AI-based pathology in clinical stage bio-pharmaceutical drug development

- Midwest Consortium for Computational Pathology (MCCP) Workshop
- Michael C. Montalto PhD, Chief Scientific Officer, PathAI
- January 28, 2021 , 1:30pm

Disclosures

- employee and shareholder of PathAI

Agenda

1. Intro: AI-based pathology in drug development
2. Examples of utility in drug development
   - Oncology PD-L1
   - Oncology CD8 topology
   - Liver Disease (NASH)
4. Regulatory environment

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Artificial intelligence based image analysis has advantages over manual microscope

Manual analyses of microscopic images		AI-powered analyses of digital whole slide images
High error rates	→	Accurate
Significant interobserver variability	→	Reproducible
Overall lack of standardization	→	Standardized
Low scalability, rarely data driven	→	Highly scalable, data-driven and predictive

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Opportunities for AI-based pathology

value drivers

Biopharma

(Basic & Clinical Research)

- Quality (precision/repro)
- Accuracy (outcomes)
- Workflow (TAT, etc)
- Archiving

Clinical Diagnostics

(Diagnosis/Prognosis)

- Quality (precision/repro)
- Accuracy (outcomes)
- Work flow efficiency
- Archiving
- Remote coverage
- Basic and translational research

Utility Drivers

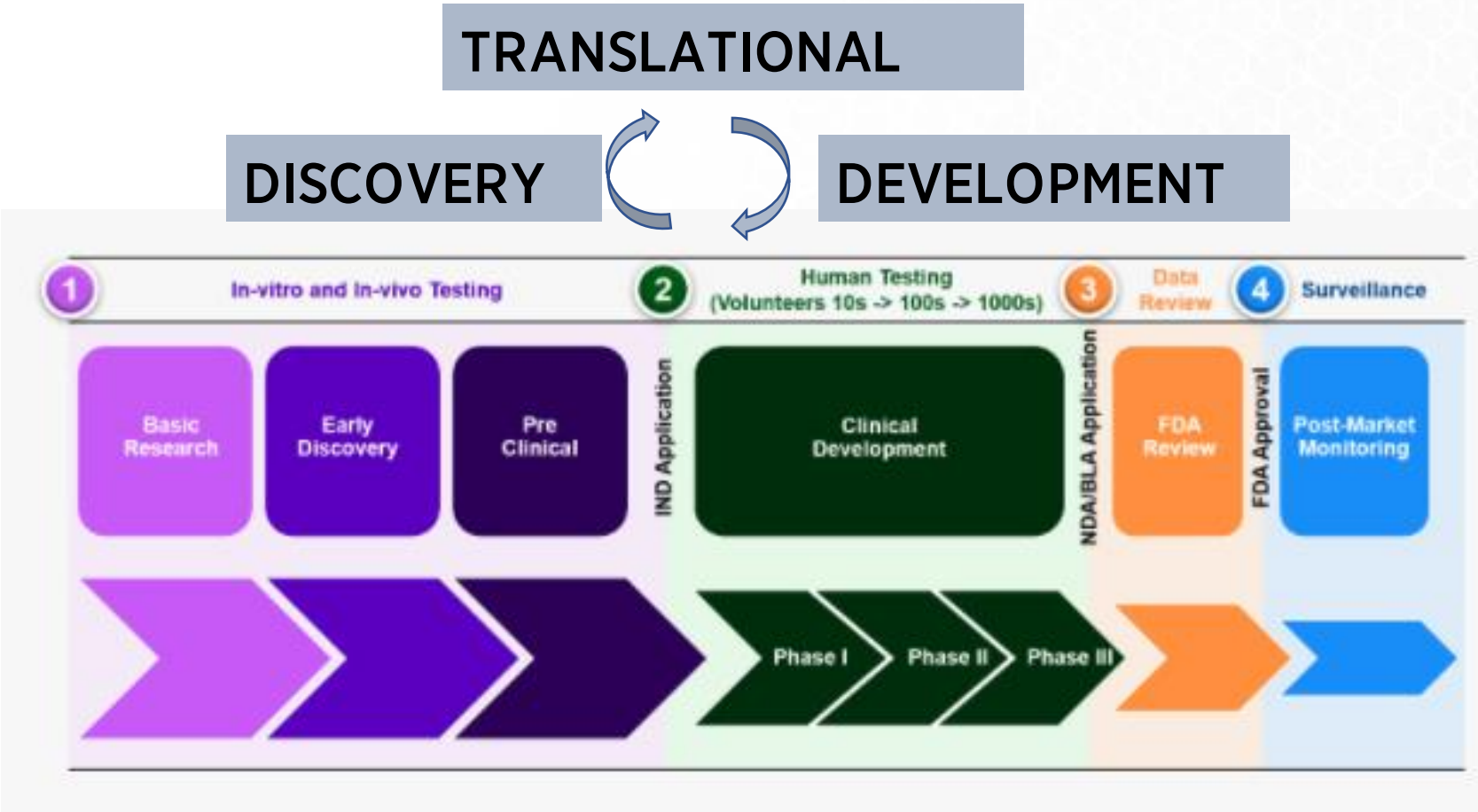
- increase probability of regulatory and technical success,
- improve patient outcomes

- improve patient outcomes
- Improve costs and quality of lab

Translational Medicine in Pharma

Multiple areas to demonstrate value across drug discovery and development.

Translational Medicine has unique needs where AI-pathology can play role



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Biomarkers in clinical stage drug development

Biomarkers Applications in Translational Medicine

Exploratory

- Retrospective Exploratory Analysis
- Target ID
- MoA
- Hypothesis Generation: Selection/Stratification
- Trial Design/Indication Selection

Early Phase PoC

- MoA validation
- Hypothesis Generation/Testing
- Dose Selection/PD
- Selection/Stratification
- Endpoints (Accelerated Approval)

Late Phase / Registration

- FDA approved IVD/CDx
- Lab Developed Test (CLIA)
- Drug Development Tool (DDT)

Retrospective ← → Prospective

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Critical role of “tradional” pathology in prospective trials

- **Enrollment & Selection**
  - diagnosis, grading and staging
  - biomarker scoring (IHC)
- **Pharmakodynamics**
  - Pre-post bx analysis for drug effect
- **Stratification**
  - grading, staging
  - biomarker scoring (IHC)
- **Efficacy Endpoints**
  - Complete Pathological Response
  - Fibrosis, NAFDL Score

