Roche since June 2022)

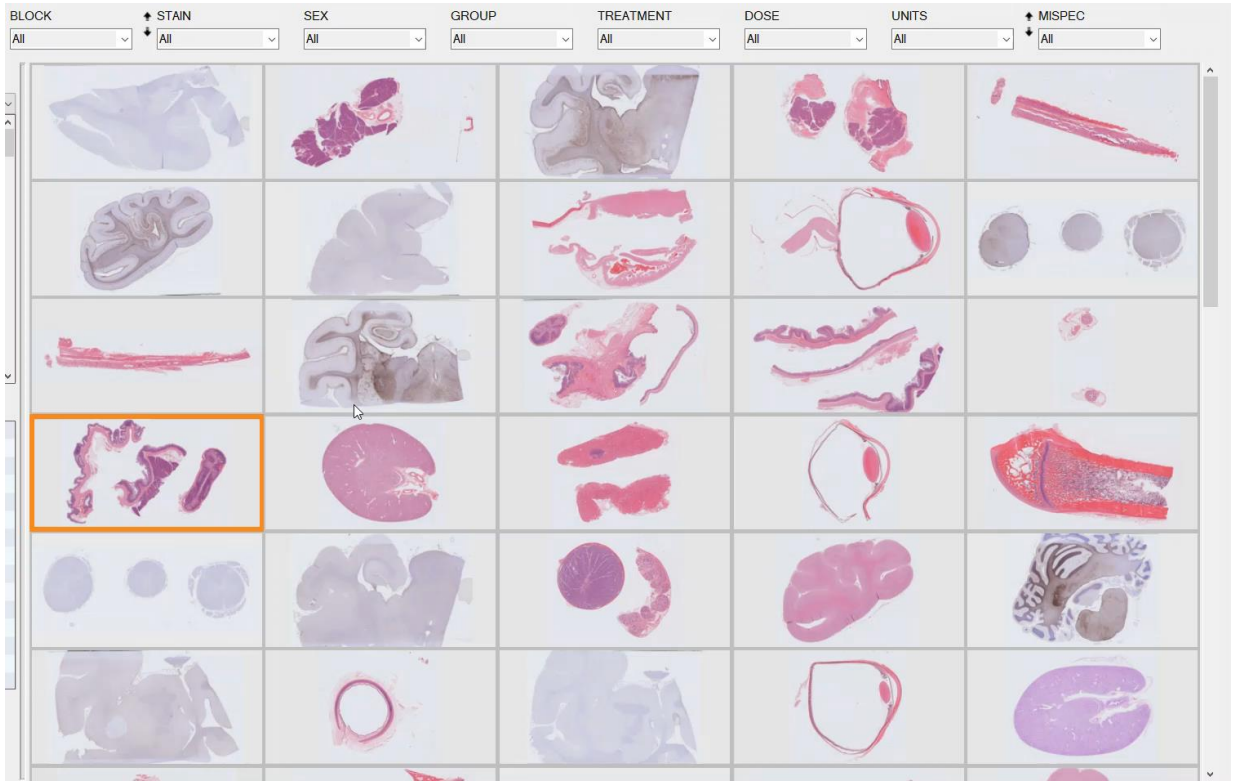


Shiny app developed to explore Microscopic Findings - https://rsconnect.roche.com/connect/#/apps/7230/info

Digitalisation in pathology: full digital pathology evaluation for preclinical tox studies (non GLP and GLP)

Combine study data with the digital scans:

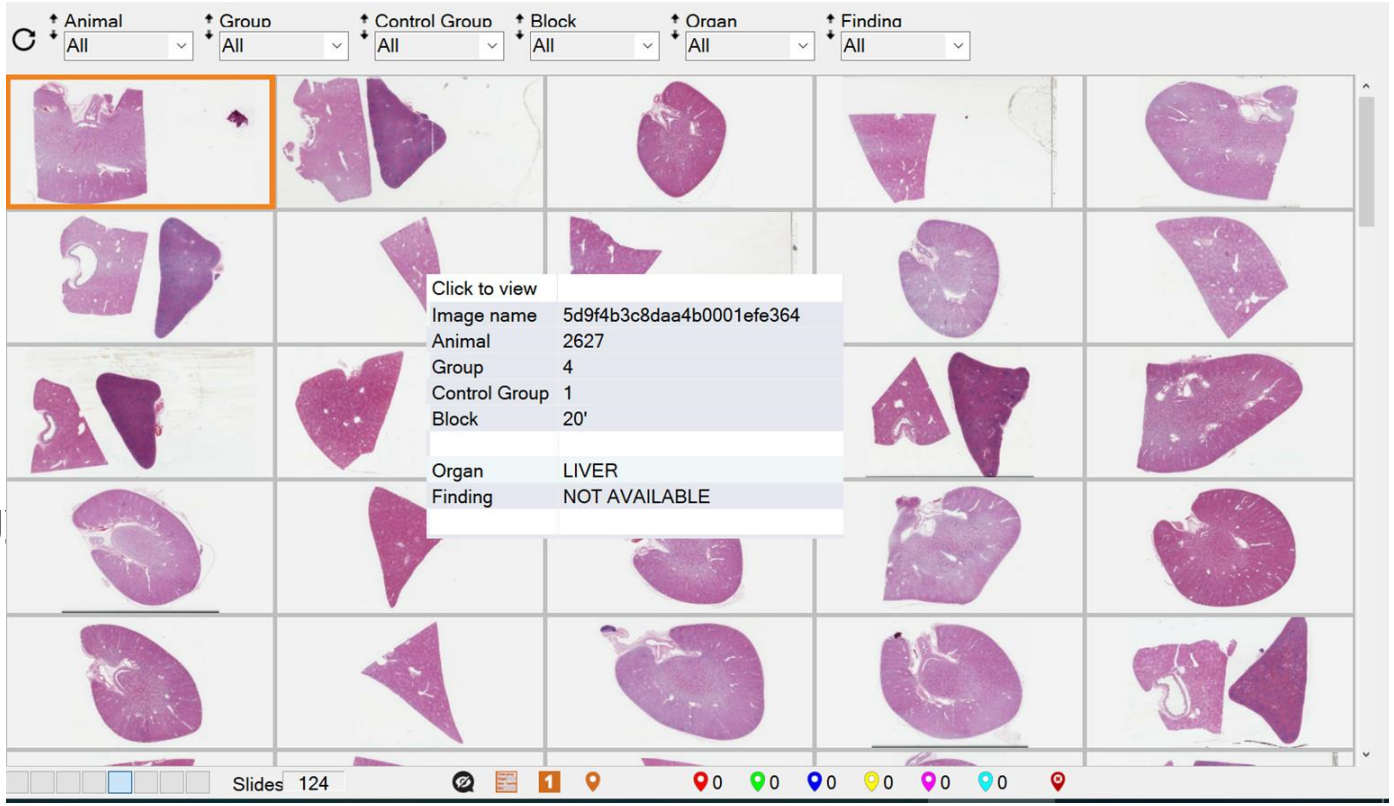
- WSI and Metadata correspondence



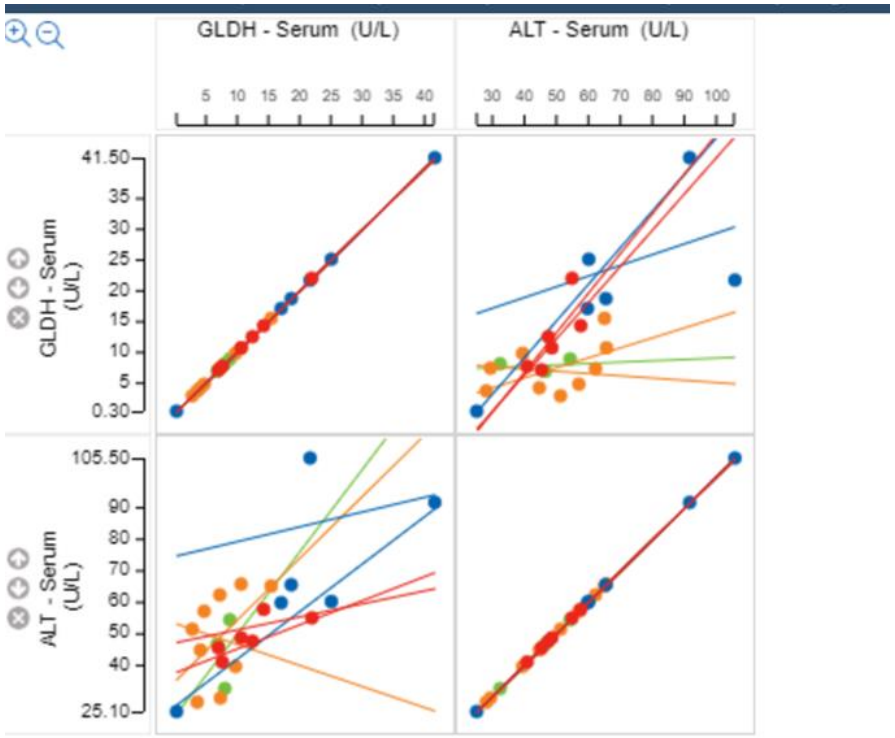
Digitalisation in pathology: towards a fully correlated digital study data evaluation?

