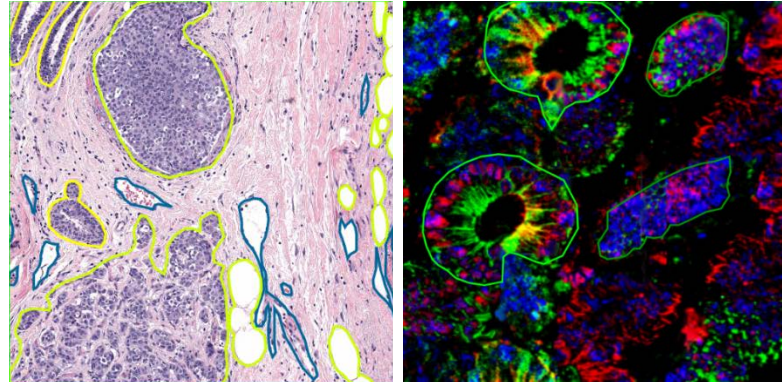


Spatial Analytics with Explainable AI for Anatomic Pathology



S. Chakra Chennubhotla, PhD

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University of Pittsburgh (on leave of absence)

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www.spintellx.com

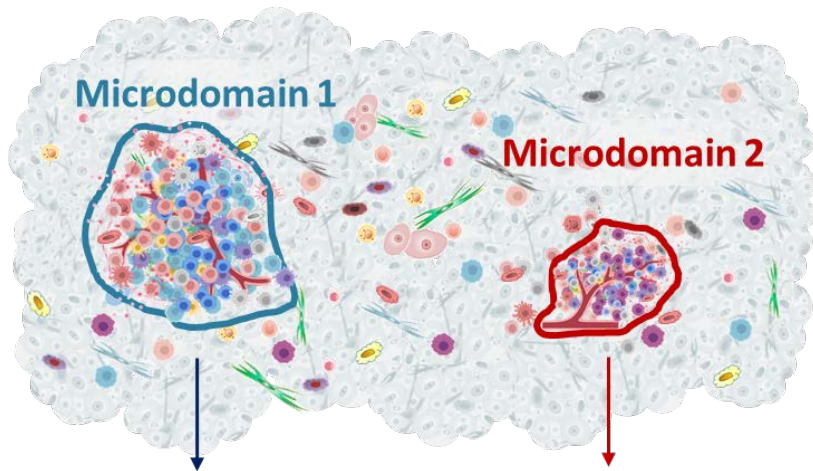
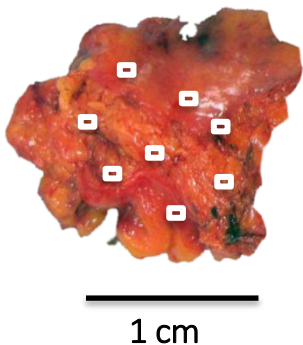
Disclosure

SpIntellx, Inc. (co-founder)

Why Advanced Unbiased Spatial Analytics Matter

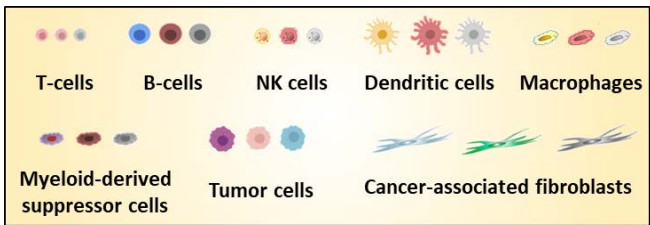
Biological spatial heterogeneity in primary tumors impacts disease progression, as well as clinical decisions and selection of therapeutic strategies

Tissue section or TMA core or needle biopsy from primary tumor



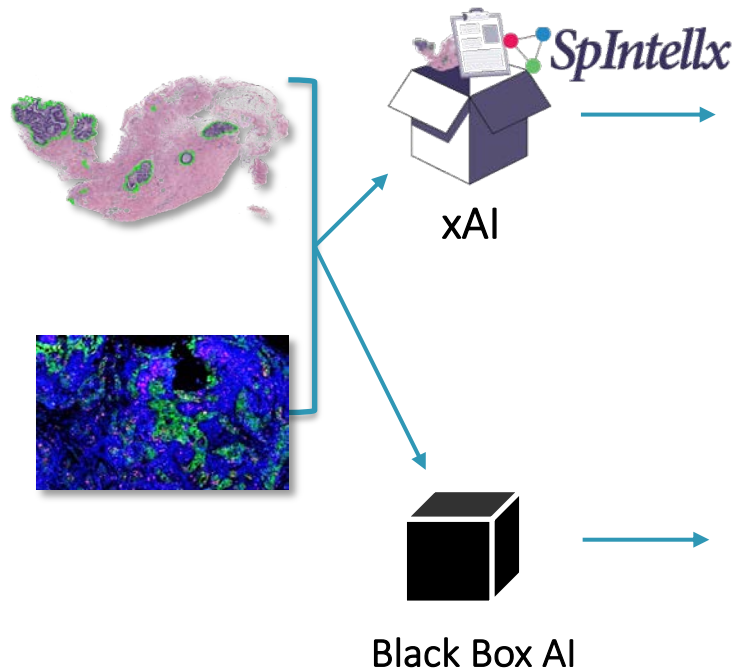
Microdomain 1: Dominance of frequently occurring tumor clone 1 with high immune infiltration and activation, and low metastatic potential

Microdomain 2: Mixed dominance of rare tumor clones 2 & 3 with low immune infiltration and high metastatic potential



Why Explainable Artificial Intelligence (xAI) Matters

Pathologists and disease experts require transparency in applying computational systems pathology



Prediction: High recurrence probability
Recommendation: Targeted therapy combining drugs 1 and 5
Why?: Spatial risk assessment has identified the rare microdomain 2 with high metastatic potential requiring targeted therapy

**PROVIDING EXPLANATIONS FOR RECOMMENDATIONS
 MAKES THE SYSTEM TRANSPARENT TO END USERS;
 BUILDS CONFIDENCE AND TRUST**

Prediction: Low recurrence probability
Recommendation: Standard therapy
Why?: N/A

**RECOMMENDATIONS WITHOUT EXPLANATIONS
 LEAVES THE END USERS IN THE DARK;
 DOESN'T BUILD CONFIDENCE AND TRUST**

Explainability for Trustworthy AI

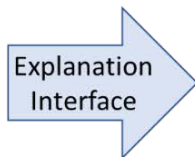


- Why did you do that?
- Why not something else?
- When do you succeed?
- When do you fail?
- When can I trust you?
- How do I correct an error?

Deep Learning Black-box AI

For Deep Learning, opening the black box is ... 'far from trivial'
– Geoffrey Hinton (New Yorker, AI vs MD 2017, S Mukherjee)

Explainability for Trustworthy AI



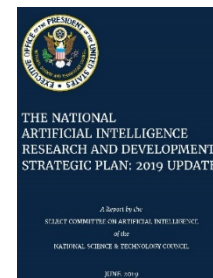
- I understand why
- I understand why not
- I know when you succeed
- I know when you fail
- I know when to trust you
- I know why you erred

Experts Require Transparency

- xAI Builds Confidence in AI Software
- Pathologist Feedback: “xAI will be the game changer in adopting Digital Pathology”

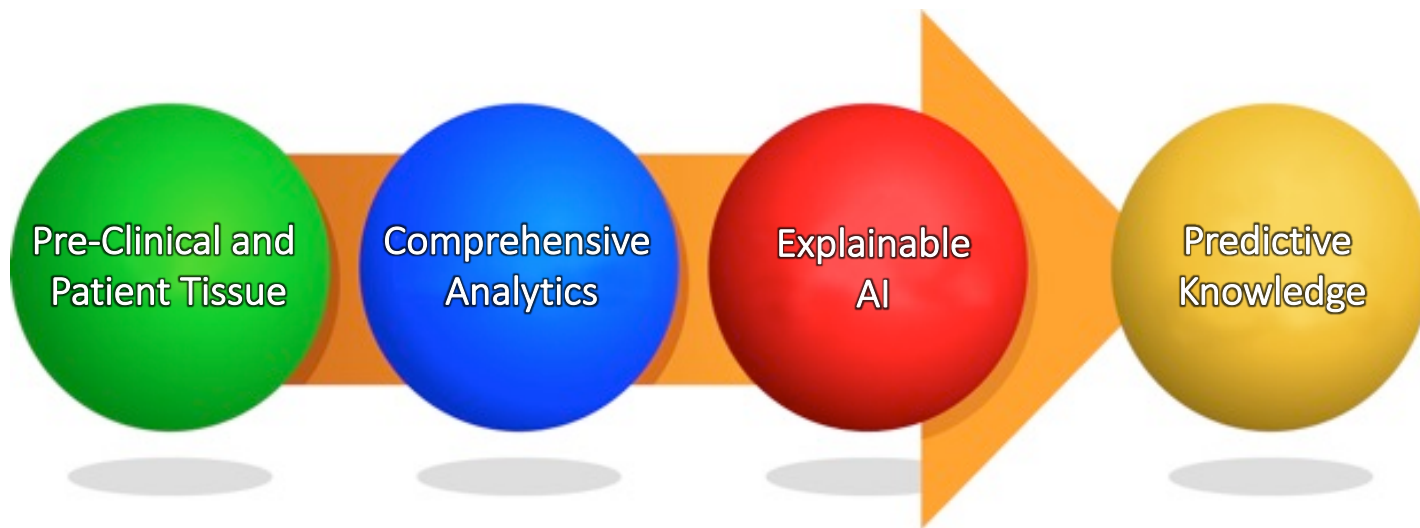
Regulatory Aspect

- Explainability is a requirement for Trustworthy AI
- White House, NIST, and EU Commission promote explainable and trustworthy AI solutions in highly regulated areas



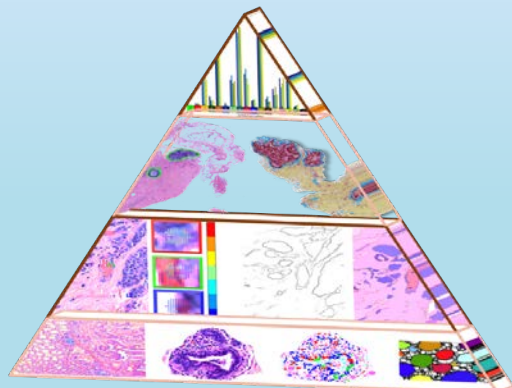
Revolutionizing Pathology

SpIntellx harnesses the computational power of proprietary spatial analytics and explainable artificial intelligence (xAI) to extract information from pre-clinical and patient primary disease pathology to create knowledge that informs therapeutic strategies and clinical decisions layered on top of basic quantitation software.



