

(Deep) learning for automated Gleason grading and disease associated molecular profiles

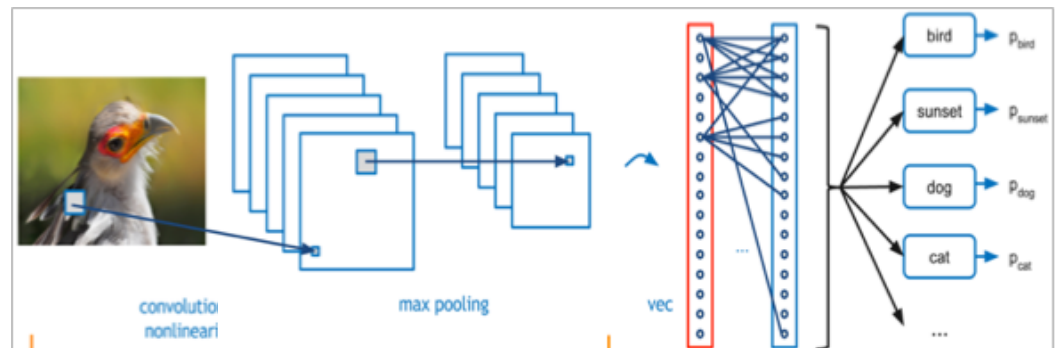
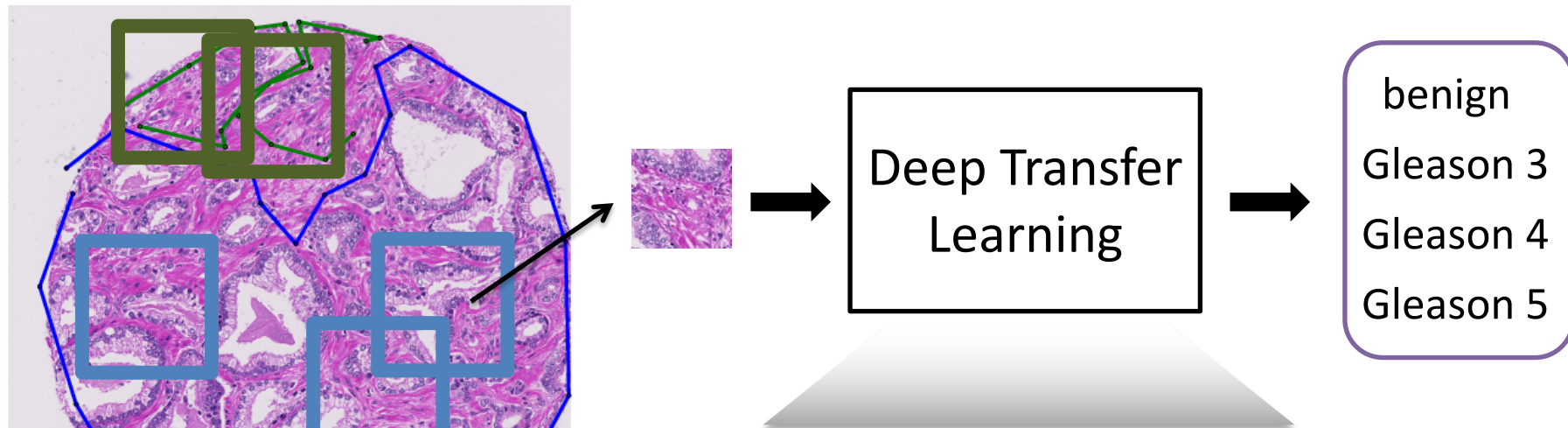
SDiPath Meeting

Bern

January 10th, 2019

Manfred Claassen
ETH Zurich

From single cell suspensions to tissue images - Computational pathology with CNNs



Peter Wild

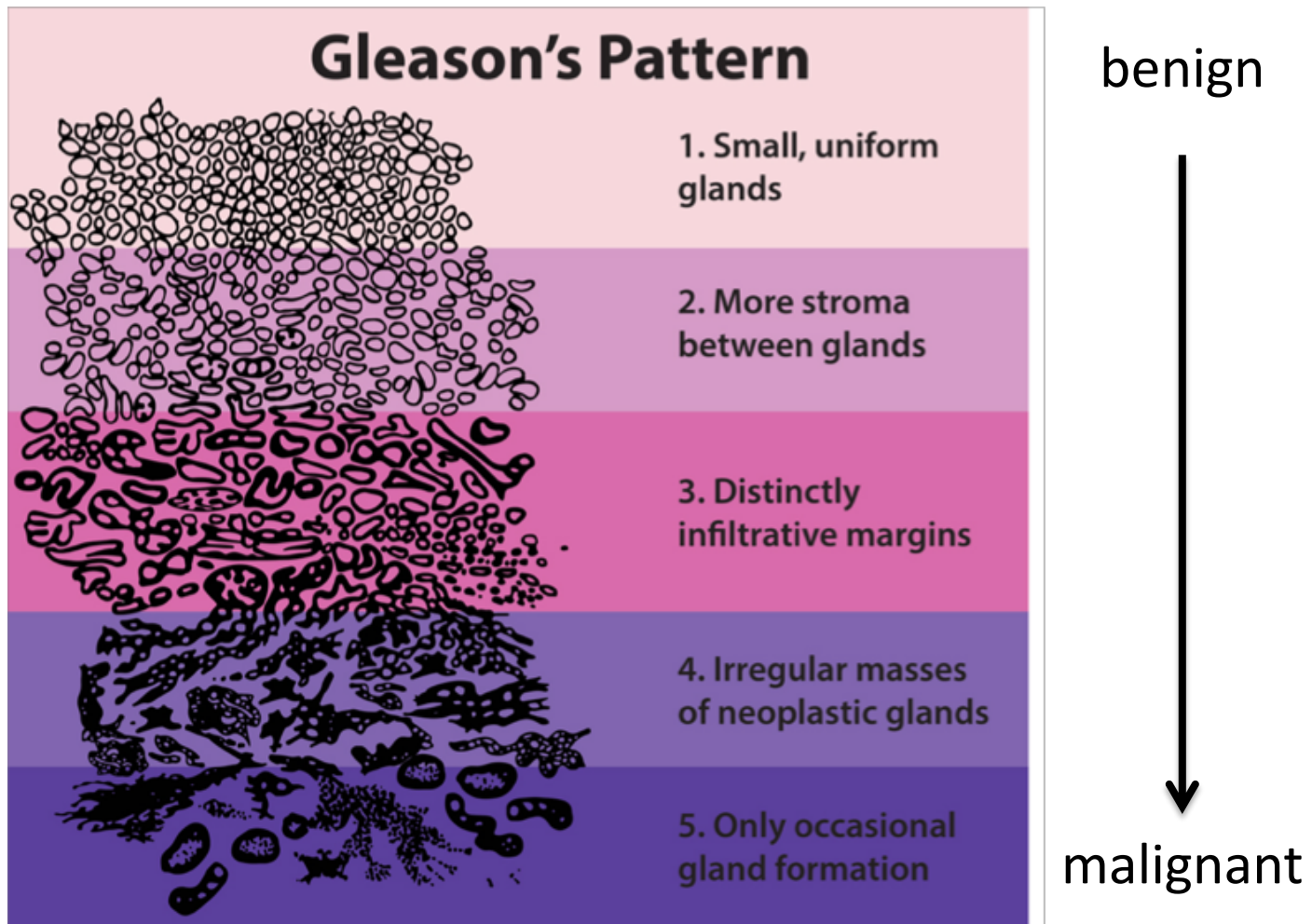


Kim Fricker

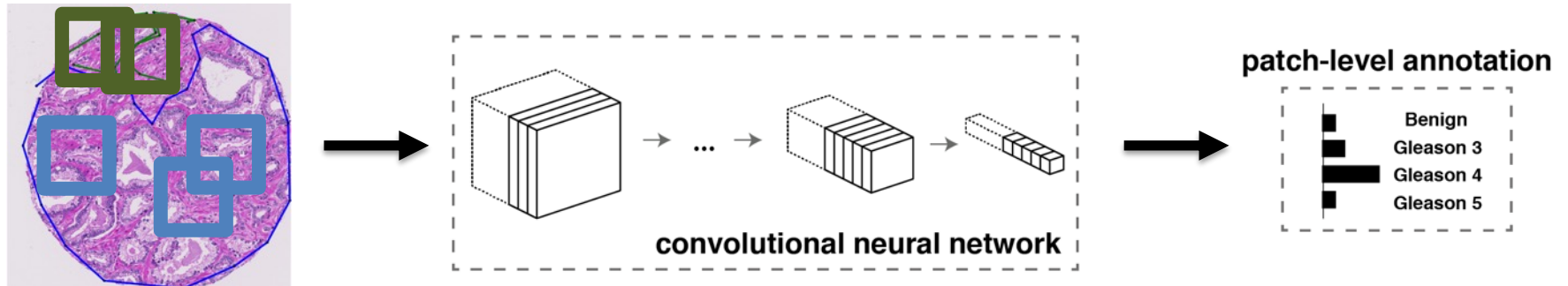


Jan Rueschoff

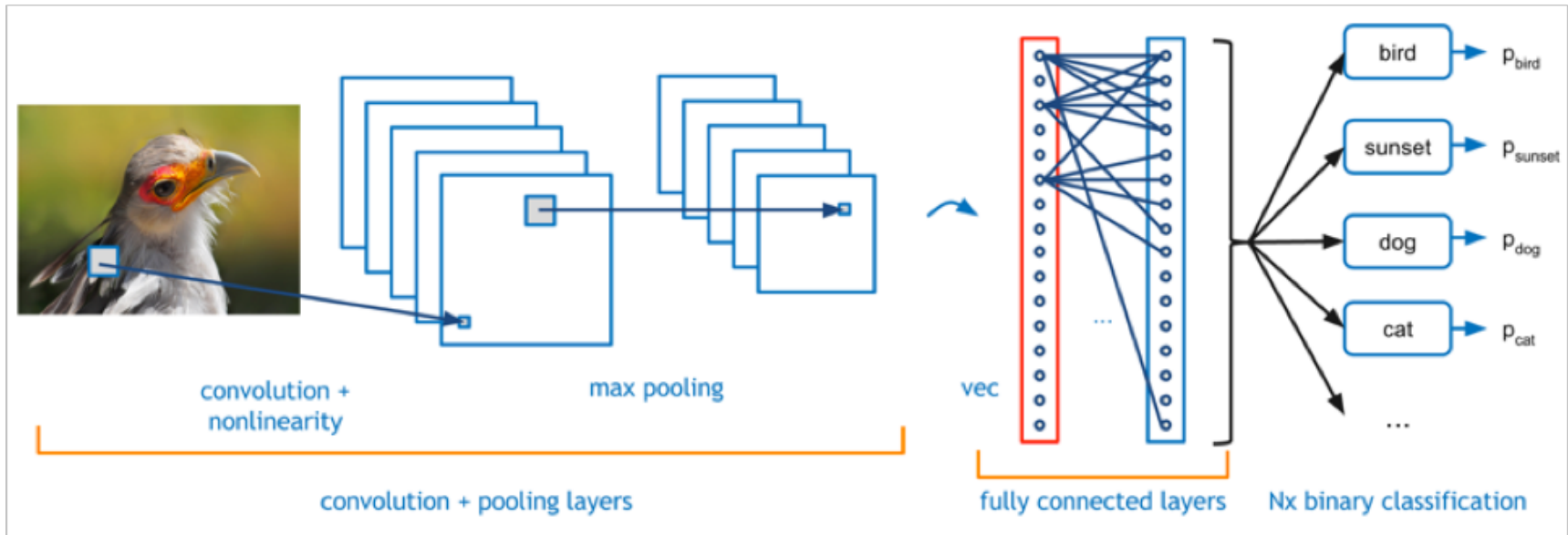
Gleason patterns for prostate cancer grading