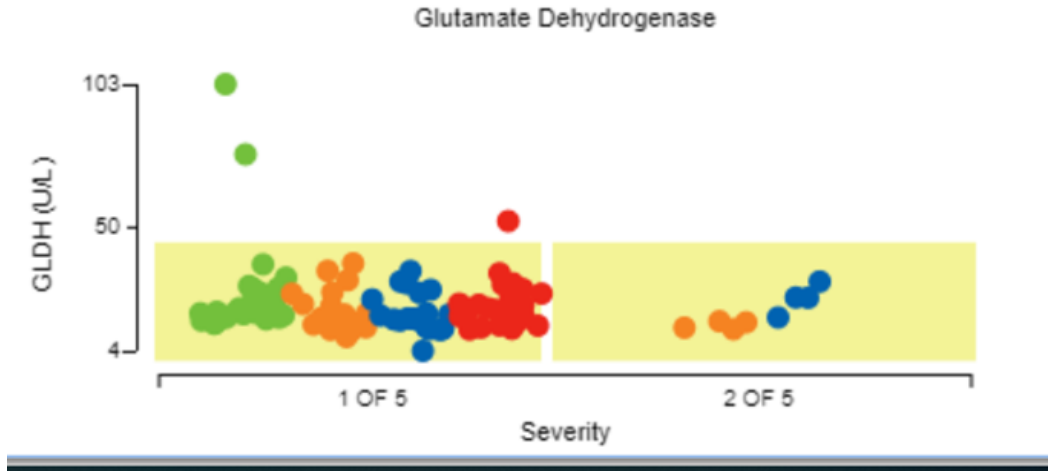
Combine study data with the digital scans

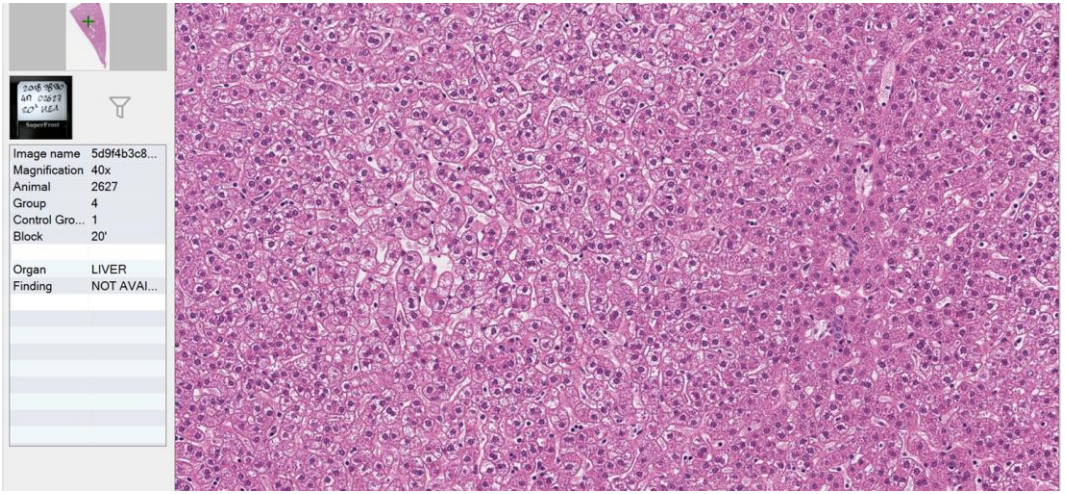
Opportunity to use the harmonized Preclinical study data set (SEND): Pathology, clinical patholog clinical signs, Body weights



Digitalisation in pathology: towards a fully correlated digital study data evaluation in preclinical safety?



