Automatic Pathology Software for Diagnosis of Non-Alcoholic Fatty Liver Disease

(OTT ID 1236)

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Shortfalls of current liver pathology assessment

Problems/Unmet Needs:

- Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common liver disease in the U.S.
- Accurate distinction of mild vs. severe phenotypes is essential and liver biopsy is the only way to accurately diagnose and stage NAFLD
- Current NAFLD scoring method relies on manual pathologist assessment and grading of histological features
- Studies demonstrate substantial pathologist disagreement and inter-observer error (Gawrieh, S., Knoedler, 2011. 15: 19-24.)
- Poor reproducibility; intra-observer error
- Does not reflect the true continuous nature of “scoring” lesions

Technological Solution:

- The inventors have utilized a supervised machine learning technique for identification of white regions in liver biopsies with 92% accuracy (based on results from 47 patients)
- This is the first work to identify white regions using machine learning and automatically quantify lobular inflammation and hepatocyte ballooning
- This technology is automatic, faster, and more accurate than human pathologists
- Applications include diagnosis of NAFLD, assessment of candidate liver donors for transplants, and biopsy index database searching

Road to Commercialization: Market, Intellectual Property, and Partnering

Market

- The global market for liver disease treatments was $400 million in 2009 and expected to increase to more than $700 million by 2014
- Computer aided detection and diagnosis (CAD), originally used in image analysis and the development of algorithms for image recognition, has evolved to offer full workflow management packages for a range of healthcare conditions
- Use of CAD can provide a more economically viable proposition for busy, cost-focused healthcare providers; CAD allows physicians to deal with enormous data sets more efficiently, making their job easier and in turn making physicians more accurate

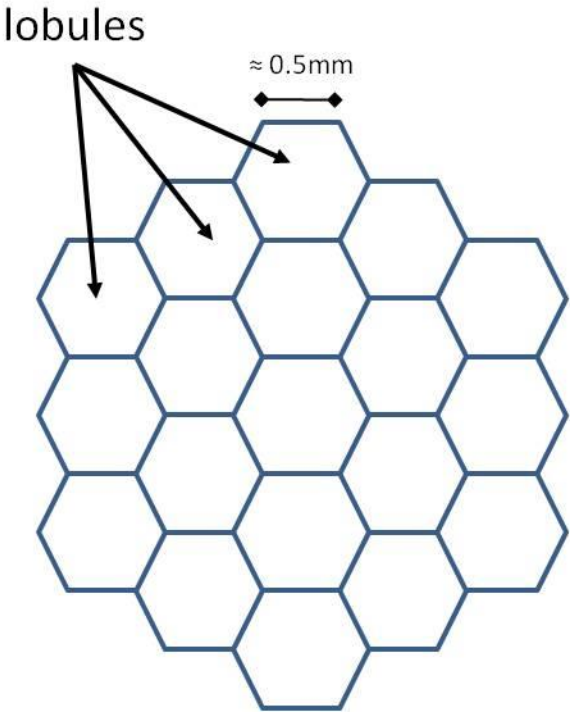
Intellectual Property

- Copyrighted Software

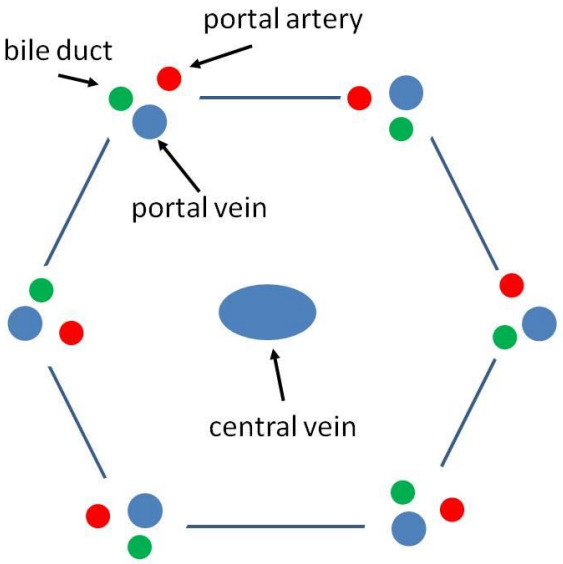
Partnering

- We are looking for a partner to license the algorithm and software and to develop the technology into a final product for use by pathologists or other end users

