Prognostication and Theranostics in Nephrology on Multimodal Datasets

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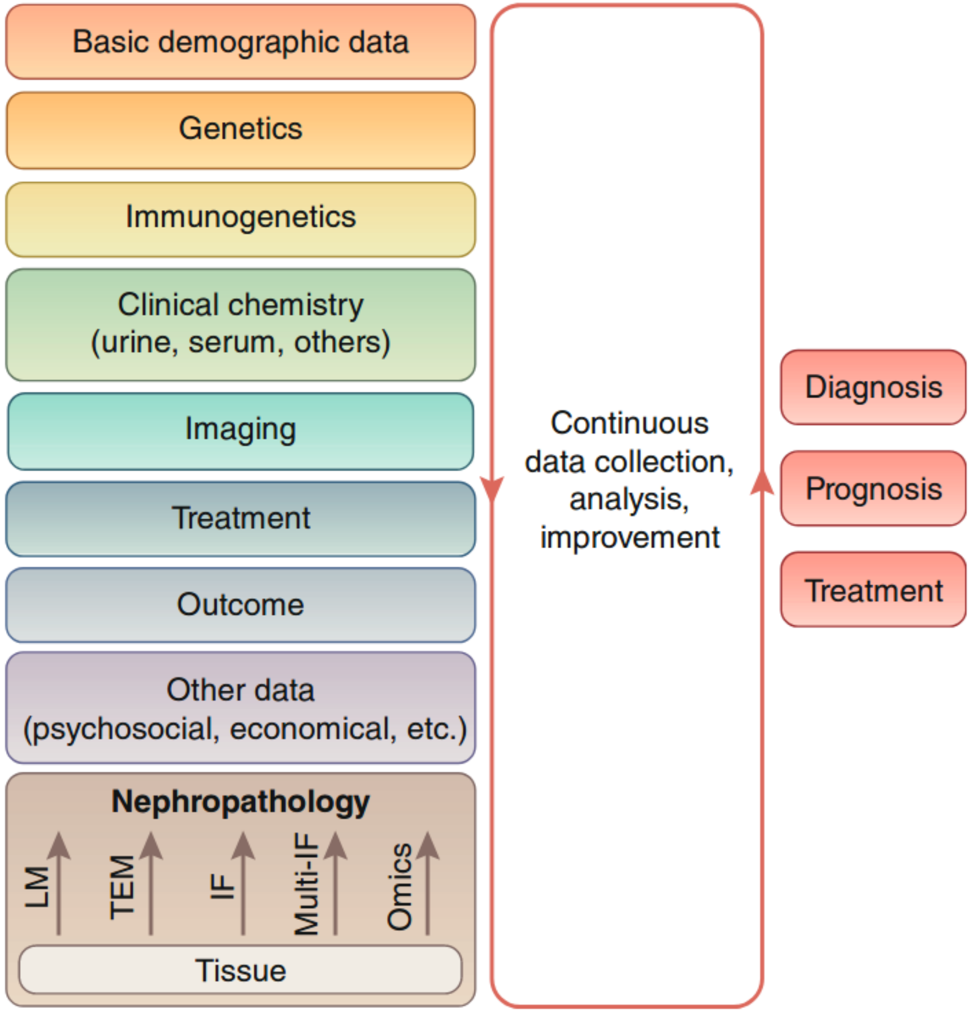
Nephropathology big data und precision medicine



Basic demographic data

Genetics

Immunogenetics

Clinical chemistry (urine, serum, others)

Imaging

Treatment

Outcome

Other data (psychosocial, economical, etc.)

Nephropathology

Continuous data collection, analysis, improvement

Diagnosis

Prognosis

Treatment

Becker et al. KI 2019

Prognostic ML in Transplant Nephrology

- Renal transplant study
- First three months
- Training set: 100,867 values
- 2 test sets: 39,999
- Input: Sequence of eGFR
- Output: future eGFR
- Architecture: Sequence-to-Sequence Deep Learning vs. Autoregressive integrated moving average (ARIMA)

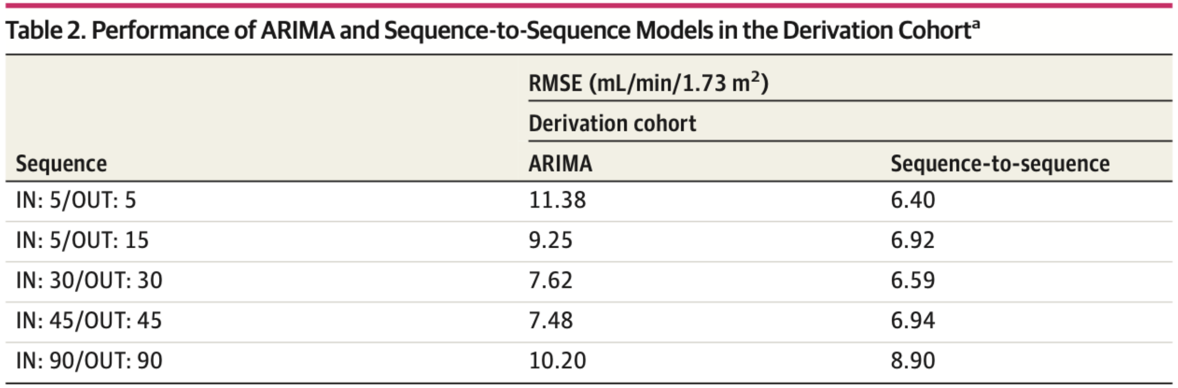
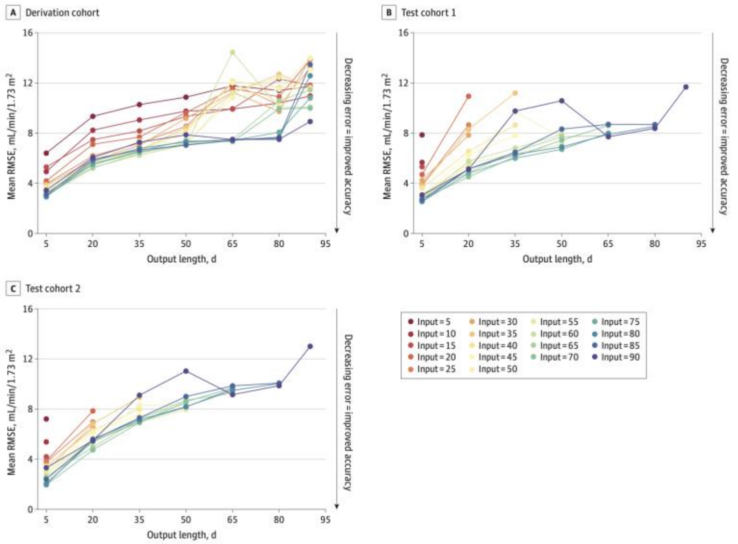


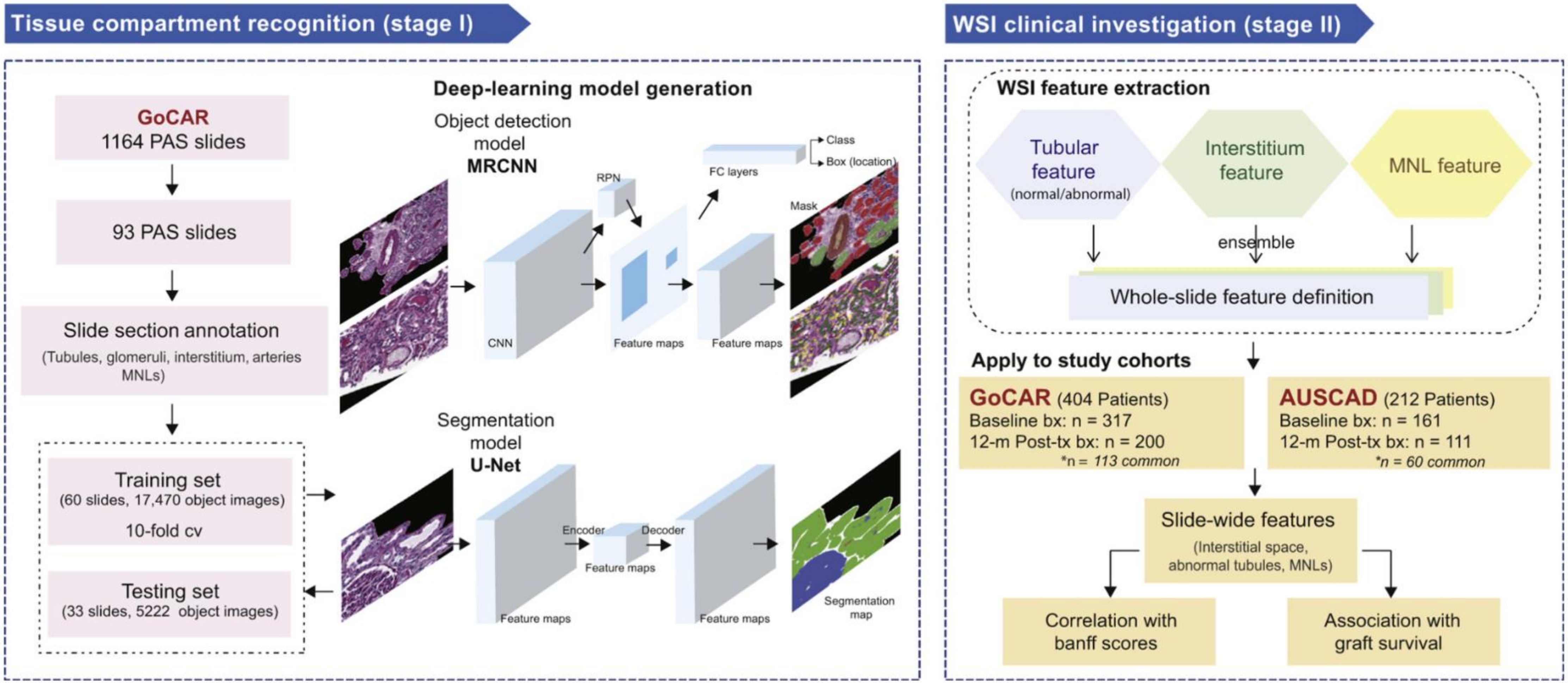
Table 2. Performance of ARIMA and Sequence-to-Sequence Models in the Derivation Cohort[a]