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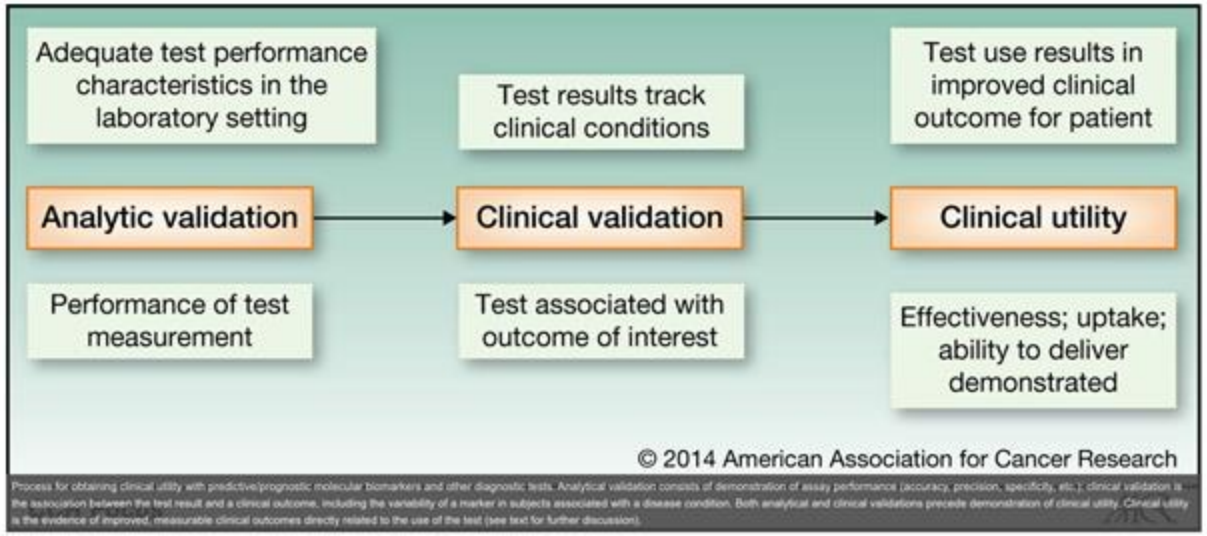
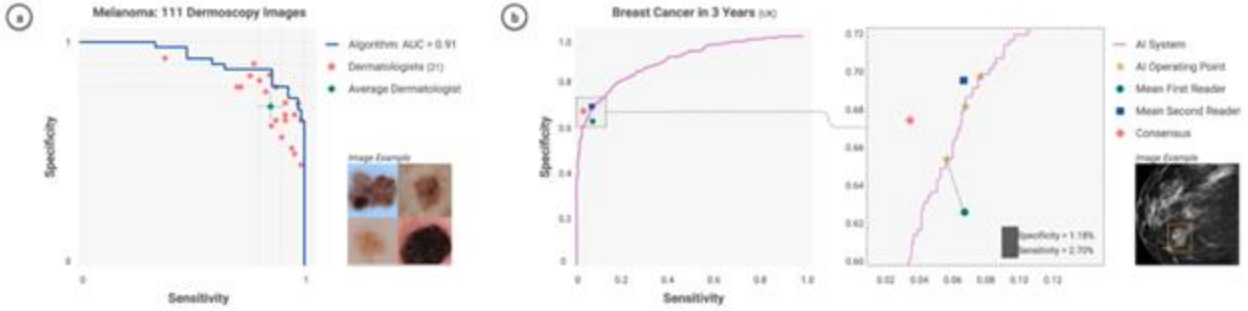
Validation vs Utility of AI in Pathology



Parkinson, DR, et al., Evidence of Clinical Utility: An Unmet Need in Molecular Diagnostics for Patients w Cancer, Clin Can Res, 20(6) 2014

Fig. 2: Physician-level diagnostic performance.

From: Deep learning-enabled medical computer vision



CNNs—trained to classify disease states—have been extensively tested across diseases, and benchmarked against physicians. Their performance is typically on par with experts when both are tested on the same image classification task. **a** Dermatology[7] and **b** Radiology[156]. Examples reprinted with permission and adapted for style.

Esteva, A, et al, Deep learning-enabled medical computer vision, Nat Dig Med, 4(5) 2021

There are important differences between clinical validation and clinical utility
- Analytical and Clinical validation do not examine test performance against patient outcomes

Image analysis in medical imaging is validated against reader performance (ie, 'accuracy')
reasons:
- utility studies are time consuming
- well curated, large data sets w outcomes are needed (randomized controlled trials)
- if trained and validated against 'gold standard readers', why expect superior performance?

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PD-L1 IHC Assays As Complementary and Companion Diagnostics

- PD-L1 expression is a biomarker associated with clinical responses to PD-1 and PD-L1 checkpoint inhibitors in some tumor types[1]
- In NSCLC, Mel, SCCHN, UC, Gastric, Cervical, TNBC PD-L1 IHC assays are approved as complementary and companion diagnostics across different lines of therapy[2-4]
  - Scoring algorithms and clinically relevant cutoffs vary across different tumor types, lines of therapy, and assays

Current FDA-Approved PD-L1 IHC Assays for NSCLC[2–4]

Assay	PD-L1 IHC 28-8 pharmDx (Dako[a])	PD-L1 IHC 22C3 pharmDx (Dako[a])	PD-L1 (SP142) Assay (Ventana)
For use with (drug)	2L nivolumab	1L pembrolizumab	2L atezolizumab
PD-L1 scoring method and clinical cutoffs	≥1%, ≥5%, ≥10% TC	≥1% TC, ≥50% TPS	≥50% TC and/or ≥10% IC
Approval status (US)	Complementary	Companion	Complementary