Liver Anatomy-Lobule



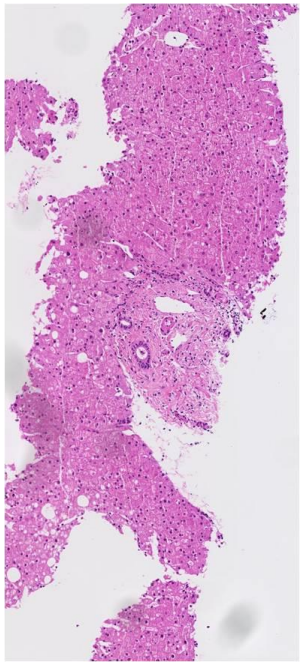
Multiple lobules



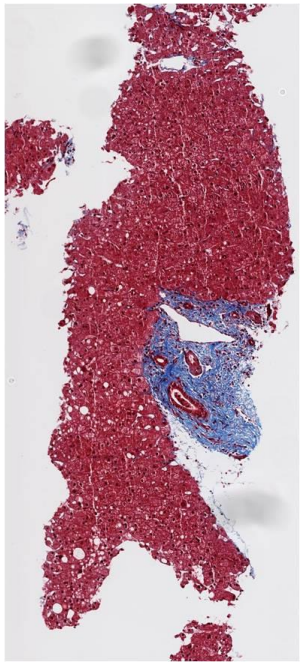
A single lobule

- The bile duct, portal artery and vein, and central vein are some of the white regions that must be distinguished from the fatty white regions in a liver lobule

Liver Biopsies for Pathological Assessment

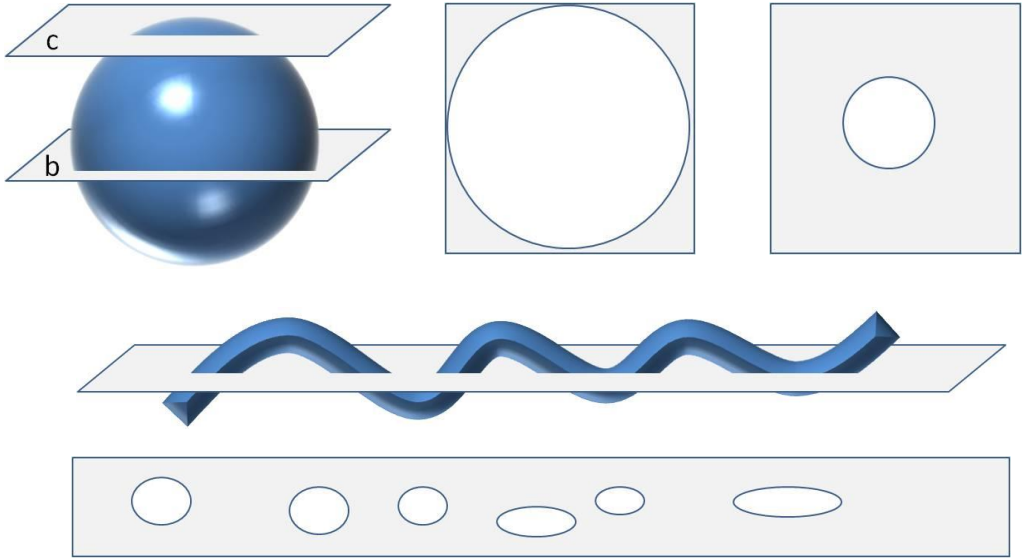


H&E Stain



Trichrome Stain

- Biopsy sections are cut into different planes for staining



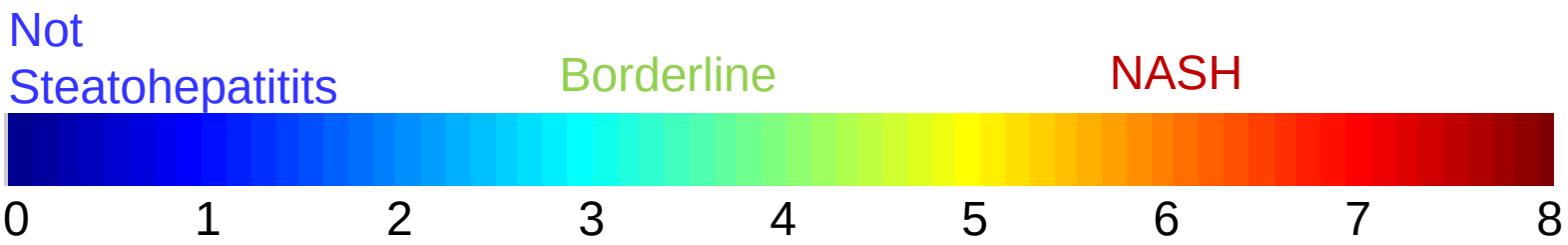
- White regions are identified from the stained biopsy sections from a patient