Automatic grading by deep learning

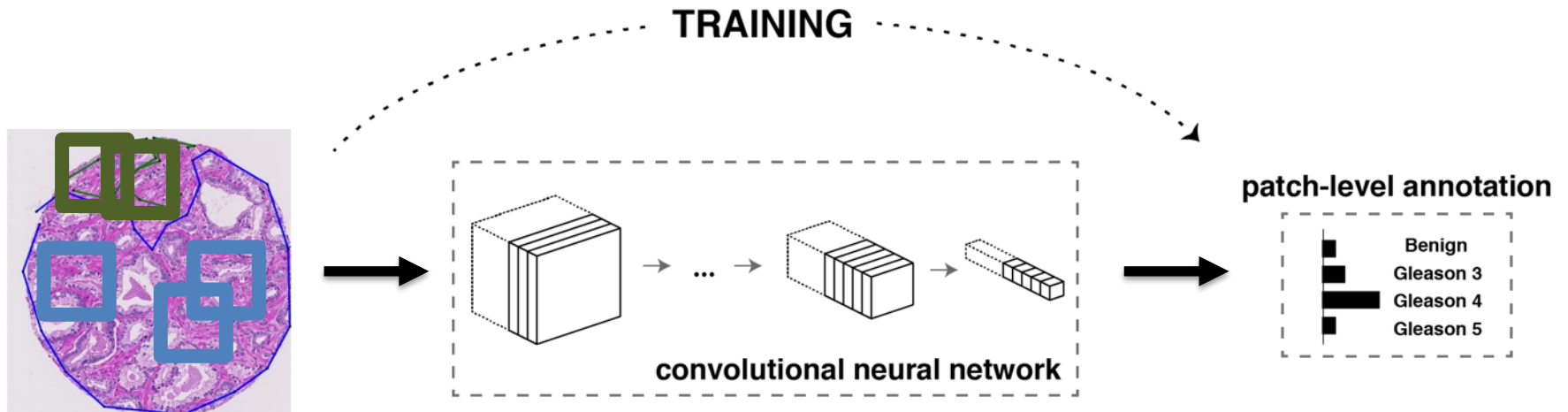


Convolutional neural networks primer for image analysis



- CNNs learn relevant image patterns by convolving over image patches

Automatic grading by deep learning

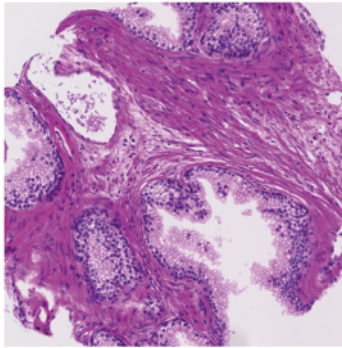


Training data:

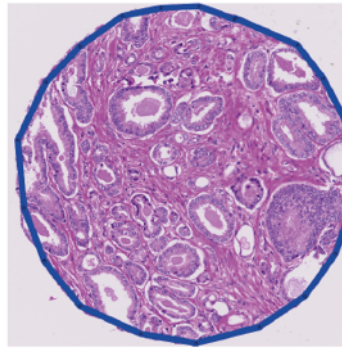
5 TMAs (864 spots) with pathology expert Gleason annotation

Pathology expert Gleason annotation

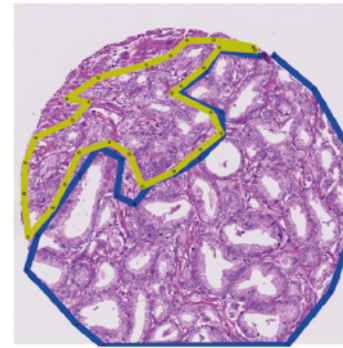
Benign



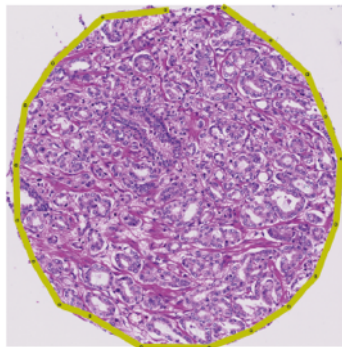
Gleason 6 (3+3)



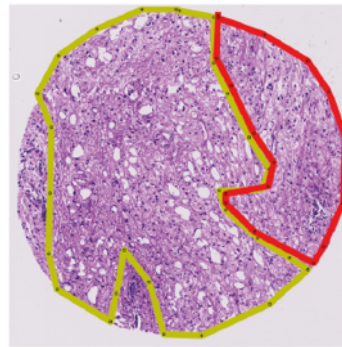
Gleason 7 (3+4)



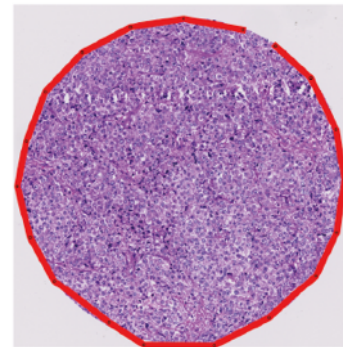
Gleason 8 (4+4)



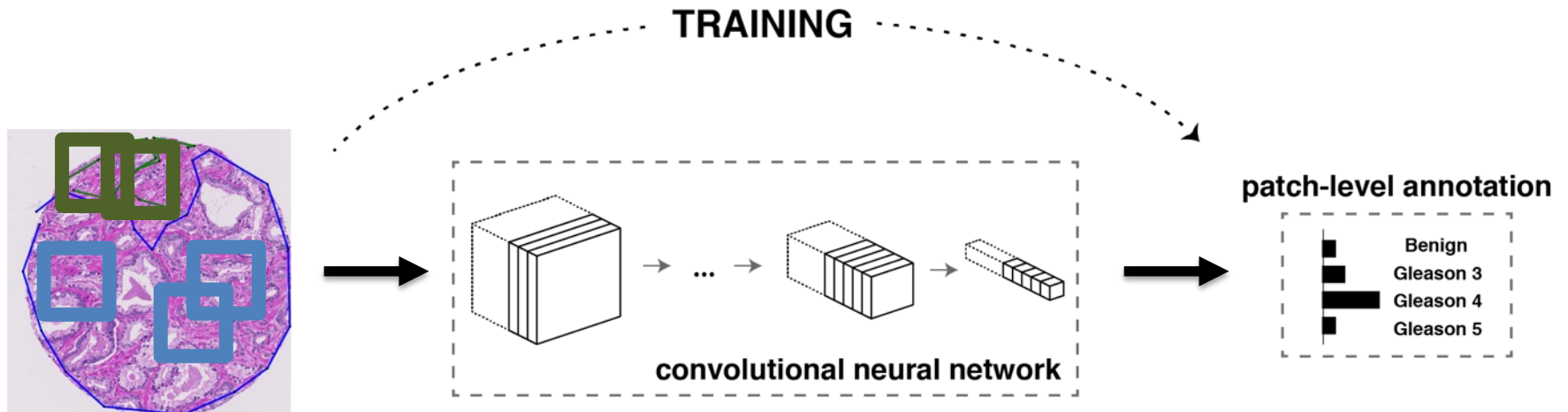
Gleason 9 (4+5)



Gleason 10 (5+5)



Automatic grading by deep learning

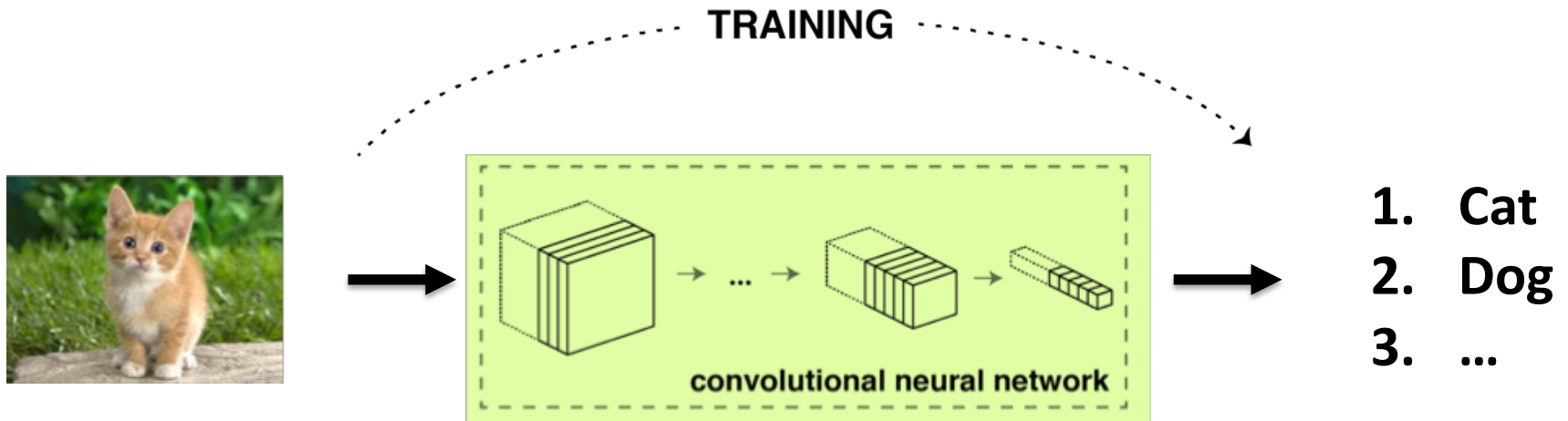


(Too little) training data:

5 TMAs (864 spots) with pathology expert Gleason annotation

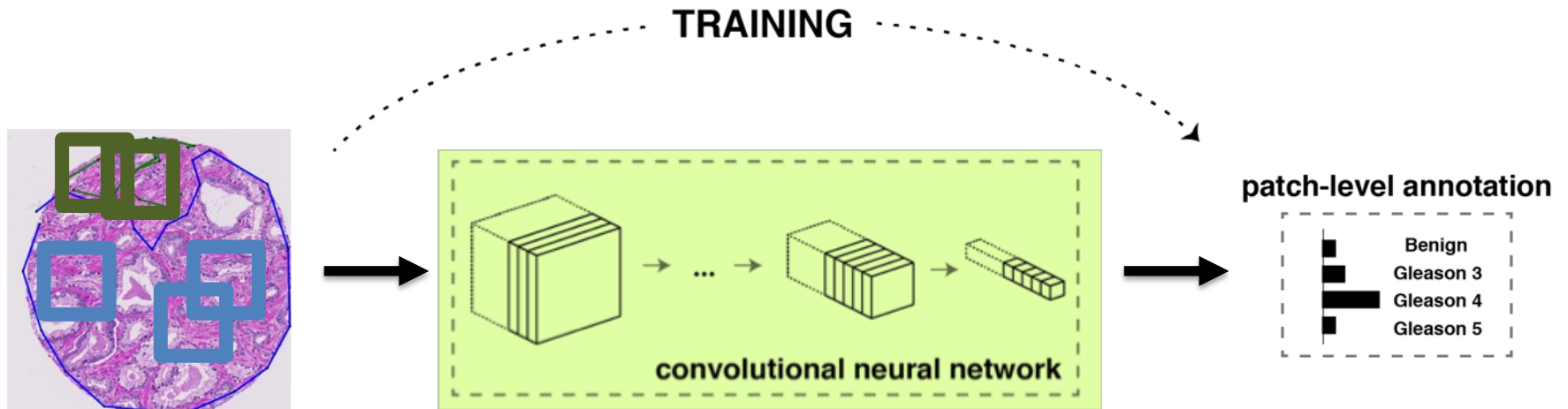
Solution: TRANSFER LEARNING !