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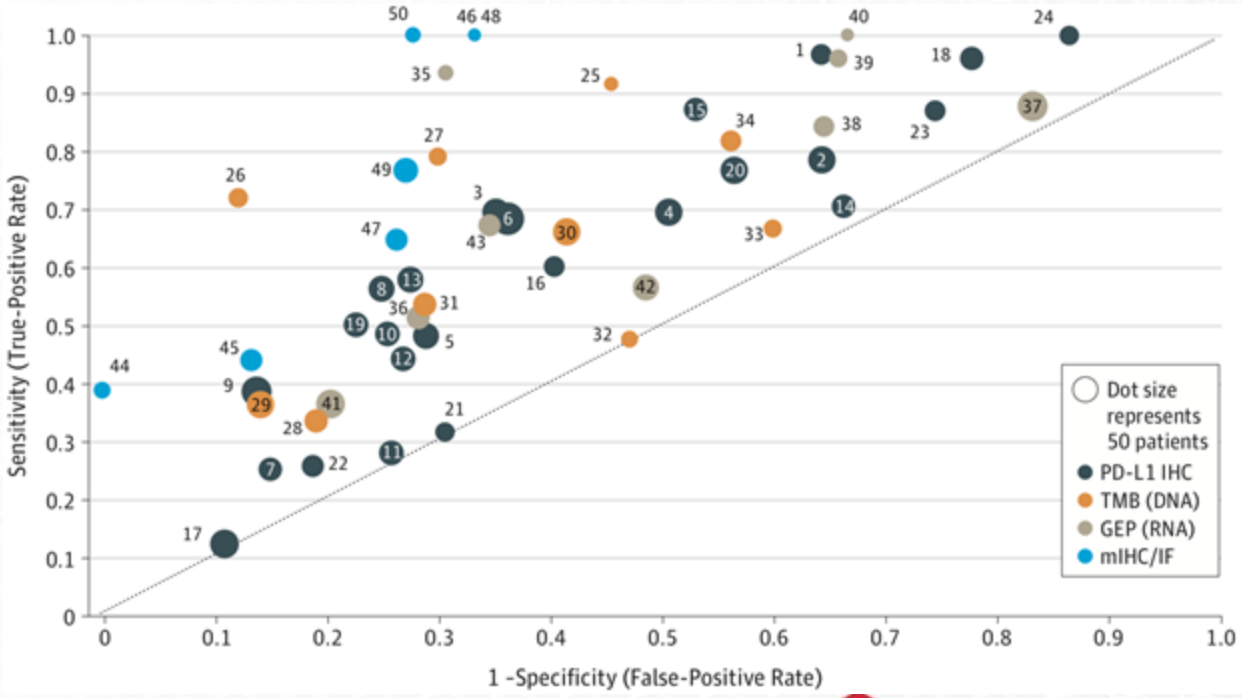
1. Rimm et al. *JAMA Oncol.* 2017;3:1051; 2. OPDIVO® (nivolumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb; April 2019. 3. KEYTRUDA® (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck & Co Inc; July 2019. 4. TECENTRIQ® (atezolizumab) [package insert]. South San Francisco, CA: Genentech Inc; May 2019.

Meta-Analysis Correlating Different Biomarker Modalities with Patient Response to anti-PD-1/PD-L1 Therapy

- 56 analyses from the primary literature highlighting *sensitivity* and *1−specificity* of assays from each individual publication.
- PD-L1 IHC had the lowest AUC (0.65, P< 0.001) compared to other biomarkers
- Limitations with PD-L1 IHC Assay:
  - Sampling bias (spatial and temporal)
  - Multiple different assays
  - Predictive significance of TC vs IC expression varies by tumor type
  - Scoring of IC PD-L1 expression by pathologists has poor interobserver reproducibility

Summary Receiver Operator Characteristic Curve[5]



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5. Lu S, et al. Comparison of Biomarker Modalities for Predicting Response to PD-1/PD-L1 Checkpoint Blockade: A Systematic Review and Meta-analysis. JAMA Oncol. 2019 Jul 18;5(8):1195–204.

Digital IA may Address Challenges of Pathologist Variability, Potentially Improving Patient Selection

- Manual assessment of tumor PD-L1 is challenging due to variability in assay and scoring methodology, complex tissue architecture, heterogeneous tumor PD-L1 expression, and difficulty in scoring immune cell PD-L1
- Digital IA has improved the precision of PD-L1 expression scoring in a number of tumor types
- We developed and validated an AI-powered IA algorithm to quantify PD-L1 expression on TCs and ICs
- The relationship between prevalence and efficacy of nivolumab monotherapy and manual vs AI-powered IA of PD-L1 expression on different cell types was retrospectively evaluated

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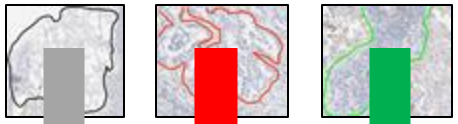
Methods for Pathology AI Platform[8]

Training

PD-L1 IHC on training slides[a]

WSIs

Normal | Tumor | Stroma



PD-L1+ | PD-L1−

TC Mac Lymph | TC Mac Lymph

250,000+ pathologist annotations

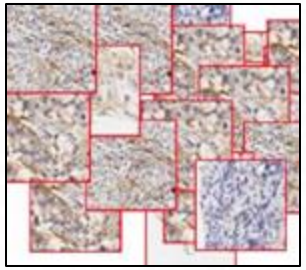
Training Classes:
- TCs (PD-L1+/−)
- Lymphs (PD-L1+/−)
- Macs (PD-L1+/−)
- Other cells

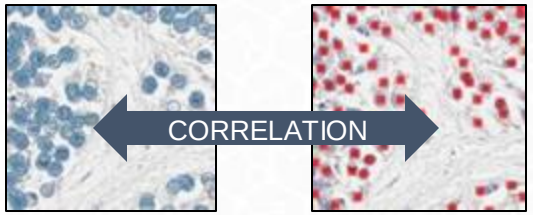
Deep-learning models

Validation

PD-L1 IHC on validation slides[a]