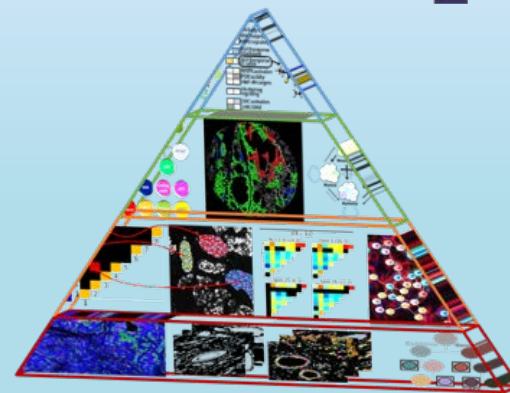
Our Solutions

HistoMapr™



For Traditional Hematoxylin & Eosin (H&E) Staining and Immunohistochemistry (IHC) Labeling and Imaging

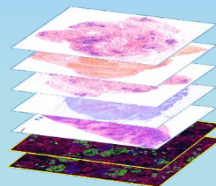
TumorMapr™



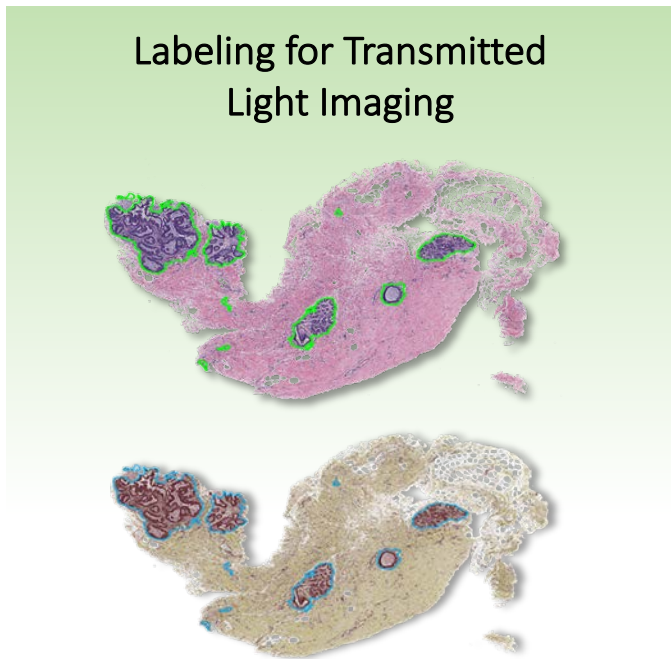
For Multi to Hyperplexed (>9) Fluorescence or Mass Spec-Based Biomarker Labeling and Imaging

Spatial Analytics & xAI

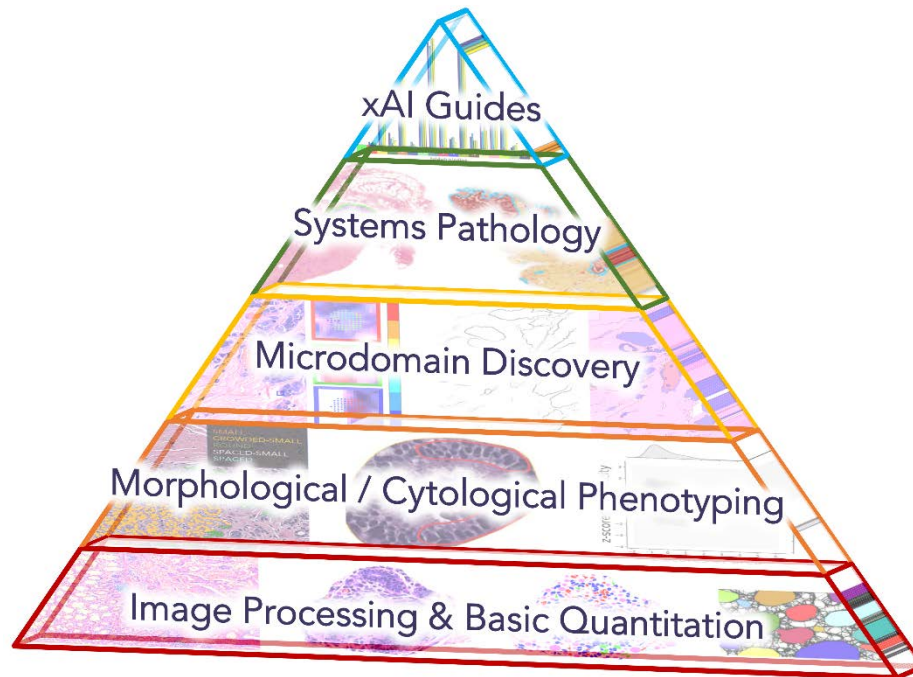
TumorMapr + HistoMapr



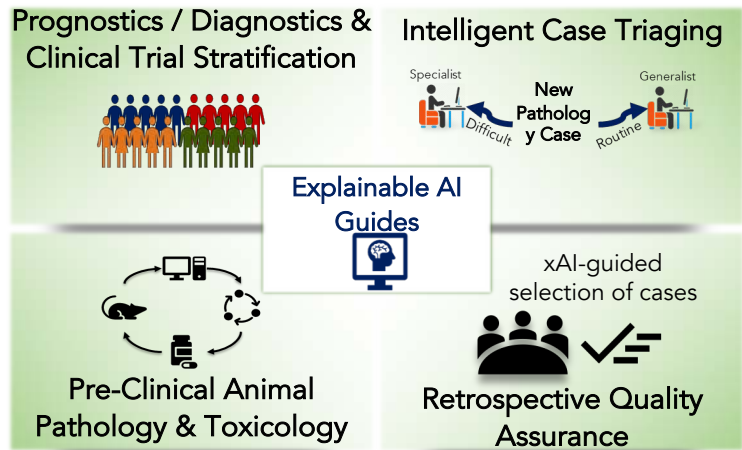
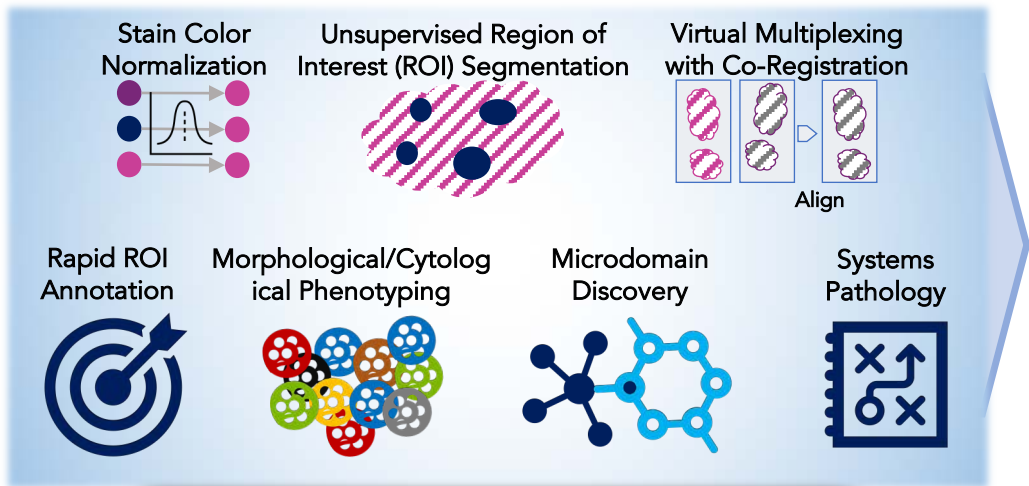
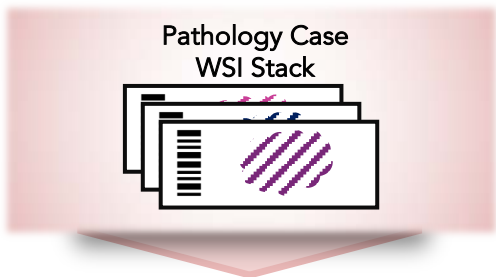
HistoMapr Offers Complete Spatial Analytics, xAI and Predictive Computational Guides on Top of Standard Analytics



 Spatial Analytics and xAI Tools



HistoMapr Offers Complete Spatial Analytics, xAI and Predictive Computational Guides on Top of Standard Analytics



