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Toward validated platforms and AI-powered digital pathology tools for evaluation of NASH histology in clinical trials

Liver Forum 15

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Institut Pasteur, Paris, France

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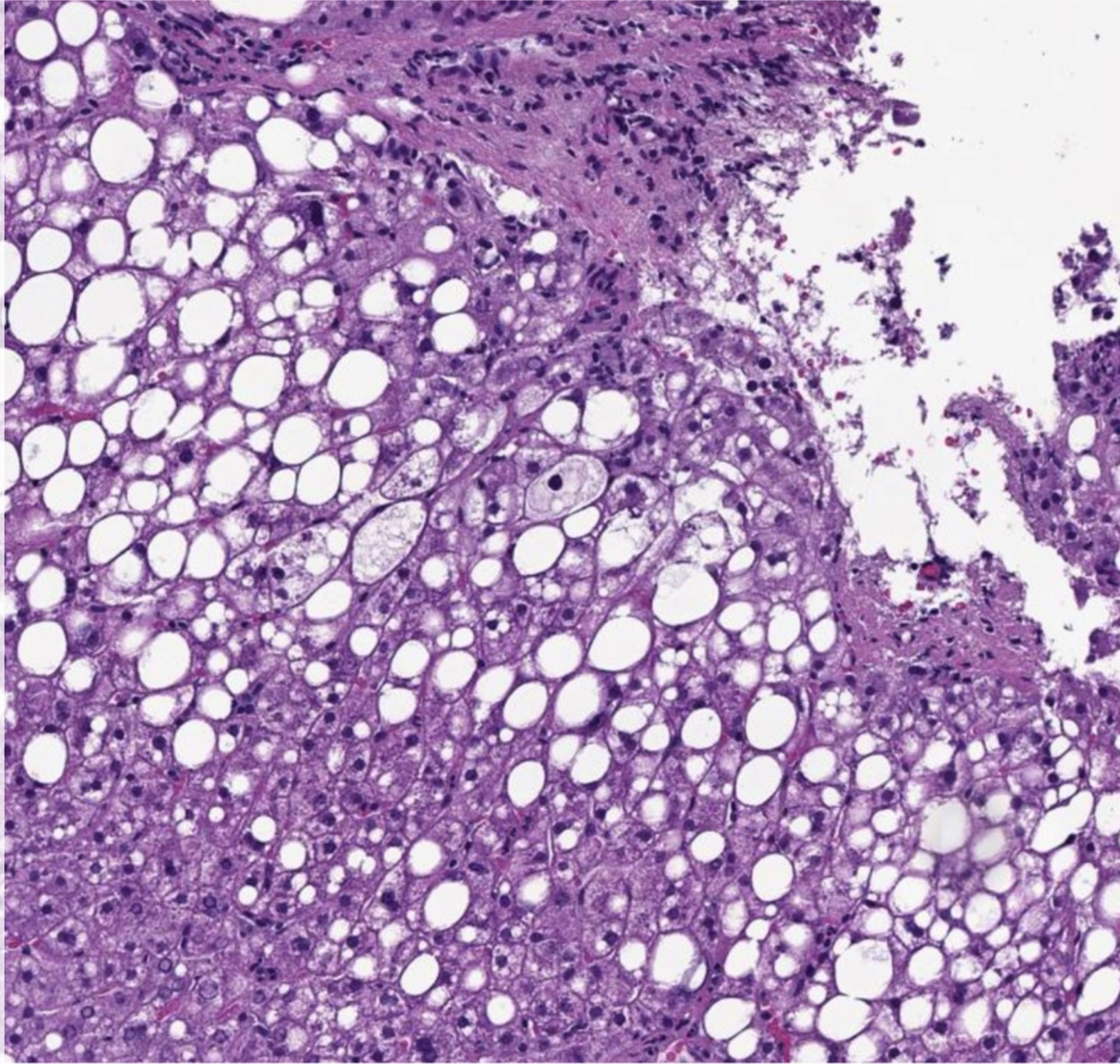
PathAI's AI-powered digital pathology solutions address unmet needs in NASH drug development

- **Immediate need** (**AIM-NASH™**):
  - Tool that assists pathologists in grading/staging of key histologic features of NASH, reducing impact of rater variability in NASH clinical trials
- **Long-term need** (**NASH Explore™**)
  - Assessment of treatment efficacy and change in disease severity over time via continuous, sub-ordinal measurement of NASH histologic features



Validation of a digital pathology platform for metabolic dysfunction-associated steatohepatitis for clinical trials

Hanna Pulaski, Shraddha S. Mehta, Laryssa C. Manigat, Stephanie Kaufman, Hypatia Hou, ILKe Nalbantoglu, Xuchen Zhang, Emily Curl, Ross Taliano, Tae Hun Kim, Michael Torbenson, Jonathan N. Glickman, Murray B. Resnick, Neel Patel, Cristin E. Taylor, Pierre Bedossa, Michael C. Montalto, Andrew H. Beck, Katy E. Wack

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Study overview

Objective: Validate a whole slide image (WSI) viewing platform that enables pathologists to perform clinical trial NASH CRN scoring in digitized slides containing liver biopsy tissue equivalently to how they perform on glass slides (i.e., “glass-to-digital” validation*)

*This study is part of PathAI’s regulatory submission to the FDA’s DDT/BQP program, to qualify the present reading platform (PathAI AISight™ Clinical Trial Services Platform) as an approved digital slide viewer for NASH clinical trials. The study design has been presented to both the FDA (CDER and CDRH) and the EMA.