High-quality 150x150-pixel images



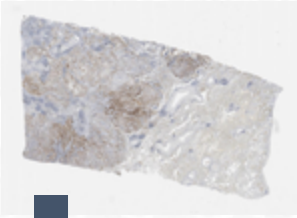


Pathologist (n=5) consensus score | Algorithm score

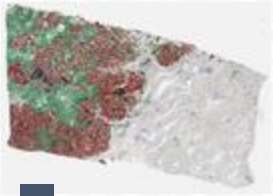
Testing

PD-L1 IHC on slides from clinical trial samples

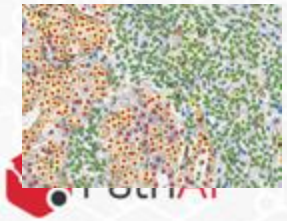
WSIs



Overlapping image patches



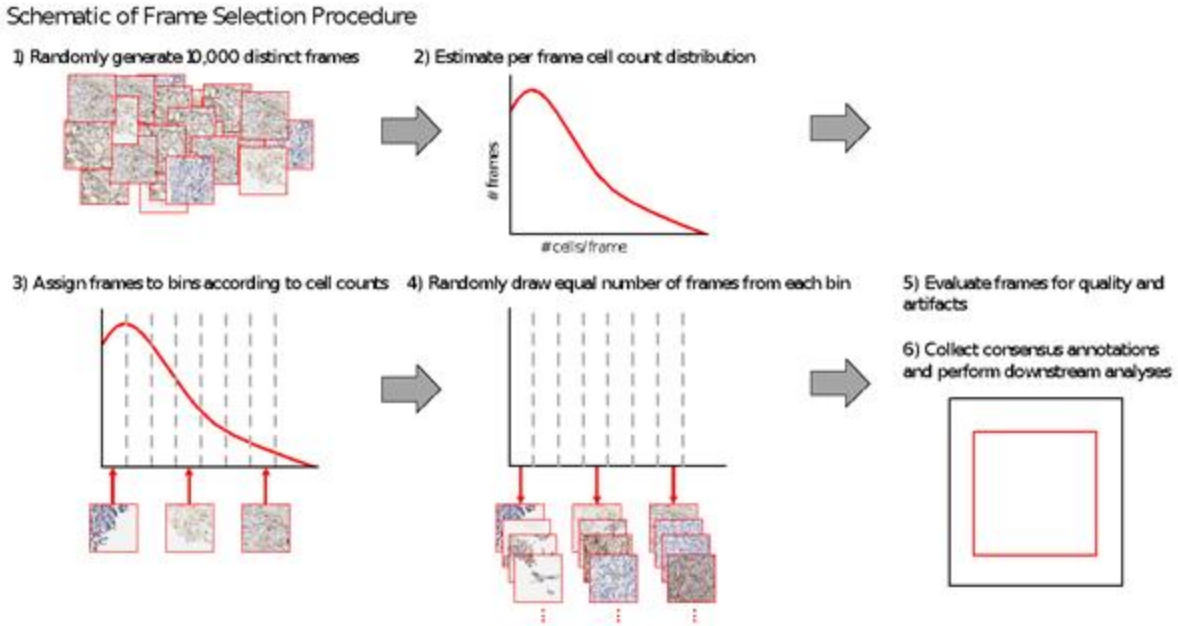
TC and IC scoring

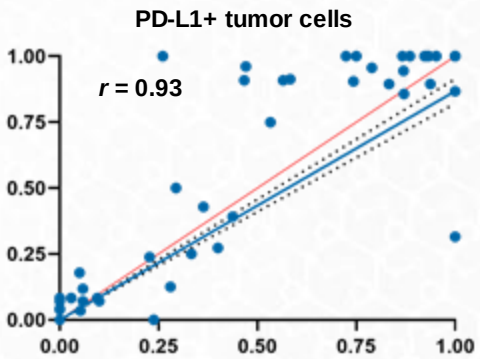


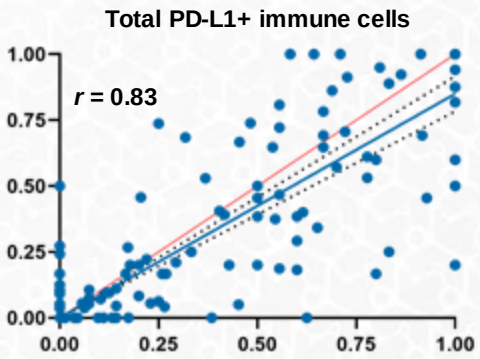
8. Baxi et al. AI-powered analysis of PD-L1 expression in nivolumab trials of NSCLC. SITC 2019 Oral Presentation

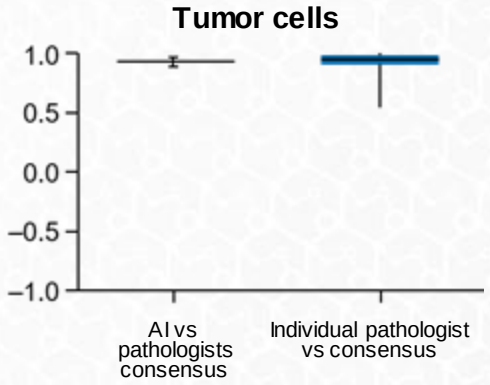
Validation of AI-Powered PD-L1 IHC Algorithm by Correlating to Pathologist Consensus on Frames[8-9]

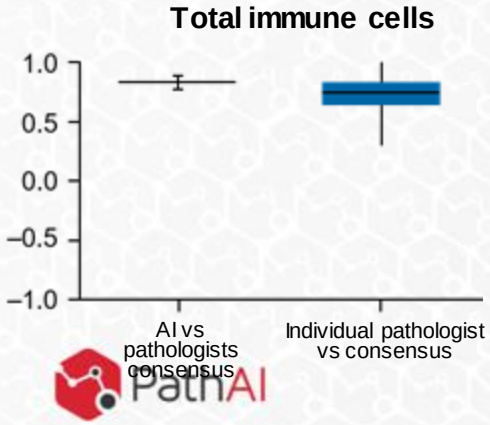
- Frames-based validation approach to measure accuracy of algorithm in detecting and classify PD-L1 +/- tumor and immune cells[8]