HistoMapr-Breast™: Spatial Analytics

Patient Data

Name

Patient 1

Age

45

Sex

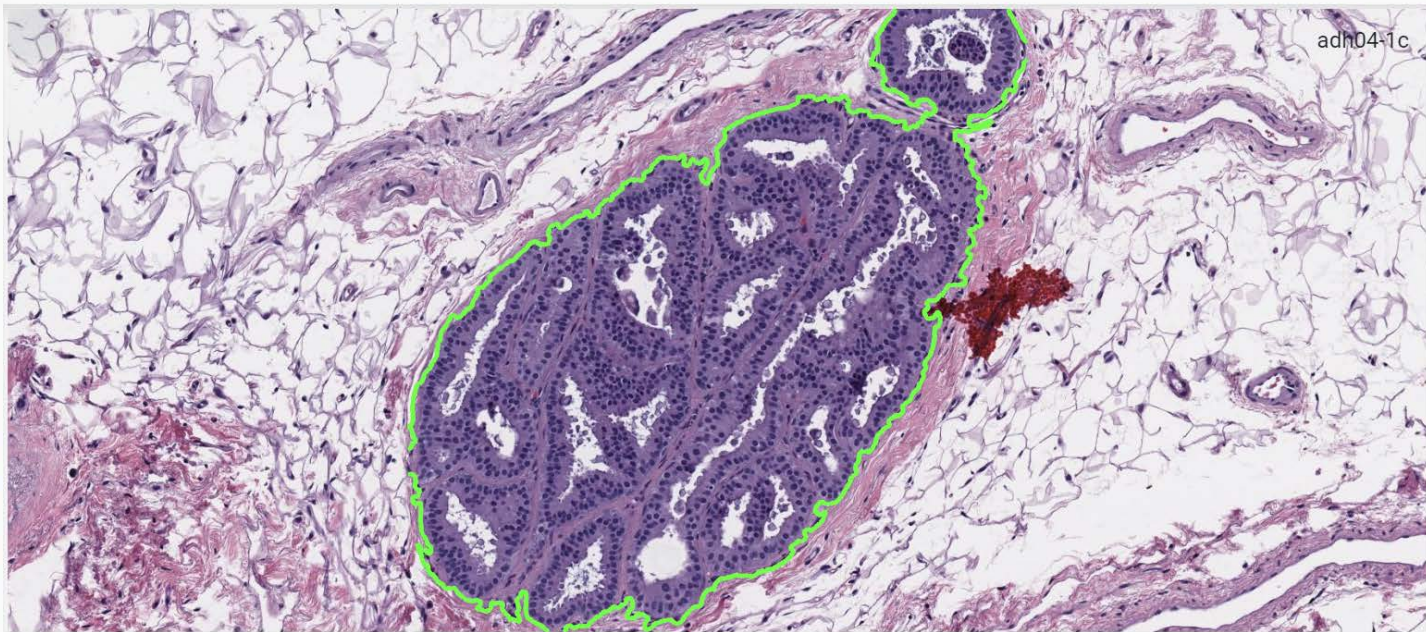
Female

Provisional
Diagnosis

Left Breast, 10:00, Ultrasound-guided Core biopsy.

A. Atypical Ductal Hyperplasia with calcifications.

B. Columnar Cell Change.

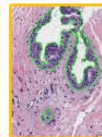
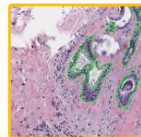
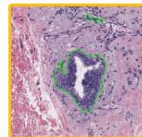
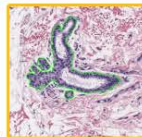
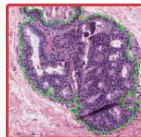
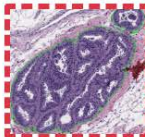
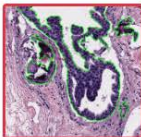
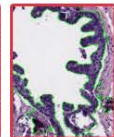
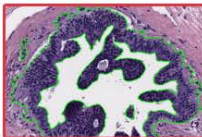
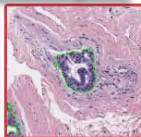


Why?

Atypical Ductal Hyperplasia

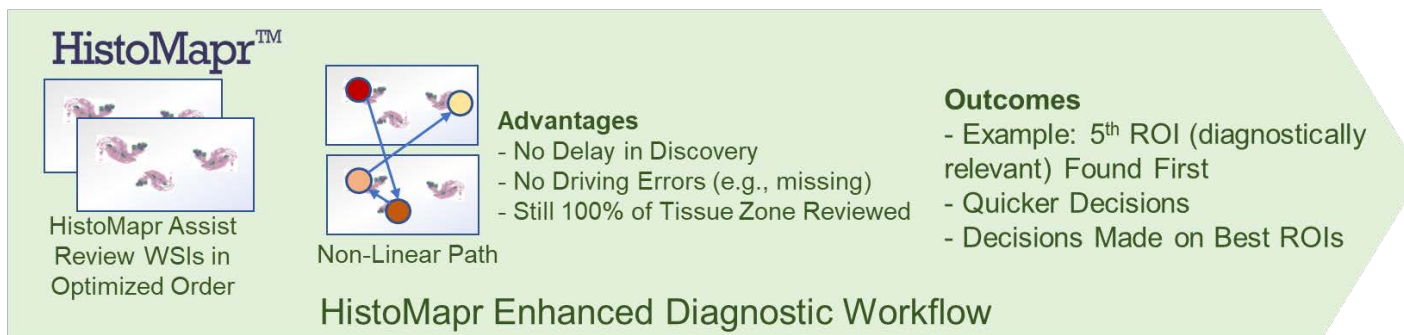
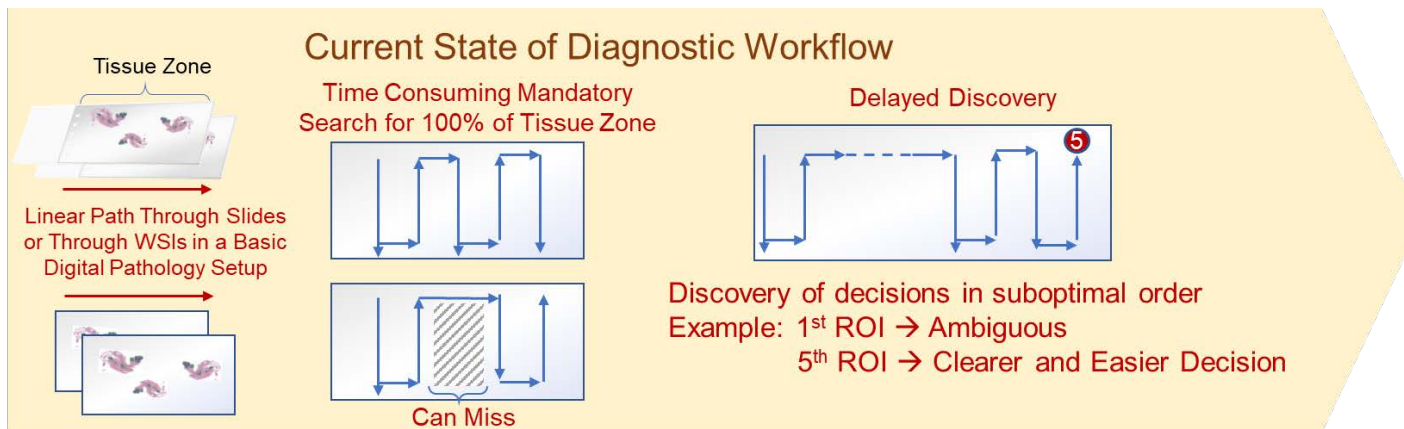
Agree Disagree Not Sure

Finalize



◀ Back to cases

HistoMapr addresses the unmet clinical need to improve the efficiency and accuracy of pathology workflows and patient cohort stratification for clinical trials



HistoMapr–Breast Impacts: Efficiency and Accuracy

- Efficiency: 56% less time
- Accuracy:
 - Enables detection of high-risk benign breast lesions

	Time (secs) per case
Microscope	221.6
HistoMapr	98.0
Time Saved	123.7
Efficiency (%)	55.8%

HistoMapr–Breast Impacts: Efficiency and Accuracy

- Efficiency: 56% less time
- Accuracy:
 - Enables detection of high-risk benign breast lesions
- N = 46 with ADH lesions (ca. 300 WSI and ca. 2000 ROIs)
- More sensitive (88%* vs 48%**) than manual calls made by pathologists without the guide

* SpIntellx Study

** Elmore, J.G., et al., Diagnostic concordance among pathologists interpreting breast biopsy specimens. JAMA, 2015. 313(11): p. 1122-32.

HistoMapr-Breast™ : Explainable AI

Patient Data
Name: Patient 1
Age: 45
Sex: Female

Provisional Diagnosis
Left Breast, 10:00, Ultrasound-guided Core biopsy:
A. Atypical Ductal Hyperplasia with calcifications.
B. Columnar Cell Change.

Key Findings

- Strong rigid architecture
- Very high stromal density
- Uniform nuclear spacing
- Apocrine & atypical nuclei
- Non-hyperplastic tissue

HistoMapr Recommendation:
Atypical Ductal Hyperplasia (ADH)
Confidence Score: 0.85

Why?

Atypical Ductal Hyperplasia

◉ Agree ◉ Disagree ◉ Not Sure Finalize

◀ Back to cases

HistoMapr-Breast™ : Explainable AI

SpIntellex™ HistoMapr™ - Breast Sign out

adh04-1c

Patient Data
Name: Patient 1
Age: 45
Sex: Female

Provisional Diagnosis
Left Breast, 10:00, Ultrasound-guided Core biopsy:
A. Atypical Ductal Hyperplasia with calcifications.
B. Columnar Cell Change.