Detour: successful image classification by deep learning with big data



(Big) training data:
e.g. millions of frames from internet videos

Successful grading by deep transfer learning



(Enough !) training data:
5 TMAs (864 spots) with Gleason annotation

Solution: TRANSFER LEARNING !

Model evaluation on test cohort and inter-pathologist variability

model vs pathologist 1

pathologist 1

benign	6	6	0	0	0	0
Gleason 6	0	32	46	1	0	0
Gleason 7	0	3	28	19	1	0
Gleason 8	0	0	27	37	20	0
Gleason 9	0	0	1	5	1	0
Gleason 10	0	0	0	0	11	1
	benign	Gleason 6	Gleason 7	Gleason 8	Gleason 9	Gleason 10

model prediction

Cohen's quadratic kappa = 0.75

model vs pathologist 2

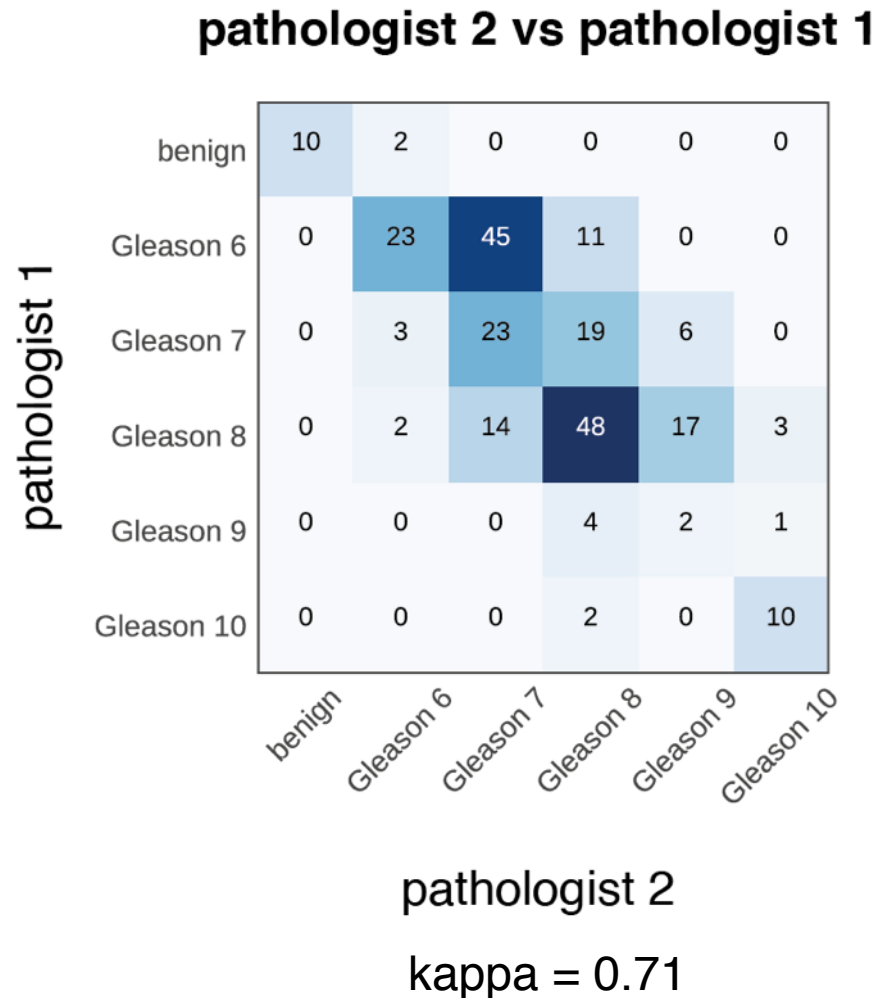
pathologist 2

benign	6	4	0	0	0	0
Gleason 6	0	17	12	1	0	0
Gleason 7	0	19	52	11	0	0
Gleason 8	0	1	29	37	17	0
Gleason 9	0	0	8	13	4	0
Gleason 10	0	0	1	0	12	1
	benign	Gleason 6	Gleason 7	Gleason 8	Gleason 9	Gleason 10