Pulaski et al. 2023, *medRxiv*

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Glass-to-digital validation study population and design considerations

- The study was designed to capture the extent of variability that occurs in NASH clinical trials, including:
  - Inclusion of both NASH and non-NASH biopsies
  - Inclusion of multiple study time points
  - Inclusion of multiple drug targets
  - Inclusion of H&E and Masson's Trichrome staining from multiple labs
  - Inclusion of a wide range of NASH CRN NAFLD Activity Scores (NASs) and fibrosis stages, with enrichment for borderline cases
  - Utilization of CAP/CLIA-qualified and -maintained scanners
- The study was powered (N = ~160 biopsies) considering the specific context of pathology evaluations in NASH clinical trials, and to account for intra- and inter-pathologist variability in NASH CRN scoring
  - Digital scoring ("WSI reads") for the present study was performed by three experienced hepatopathologists per case. All pathologists passed NASH CRN scoring proficiency testing. Scoring was performed on PathAI's AISight™ Clinical Trial Services (CTS) Platform.
  - Ground truth (GT) glass slide scoring was performed by an independent group of experienced hepatopathologists who also passed NASH CRN scoring proficiency testing. These pathologists performed NASH CRN scoring on glass slides.

Pulaski et al. 2023, *medRxiv*

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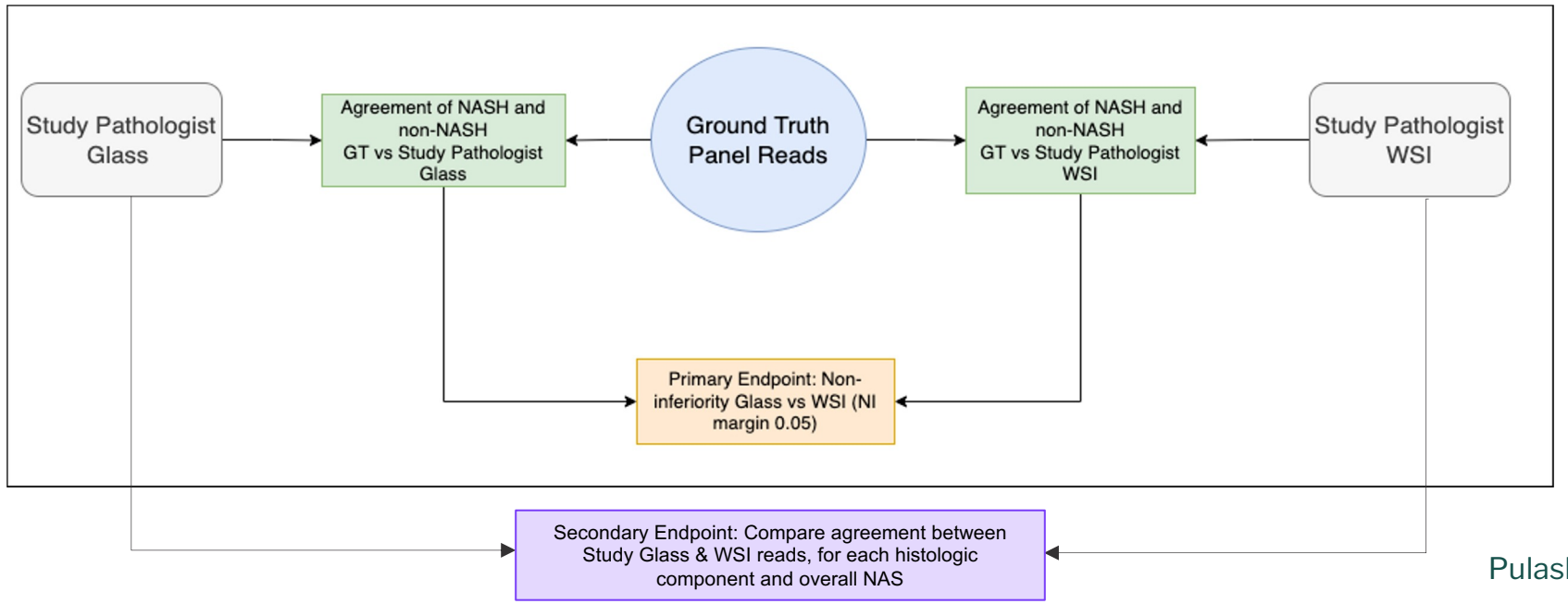
Glass-to-digital validation study design

Primary endpoint: Agreement between digital scoring and ground truth (GT) glass scoring of NASH CRN clinical trial inclusion criteria is **non-inferior** to agreement between individual pathologist glass scoring and GT glass scoring

Secondary endpoint: Per histologic component and for overall NAS, agreement between digital scoring and ground truth (GT) glass scoring is **non-inferior** to agreement between individual pathologist glass scoring and GT glass scoring. Agreement rates are within published ranges for intra-pathologist agreement.



Pulaski et al. 2023, *medRxiv*

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Glass-to-digital validation study met its primary endpoint

Primary endpoint: Agreement between digital scoring and ground truth (GT) glass scoring of NASH CRN clinical trial inclusion criteria is **non-inferior** to agreement between individual pathologist glass scoring and GT glass scoring

Test	N	*Agreement Rate (95% CI)	Difference (95% CI)	P-value
Digital vs. GT Glass	159	0.743 (0.7, 0.788)	-0.001 (-0.027, 0.026)	<0.0001
Individual Pathologist Glass vs. GT Glass	159	0.745 (0.703, 0.786)		

*Agreement rates were measured for identification of steatohepatitis, defined as NAS ≥ 4 with ≥ 1 in each of Steatosis, Lobular Inflammation, and Hepatocellular Ballooning, and absence of features indicative of other liver diseases