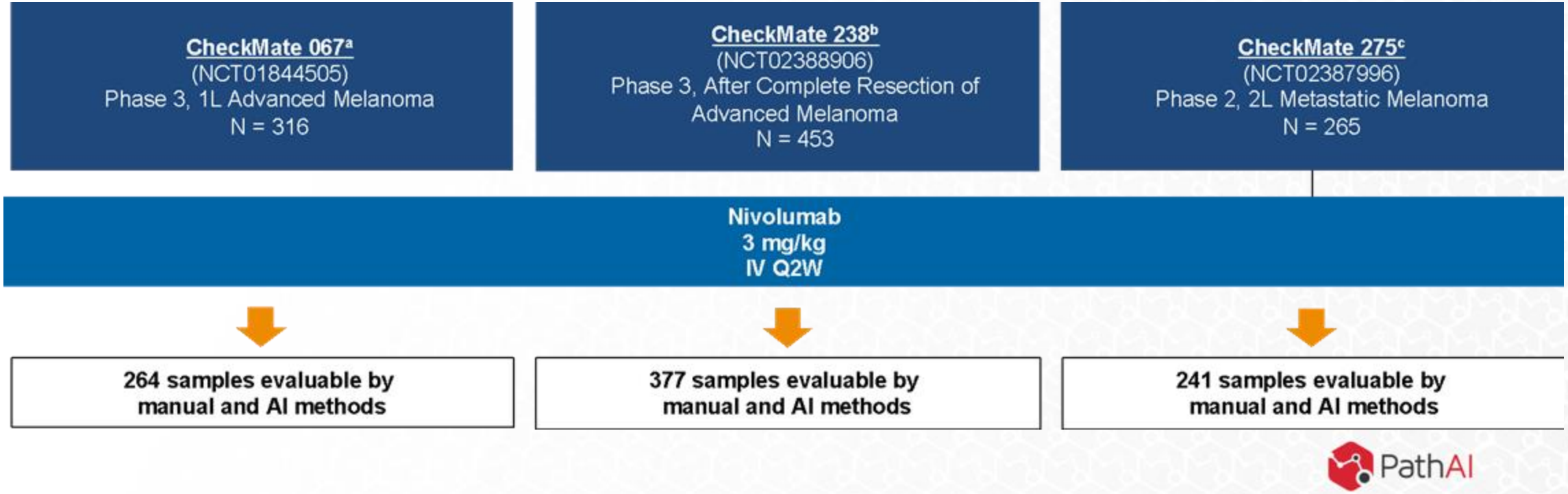




8. Baxi et al. AI-powered analysis of PD-L1 expression in nivolumab trials of NSCLC. SITC 2019 Oral Presentation. 9. Beck A, et al. Poster presented at the 34th SITC Annual Meeting 2019, #P730.

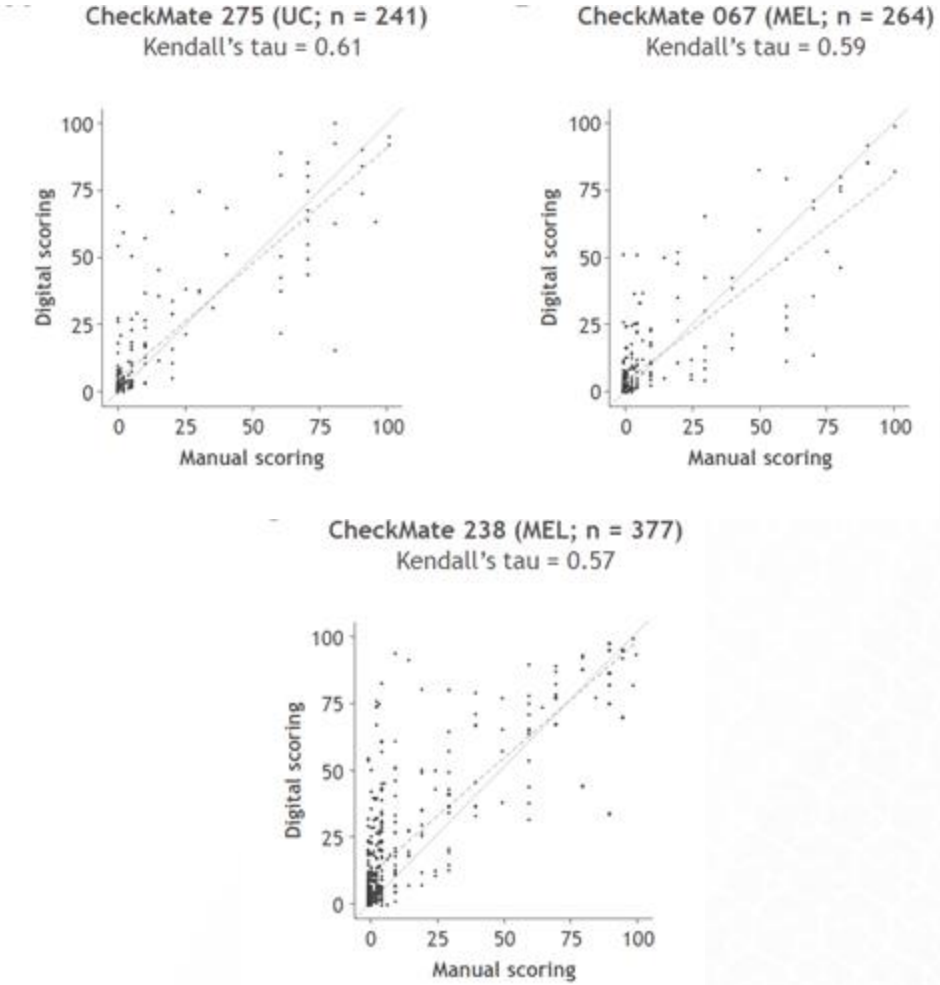
Test of PD-L1 IHC Algorithms for Efficacy of Nivolumab Monotherapy in Patients With Melanoma & Urothelial Cancer

- In exploratory post-hoc analyses, locked algorithms were applied to PD-L1–stained images of baseline NSCLC samples from nivolumab clinical trials



a. Hodi FS, et al. Lancet Oncol 2018;19:1480–1492. b. Weber JS, et al. Ann Oncol 2019;30(suppl 5). Abstract 1310O. c. Sharma P, et al. Lancet Oncol 2017;18:312–322.

Correlation between Digital and Manual Assessment[10]



	Evaluable samples, n	Prevalence, n (%)		Additional samples identified by digital only, n (%)[a]	Additional samples identified by manual only, n (%)
		Digital	Manual		
≥ 1% PD-L1+ TCs					
CheckMate 275 (UC)	241	166 (69)	113 (47)	58 (24)	5 (2)
CheckMate 067 (MEL)	264	173 (66)	160 (61)	36 (14)	23 (9)
CheckMate 238 (MEL)	377	307 (81)	259 (69)	66 (18)	18 (5)
≥ 5% PD-L1+ TCs					
CheckMate 275 (UC)	241	90 (37)	74 (31)	28 (12)	12 (5)
CheckMate 067 (MEL)	264	103 (39)	76 (29)	36 (14)	9 (3)
CheckMate 238 (MEL)	377	234 (62)	139 (37)	104 (28)	9 (2)