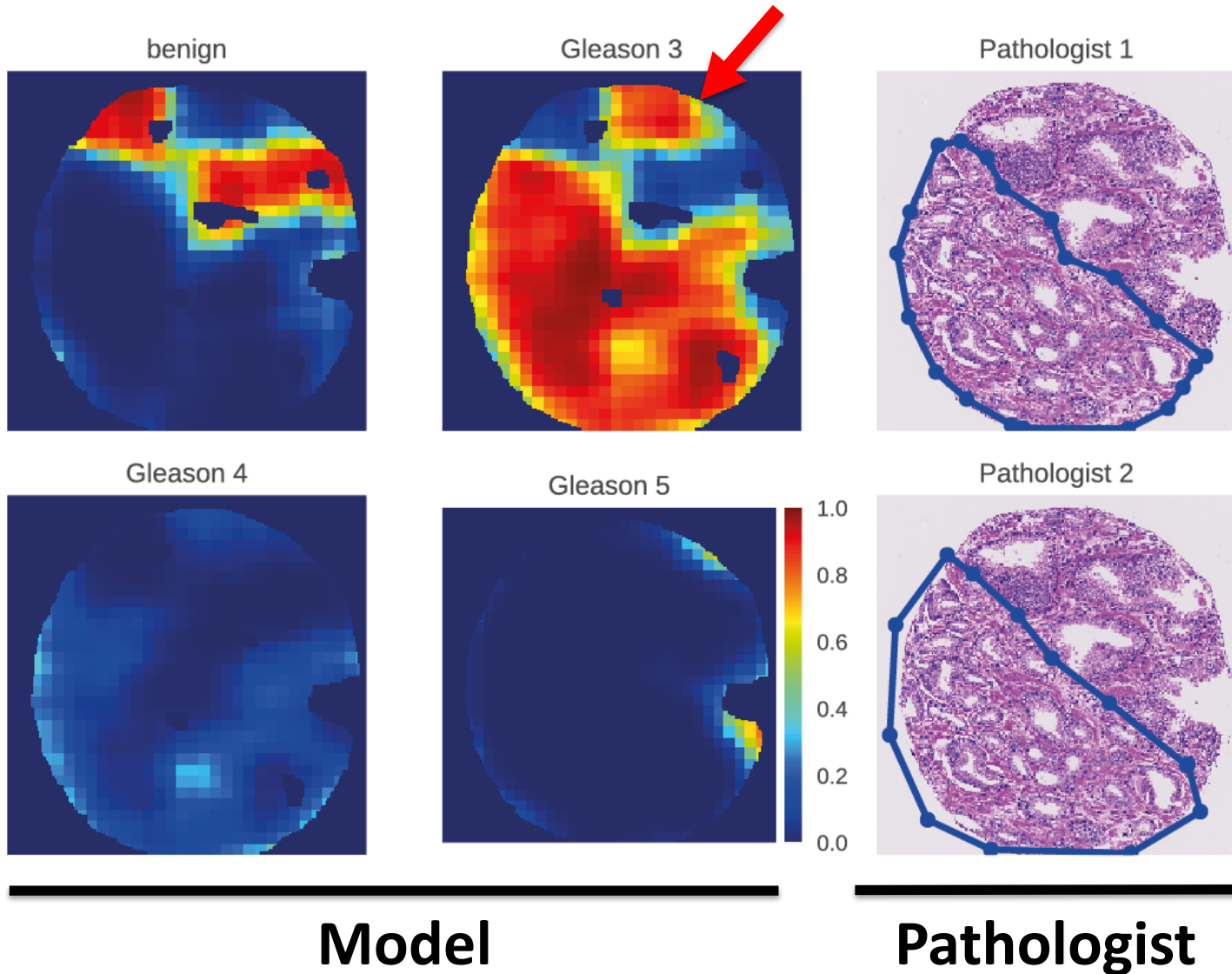
model prediction

kappa = 0.71

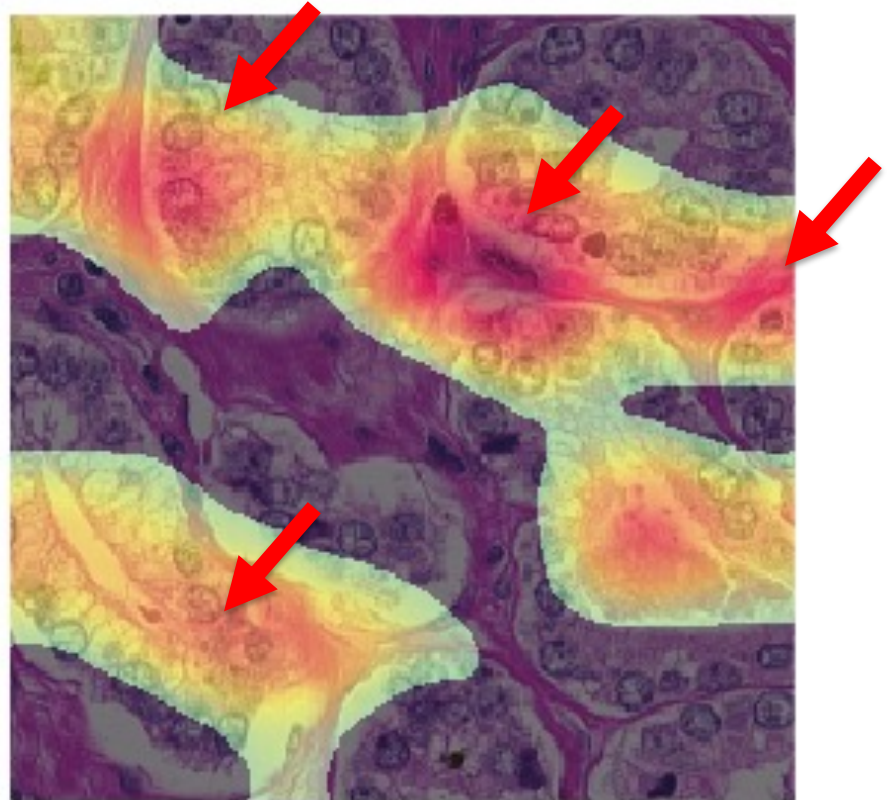
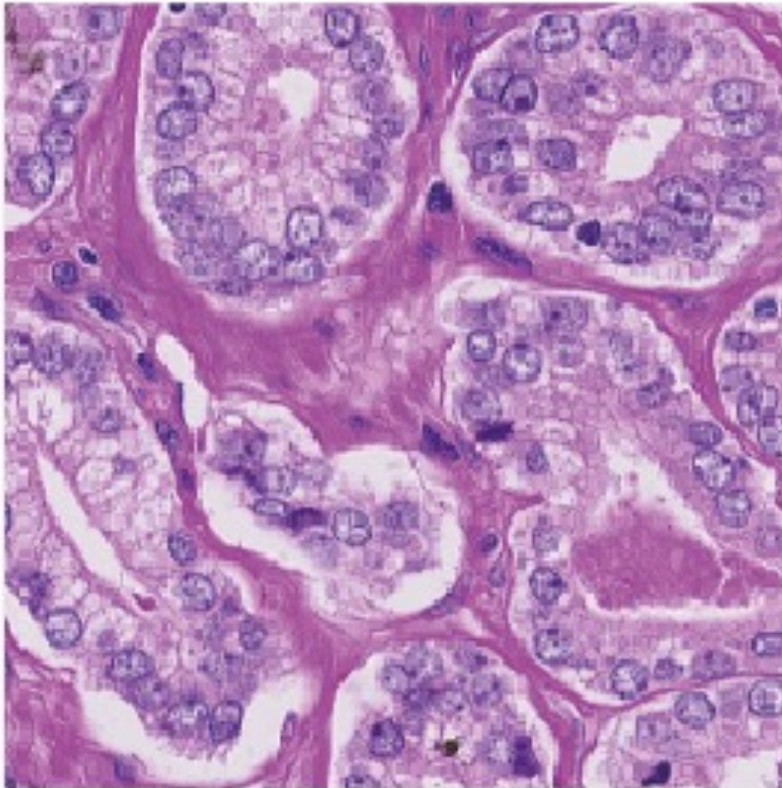
Model evaluation on test cohort (TMA) and inter-pathologist variability



Model predictions as pixel-level probability maps

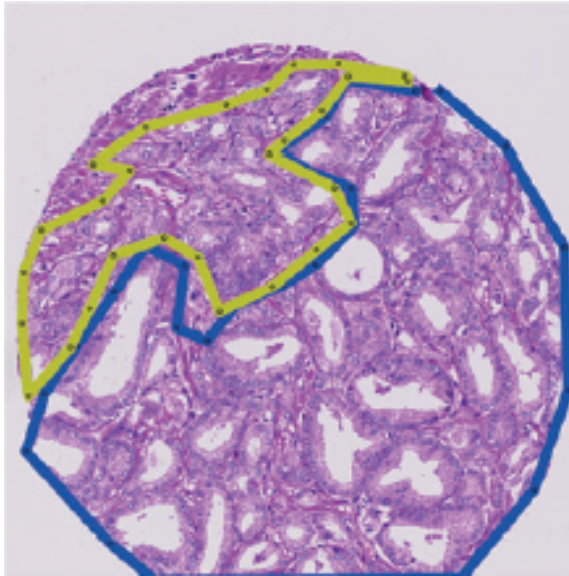


Model predictions are triggered by epithelial structures

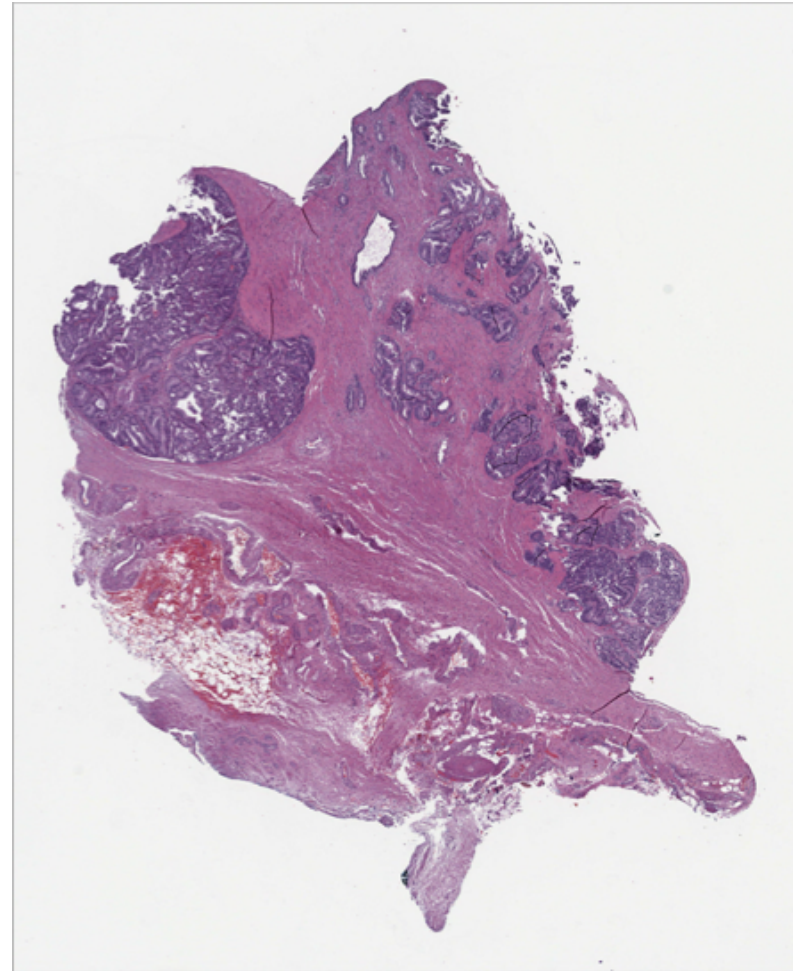


Gleason 3: unfused gland junctions to dissect from Gleason 4

Can we reduce the need for detailed pathologist annotations?



VS

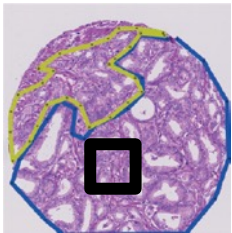


Local-level weak labels: e.g. Gleason 3+4

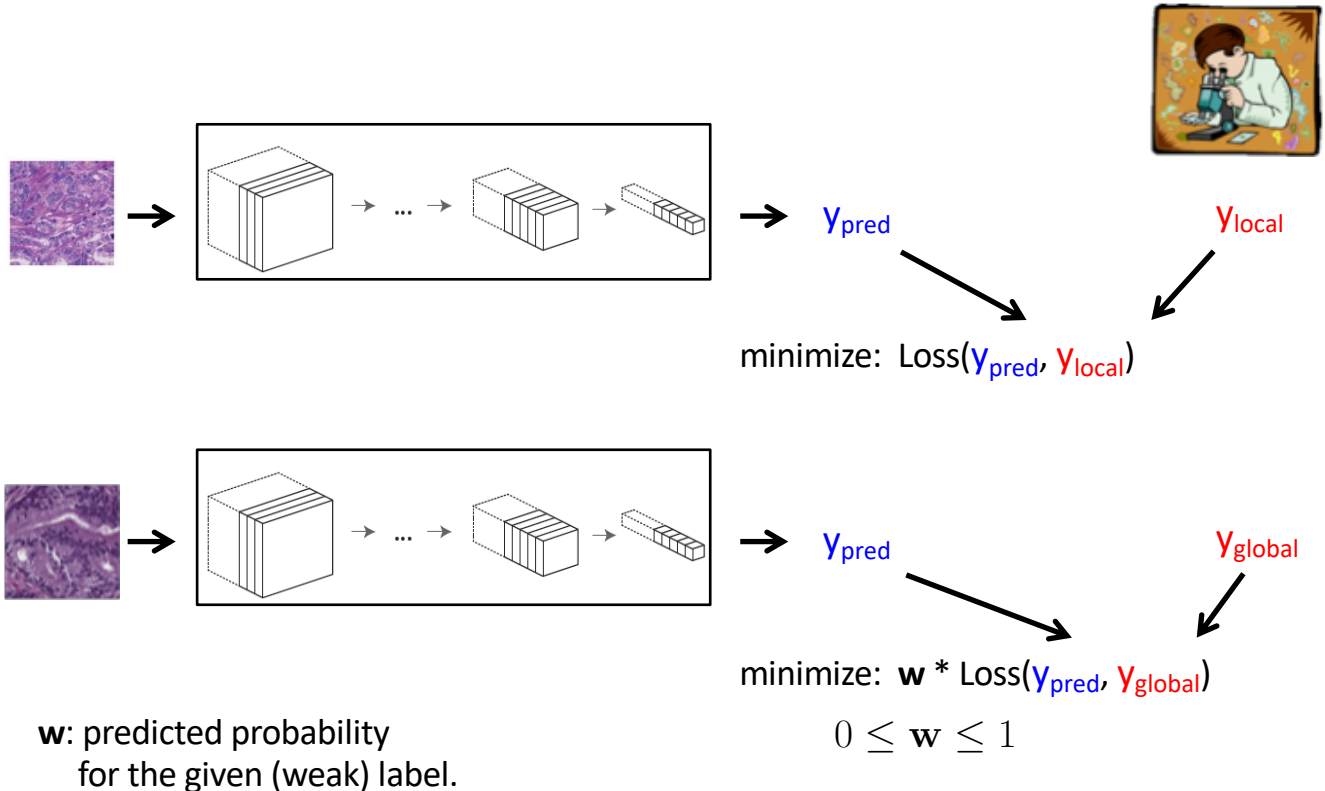
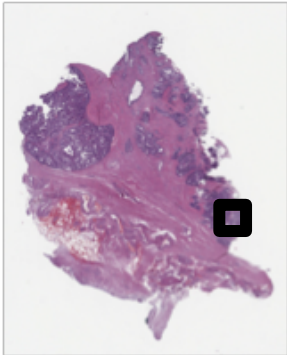
Global-level weak label: e.g. Gleason 7