Key Findings

- Strong rigid architecture
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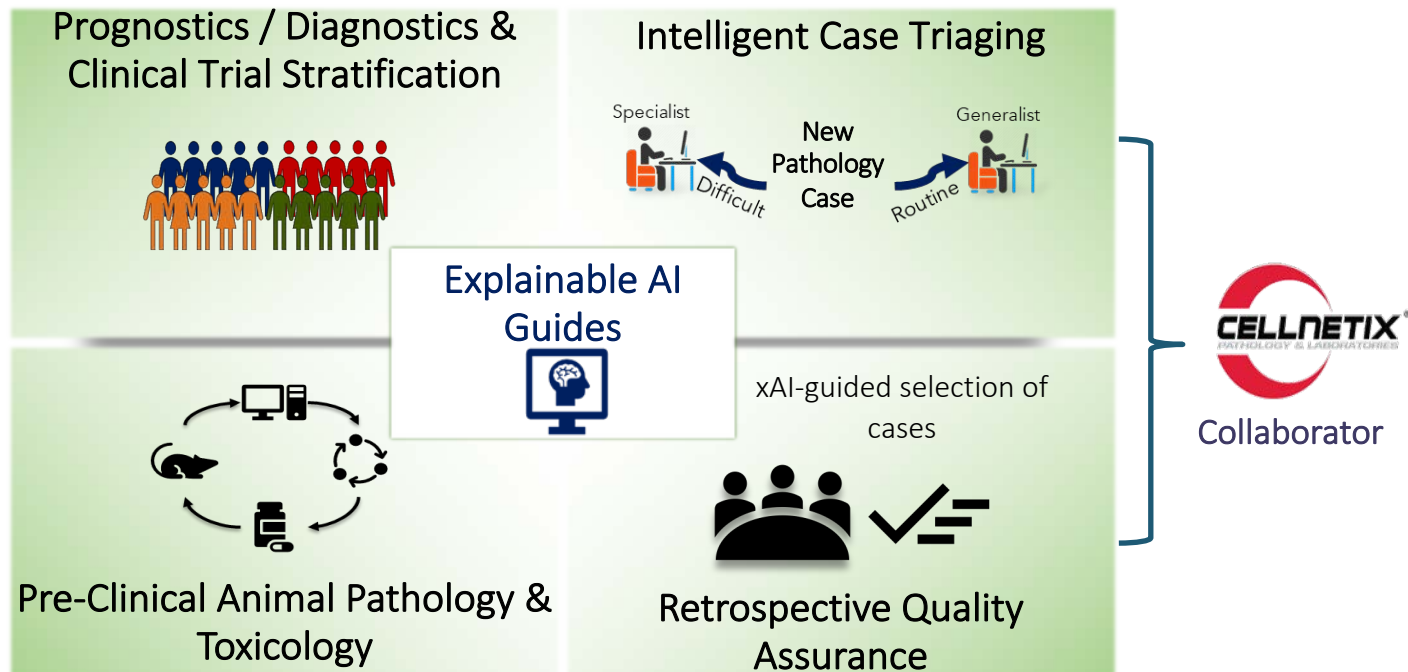
HistoMapr Recommendation:
Atypical Ductal Hyperplasia (ADH)
Confidence Score: 0.85

Why?

Atypical Ductal Hyperplasia

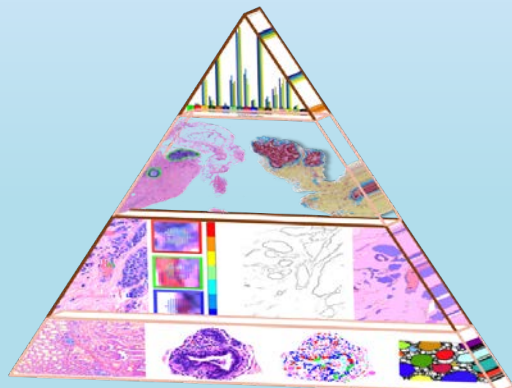
Agree Disagree Not Sure

Near-Term HistoMapr Applications



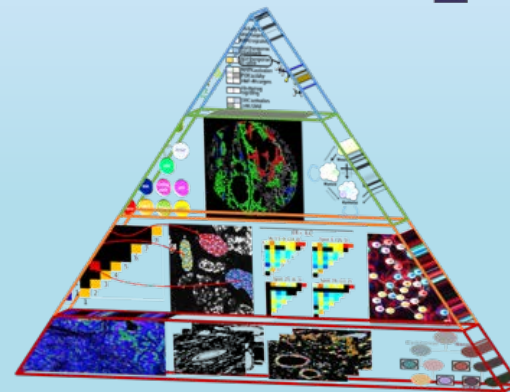
Our Solutions

HistoMapr™



For Traditional Hematoxylin & Eosin (H&E)
Staining and Immunohistochemistry (IHC)
Labeling and Imaging

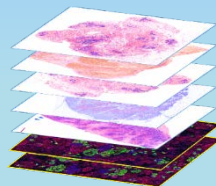
TumorMapr™



For Multi to Hyperplexed (>9)
Fluorescence or Mass Spec-Based
Biomarker Labeling and Imaging

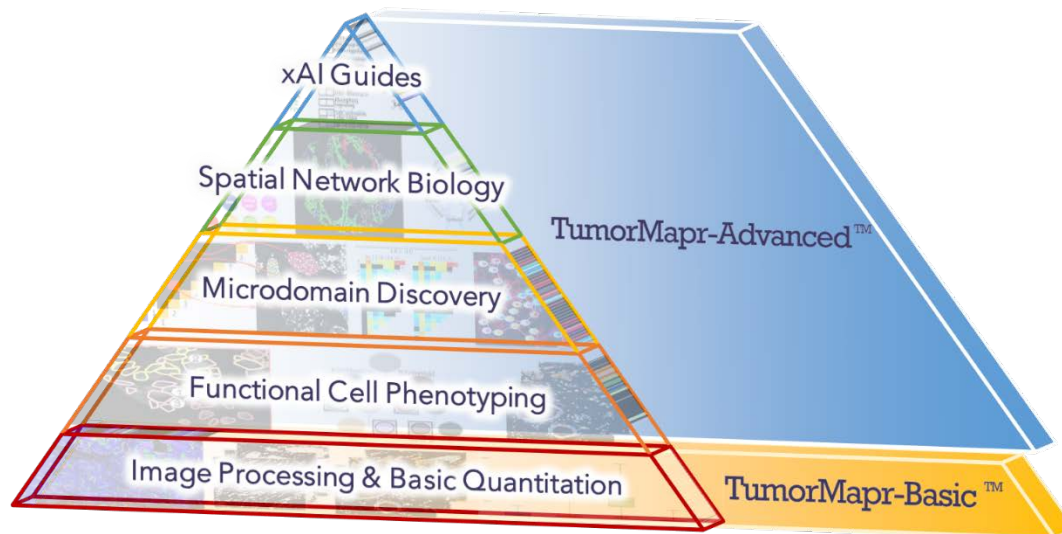
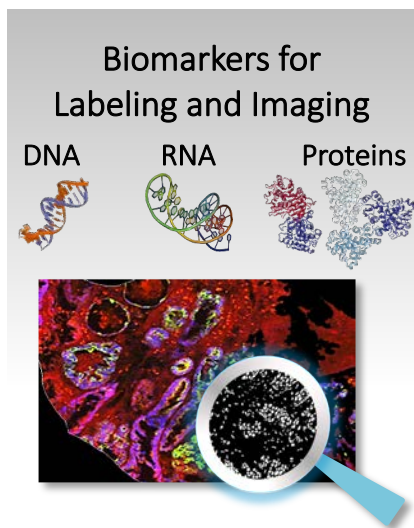
Spatial Analytics & xAI

TumorMapr + HistoMapr



TumorMapr™ Feature Pyramid

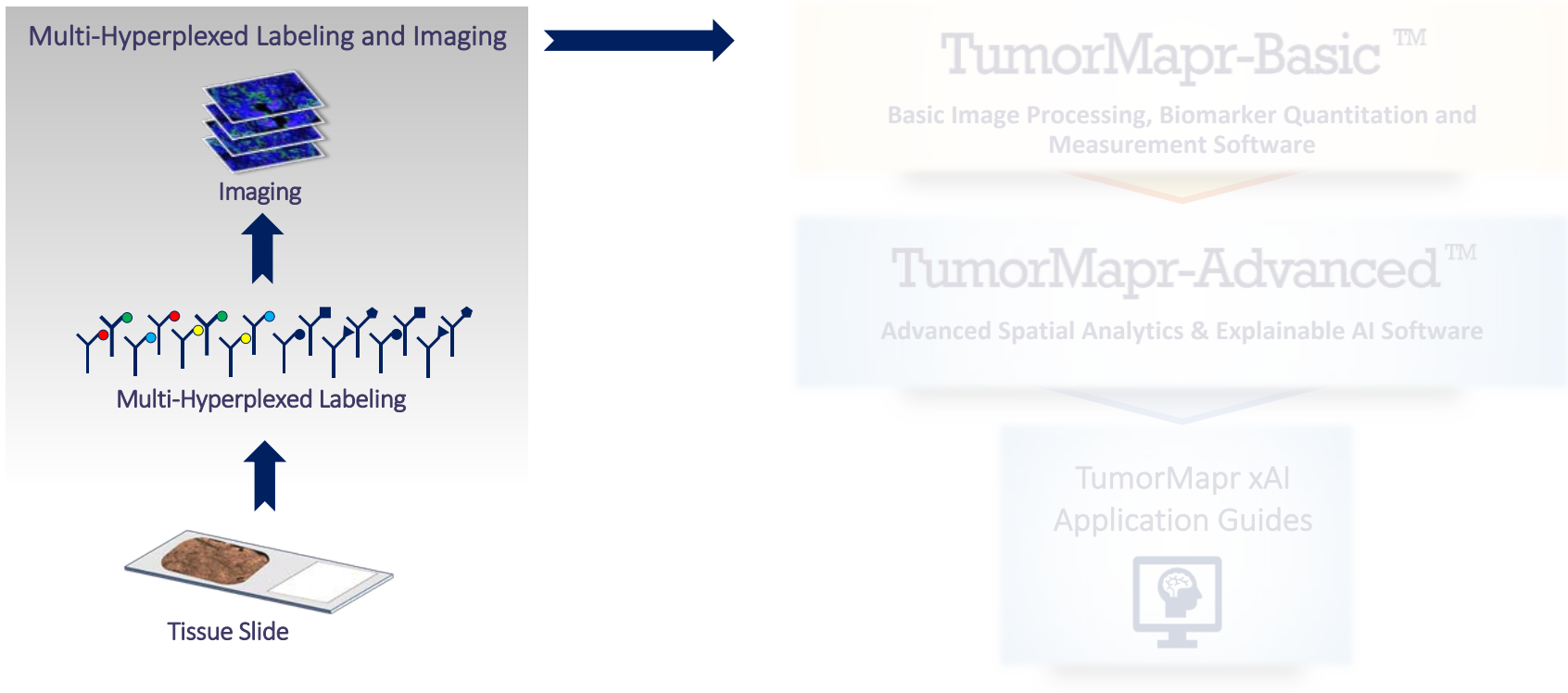
TumorMapr-Basic Offers Rapid and Basic Measurements, and TumorMapr-Advanced Features Functional Phenotyping, Spatial Analytics in Tumor Microdomains, Systems Biology and xAI Guides