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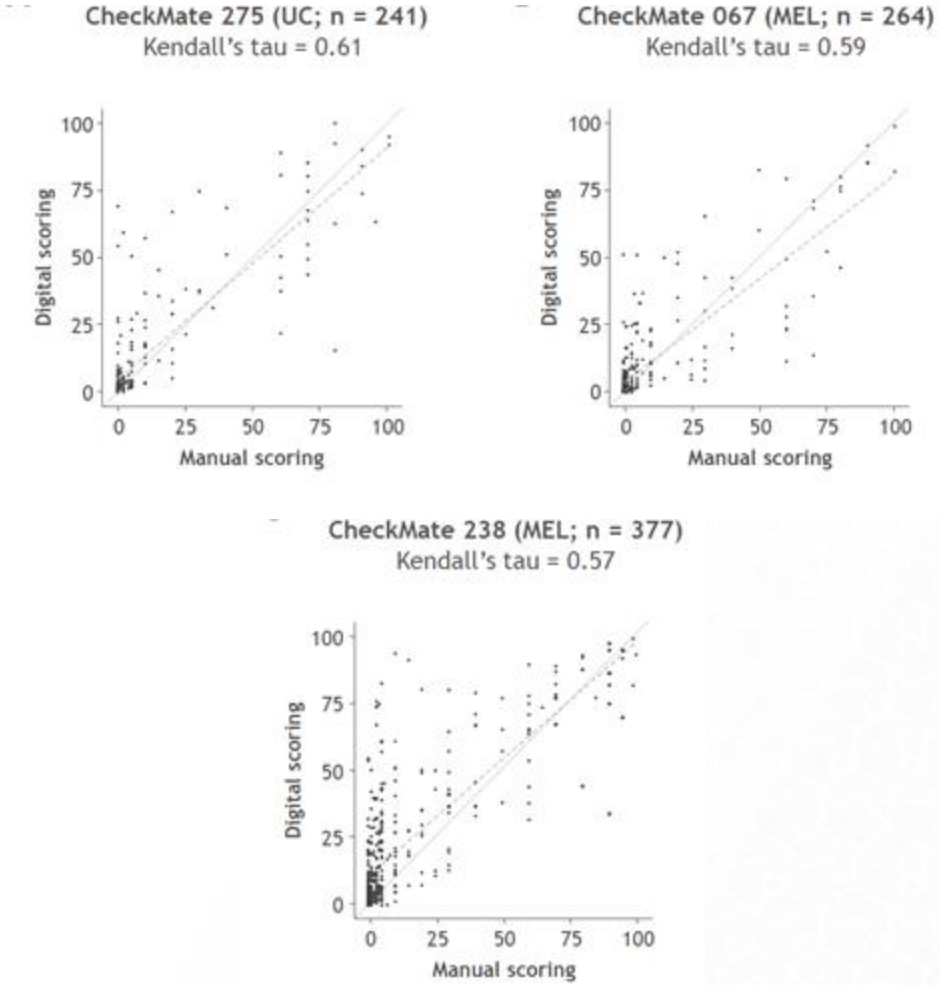
10. Duan et al., Association of digital and manual quantification of tumor PD-L1 expression with outcomes in nivolumab-treated patients. Poster presented at AACR 2020

Correlation between Digital and Manual Assessment[10]



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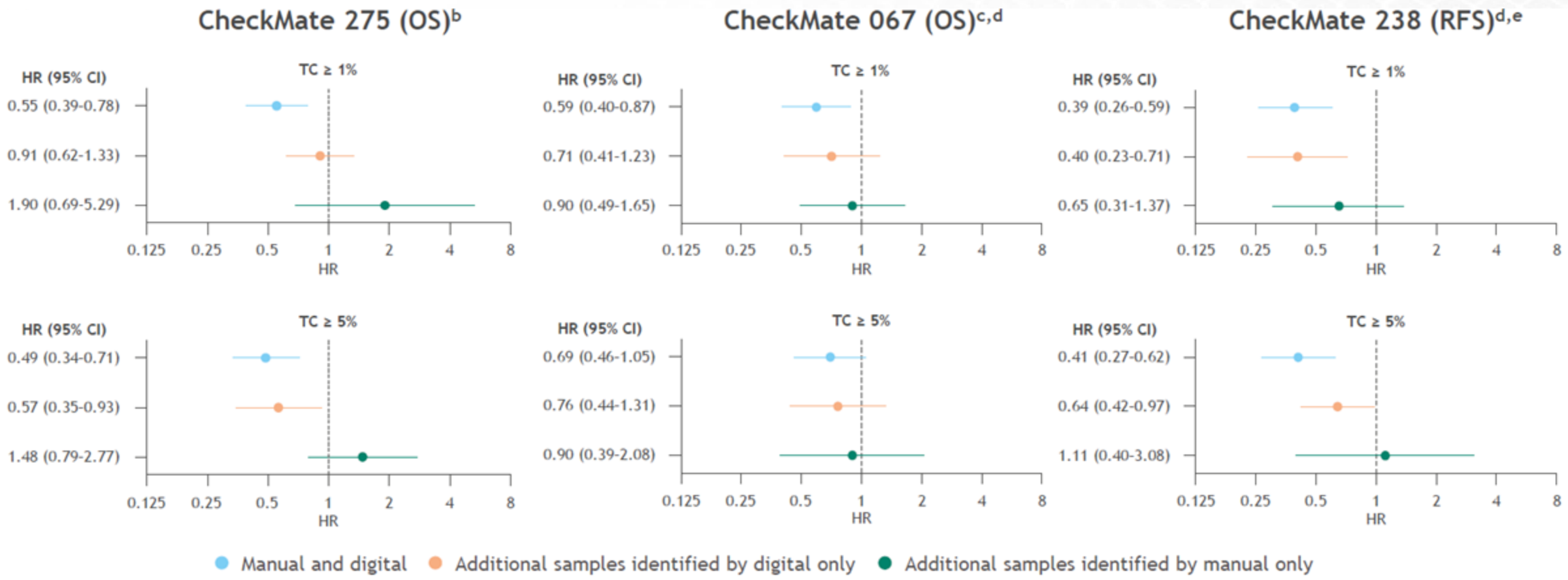
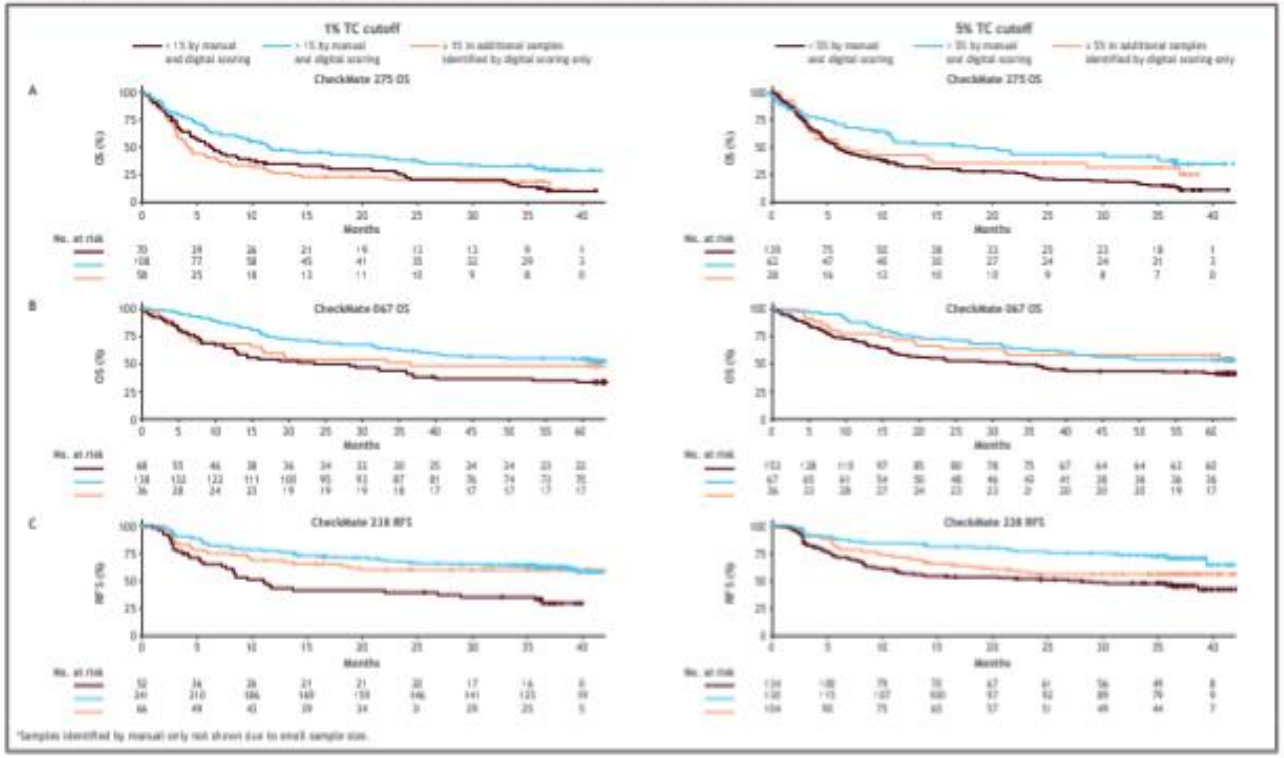
OS/RFS Assessment Using Manual and AI-Powered Tumor PD-L1 Scoring[10]