Pulaski et al. 2023, *medRxiv*

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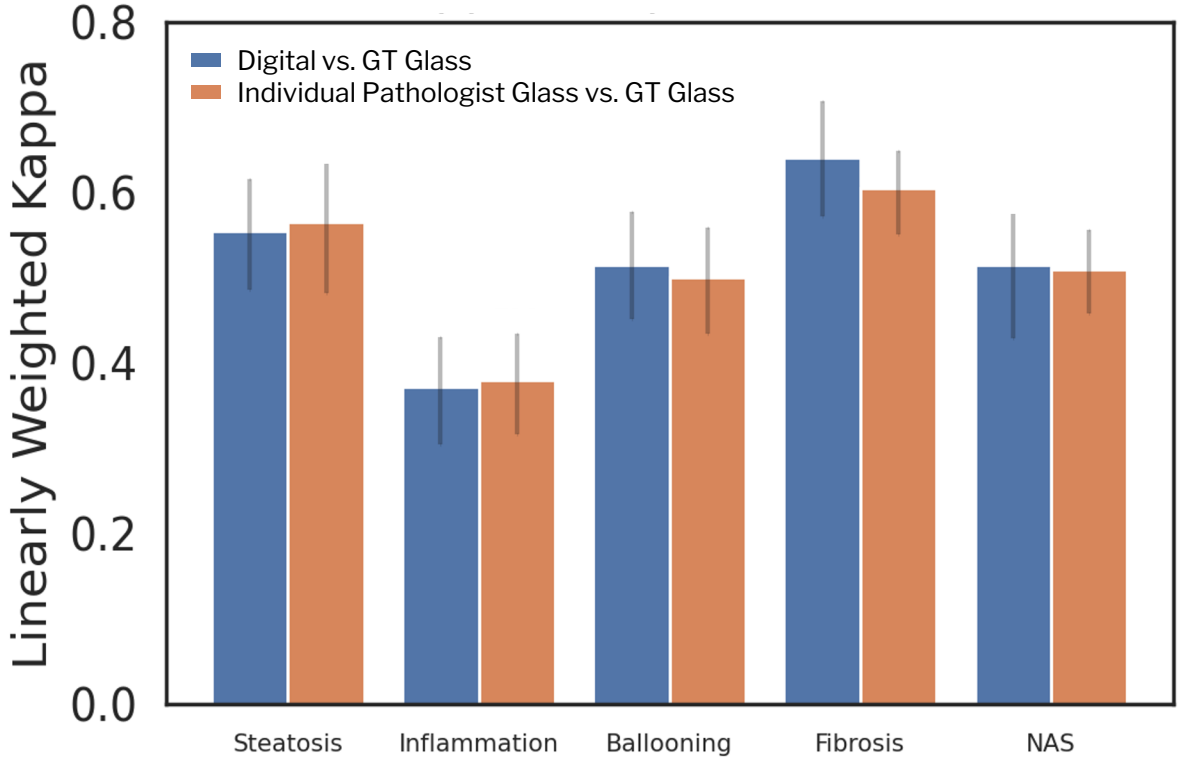
Glass-to-digital validation study met its secondary endpoint

Secondary endpoint: Per histologic component and for overall NAS, agreement between digital scoring and ground truth (GT) glass scoring is **non-inferior** to agreement between individual pathologist glass scoring and GT glass scoring. Agreement rates are within published ranges for intra-pathologist agreement.



Histologic component	Publication	Intra-reader variability*	Digital vs. GT Glass (95% CI)*
Steatosis	Kleiner et al. 2005	0.83	**0.882** (0.844, 0.916)
	Gawrieh et al. 2011	0.72-0.75	
	Davison et al. 2020	0.666	
Lobular Inflammation	Kleiner et al. 2005	0.60	**0.761** (0.707, 0.809)
	Gawrieh et al. 2011	0.37-0.48	
	Davison et al. 2020	0.227	
Hepatocellular Ballooning	Kleiner et al. 2005	0.66	**0.788** (0.732, 0.835)
	Gawrieh et al. 2011	0.32-0.56	
	Davison et al. 2020	0.487	
Fibrosis	Kleiner et al. 2005	0.85	**0.872** (0.837, 0.901)
	Gawrieh et al. 2011	0.64-0.75	
	Davison et al. 2020	0.679	
Overall NAS	Davison et al. 2020	0.372	**0.795** (0.76, 0.825)

*All reported values are linearly-weighted kappa statistics

Pulaski et al. 2023, *medRxiv*

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Conclusions

- Experienced liver pathologists are equivalently capable of scoring the following NASH histologic parameters via glass slides vs. PathAI's AISight™ Clinical Trial Services digital platform (in addition to identifying additional findings):
  - Macrovesicular steatosis
  - Lobular inflammation
  - Hepatocellular ballooning
  - Fibrosis

- Agreement between digital scoring and ground truth (GT) glass scoring of NASH CRN clinical trial inclusion criteria is **non-inferior** to agreement between individual pathologist glass scoring and GT glass scoring

- Per histologic component and for overall NAS, agreement between digital scoring and ground truth (GT) glass scoring is **non-inferior** to agreement between individual pathologist glass scoring and GT glass scoring. Agreement rates are within published ranges for intra-pathologist agreement.

We're ready to move beyond glass vs. digital reading concerns to discuss how AI can **1)** help pathologists achieve reproducible scoring in NASH clinical trials, and **2)** help drug developers characterize the histologic response to their therapeutics!