Training with both local- and global-level annotations

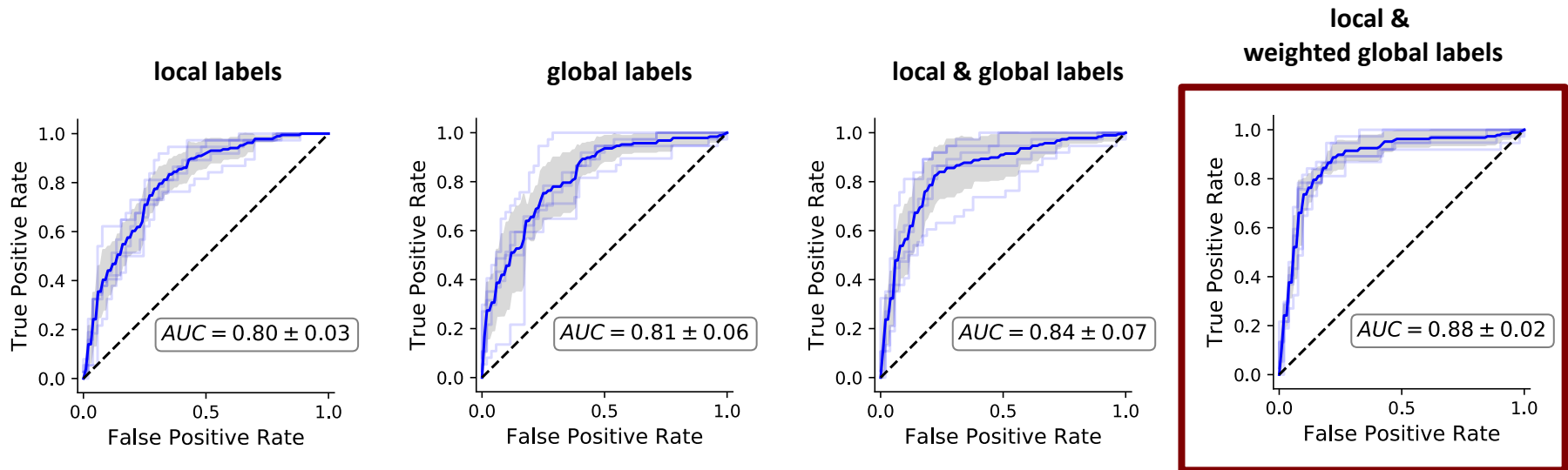
Local annotations



Global (weak) annotation



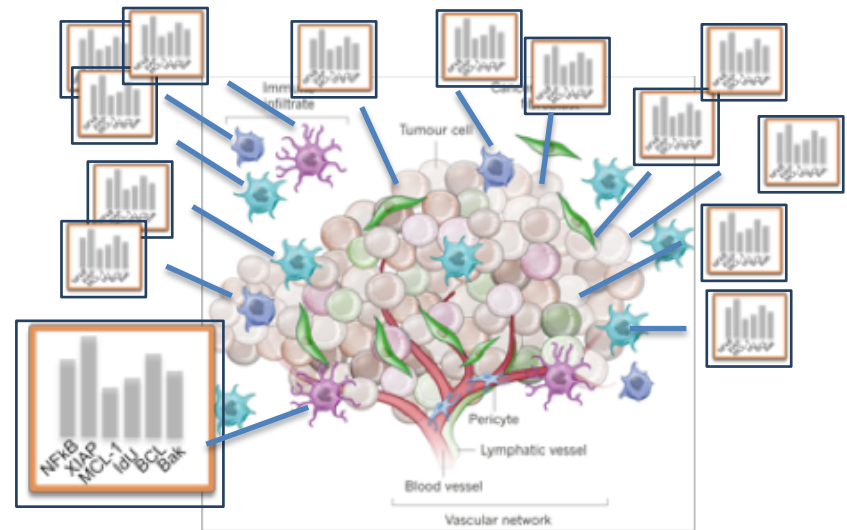
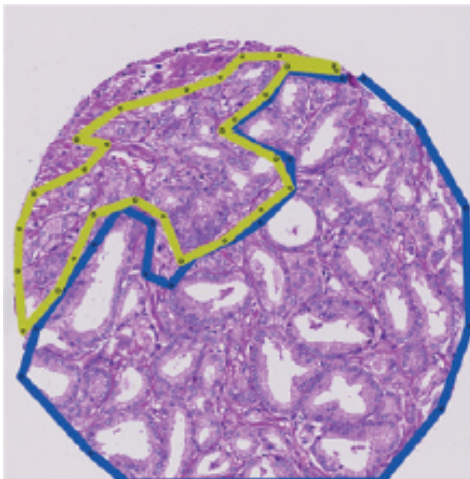
Weighted weak supervision outperforms simpler approaches



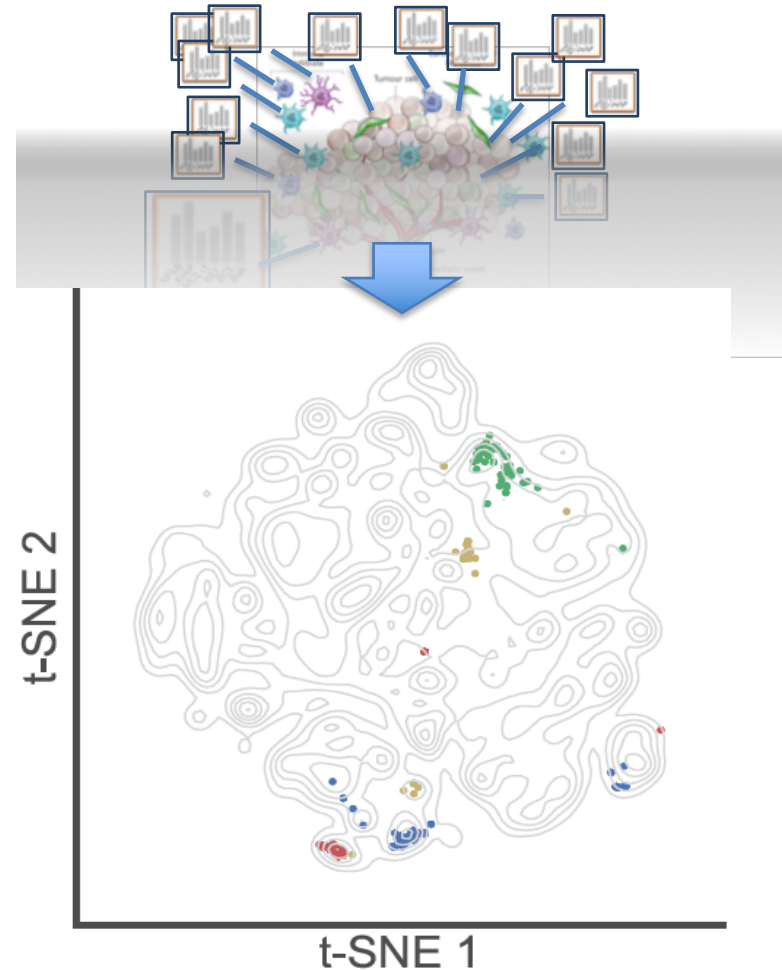
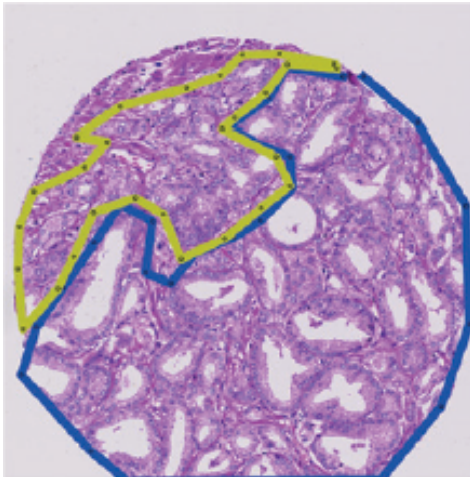
➤ **Task:** classify *low vs high Gleason score* cases from The Cancer Genome Atlas (TCGA) WSI.

				low grade			high grade	
dataset	# patches	# cases	Gleason low/high	≤ 6	7=3+4	7=4+3	8	9-10
TCGA	$\sim 300'000$	447	261/186	44	125	92	65	121
TMA	$\sim 25'000$	886	524/362	403	121		226	136

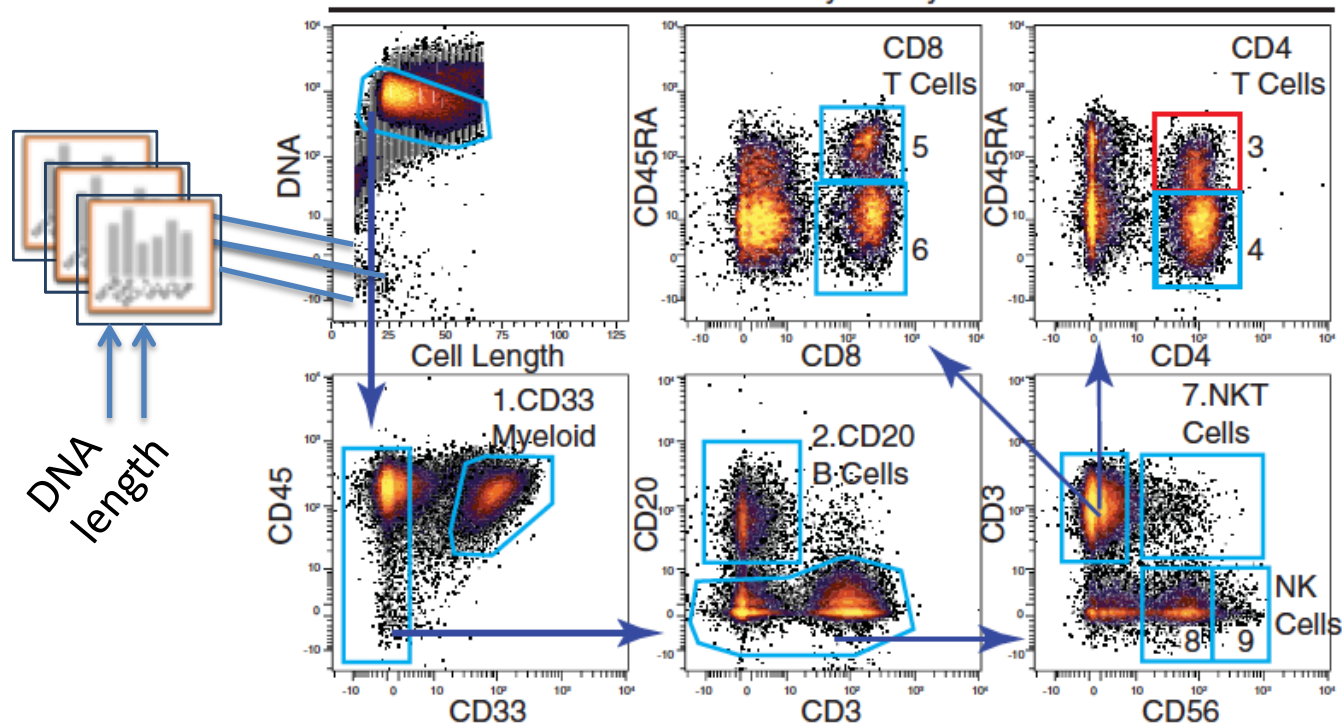
Images and single-cell data have a lot in common