Analyze Image Data Sets from Any Imaging Platform, Any Reagent Type and Any Disease

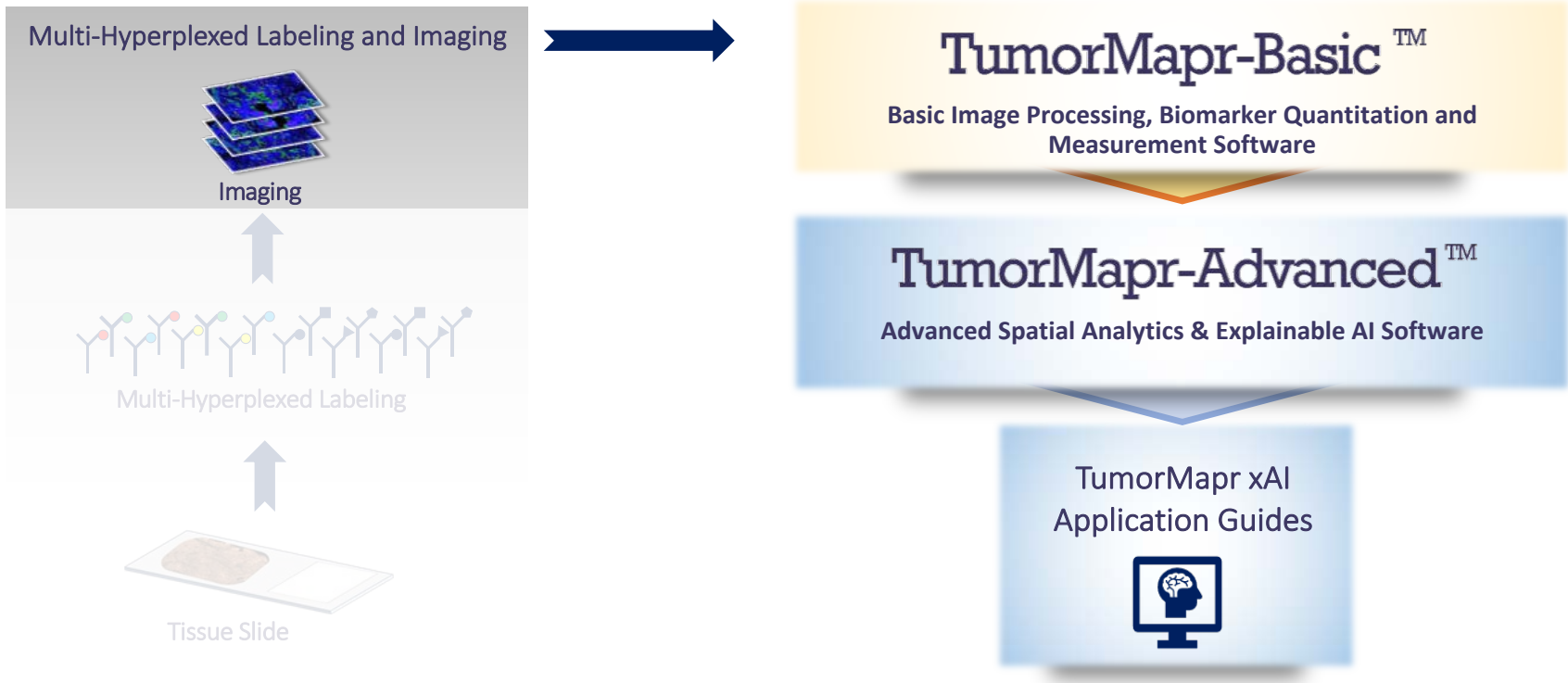
TumorMapr™ Pipeline

TumorMapr™ combines TumorMapr-Basic™ and TumorMapr-Advanced™ to develop powerful applications in drug target identification, clinical trial stratification, prognostic/diagnostic tests, and personalized therapeutic strategies.



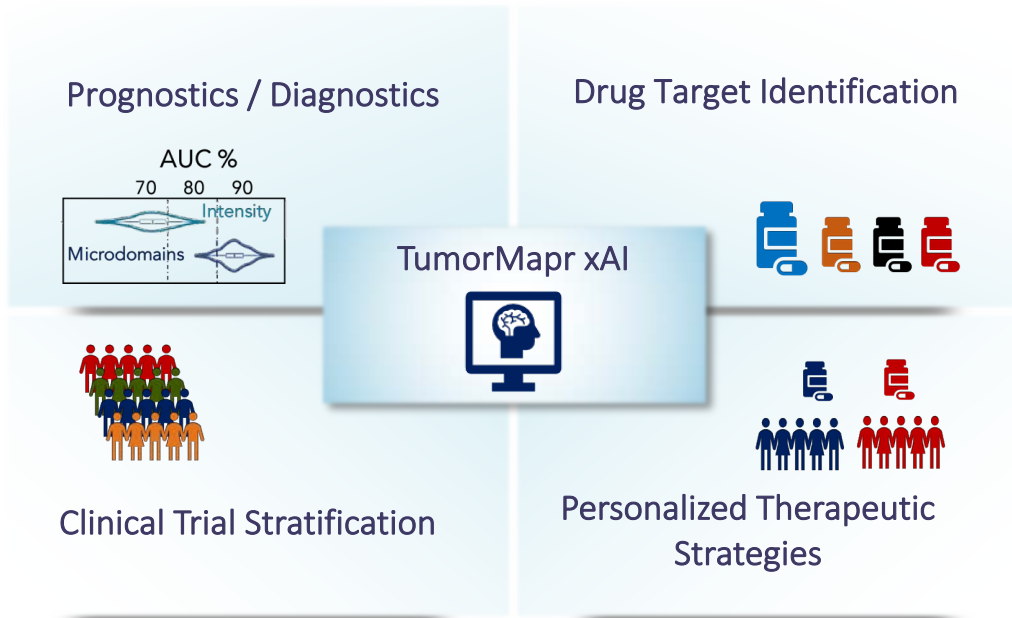
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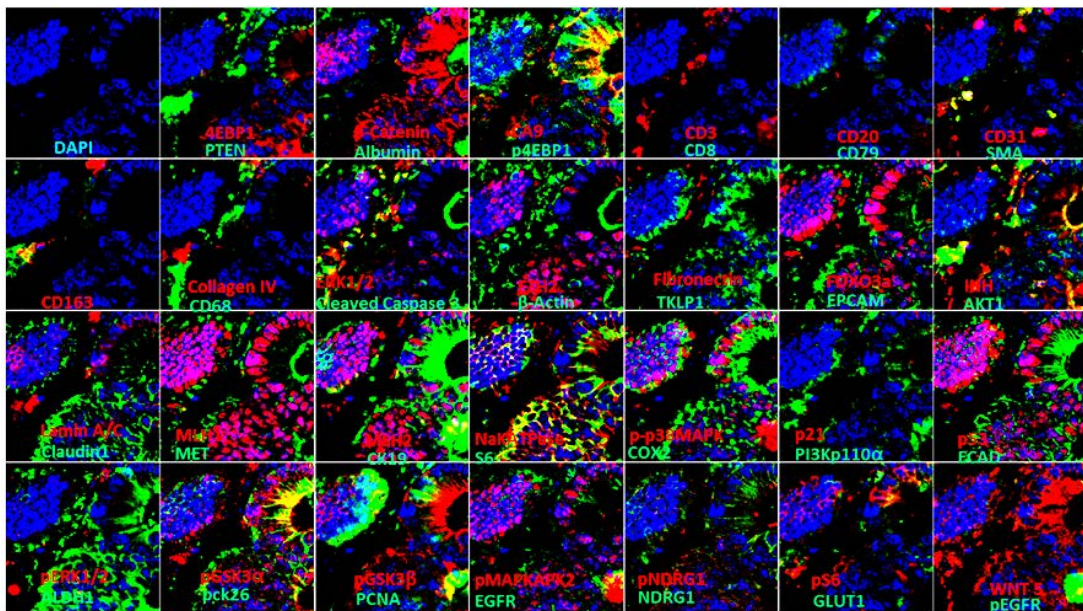
TumorMapr™ xAI Application Guides