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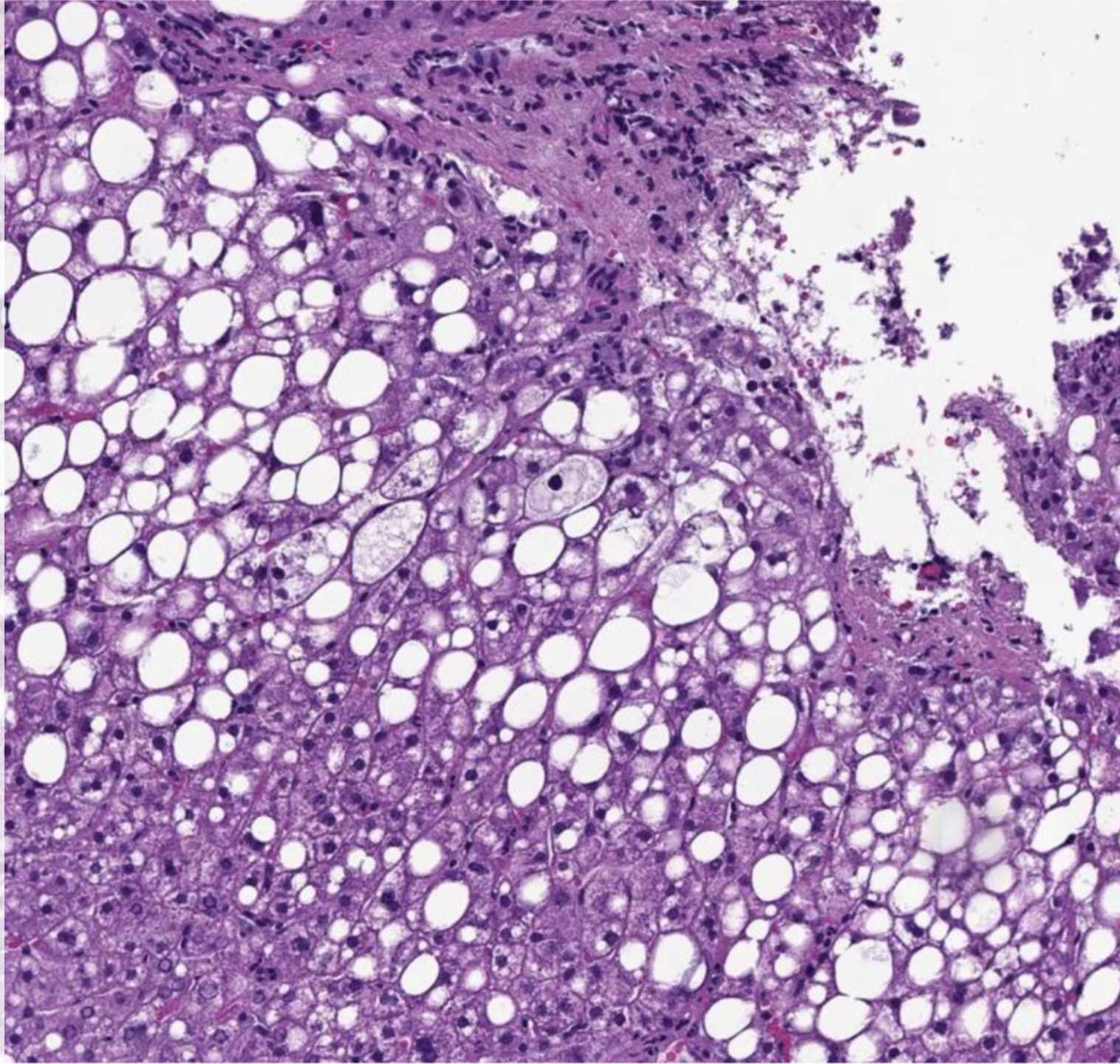
PathAI's AI-powered digital pathology solutions address unmet needs in NASH drug development

- **Immediate need** (**AIM-NASH™**):
  - Tool that assists pathologists in grading/staging of key histologic features of NASH, reducing impact of rater variability in NASH clinical trials
- **Long-term need** (**NASH Explore™**)
  - Assessment of treatment efficacy and change in disease severity over time via continuous, sub-ordinal measurement of NASH histologic features



AIM-NASH Drug Development Tool (DDT) for clinical trial biopsy scoring

PathAI NASH DDT provides the standard EMA- and FDA-recommended scores:

- NAFLD activity score
- CRN fibrosis stage

Validated Whole Slide Image (WSI) viewer:
AISight | Clinical Trials

- AISight Clinical Trials, validated for pathologist evaluation of biopsies in NASH trials.
- Overlay features validated for accuracy in highlighting the NAS and CRN fibrosis scores

Context of Use: A monitoring biomarker as an adjunct that aids the pathologist in assessing NASH disease activity (at baseline and subsequent time points) to produce the Nonalcoholic Fatty Liver disease activity score (NAS) components and fibrosis stage in liver biopsies in NASH clinical trials.

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PathAI is proud to introduce

NASH Explore™

for AI-powered fibrosis detection + subtyping, zonal quantification of histologic features, and cellular-level characterization of NASH tissue microarchitecture in H&E whole slide images.

Achieving model performance domain generalization using ContriMix

- PathAI has developed and launched **ContriMix**, a domain generalization technique that learns to disentangle biological content (e.g. tissue and cell features) from technical variations (e.g. scanner/stain-specific noise) in microscopy images. This is an operation that pathologists perform naturally, but computers have to learn to do effectively.

- Training our portfolio of NASH AI products using ContriMix allows for excellent model performance generalization across the extent of stain variability encountered in NASH clinical trials and in real world data.

Nguyen et al. 2023, *medRxiv*, "ContriMix: Unsupervised disentanglement of content and attribute for domain generalization in microscopy image analysis"

This approach allows us to perform accurate, reproducible, quantitative AI-powered digital pathology in whole slide images of **stained** liver biopsy tissue sections with **limited concerns surrounding performance generalizability.**