Images and single-cell data have a lot in common

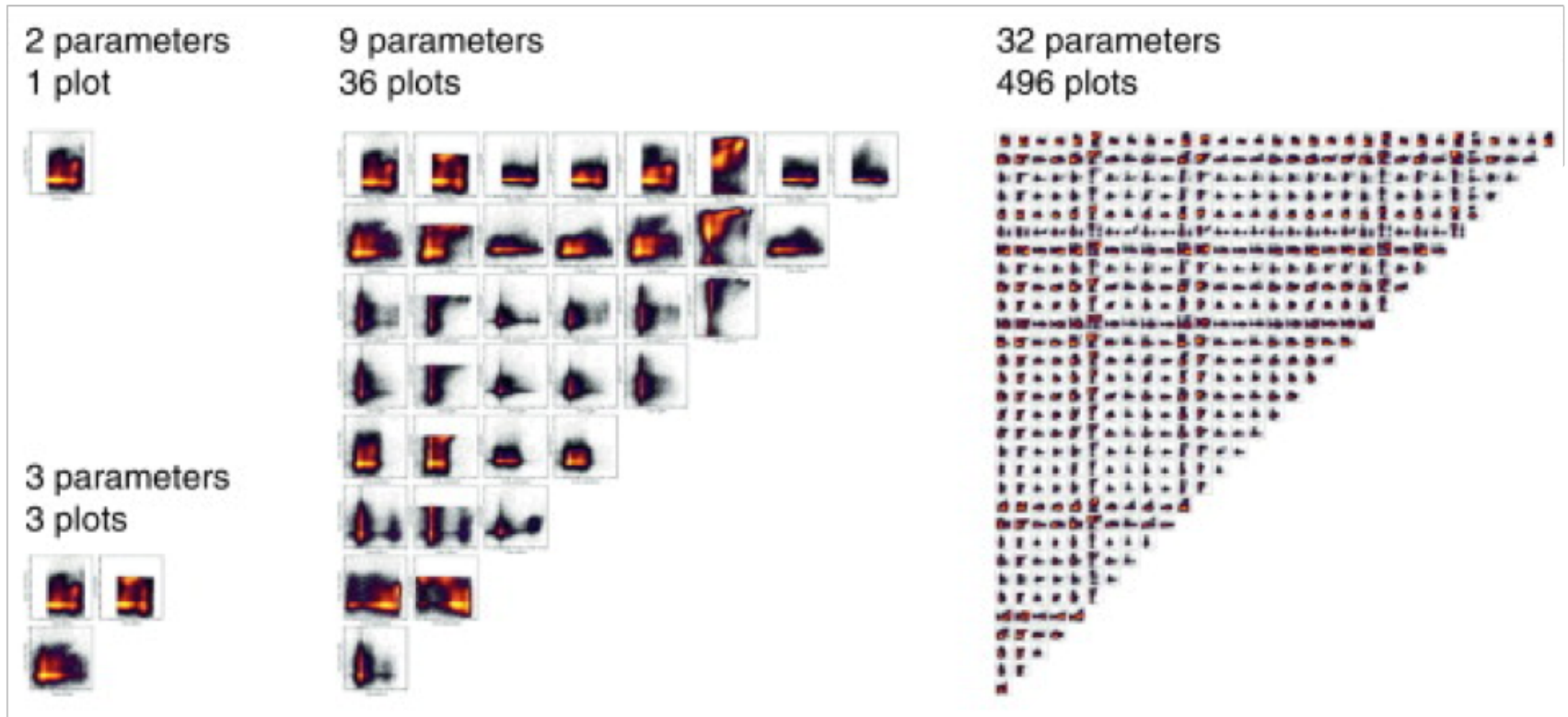


Flow cytometry primer

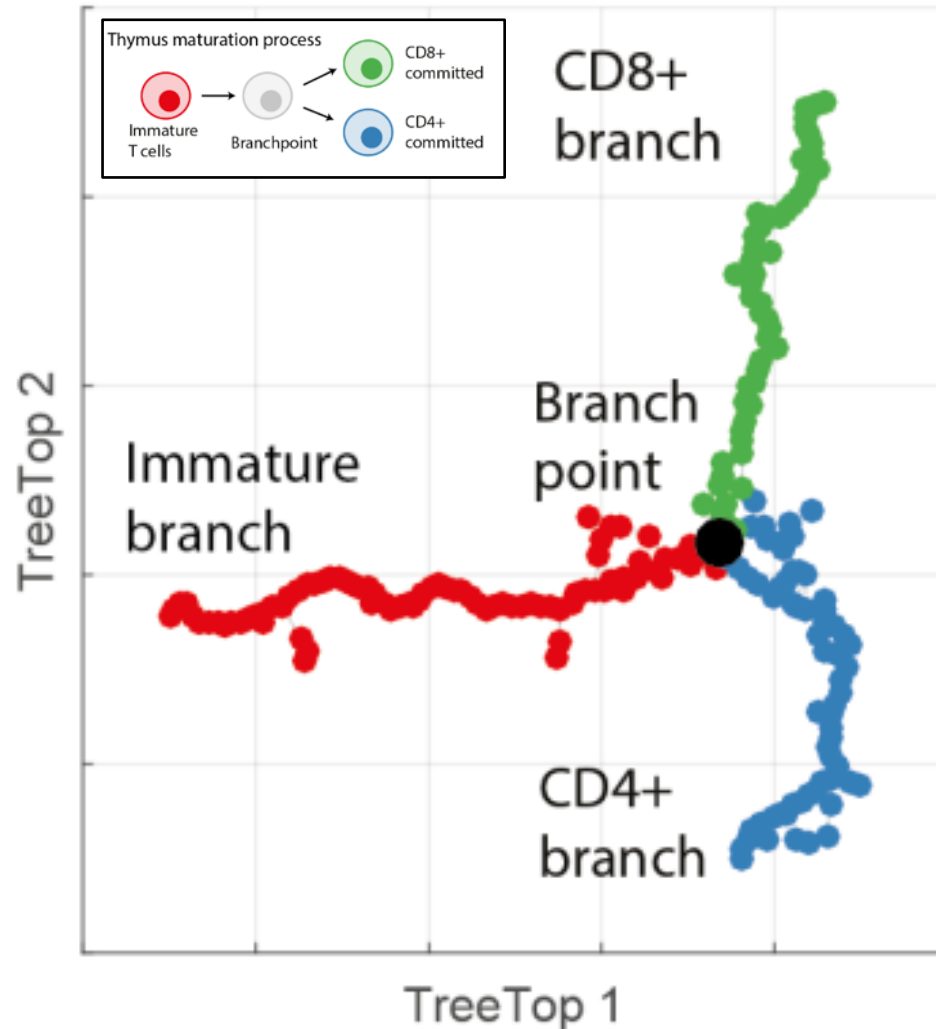
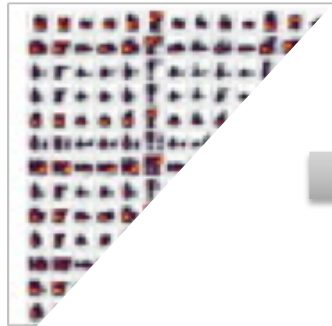


- ~10/30+ protein panel (flow/mass)
- $> 10^6$ cells/experiment
- Definition/quantification cell types by manual gating

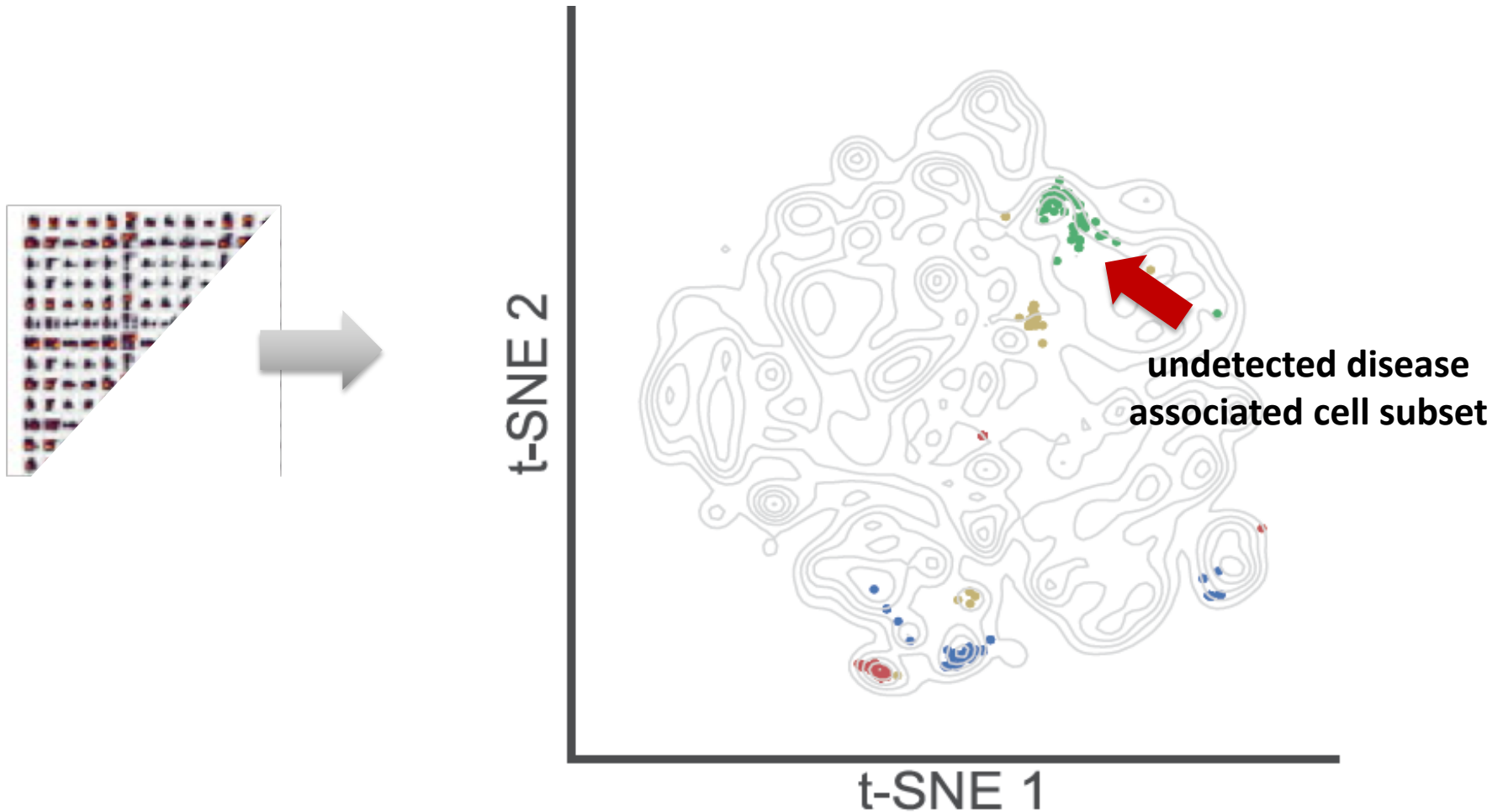
Curse of dimensionality in flow cytometry