TumorMapr-Basic coupled with TumorMapr-Advanced meets the rigorous clinical needs for precision medicine



TumorMapr-Colon™

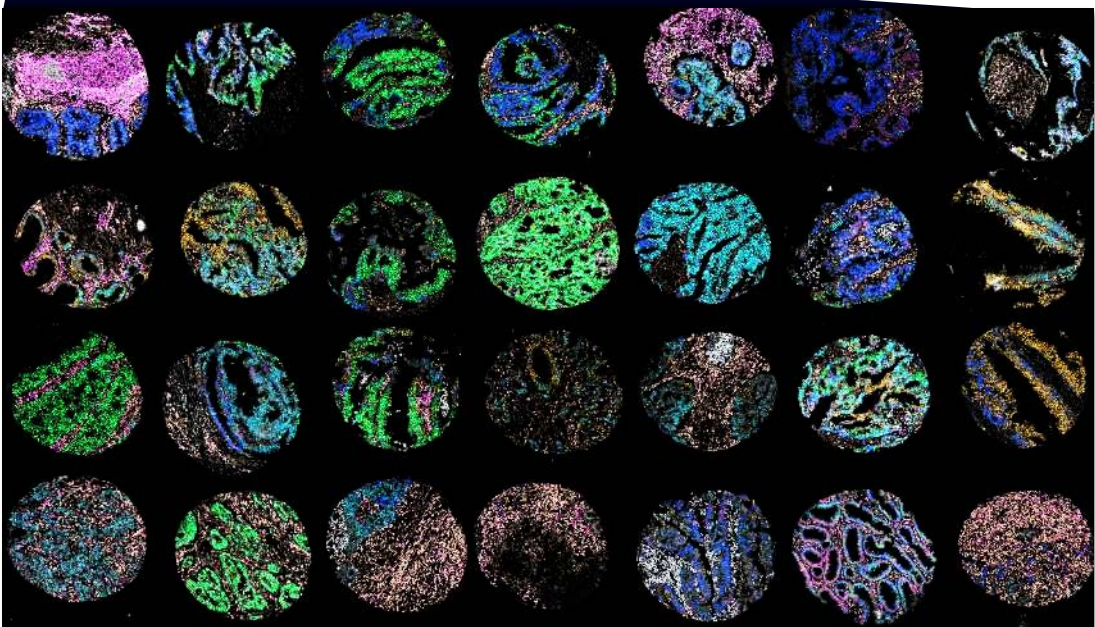
Using Cell DIVE, one of multiple hyperplexing imaging platforms, to sample colon cancer TME



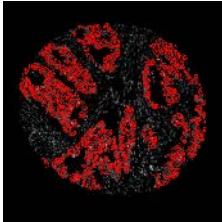
Post Translational Modifications	Cell Types and States
Oncogenic	Tumor Suppressive
Extracellular Transport and Metabolism	Growth and Transcription Factor, Cell Migration and Proliferation
Signaling Pathways:	
- RAS/RAF/MAPK	- Apoptosis
- PI3K/AKT/MTOR	- Hypoxia
- Mismatch Repair	- Hedgehog

	All	StageI	StageII	StageIII
<i>Patients</i>	432	175	190	67
<i>Age (median years)</i>	75	67	73	70
<i>Age (std)</i>	6.7	11.7	11.4	13.4
<i>Gender (Male)</i>	220	88	101	31
<i>Gender (% Male)</i>	50.9	50.3	53.2	46.3
<i>No. of Recurrences</i>	65	10	30	25
<i>Recurrence (%)</i>	100	15.4	46.2	38.5
<i>Recurrence Time (median days)</i>	1651	1899	1574	1098
<i>Survival Time (median days)</i>	1695.5	1899	1658	1280