Pathologists use the NAFLD Activity Score (NAS)

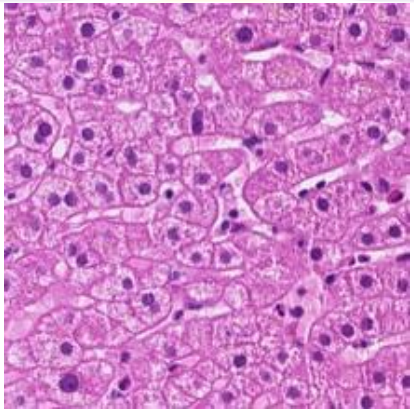
- State-of-the-art scoring system for NAFLD (Kleiner et al., 2005)

- Based on 3 key histological features:
  - Steatosis [0-3]
  - Lobular Inflammation [0-3]
  - Hepatocyte Ballooning [0-2]

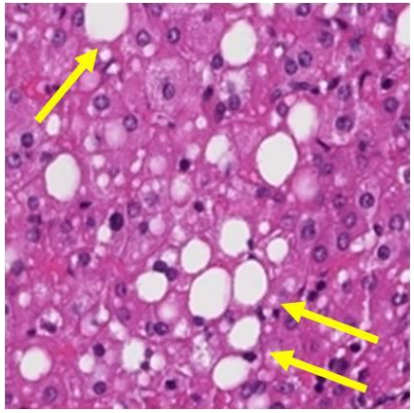
- NAS = Steatosis + Lobular Inflammation + Hepatocyte Ballooning