	RMSE (mL/min/1.73 m^2)	
	Derivation cohort	
Sequence	ARIMA	Sequence-to-sequence
IN: 5/OUT: 5	11.38	6.40
IN: 5/OUT: 15	9.25	6.92
IN: 30/OUT: 30	7.62	6.59
IN: 45/OUT: 45	7.48	6.94
IN: 90/OUT: 90	10.20	8.90



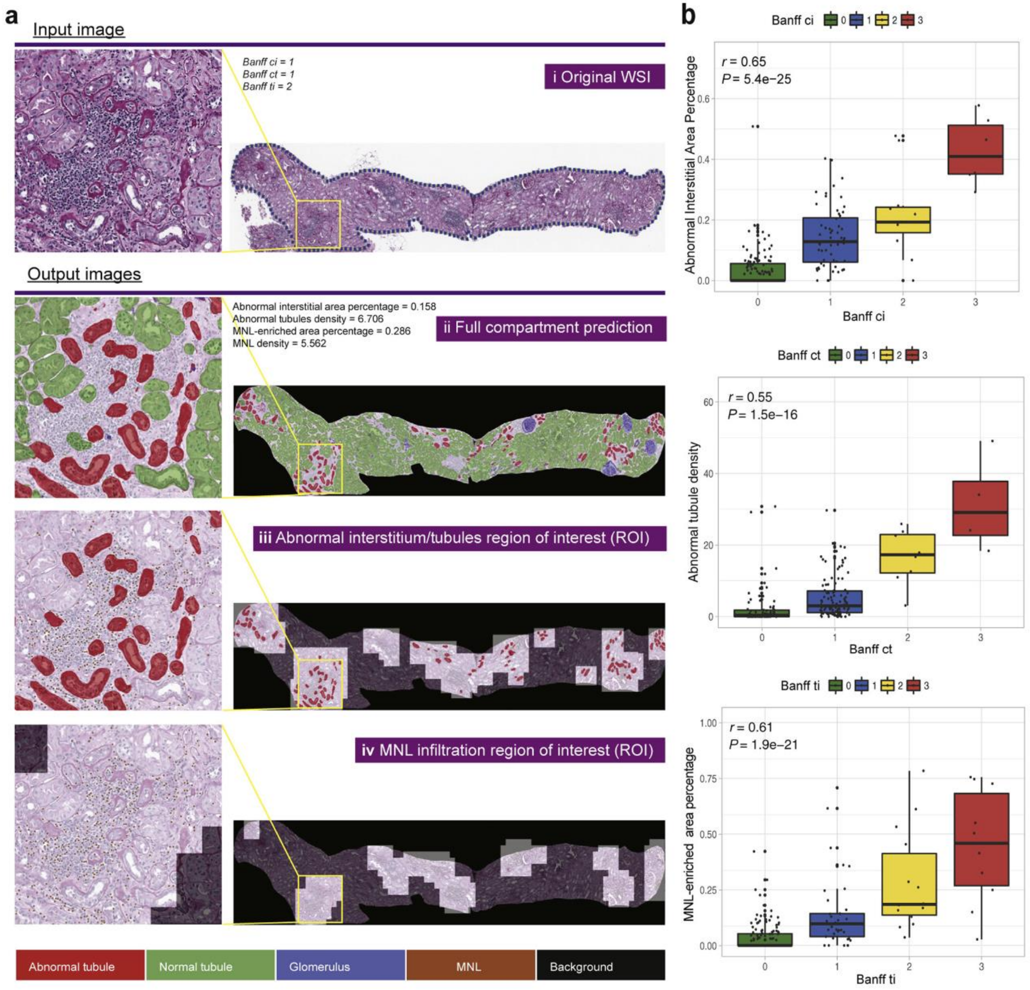
Van Loon, JAMA Network Open 2021

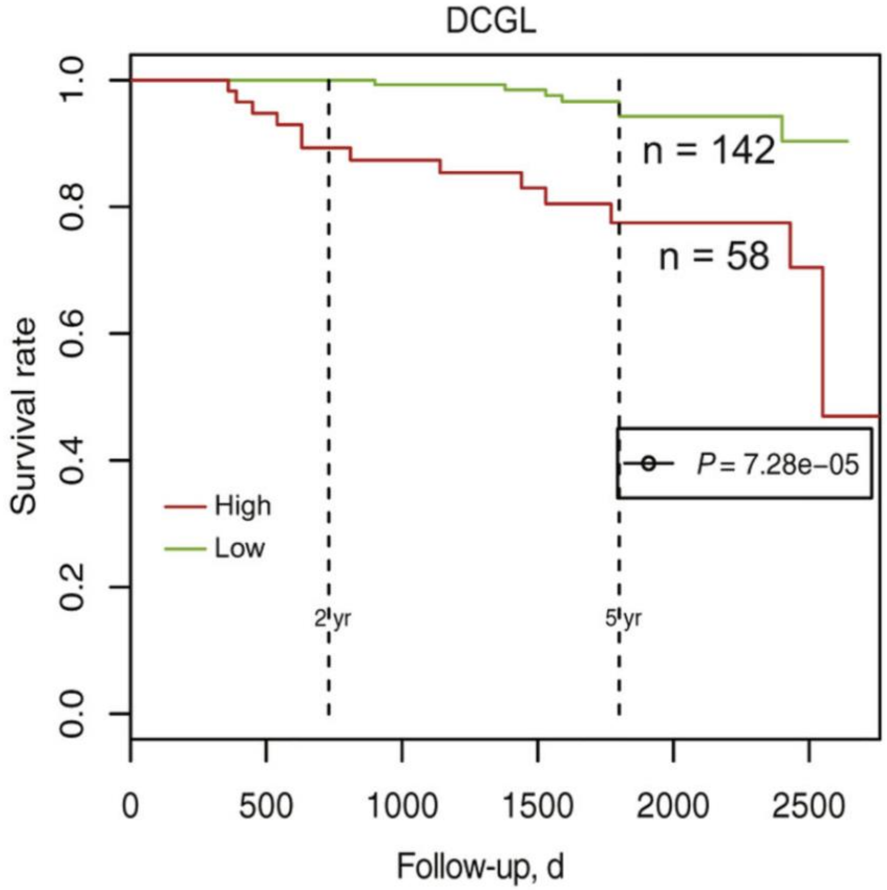
Prognostic ML in Transplant Nephropathology