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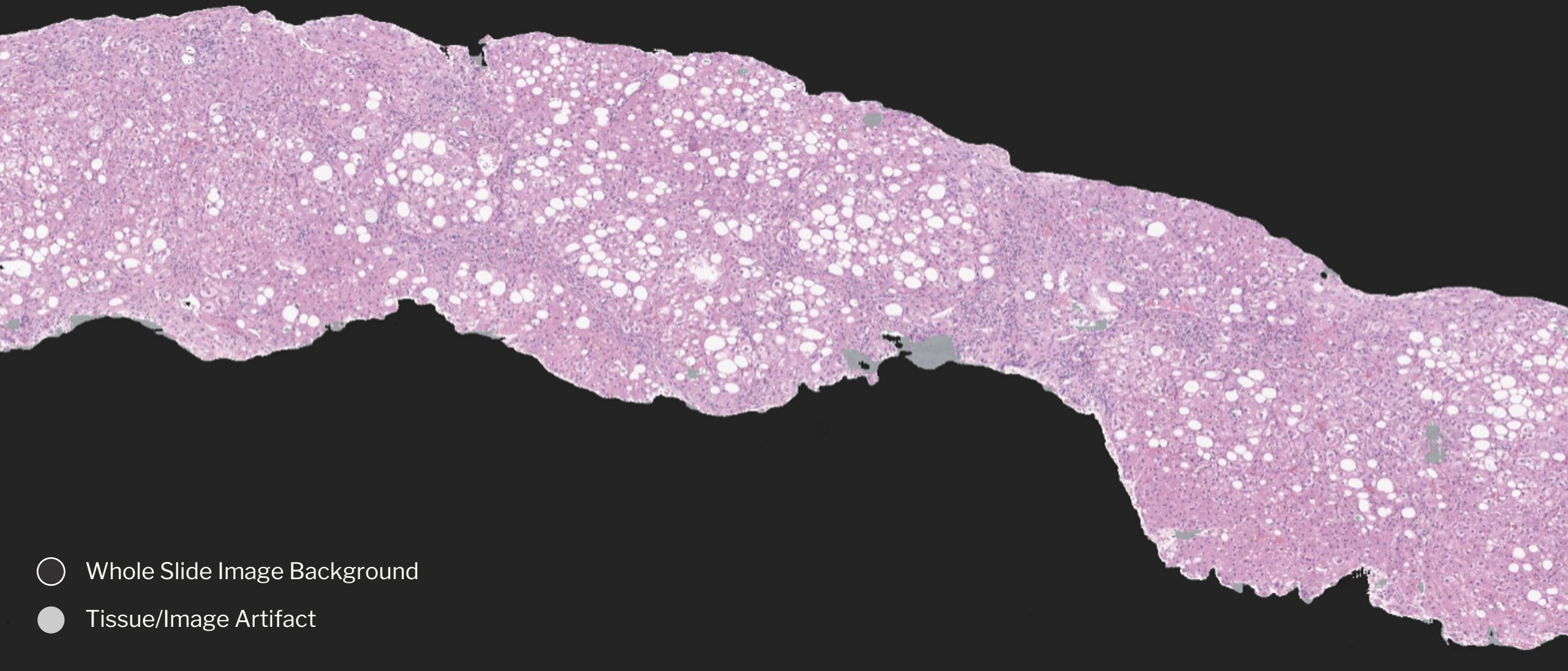
NASH Explore™

ARTIFACT DETECTION: AI-powered, automated detection and exclusion of tissue and image artifact in H&E whole slide images



Whole Slide Image Background

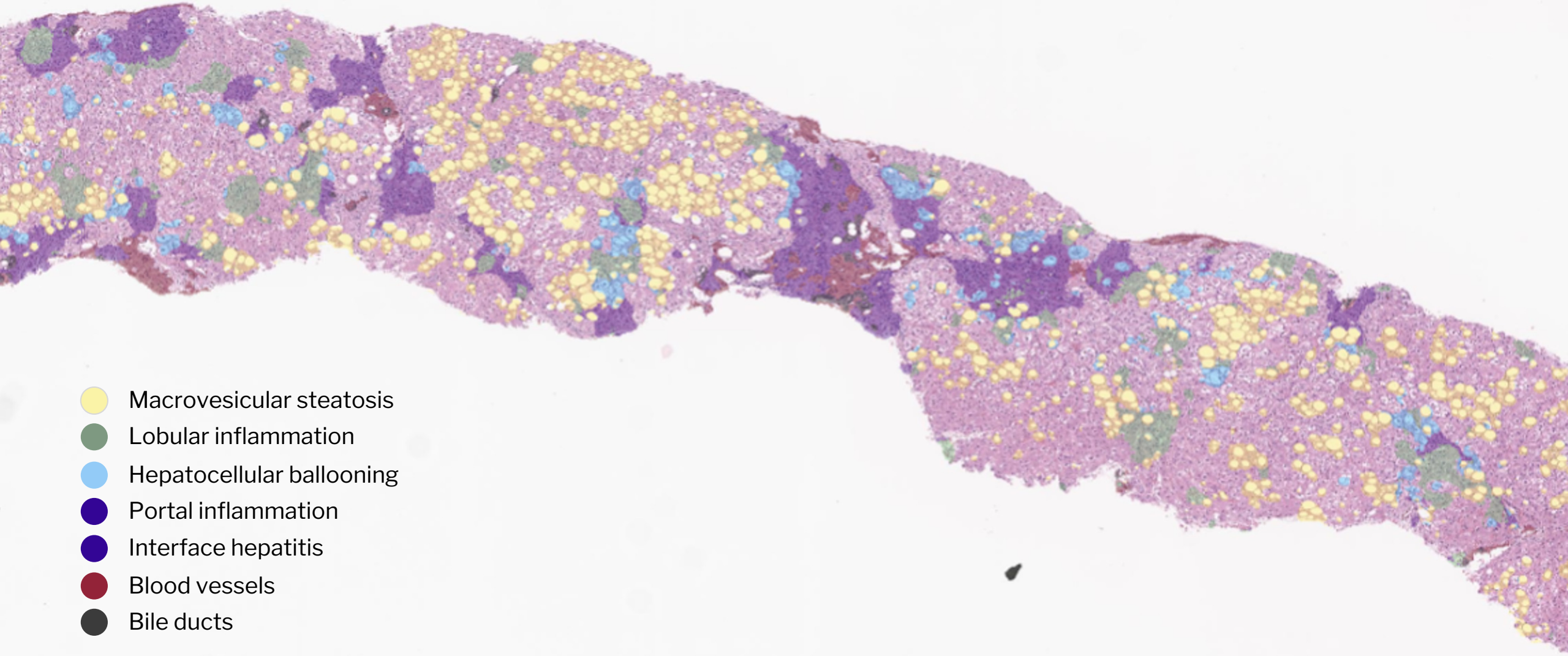
Tissue/Image Artifact

NASH Explore™

LANDMARK SEGMENTATION: AI-powered, automated detection of portal tracts and central veins, and segmentation of liver lobular zones for zonal quantification of histologic features