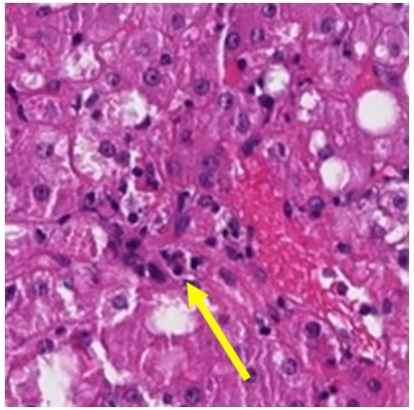
Examples of Histological Legions



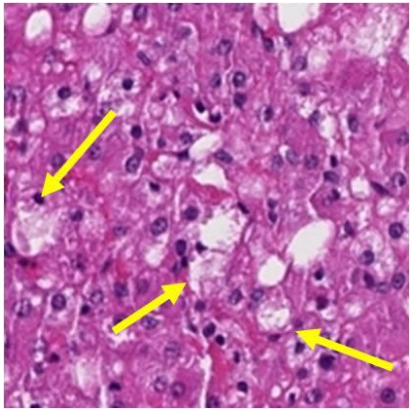
Normal



Steatosis

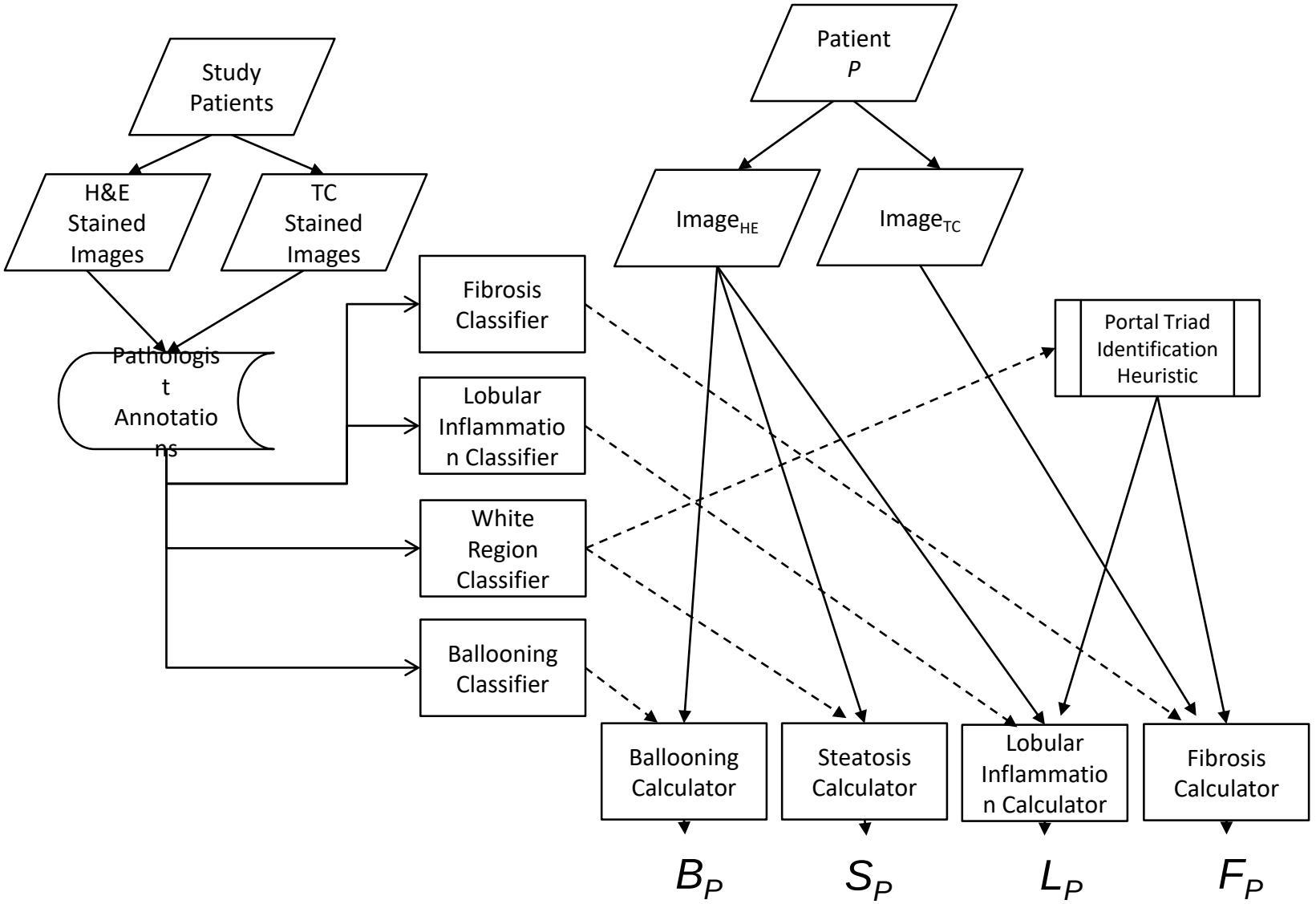


Lobular Inflammation

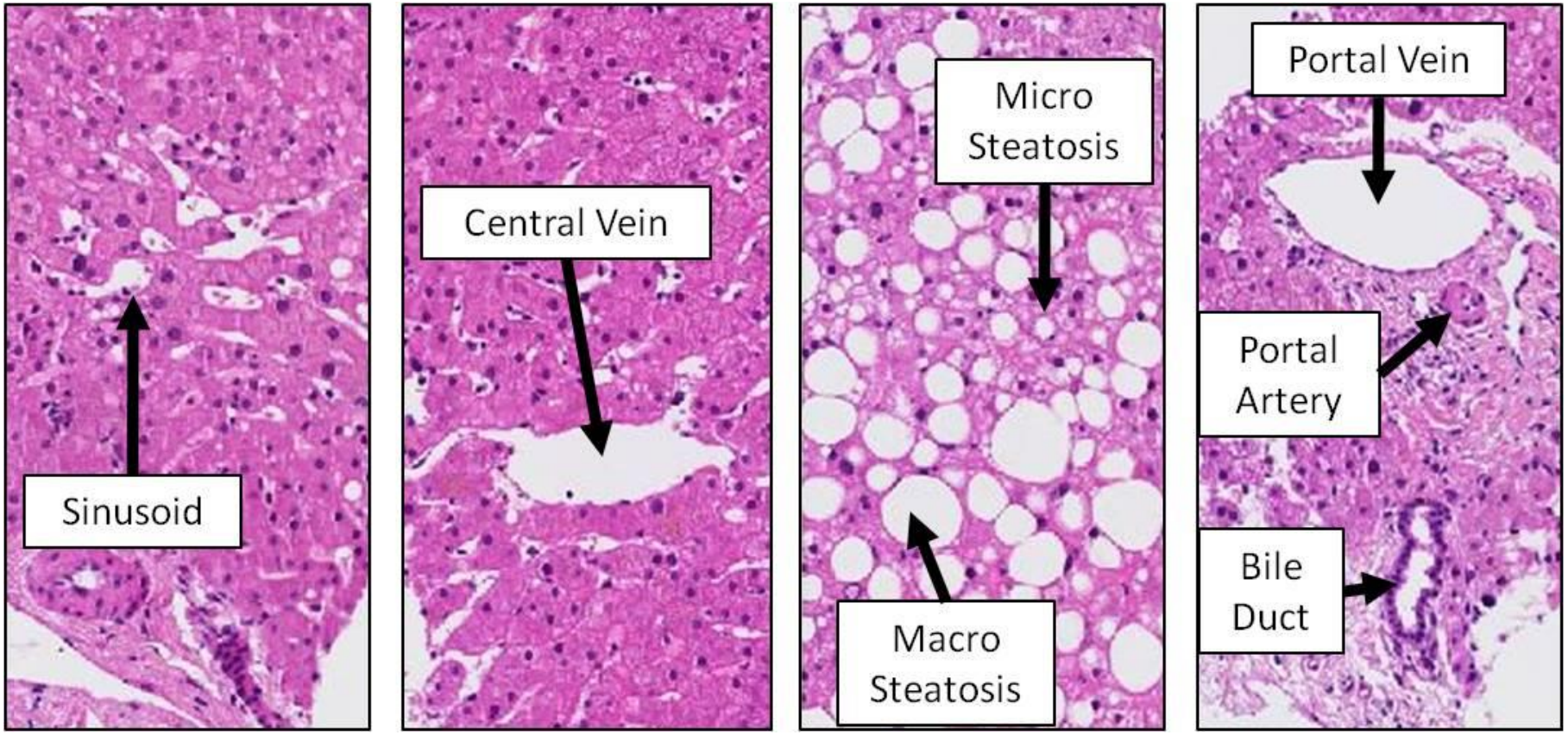


Hepatocyte Ballooning

Approach for Machine Learning



Classification of White Regions



- Motivation
  - Classifying all white regions provides a direct methods for quantifying steatosis
  - Many anatomical land markers manifest as white or with a white center. This is useful for other tasks

Method for Classification of White Regions

Hypothesis:

- Comparing previous methods that use hand crafted rules based purely on morphology, to a supervised machine learning approach that uses a richer feature vector representation
- Richer feature vector representations lead to more accurate classifications than ones based purely on morphology
  - We compare 2 representations:
    1. Morphology Only
    2. Advanced feature set

Approach

- Represent each white region by a fixed length feature vector