Yi, Kidney International 2022

Prognostic ML in Transplant Nephropathology

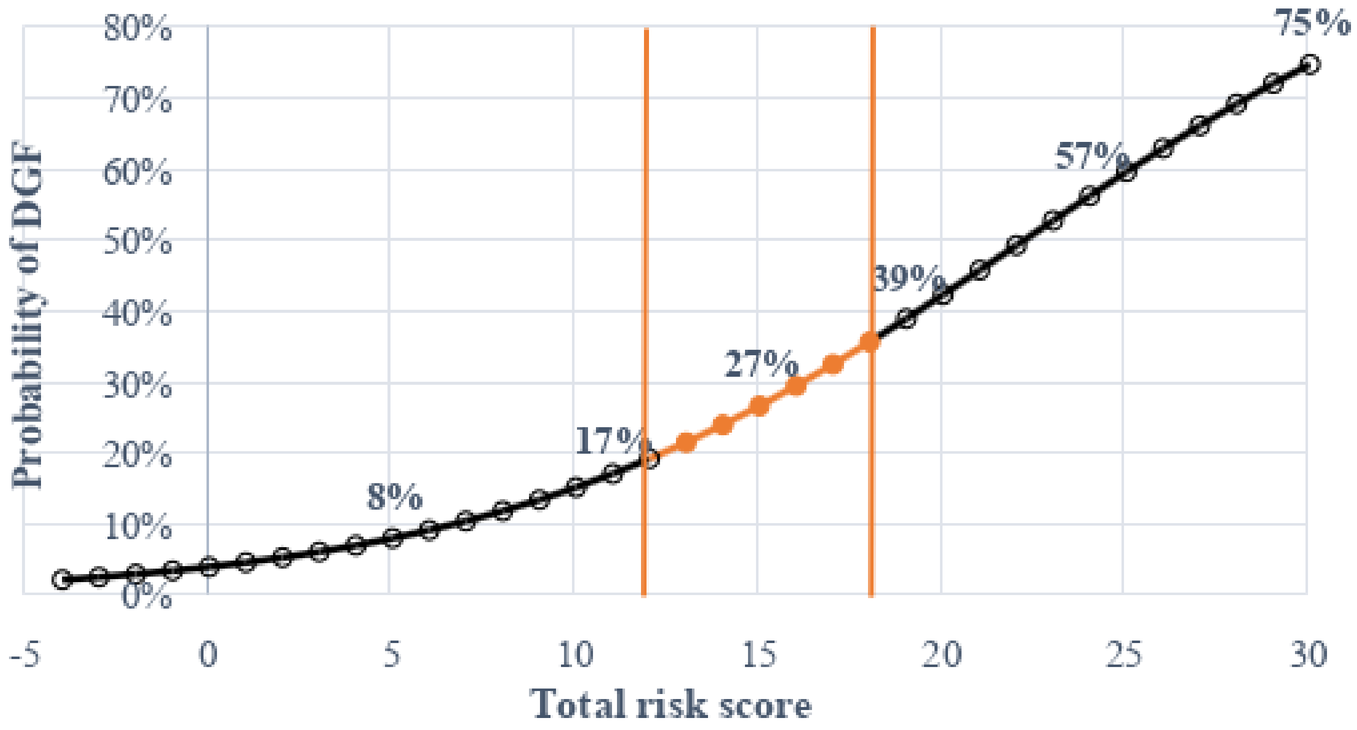




Yi, Kidney International 2022

2-Step-Score for the Prognostication of Delayed Graft Function

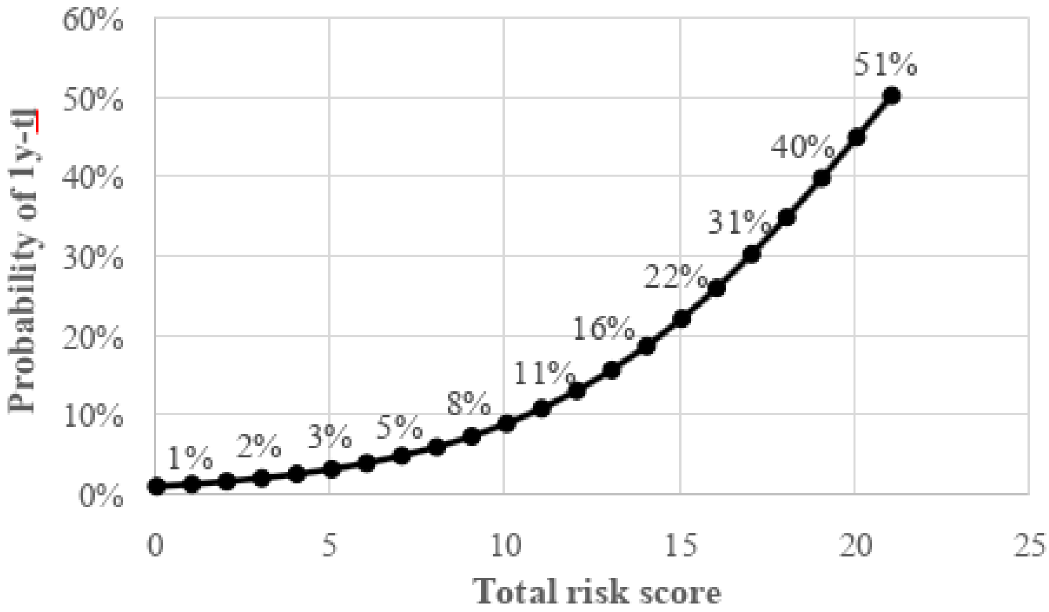
Risk factor	**Addition to risk score**						**Risk score**
Donor BMI (kg/m²)	< 18.5	18.5 to < 25		25 to < 30		>= 30	
	-2	0		+3		+6	
Recipient BMI (kg/m²)	< 18.5	18.5 to < 25		25 to < 30		>= 30	
	-2	0		+2		+3	
Recipient CVM IgG	Negative			Positive			
	0			+5			
Number of HLA-DR mismatches	Less than two			Two			
	0			+6			
Dialysis vintage in years	< 1	1 to < 3	3 to < 4		4 to < 6	>= 6	
	0	+1	+2		+3	+5	
Cold ischaemia time in hours	< 2	2 to <6	6 to <10	10 to < 14	14 to < 18	>= 18	
	0	+1	+2	+3	+4	+5	
Total score without histological assessment	- 4 to 11 points		12 to 18 points (18% to 36% risk)		19 to 30 points		
	Low risk		Medium risk: histological assessment advised		Increased risk		
Number of glomeruli	< 20		20 to < 30		30 to < 40	>= 40	
	0		-2		-4	-7	
Banff cv	cv0, cv1 or cv2				cv3		
	0				+5		
						Total score =	



Ernst, NCT, in press

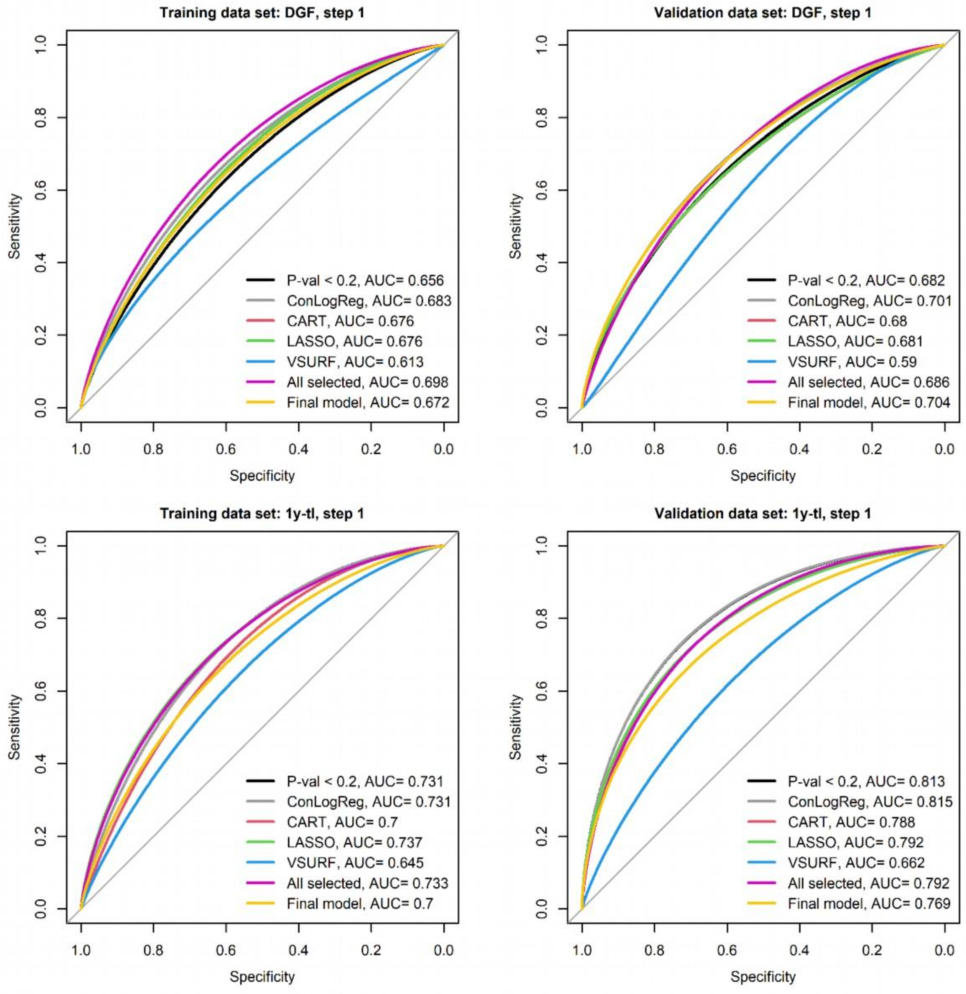
2-Step-Score for the Prediction of 1-Year Transplant Survival

Risk factor	**Addition to risk score**						**Risk score**
Donor age in years	< 30	30 to < 40	40 to < 50	50 to < 60	>= 60		
	0	+1	+3	+4	+6		
Sum of HLA-A, -B and -DR mismatches	0	1	2	3	4 or 5	6	
	0	+1	+2	+3	+4	+5	
Cold ischaemia time in hours	< 2	2 to <6	6 to <10	10 to < 14	14 to < 18	>= 18	
	0	+1	+2	+3	+4	+5	
Total score without histological assessment							
Banff ct	ct0 or ct1	ct2 or ct3					
	0	+6					
	Total score =						