10. Duan et al., Association of digital and manual quantification of tumor PD-L1 expression with outcomes in nivolumab-treated patients. Poster presented at AACR 2020

OS Assessment Using Manual and AI-Powered Tumor PD-L1 Scoring[10]

Figure 4. Additional survival analyses: digital or manual assessment of PD-L1 expression[a]



Summary

- accurate ML models were developed to score PD-L1
- models correlated to original trial pathologist scores
- AI-PD-L1 identified additional patients who were classified as negative by manual
- additional patients appeared to have similar response rates as double positive patients

AI-PD-L1 score has utility compared to manual scores at predicting response to anti-PD1 therapy

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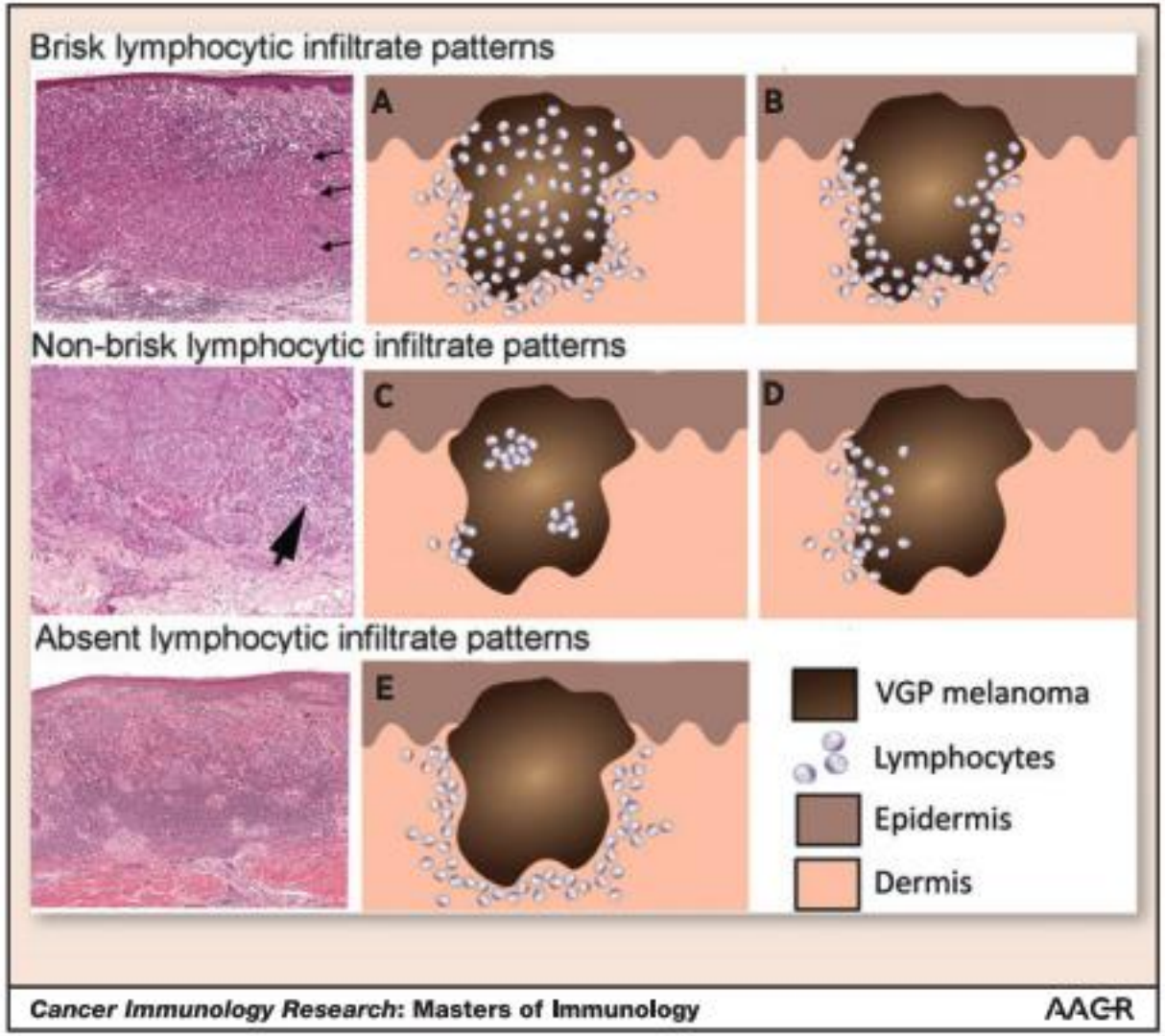
Role T-cell topology in I/O resistance