- 10 fold cross validation

Results of White Region Classification

Accuracy

Model	Overall Accuracy	P-Value
Morphology	74.8%	
Advanced feature set	92.1%	0.0007

Supervised Machine Learning Results

	Predicted							
Actual	Bile Duct	Central Vein	Macro Steatosis	Micro Steatosis	Portal Artery	Portal Vein	Other	Sinusoid
Bile Duct	45	1	0	1	4	2	0	0
Central Vein	0	41	2	0	2	3	0	4
Macro Steatosis	0	0	419	9	0	0	0	2
Micro Steatosis	0	0	15	281	1	0	0	6
Portal Artery	3	3	0	1	33	2	0	1
Portal Vein	2	5	0	1	1	73	0	1
Other	0	1	0	0	0	0	6	0
Sinusoid	0	5	3	9	1	1	0	170

The results show that the algorithm is predicting the white regions with very high accuracy.

Results of White Region Classification-Cont'd

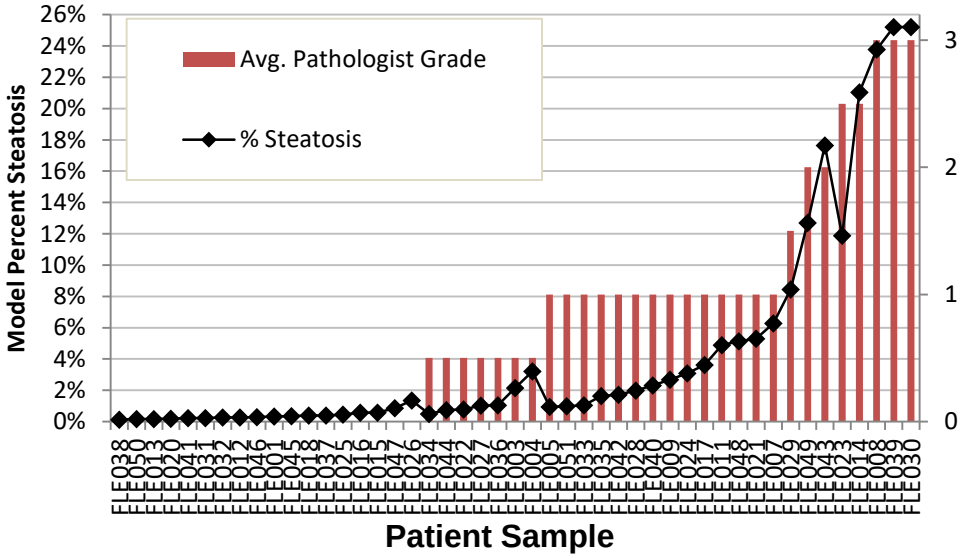
Feature	Precision	Recall	ROC Area
Bile Duct	0.900	0.849	0.981
Central Vein	0.732	0.788	0.938
Macro Steatosis	0.954	0.974	0.980
Micro Steatosis	0.930	0.927	0.967
Other	1.000	0.857	0.994
Portal Artery	0.786	0.767	0.973
Portal Vein	0.901	0.880	0.976
Sinusoid	0.924	0.899	0.982
OVERALL	**0.921**	**0.921**	**0.974**