Ernst, NCT, in press

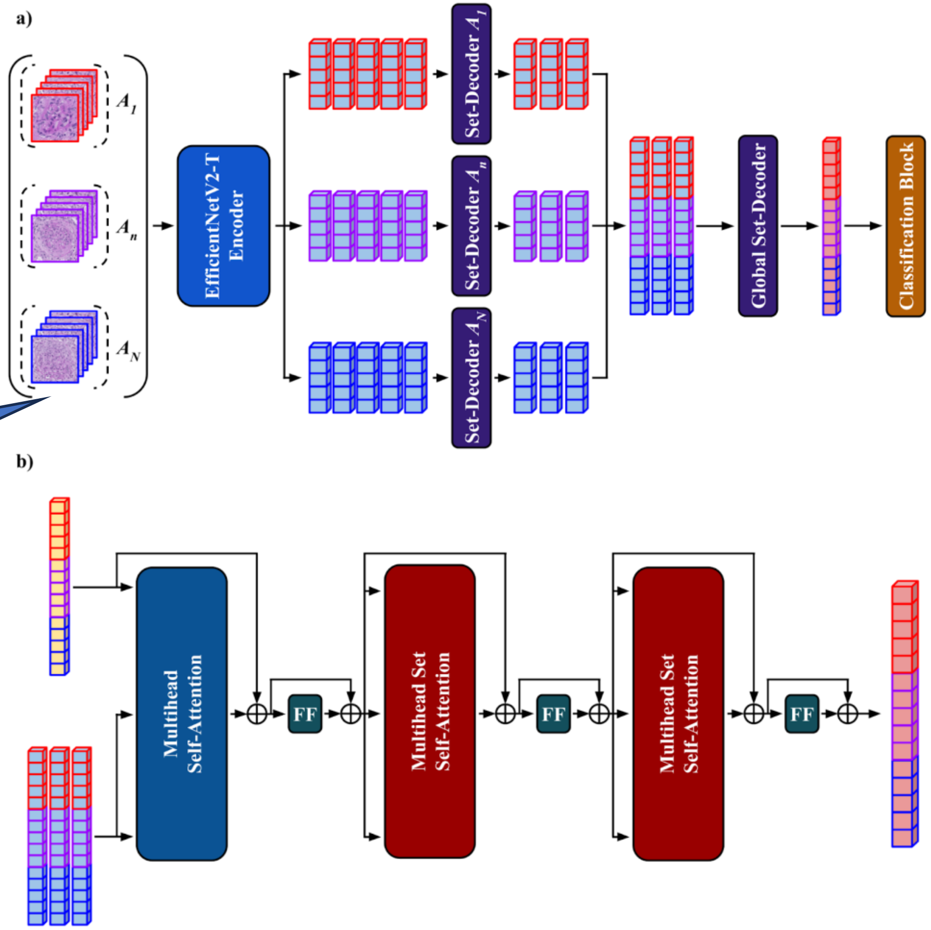
LogReg superior to ML in 2-Step-Score Development



Multimodal Machine Learning

- Use every source of information available for the task
- Not just histology images
  - Paraffin histology
  - Immunohistology
  - Electron microscopy
- But also clinical parameters
- Including e.g. immunogenetic data for transplants
- Parametrisation of such data?