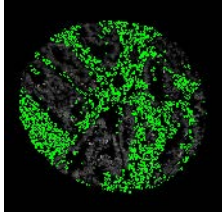
TumorMapr-Colon: User-Interface



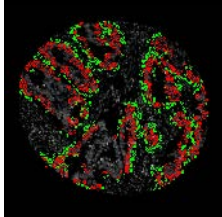
Microdomains



Epithelial

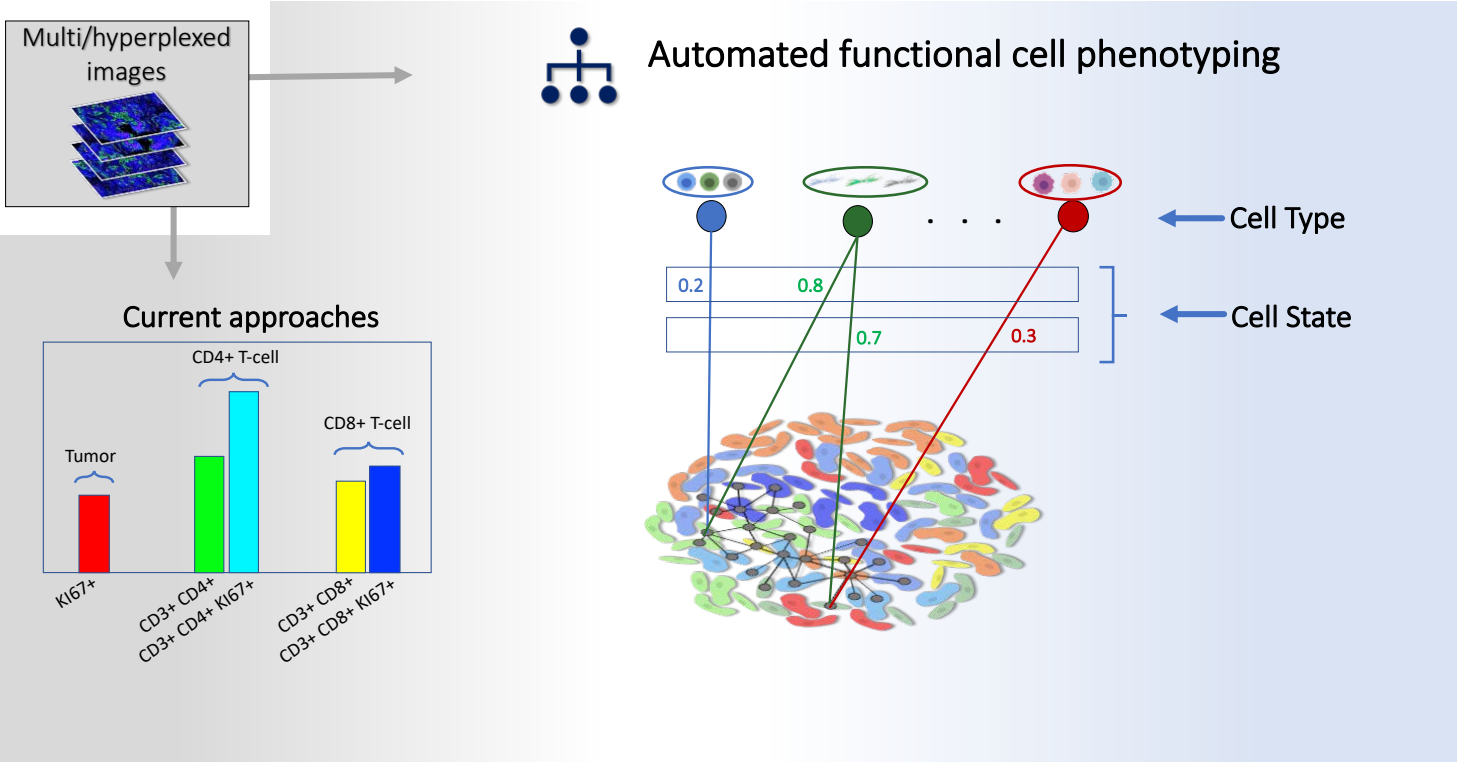


Stromal

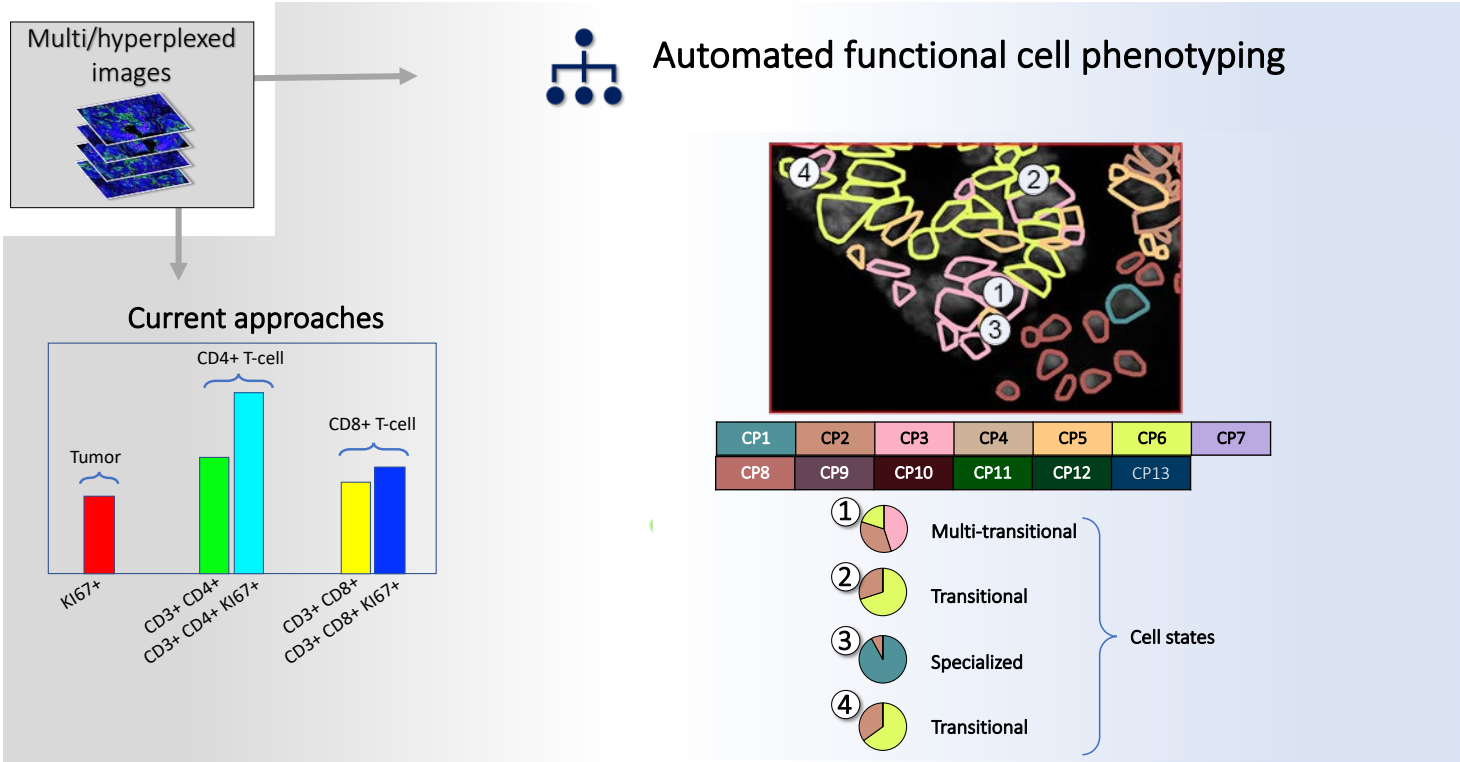


Epi-Stroma Interface

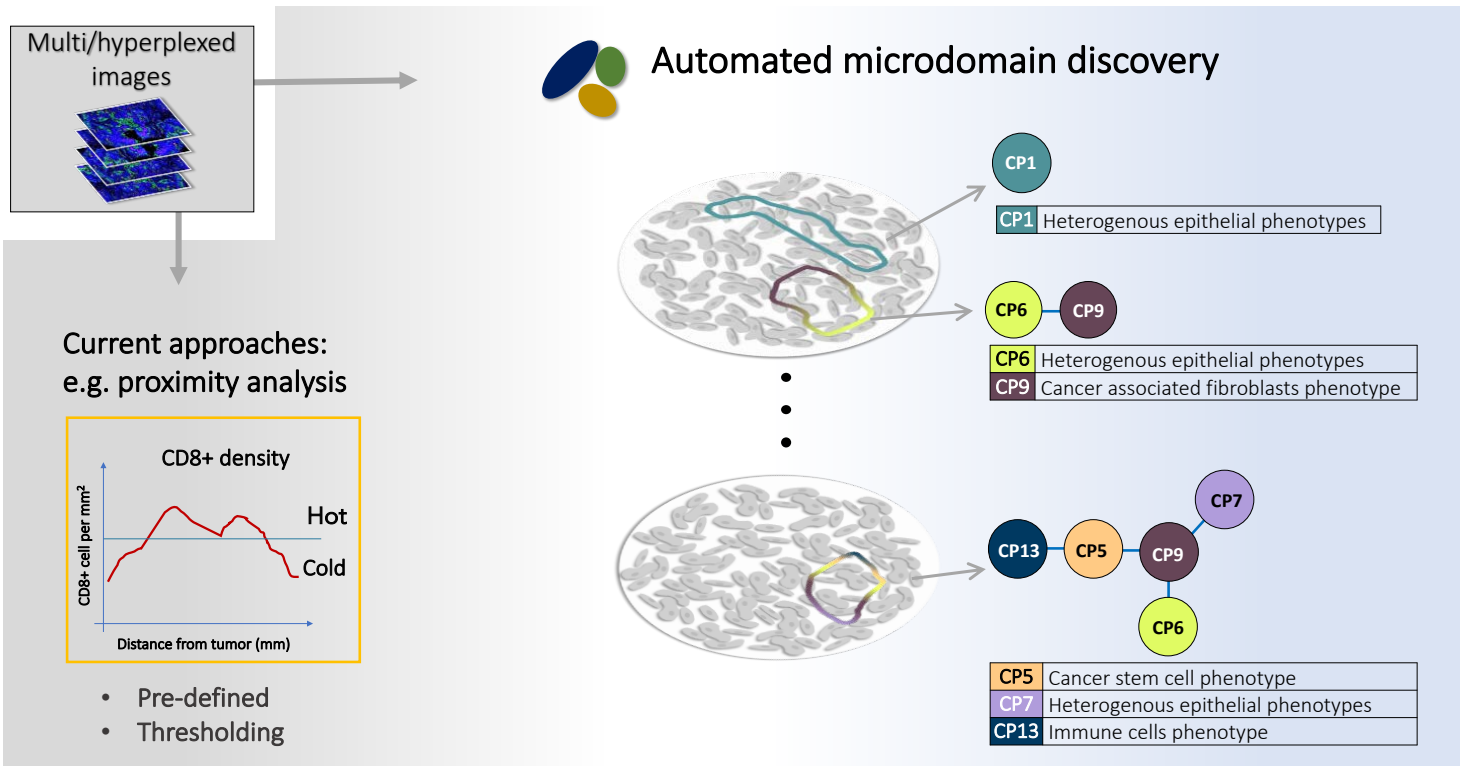
TumorMapr-Colon: Automated Functional Cell Phenotyping



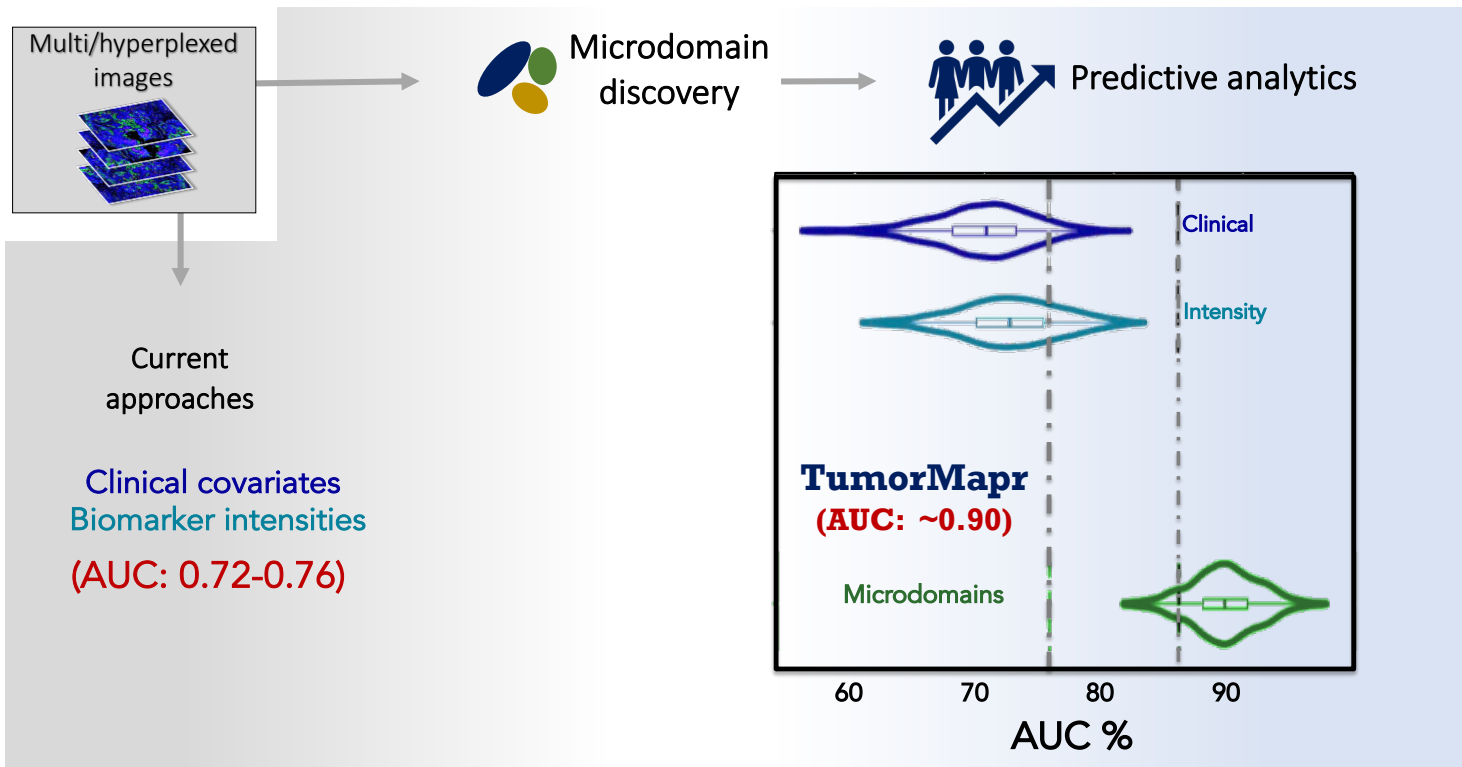
TumorMapr-Colon: Reveals a Phenotypic Hierarchy of *Specialized, Transitional* and *Multi-Transitional* Cell States