- Results again show that the algorithm is classifying white regions with very high accuracy. Of particular interest is how well it performs for macro and micro steatosis (fat)

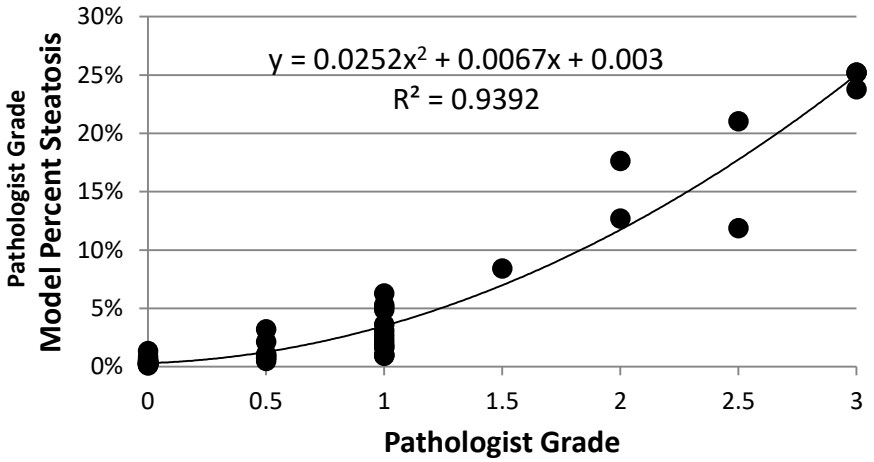
Steatosis Grade Machine Learning

- Percent Steatosis = total steatosis area / total tissue area
- Learn a different model for each patient using a leave one out approach
- The model is able to correlate best with the average grade