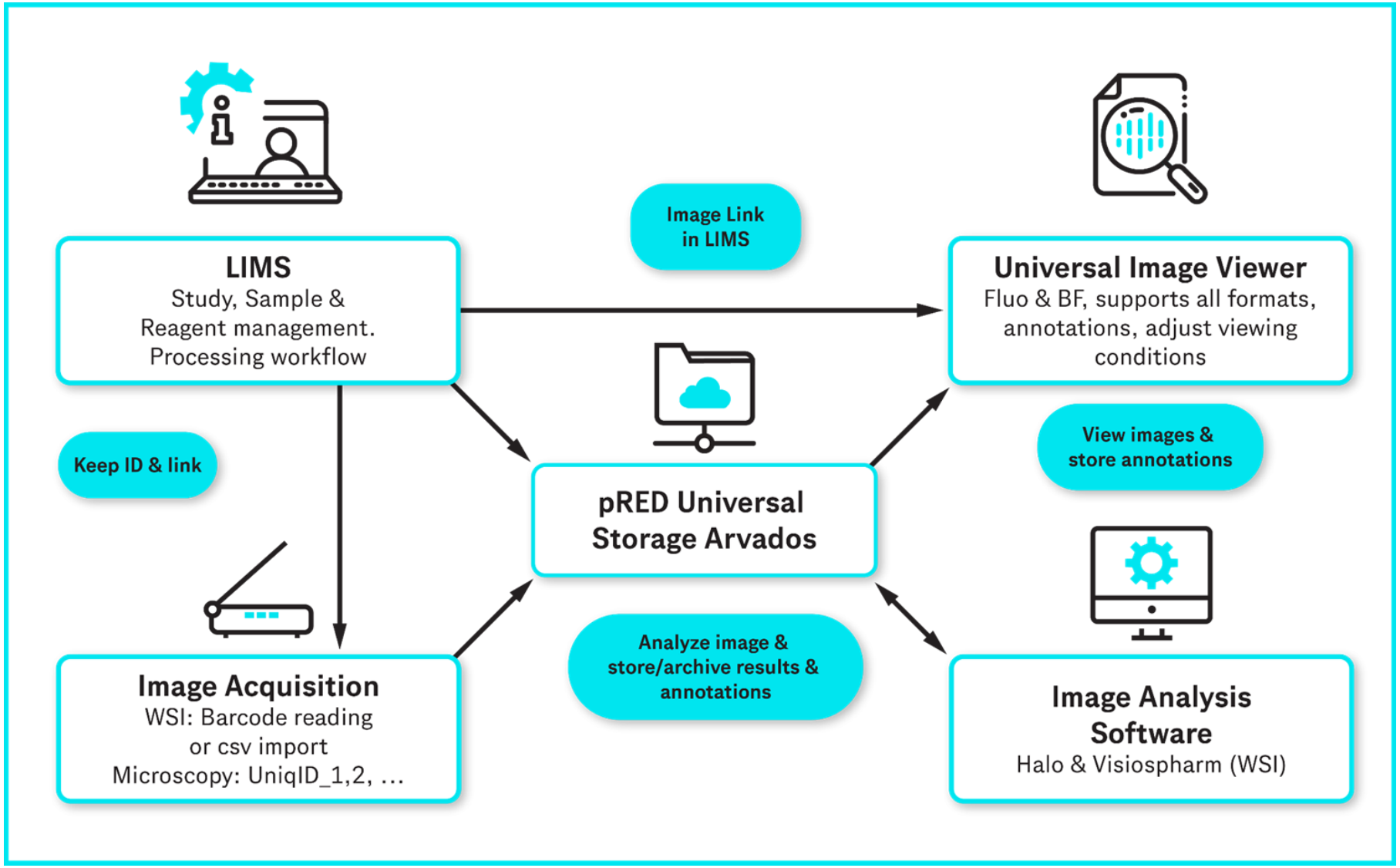




➢ **Digital pathology is part of a comprehensive, integrative preclinical study data evaluation in drug development**