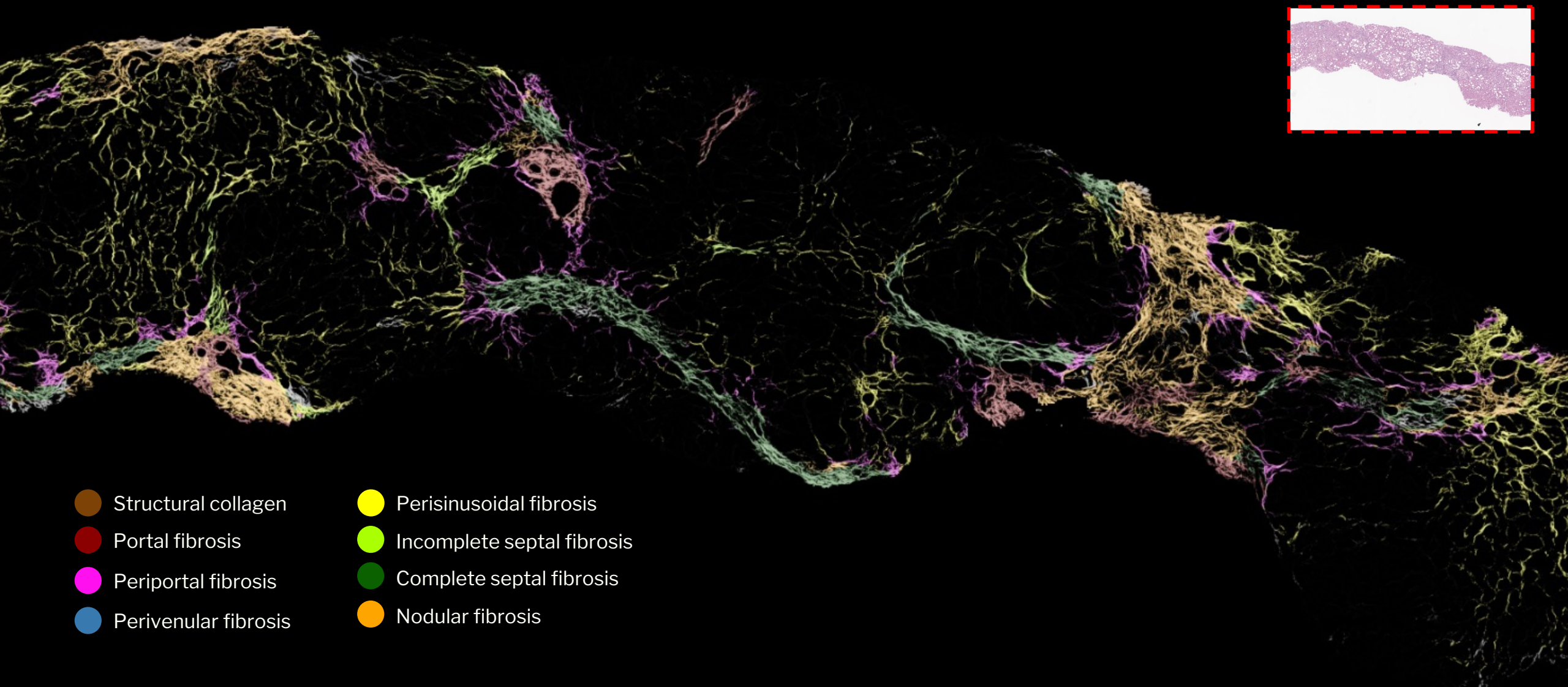
NASH Explore™

TISSUE DETECTION: AI-powered, automated tissue region detection and quantification in H&E whole slide images