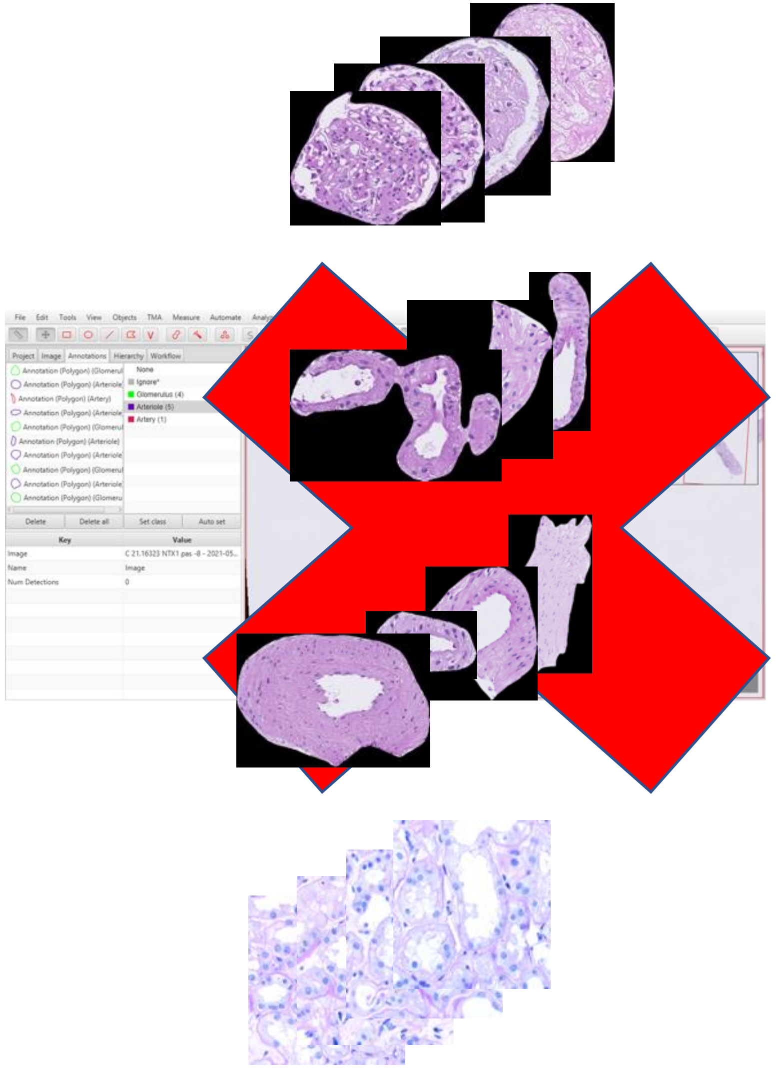
MILxFormer Architecture

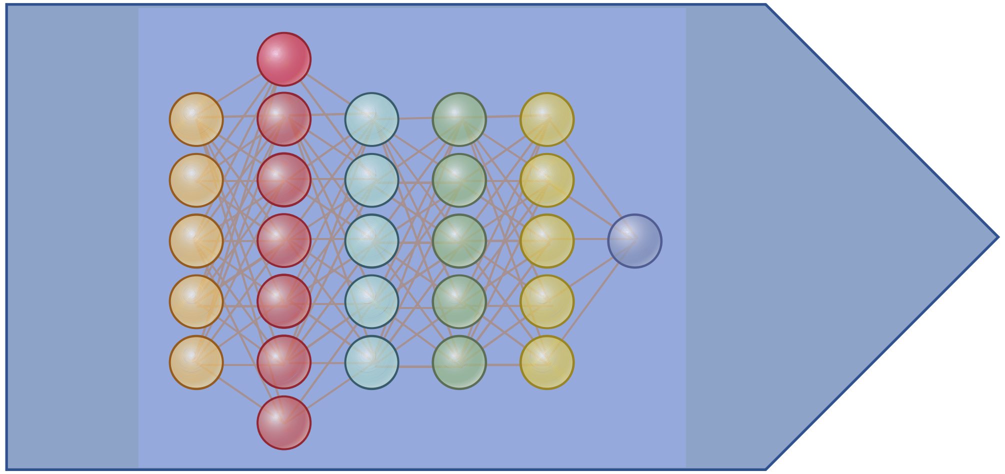


Unlimited input channels, combining different modalities

Cicalese et al. in revision

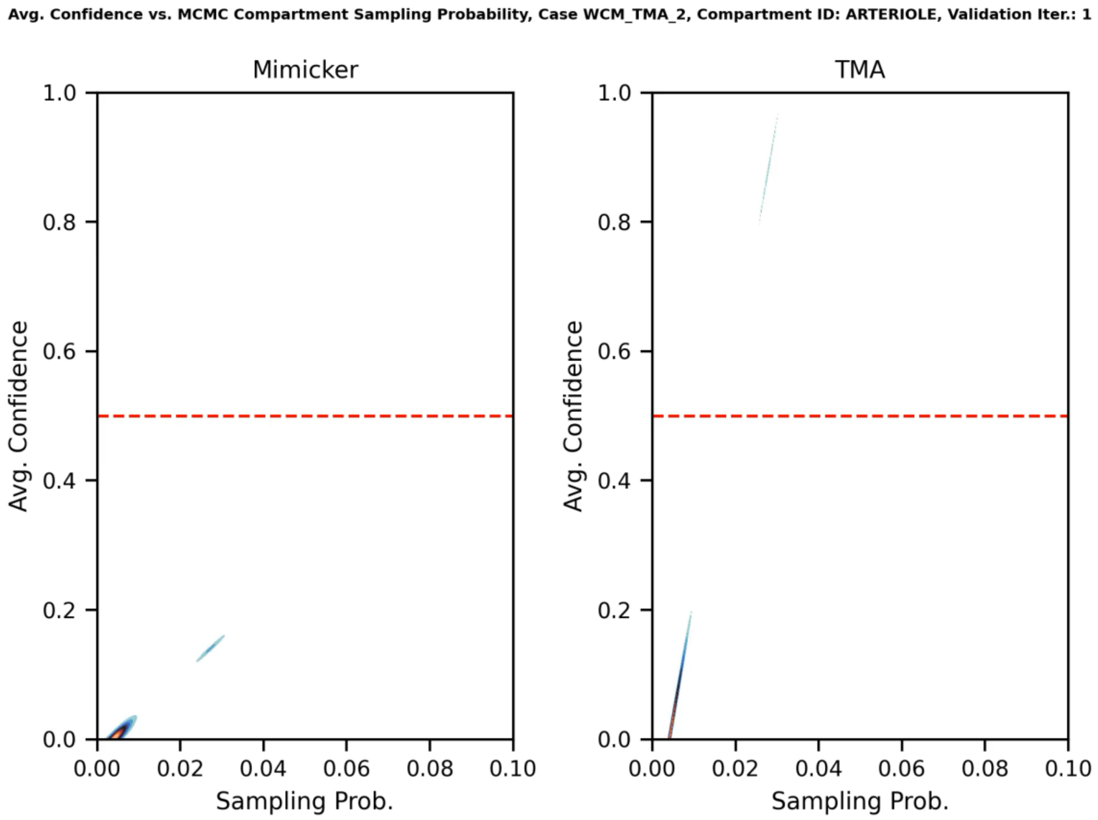
ML as Multiple-Instance Learning

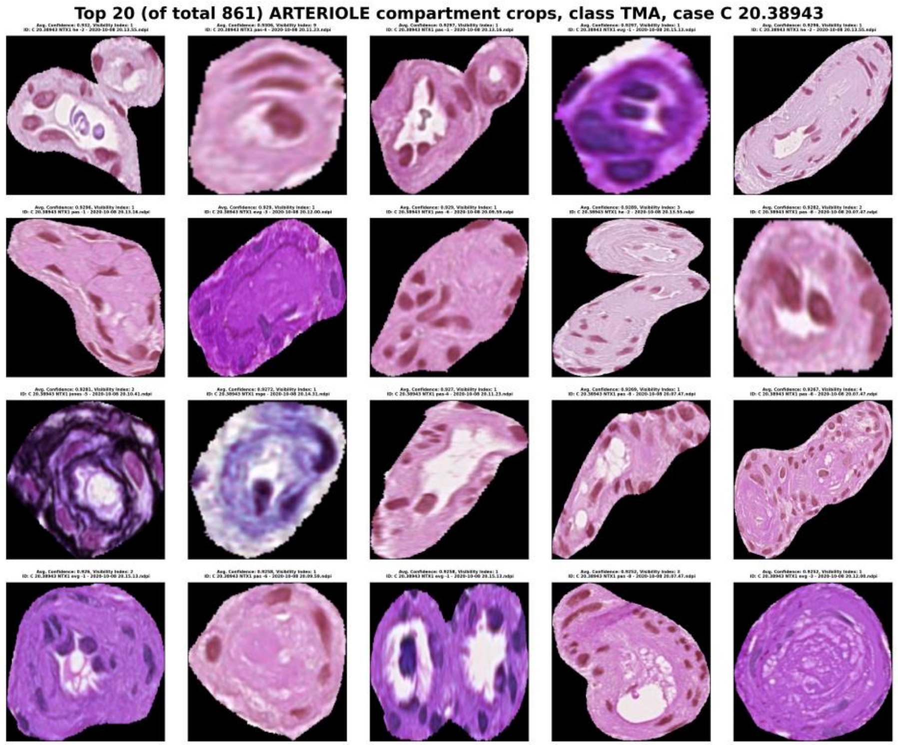




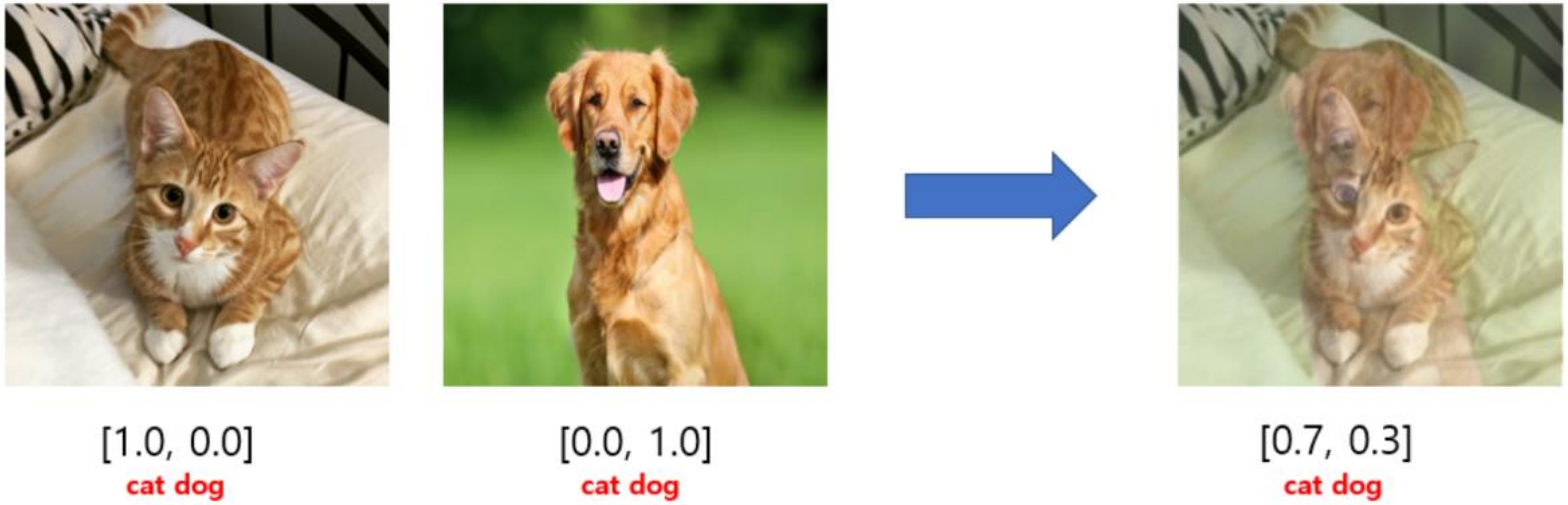
Meaningful output

Soft Markov Chain Monte Carlo Sampling





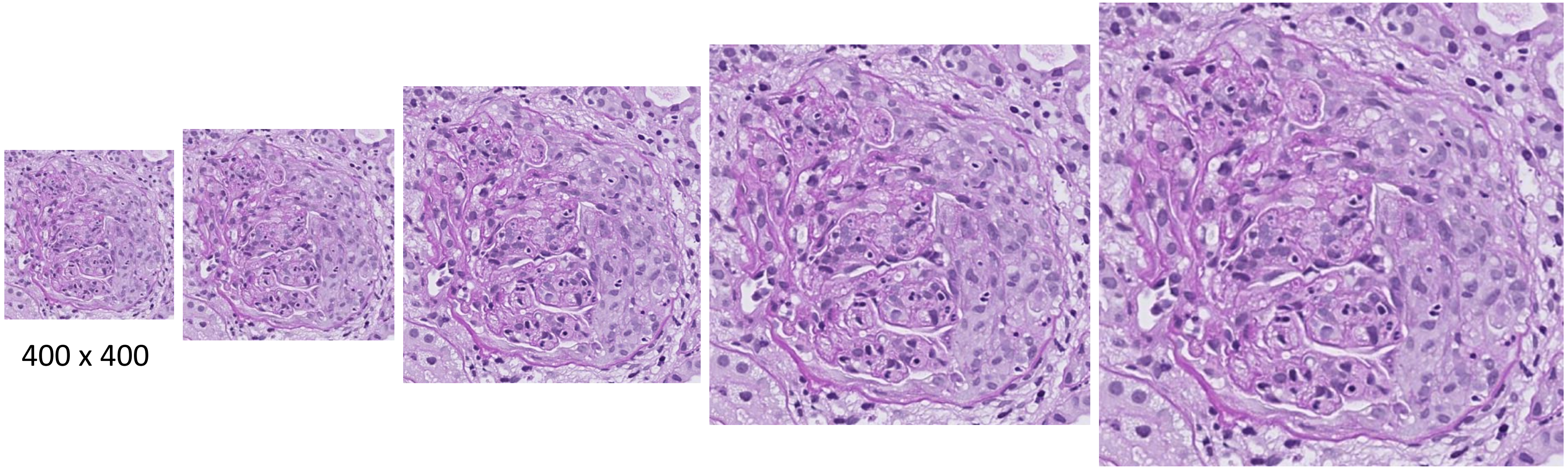
Advanced Methods of Sample Size Augmentation for MILxFormer: MixUp



Zhang et al arXiv 2020

Advanced Methods of Sample Size Augmentation for MILxFormer: MILxScale

4 different resolutions from to 1100 x 1100



Cicalese et al. in revsision

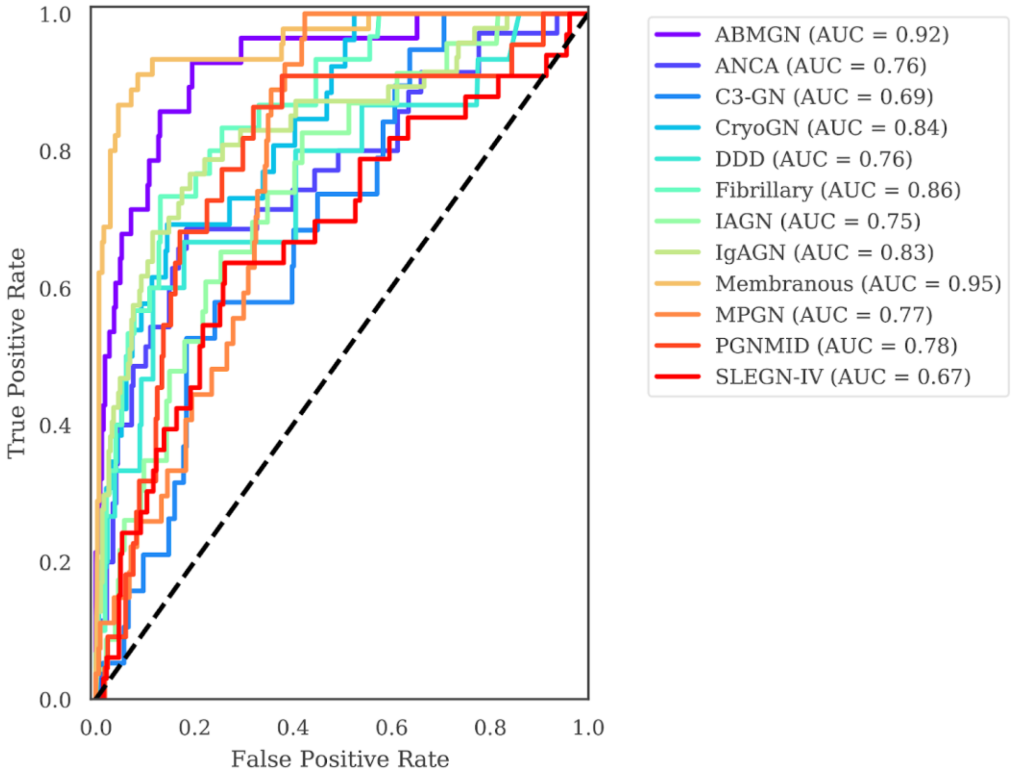
Development of MILxFormer from MorphSet

- Soft Markov Chain Monte Carlo Sampling instead of MC Sampling
- MILxUp: implementation of MixUp Zhang et al arXiv 2020 sample size augmentation
- MILxScale: 4 different resolutions from 400 x 400 to 1100 x 1100 as sample size augmentation
- MILxDrop: dropout (removal of corrupted filter nodes) in order to improve generalisation