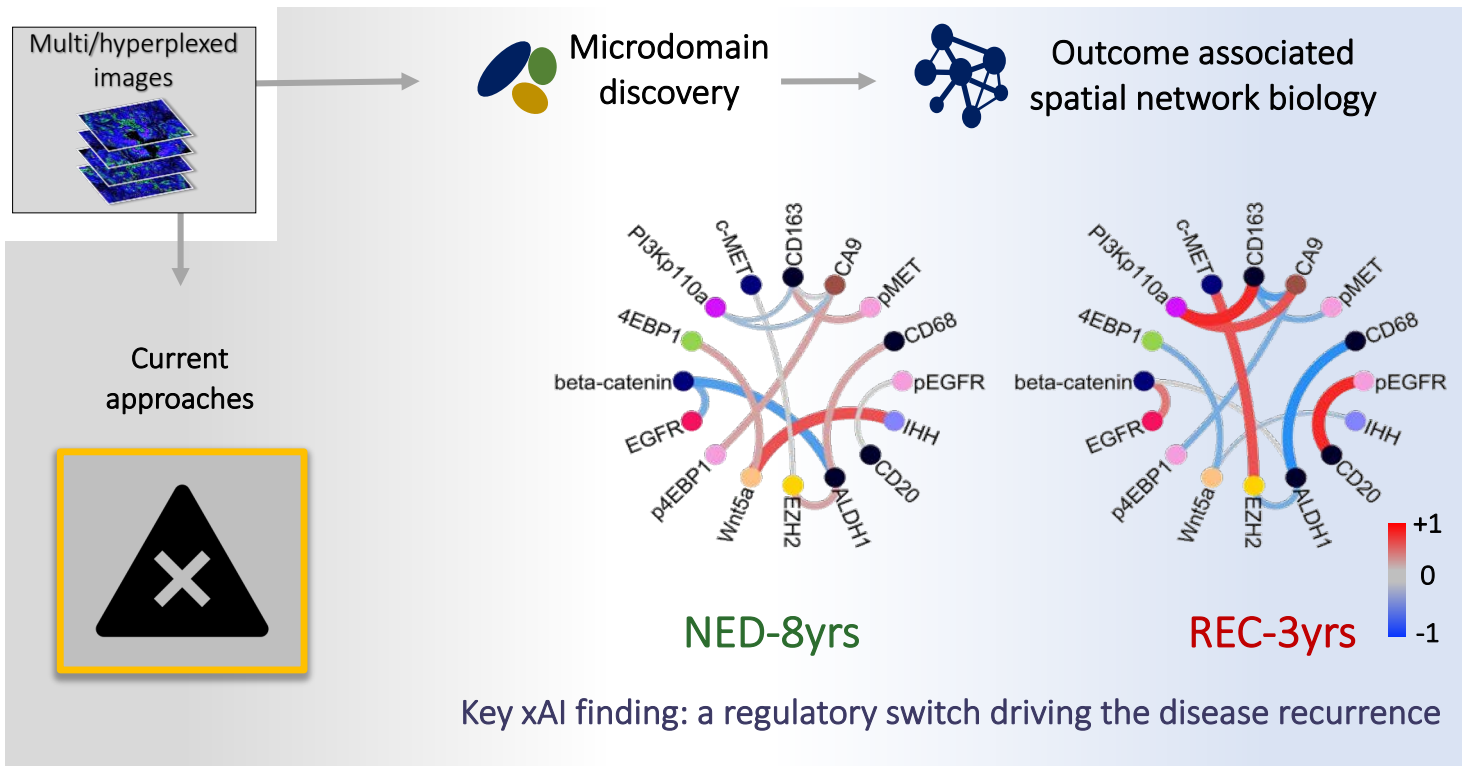
TumorMapr-Colon: Discovers Microdomains Associated w/ Recurrence Outcomes



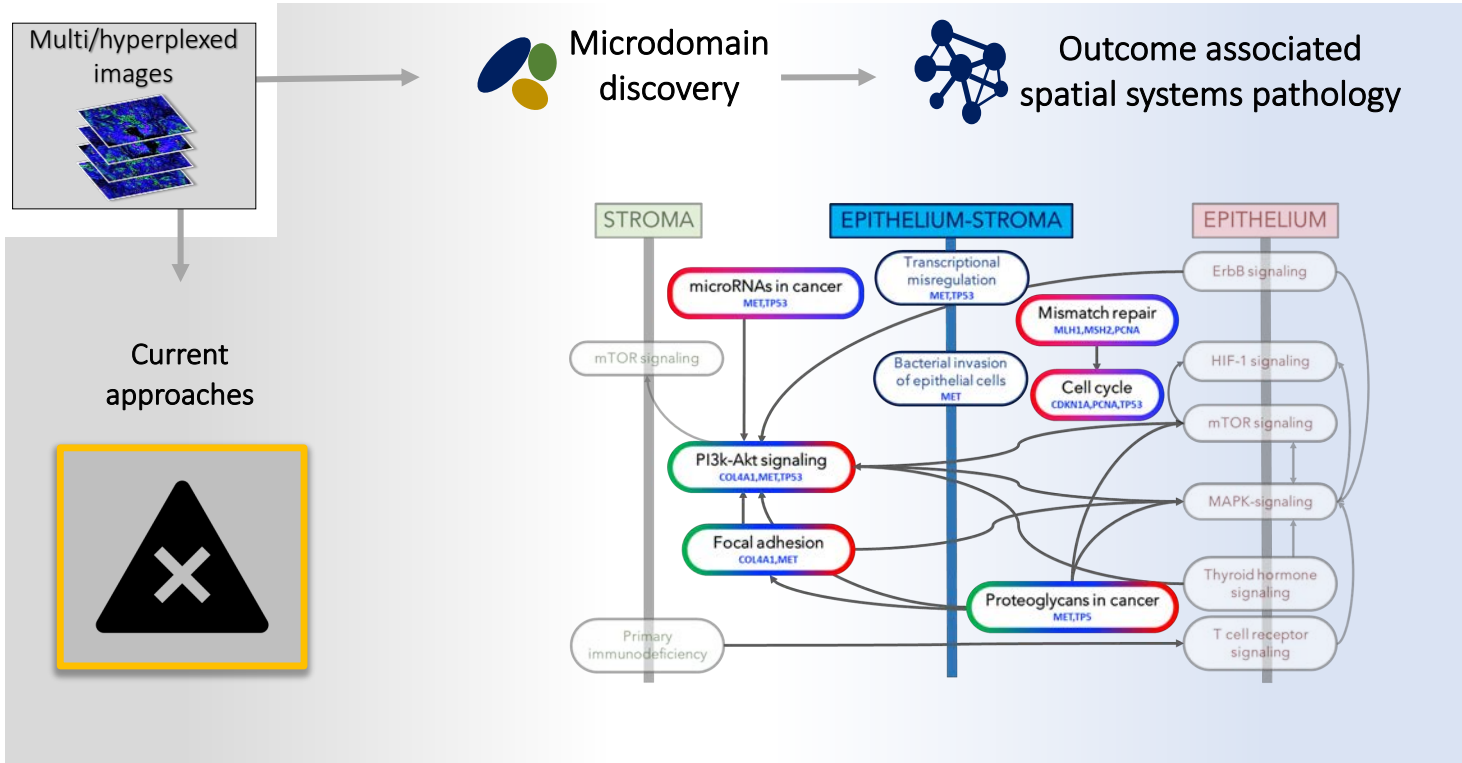
TumorMapr-Colon: Superior Prognostic Predictive Performance with Spatial Analytics & xAI



TumorMapr-Colon: Explains Spatial Network Biology Driving Recurrence



TumorMapr-Colon: Provides Mechanistic Insights Into Disease Biology



Spatial Analytics and xAI References

Spatial Analytics and xAI Pipelines

Tosun AB, et al – Springer Nature, LNAI 2020 [DOI Link](#)

Parvatikar A, et al – MICCAI 2020 [DOI link](#)

Tosun AB, et al – MICCAI 2017 [DOI link](#)

Nguyen L, et al – ISBI 2017 [PMID](#)

Nguyen L, et al – IEEE Trans Med Imaging 2017 [PMID](#)

Spagnolo DM, et al – J Pathol Inform 2016 [PMID](#)

Fine JL et al – Arch Pathol Lab Med 2017 [PMID](#)

Fine JL – J Pathol Inform 2014 [PMID](#)

Spatial Analytics and xAI Applications

Tosun AB, et al – xAI for Anatomic Pathology 2020 ([Adv Anat Pathol](#))

Uttam S, et al – Spatial colon cancer recurrence 2020 ([Nature Communications](#))

Furman S, et al – Unsupervised cellular phenotyping 2020 (bioRxiv [DOI link](#))

Spatial Analytics and xAI Conclusions

- Computational and systems pathology is here but we need trust
- Explainability means accountability and transparency, which will enable Trustworthy AI and will be critical for early clinical applications
- xAI will augment and not replace pathologists
 - Automation of easy tasks to allow pathologists to focus
 - Situational awareness for pathologists to make the best diagnoses possible
 - Improve the quality of pathology’s “product”; help patients
 - Pathologists and clinicians remain in control of the process and final decisions

Acknowledgements



Mike Becich



Lans Taylor



Jeffrey Fine



A. Burak Tosun



Filippo Pullara



Akash
Parvatikar



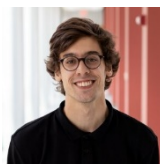
Om
Choudhary



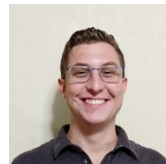
Luong
Nguyen



Dan
Spagnolo



Brian
Falkenstein



Maurice
Marx



Shikhar
Uttam



Samantha
Furman



- NIH-NCI U01 CA204826
- NHGRI BD2K U54HG00854
- UPMC & Center for Commercial Applications of Healthcare Data Grant #711077
- NSF SBIR Phase I Award #1843825