Correlation of Computed Percentage Steatosis with Pathologist Grade



Relationship of Computed Percentage Steatosis with Pathologist Grade

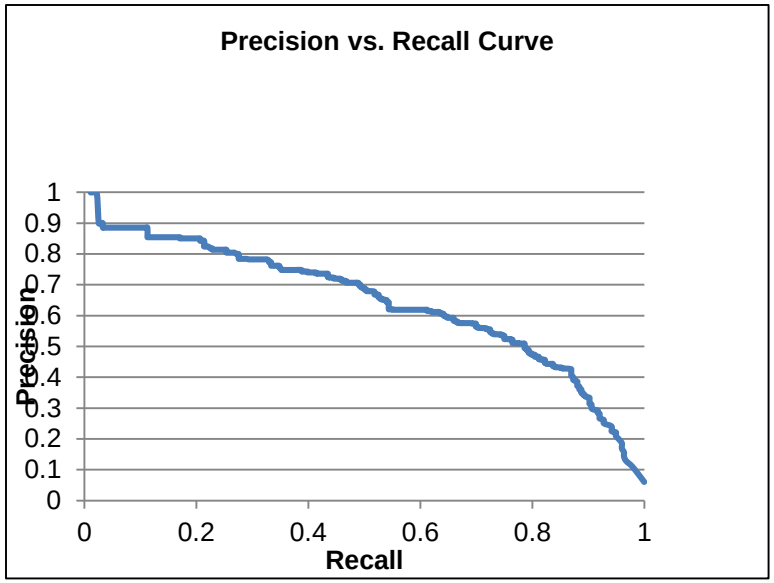


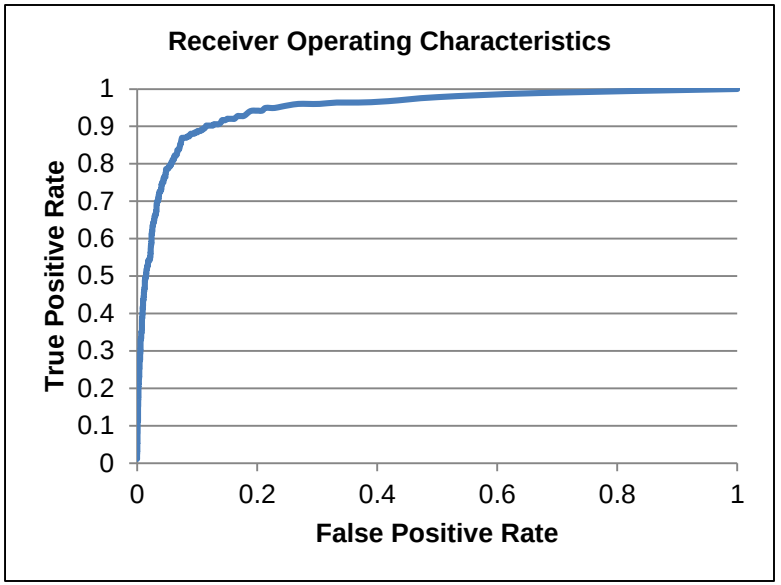
Lobular Inflammation Classification

Hypothesis/Approach:

- Lobular inflammation classification can be performed by supervised machine learning
- Provide a representative quantification for actual lobular inflammation regions
- Use a feature vector very similar to the one used for white regions
- 10 fold cross validation

Approach for Lobular Inflammation Classification: 95.6% accuracy (vs. 94.0% baseline)



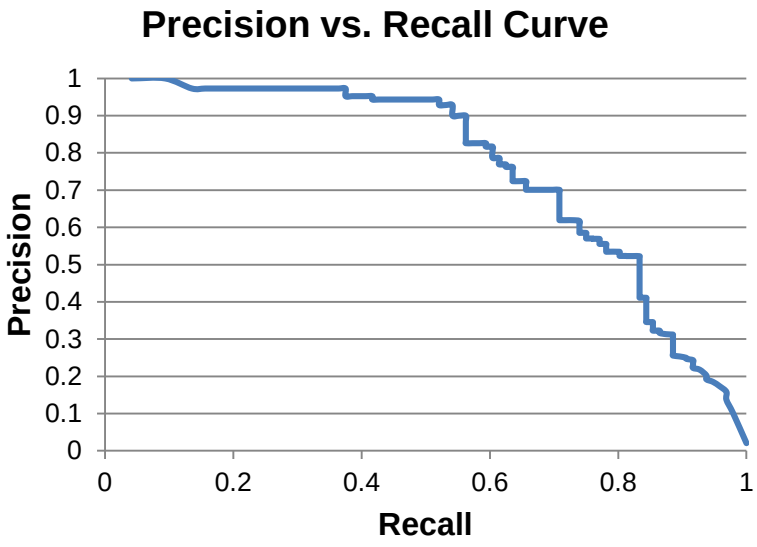


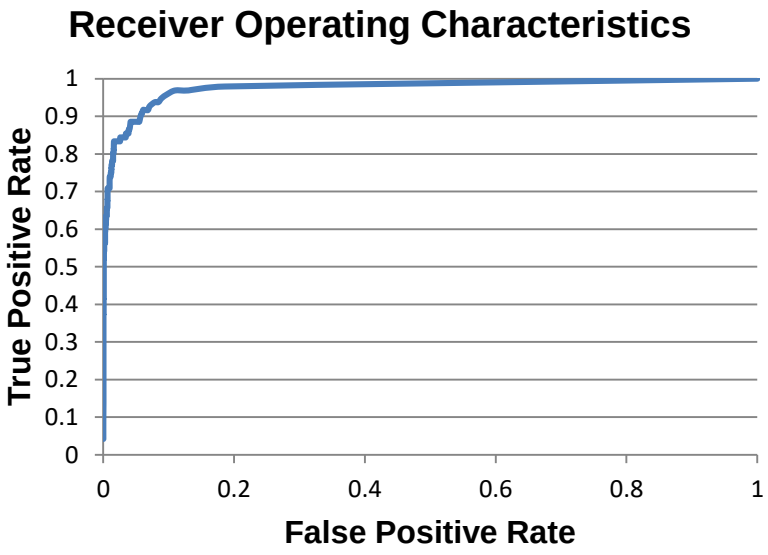
Feature	Precision	Recall	ROC Area
Lobular Inflammation	0.696	0.489	0.946
Not-Lobular Inflammation	0.968	0.986	0.946
OVERALL	**0.952**	**0.956**	**0.946**

Hepatocyte Ballooning: Classification Results

- 98.9% accuracy (vs. 97.9% baseline)