Cicalese et al. in revision

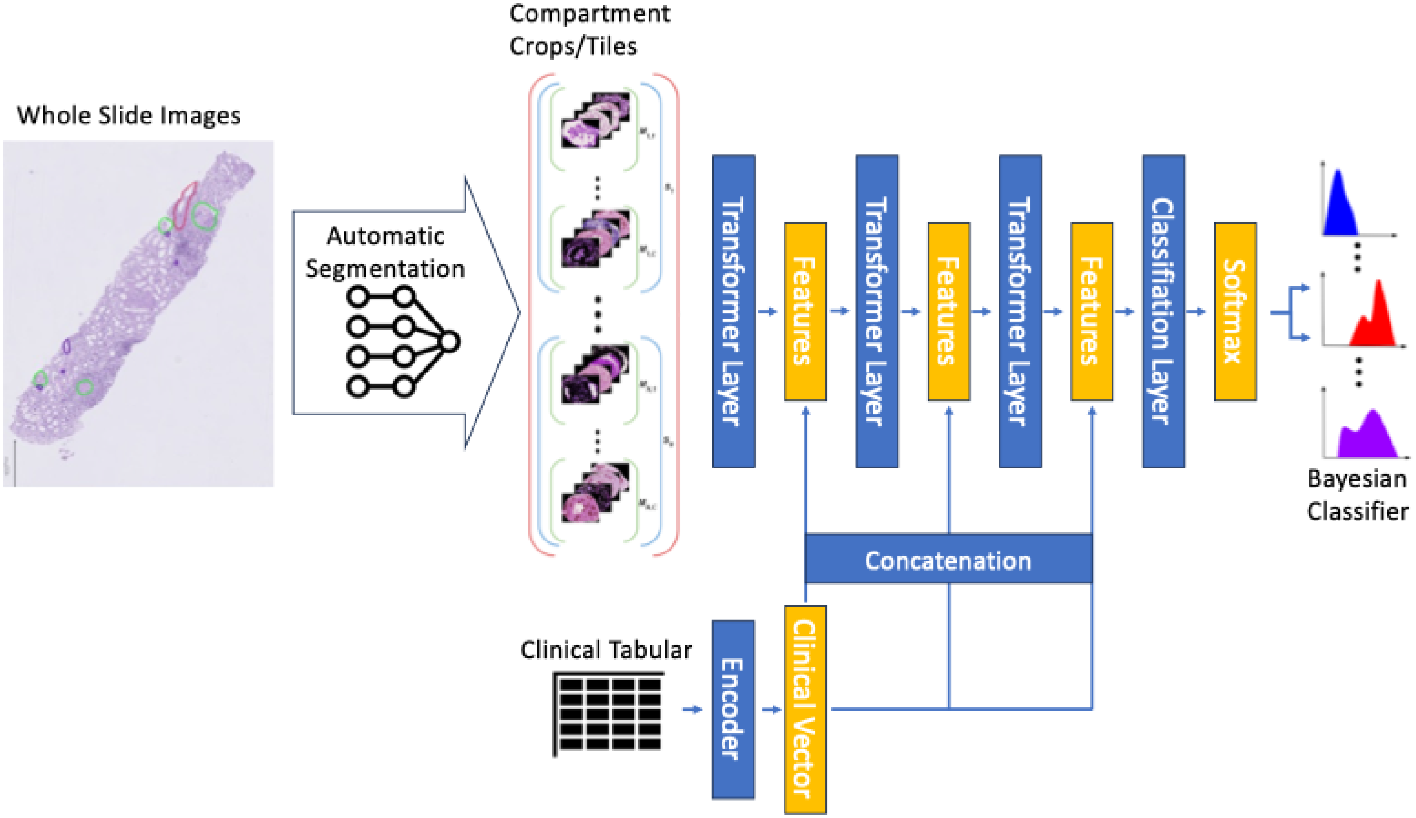
MILxFormer Architecture for Advanced Classification tasks

- Input: PAS glomerular transections (crops)
- Output: 12 classes of GN
- Training set: glomerular crops from 350 biopsies
- Weakly supervised training
- MILxFormer architecture
- Internal cross-validation