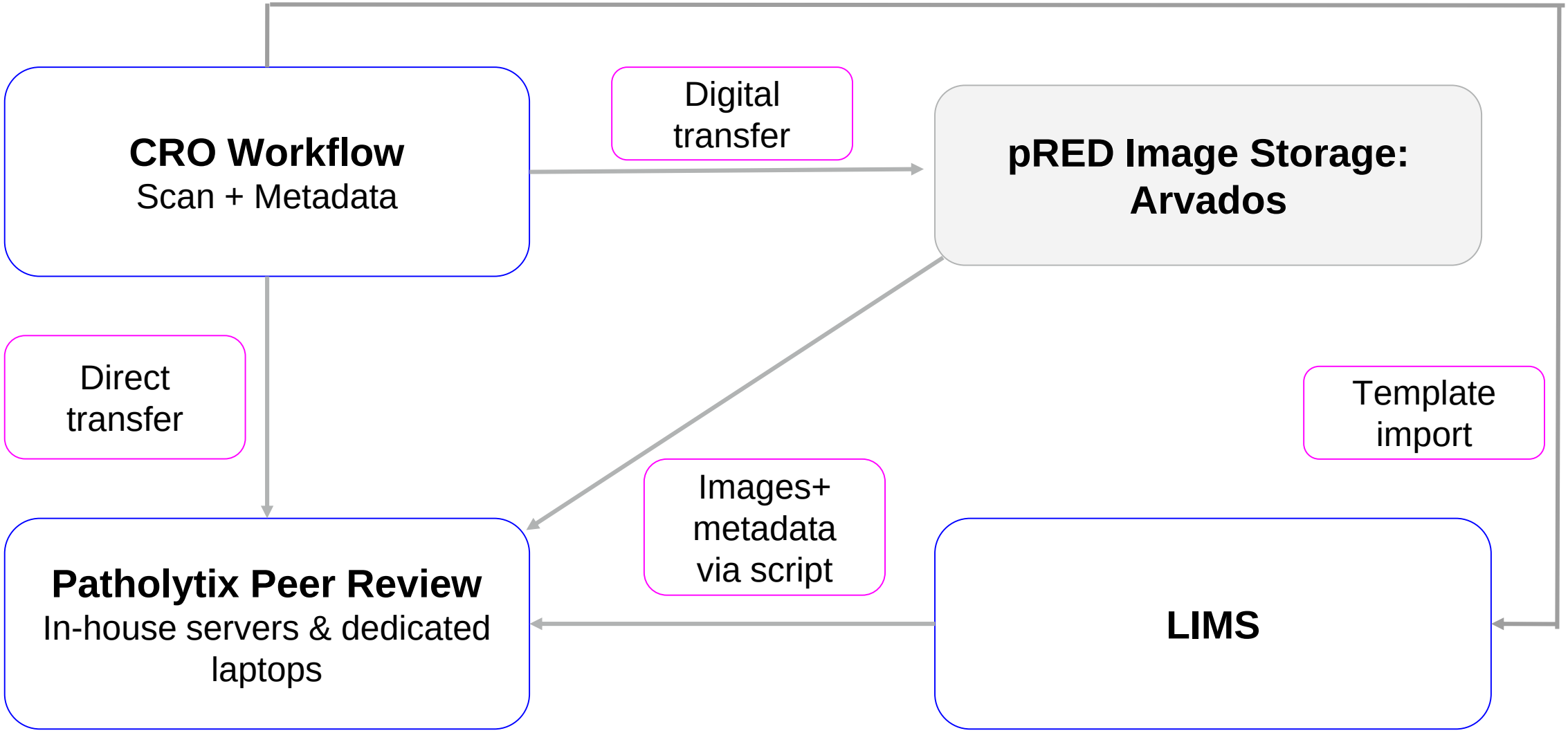
Digitalisation in Pathology requires a state of the art IT platform (infrastructure, software, hardware)

End to End Platform outcome



WSI: whole slide image

Peer review platform/process outcome

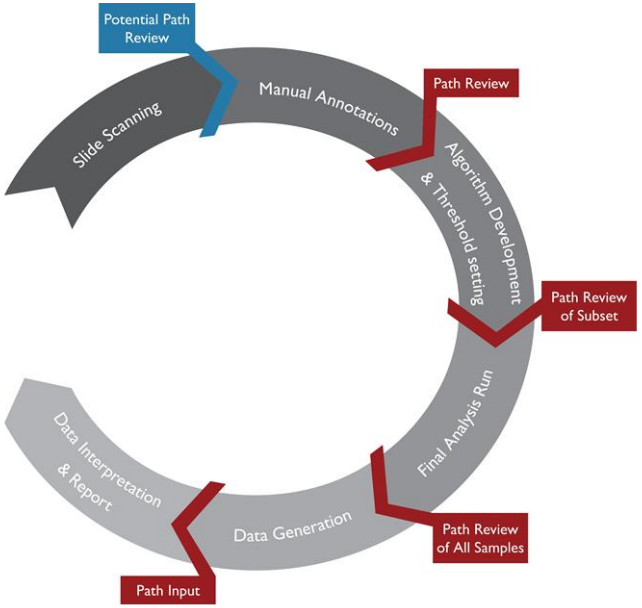


What is the role of the pathologist in the digitalisation process?

Where does the pathologist fit in?

All stages of the Digital Pathology/Digitalisation Workflow!

- Study **design**
- Sample **quality** verification
- «Wet Lab» assay **development**: IHC, ISH
- Review and **quality control** of algorithms
- **Interpretation** of image analysis results
- Pathology and clinical Pathology data management (SEND)
- IT system integration / WSIs and data storage/FAIR
- Regulatory acceptance / Quality Assurance



- PS: Pathologists do train in algorithm programming!

Many thanks to all Pathology chapter and PS colleagues involved in the Pathology digitalisation, especially:

Vanessa Schumacher

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Marco Tecilla

Fernando Romero Palomo

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Shanon Seger

All lab colleagues

Guillemette Duchateau-NGuyen

Dragomir Ivanov

Doing now what patients need next