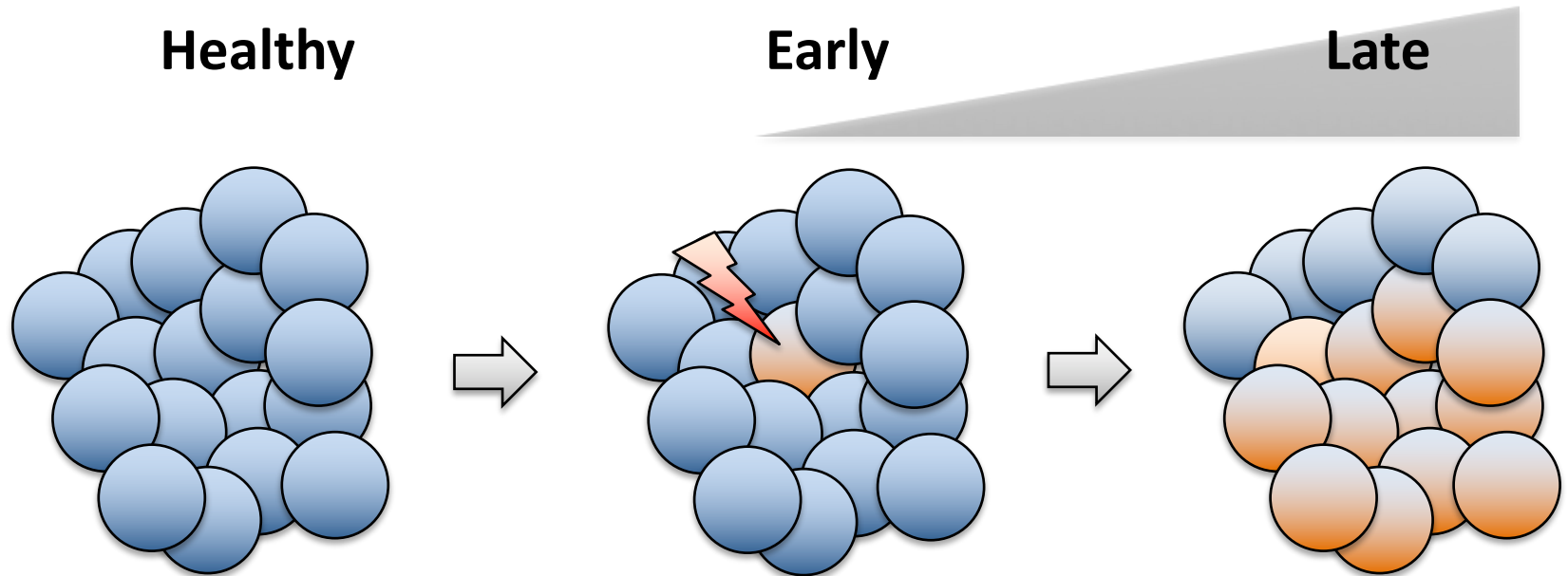
TreeTop visualization of mass cytometry thymus data



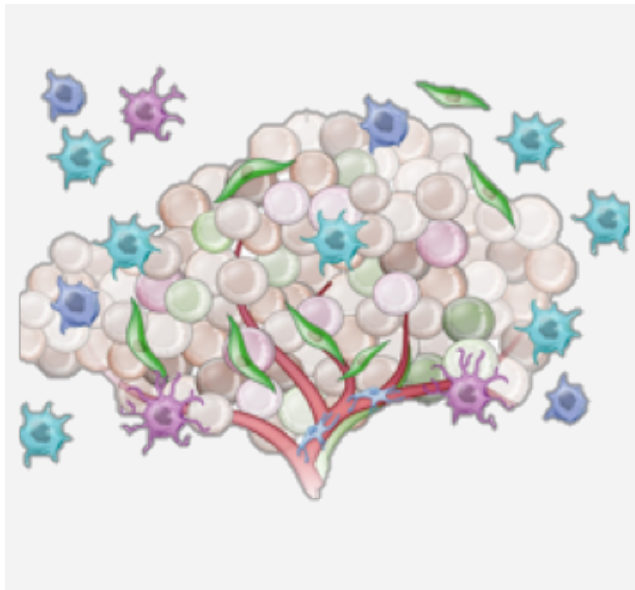
Global unsupervised analysis of cell population heterogeneity is ambitious



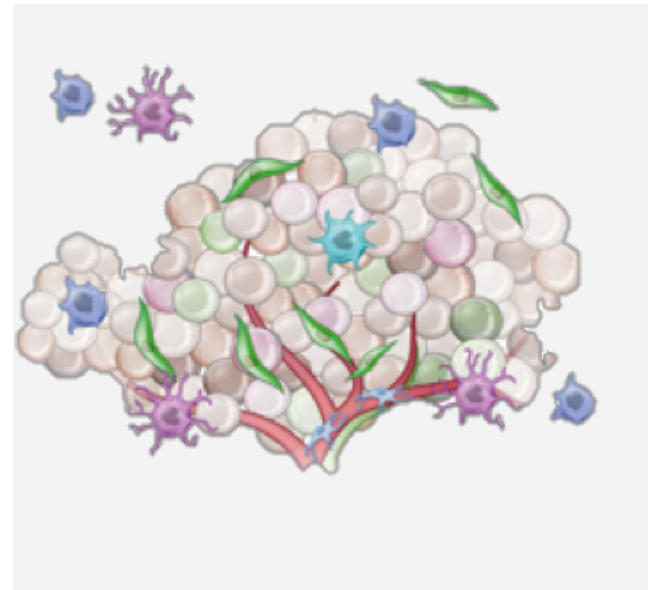
Cell population differences across conditions



(Immune) therapy response is difficult to predict

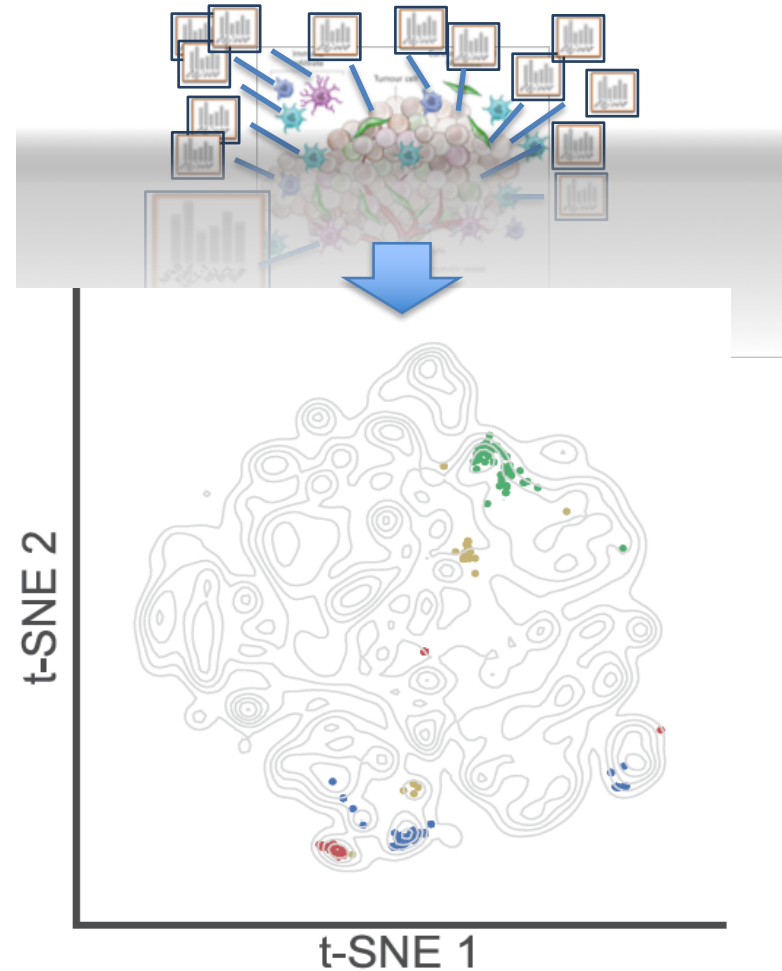
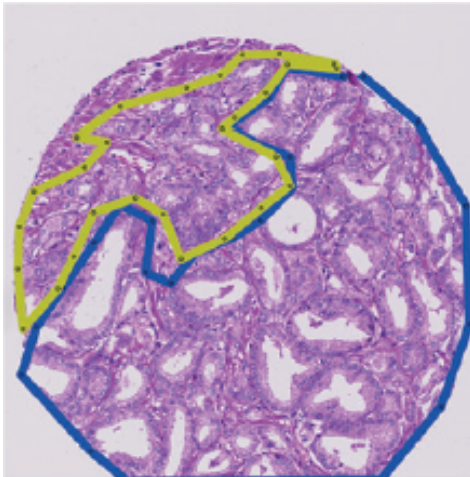