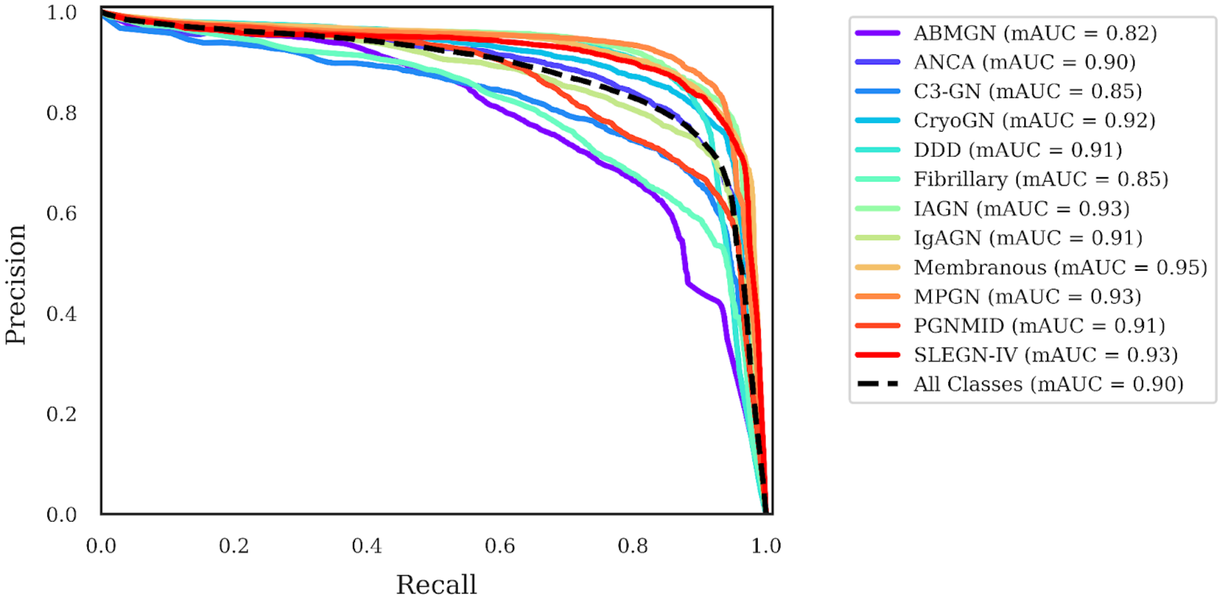


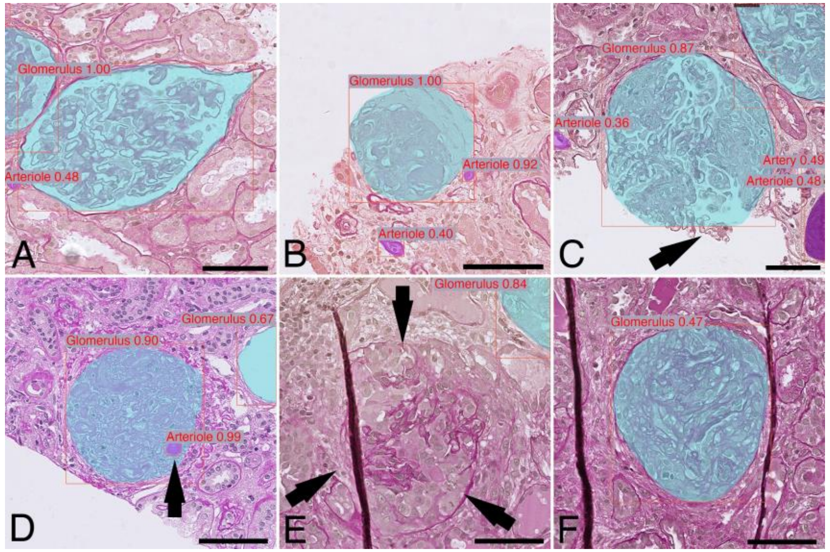
Cicalese et al. in revision

MILxFormer+ for Multimodal Data



Automatic Segmentation

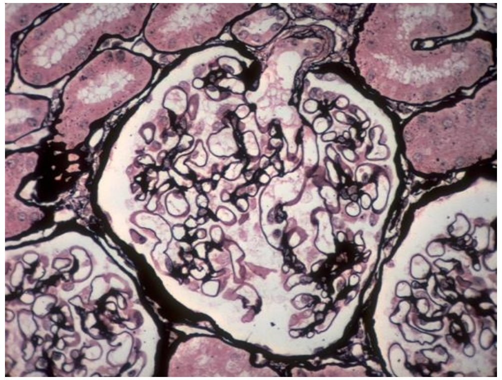


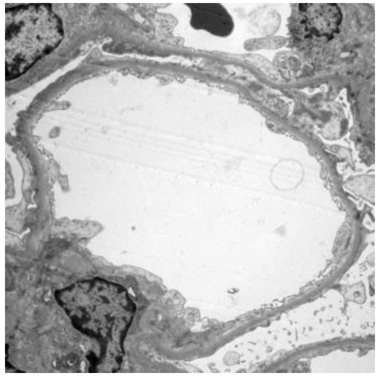


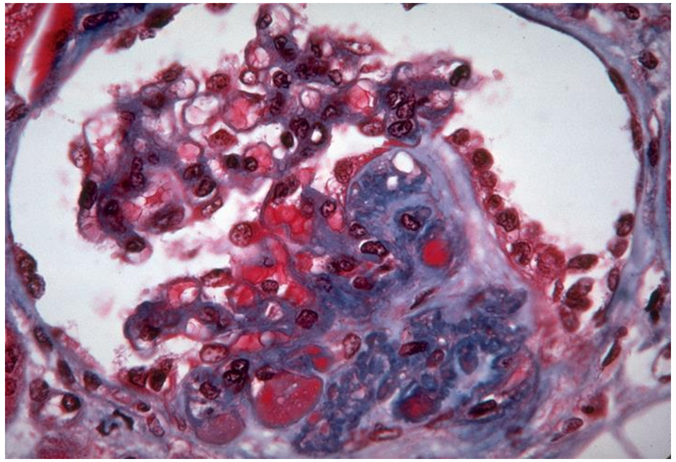
Cicalese et al. in preparation

Integration of clinical tabulation with histology: Treatment response with SRNS

- Steroid resistant nephrotic syndrome: podocytopathy predominantly in children
- Cause: defect in podocyte-relevant genes or unknown circulating factor (T cell-secreted?)
- Histology: minimal change-nephropathy, FSGS, diffuse mesangial sclerosis (DMS)

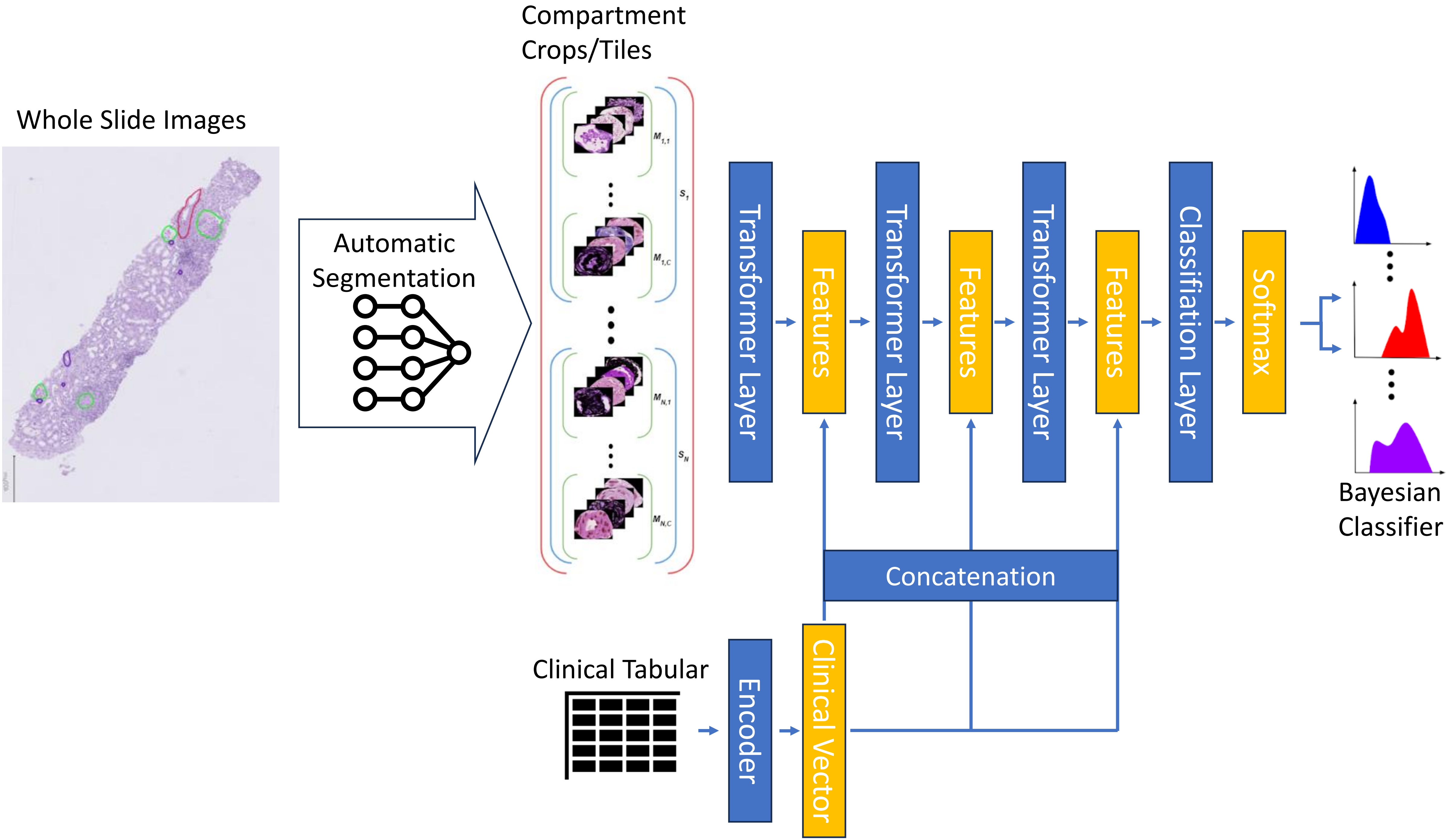




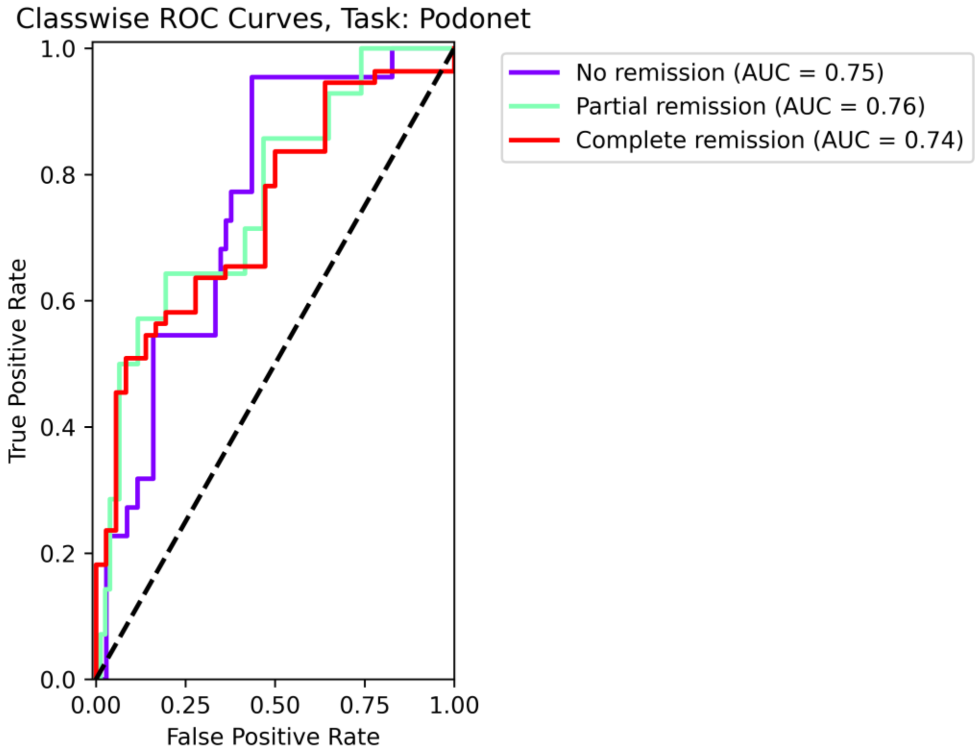


Steroid Resistant Nephrotic Syndrome

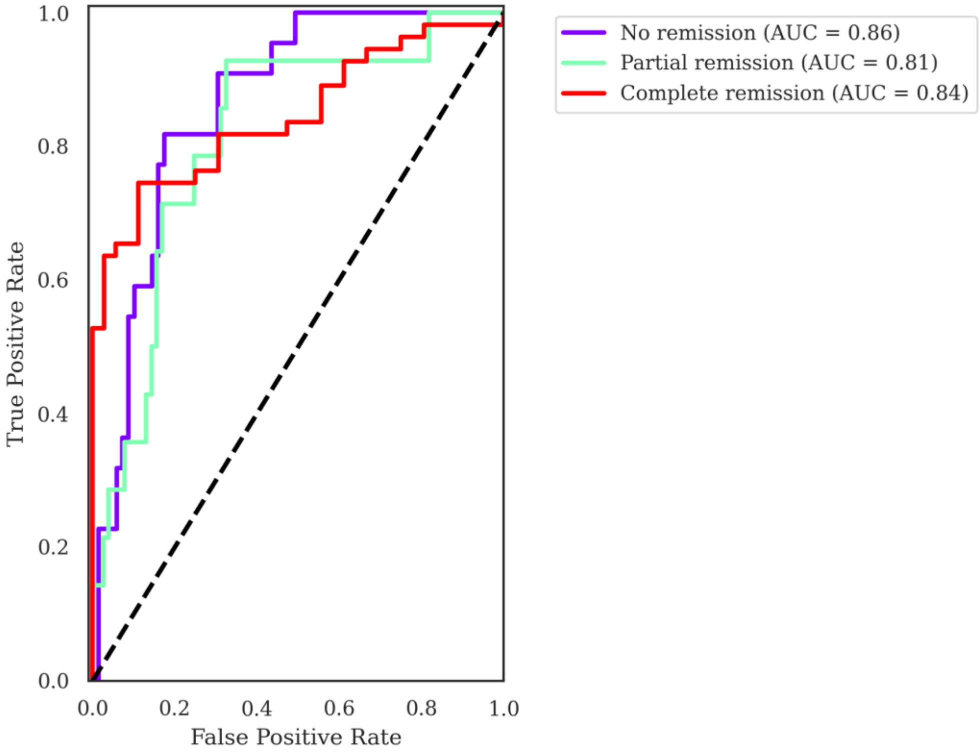
- Steroid resistance: max. 14 weeks without response to immunosuppression
- Then „intensified immunsuppression“ with e.g. CNIs
- Current paradigm: conventional histology inferior for prognosis and theranostic compared to genetics
- PodoNet cohort, 14 centres (Izmir to Vilnius), very large domain shifts
- n=201 biopsies, n=114 no remission, n=42 partial remission, n=45 complete remission