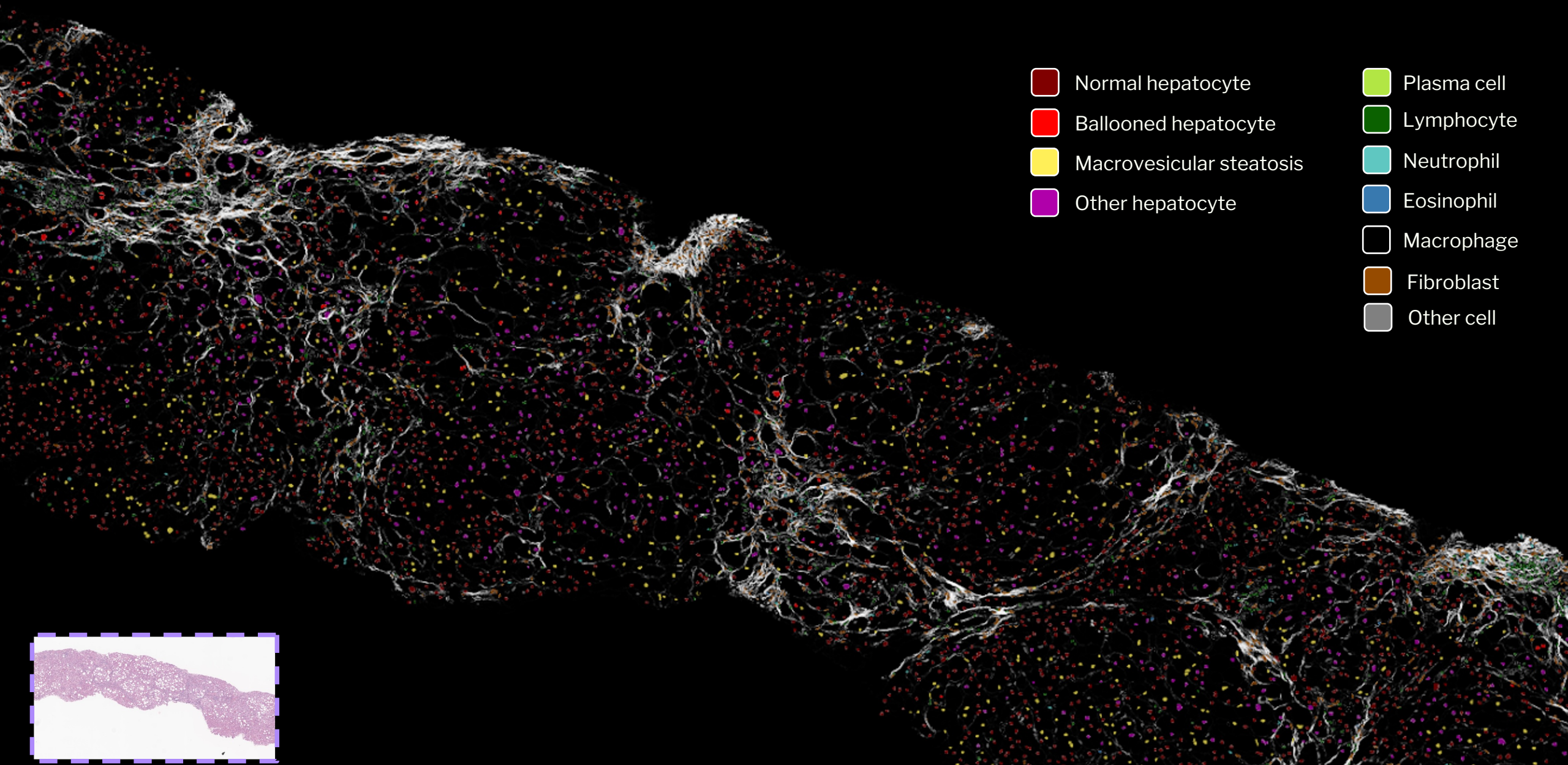
NASH Explore™

FIBROSIS SUBTYPING: AI-powered, automated subtyping of fibrosis into clinically-relevant patterns in H&E whole slide images



NASH Explore™

CELL DETECTION: AI-powered, automated cell detection and quantification in H&E whole slide images



NASH Explore™ complements AIM NASH™ by delivering a structured panel of >1000 quantitative Human Interpretable Features (HIFs) per H&E whole slide image for scalable, standardized, reproducible analysis

Quantitative Human Interpretable Features (HIFs) measured across each cell type, tissue type, fibrosis subtype, and zonal location

Total Area of **Perisinusoidal Fibrosis**

- Periportal Fibrosis
- Complete Septal Fibrosis
- Nodular Fibrosis

Total Area of **Perisinusoidal Fibrosis** area in **Total Tissue Area**

- Periportal Fibrosis
- Nodular Fibrosis
- Pathologic Fibrosis

Count of **Steatotic Hepatocytes** in proximity of **Septal Fibrosis** in **Zone 2**

- Ballooned Hepatocytes
- Normal Hepatocytes
- Lymphocytes
- Macrophages
- Perisinusoidal Fibrosis
- Nodular Fibrosis
- Zone 1
- Zone 3

Density of **Lymphocytes** in **Portal Tract**

- Neutrophils
- Eosinophils
- Macrophages
- Interface Hepatitis
- Zone 2

H&E Slide ID	AREA PROP [PERISINUSOIDAL FIBROSIS] IN [ALL FIBROSIS]_H&E	DENSITY [ALL IMMUNE CELLS] IN [PORTAL TRACT]_H&E	TOTAL [BALLOONED HEPATOCYTES] IN [USABLE TISSUE]_H&E	AREA PROP ([MACROVESICULAR STEATOSIS] IN [USABLE TISSUE]) NEAR [NODULAR FIBROSIS]_H&E
257785	0.35536164	184.3284696	12.00000000	0.74893501
257682	0.69919819	105.7626842	7.00000000	0.47892043
257722	0.75522328	106.5570013	5.00000000	0.23048759
257812	0.04953395	135.196.477	8.00000000	0.08749367
257664	0.70388323	362.1587609	2.00000000	0.20948574
257779	0.54496612	215.9119680	9.00000000	0.39475873
257842	0.20255.414	187.9219654	6.00000000	0.21769405
257710	0.66805131	107.1449498	8.00000000	0.01928347
257772	0.04857480	104.5795653	1.00000000	0.00283765
257661	0.65090889	190.4890243	0.00000000	0.95890648
257675	0.21158807	118.4339708	3.00000000	0.84567302
257768	0.35020110	139.4641664	3.00000000	0.73892473
257655	0.19666099	200.8956839	5.00000000	0.18973246
257715	0.26749427	314.3395106	3.00000000	0.98273463
2578.47	0.51483537	136.3118490	2.00000000	0.12984364
257787	0.22957260	531.3859510	4.00000000	0.72398746
257717	0.57409153	124.1346719	5.00000000	0.23487320
257810	0.41735203	115.2742895	6.00000000	0.39873249
257831	0.42164019	208.1559374	1.00000000	0.73639283
257777	0.07660992	107.6967374	4.00000000	0.00278927
257728	0.00215114	102.9368179	2.00000000	0.83279238
257837	0.14516027	89.7637331	3.00000000	0.72384958
257719	0.00317080	98.6636485	2.00000000	0.55567483
257671	0.13924442	107.7011635	3.00000000	0.23736938

>1000 Quantitative HIFs enable...