Responder

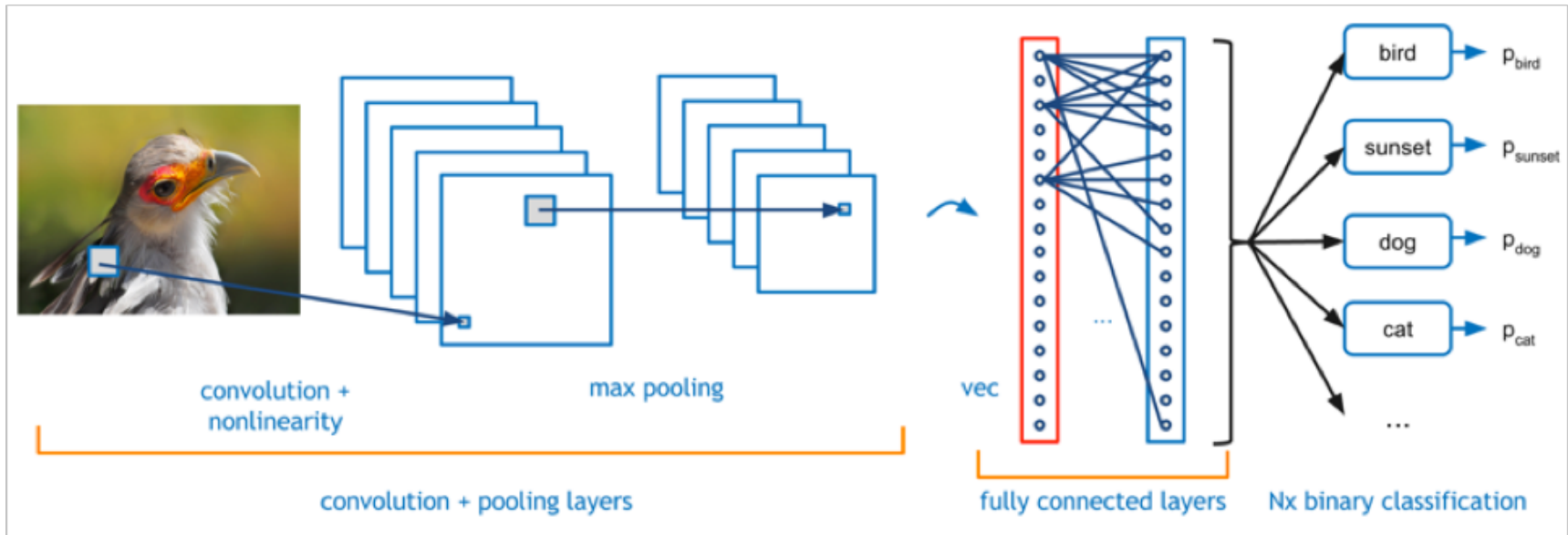


Non-responder

Images and single-cell data have a lot in common

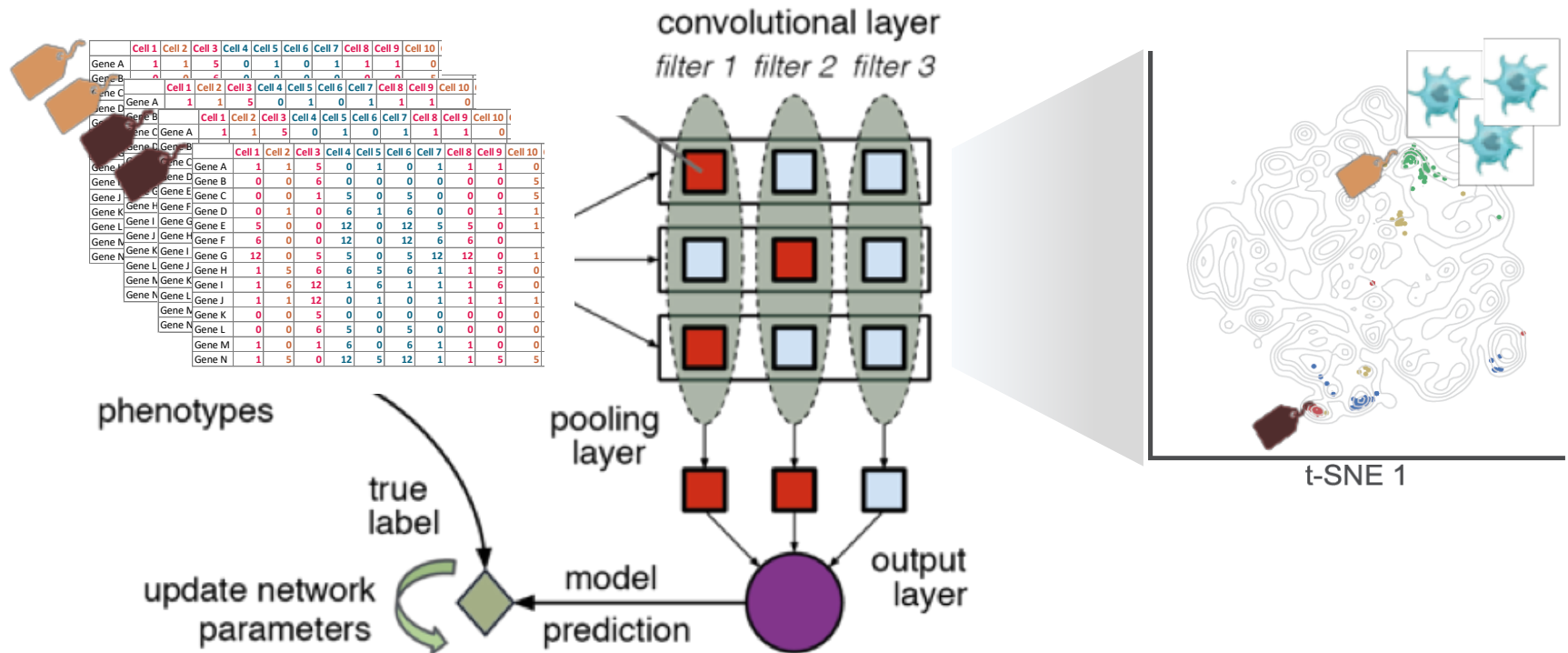


Convolutional neural networks primer for image analysis

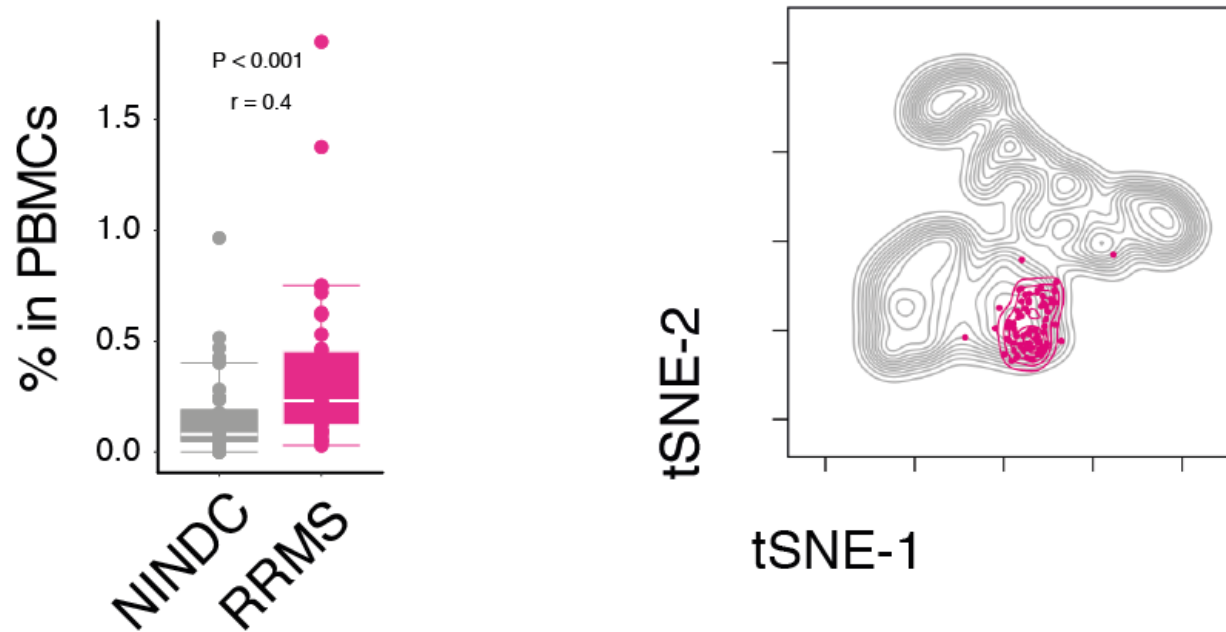


- CNNs learn relevant image patterns by convolving over image patches
- Idea: convolve over single cells and learn relevant cell profiles

CellCnn: Convnets for discovery of cell identity biomarkers



Pathogenic T_H cell signature associated with multiple sclerosis

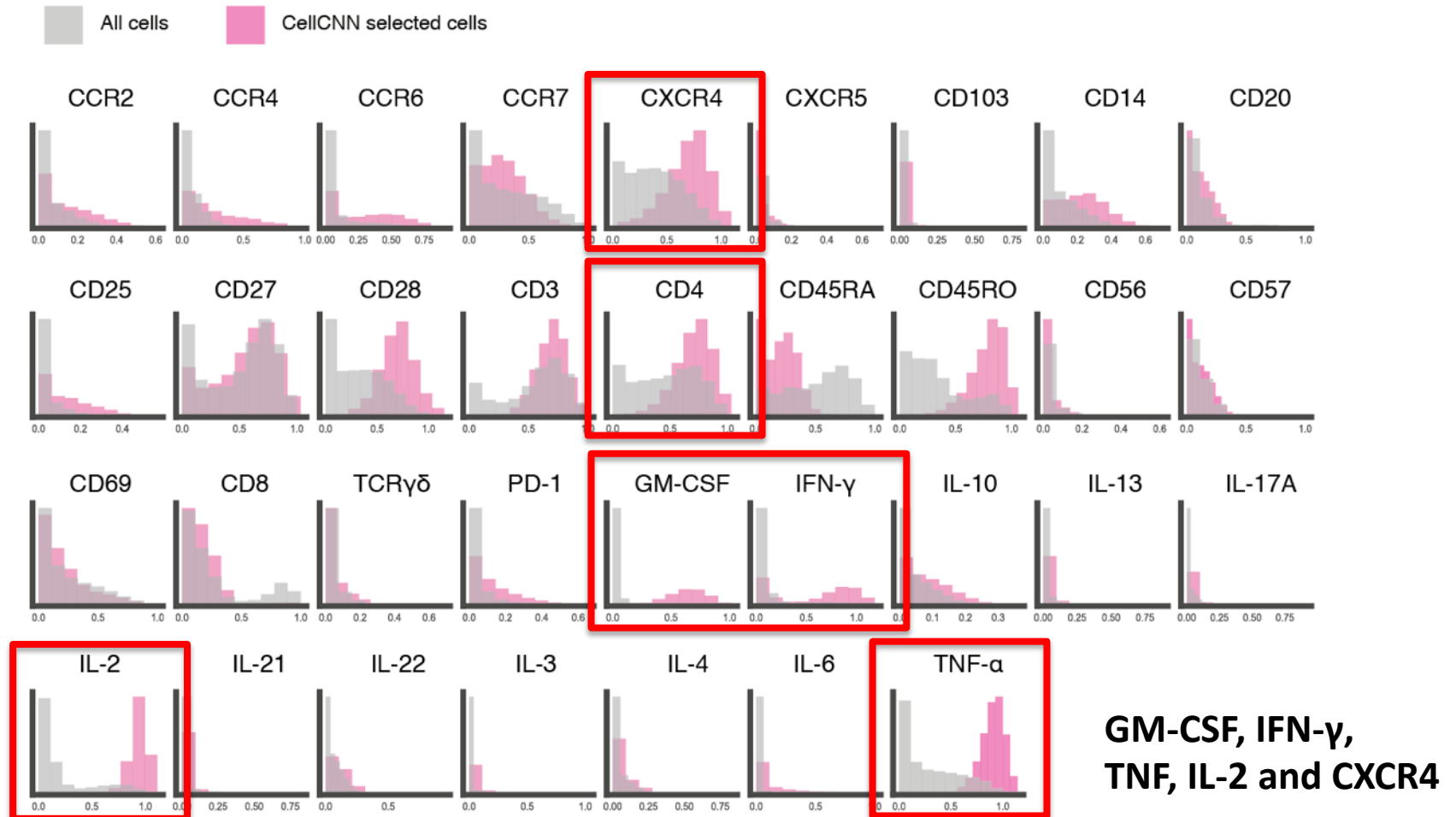


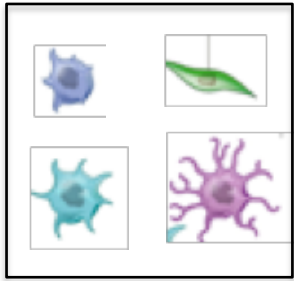
- Non-inflammatory neurological disease control (n = 36) vs relapse-remitting MS (n = 37)
- PBMC, restimulated (PMA/ionomycin)
- 34 marker CyTOF: lineage markers, cytokines, chemokines



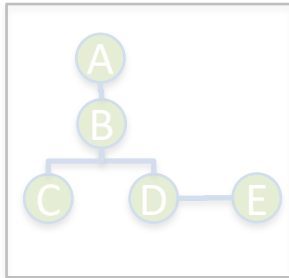
Burkhard Becher
Felix Hartmann
(UZH)

Pathogenic T_H cell signature associated with multiple sclerosis

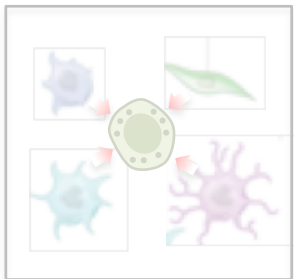




Cell types



Intracellular
Mechanisms



- **Computational Pathology** with CNNs
 - Gleason score estimation & survival stratification
 - Weak & strong supervision
- **TreeTop** for visualization of high dimensional data
- **CellCnn**: Cell identity biomarkers for precision medicine
 - MS associated T_H cell subset