Whole Slide Images
Automatic Segmentation
Compartment Crops/Tiles
$M_{1,1}$
$M_{1,C}$
S_1
$M_{N,1}$
$M_{N,C}$
S_N
Transformer Layer
Features
Transformer Layer
Features
Transformer Layer
Features
Classifiation Layer
Softmax
Bayesian Classifier
Concatenation
Clinical Tabular
Encoder
Clinical Vector

Theranostics for SRNS with MILxFormer

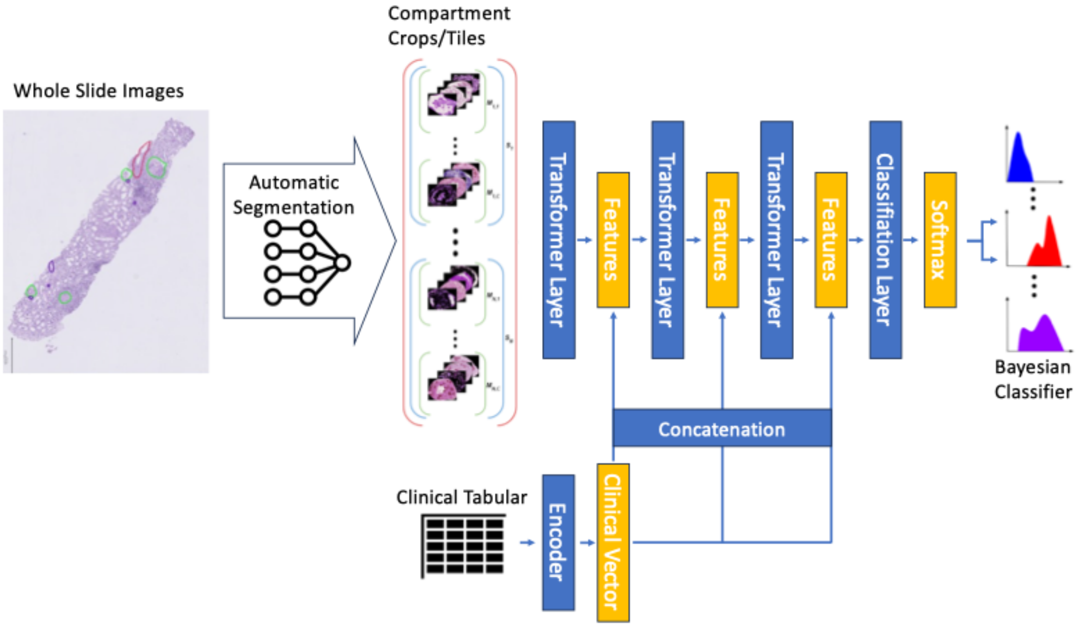


Gaussian naive Bayes classifier
Only clinical data at biopsy (incl. binary Mutation)

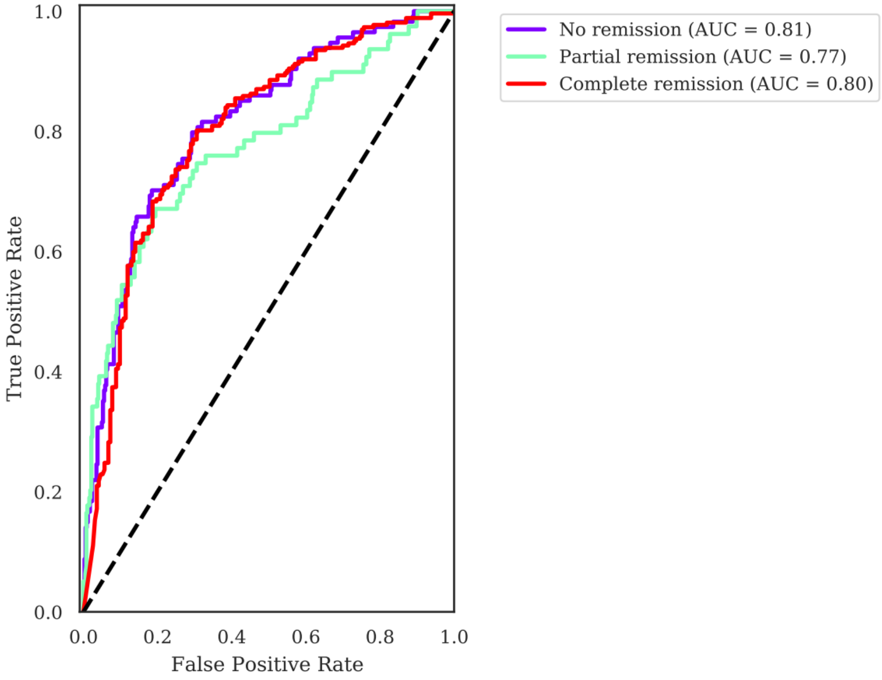


MILxFormer
Only histology

Theranostics for SRNS with MILxFormer

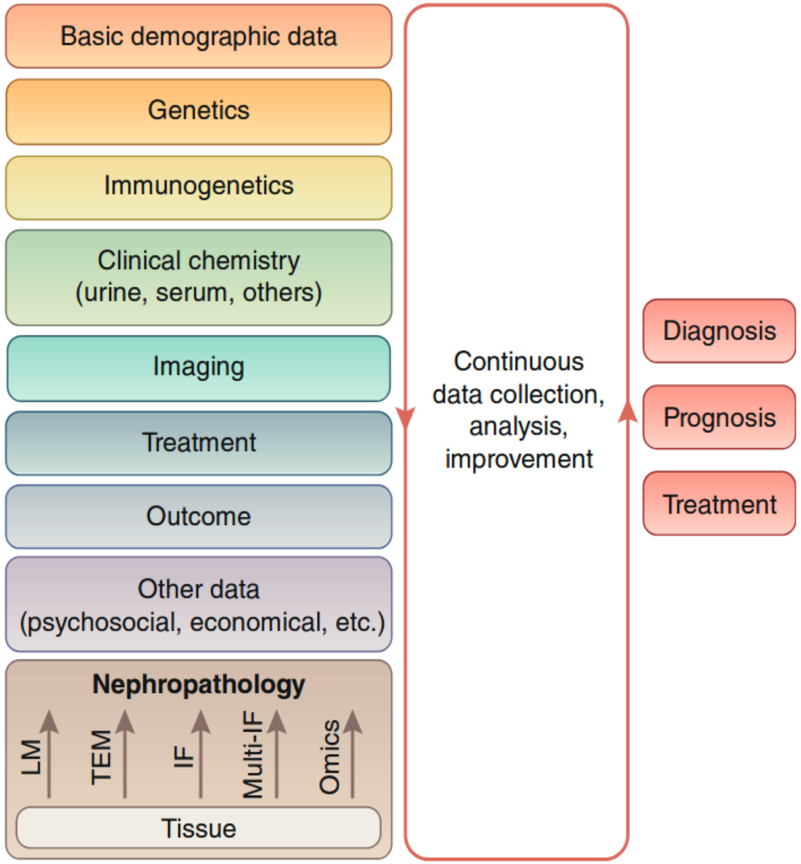


Response to intensified IS in SRNS
(5-fold internal cross-validation)



Vo, Gimpel et al., manuscript in preparation

Nephropathology,
Big Data and Precision Medicine



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Other data (psychosocial, economical, etc.)

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Continuous data collection, analysis, improvement

Diagnosis

Prognosis

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Becker et al. KI 2019

Summary/Outlook

- Weakly supervised ML ist currently the only realistic option for the evaluation of large clinico-pathological datasets for diagnostics, prognostication and theranostics
- A framework of segmentation followed by classification allows for rapid and efficient, training, upscaling and expansion with large datasets from trusted institutions
- We need large reference datasets with ERKNet‘s ERKReg, CERTAIN/CTS as go-to platforms for native and transplant nephrology
- Integration of (multimodal) foundation models next frontier

Datasets with (treatment) outcome needed

Thank you!

- Houston: Hien V. Nguyen, Pietro A. Cicalese, Syed Rizvi, Chandra Mohan, Badri Roysam
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- Szeged: Béla Ivanyi, Sándor Turkevi-Nagy
- New York: Surya Seshan, Ibrahim Batal
- Baltimore: Avi Rosenberg
- ERKNet, PodoNet (F. Schäfer), CERTAIN (B. Tönshoff)
- DFG and Köln Fortune