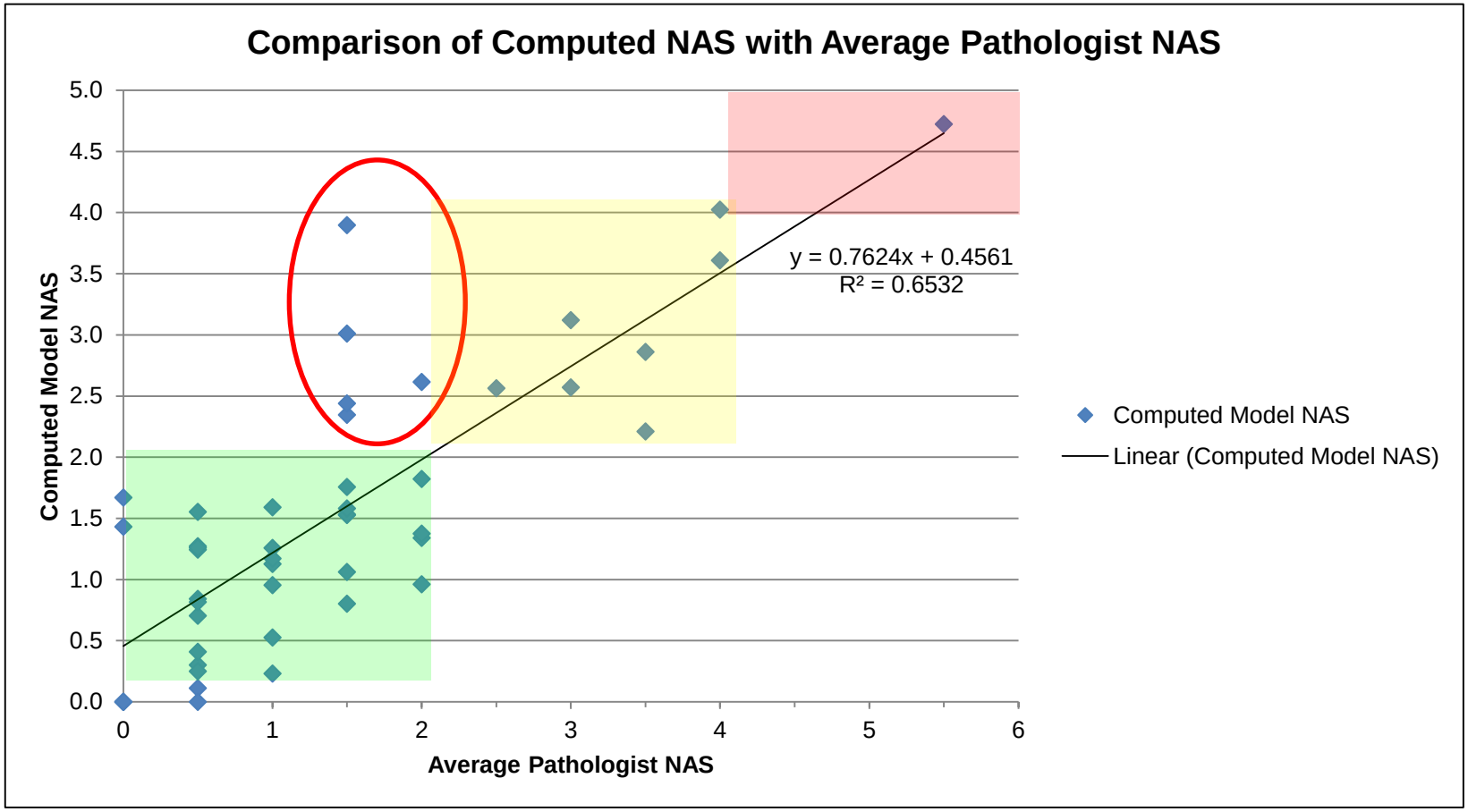
Feature	Precision	Recall	ROC Area
Hepatocyte Ballooning	0.912	0.542	0.983
Not-Hepatocyte Ballooning	0.990	0.999	0.983
OVERALL	**0.989**	**0.989**	**0.983**





Overall Results for NAFLD Activity Score (NAS)

- 73.8% Correlation with Pathologists



- Circled region accounts for diagnosis by software of a worse case than that predicted by pathologist

Summary

- Computer imaging techniques can effectively be used as a diagnostic aid for NAFLD / NASH
- Supervised learning techniques are superior to hand crafted computational rules
- Steatosis grading accurate enough for clinical use
- Next Steps
  - Additional data to study lobular inflammation and ballooning
  - Model refinement, tile size, etc.
  - Features in other domains (FFT, Wavelets, etc)
  - Impact of magnification of scan

Next Steps: Product Development

- Company must convert Matlab algorithms into a production software environment for commercial use

- Estimated 500 hours of development to move this technology into production

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