- Identification of histologic biomarkers of trial endpoint response and predictors of disease progression and regression
- Characterization of mechanism-of-action-specific histologic response to therapy
- Seamless correlation with non-invasive biomarker data

PathAI has published extensively on the utility of its NASH quantitative histologic features for detecting therapeutic response and predicting patient outcomes

- The ratio of portal to lobular inflammation stratifies cirrhotic NASH patients into rapid vs. slow progressors
  - *Pokkalla et al. 2019*
- The proportionate area of patterns of advanced fibrosis at baseline in F3 patients is highly predictive of which will progress to cirrhosis
  - *Pokkalla et al. 2020*
- Distinguishing between and quantifying patterns of advanced vs. early-stage fibrosis facilitates detection of drug effect that is not detected via categorical scoring
  - *Loomba et al. 2020*
- Continuous scoring is more predictive of patient progression to poor outcomes than ordinal scoring
  - *Iyer et al. 2022*
- Integration of quantitative histologic features and transcriptomic data identifies key genes associated with fibrogenesis in NASH
  - *Pouryahya et al. 2023*

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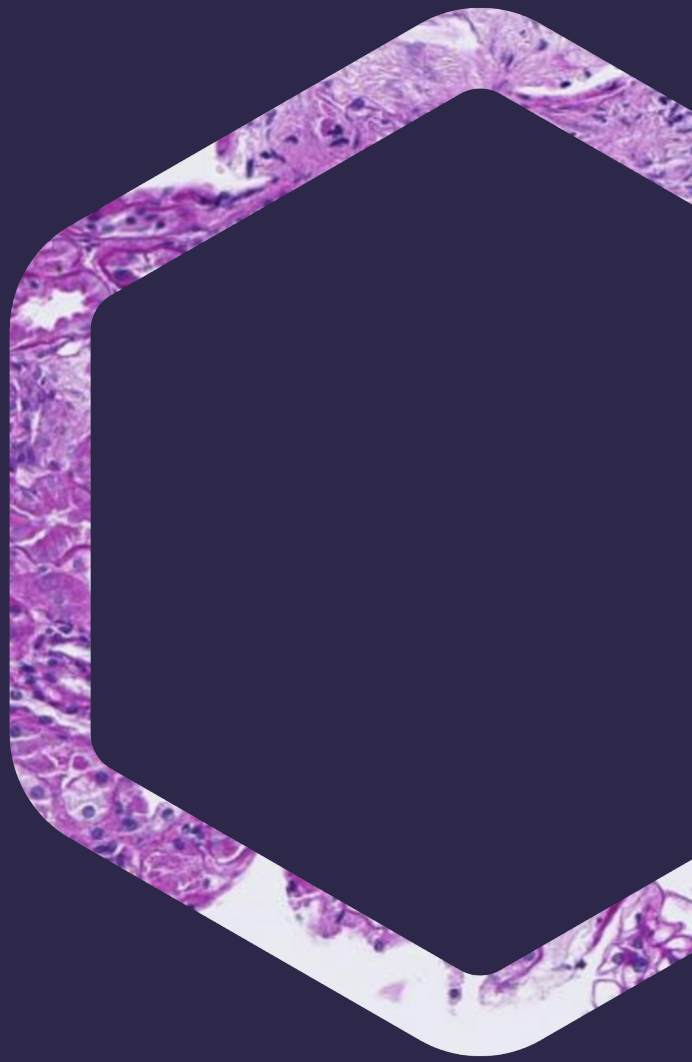
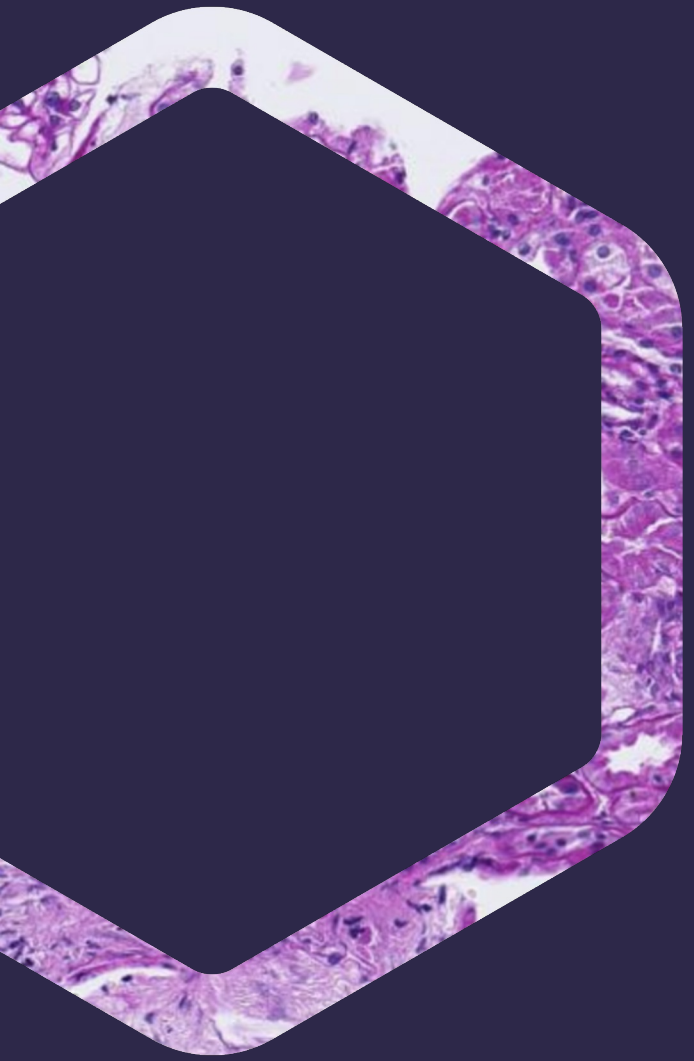
Thank you





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