Figure 3.
Brisk, non-brisk, and absent lymphocytic infiltration in primary melanoma nodules. The three photomicrographs in the left column exhibit the brisk, non-brisk, and absent patterns. The brisk pattern is defined by lymphocytes present throughout the tumor as shown by arrows (top left). Non-brisk is defined by scattered, focal groups of lymphocytes (arrow). The word "absent" above the bottom row of images is defined as "containing no lymphocyte infiltration in the tumor." A–E (middle and right), schematic renderings of different types of TIL patterns in primary melanoma. A, the brisk lymphocytic response may involve the entire tumor nodule or B, be present along the advancing edge of the entire peripheral nodule. The focal nature of the non-brisk pattern is sjpwm in C and D. In the rendering of the absent lymphocytic response, there are either no lymphocytes in the tumor, or if lymphocytes are present (E), they do not interact with melanoma cells. Panels A–E are adapted from Fig. 4 of chapter 16 by Schatton et al., Tumor infiltrating lymphocytes and their significance in melanoma prognosis. In: Thurin M, Marincola FM, editors. Molecular diagnostics for melanoma. New York: Humana Press; 2014. p. 287–324.



brisk phenotype associated w enhanced survival and response to I/O therapy

non-brisk (excluded) less association w survival

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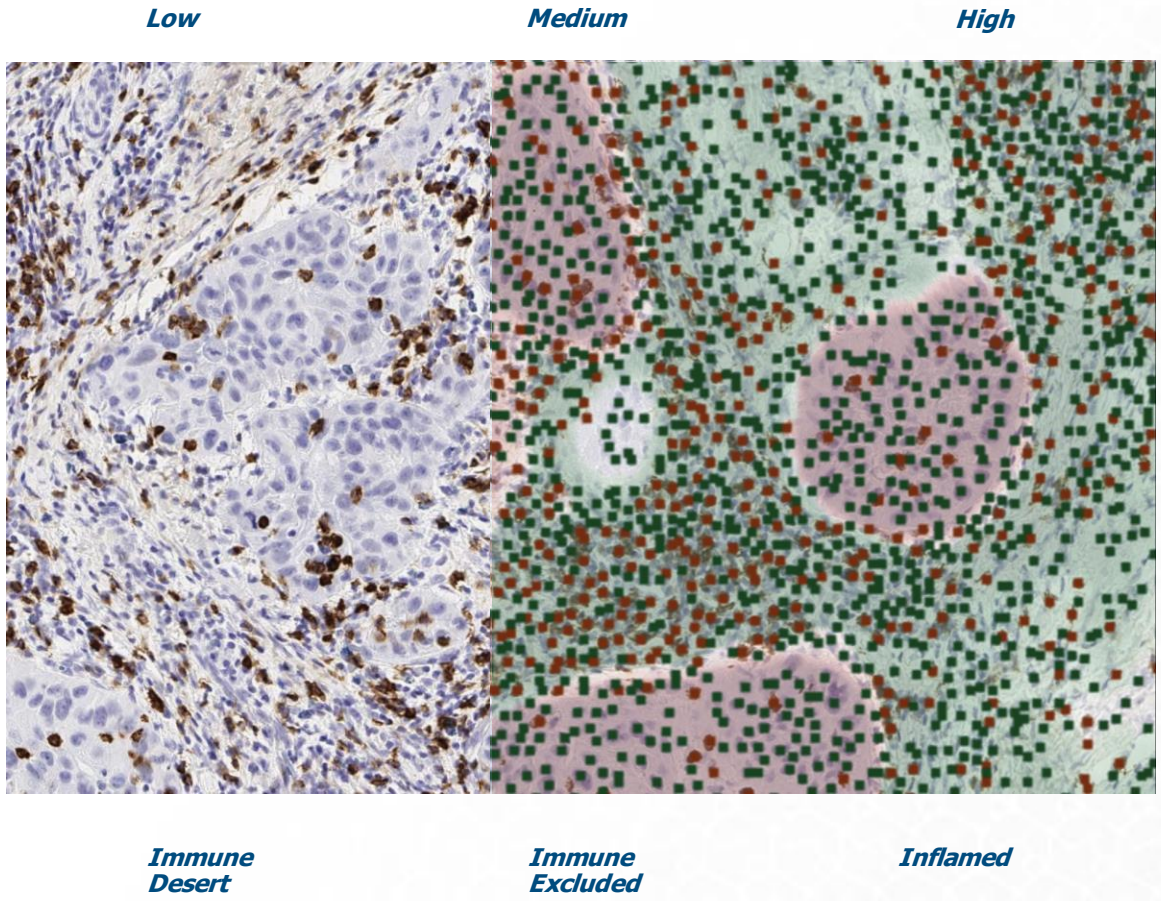
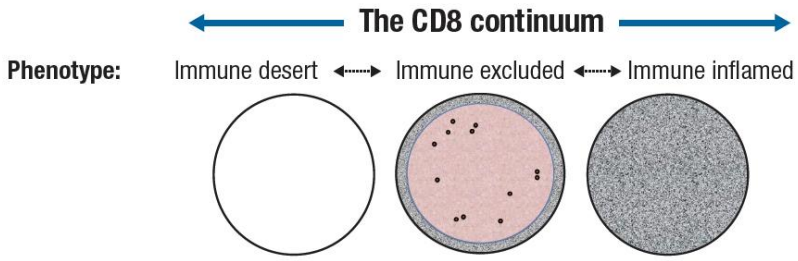
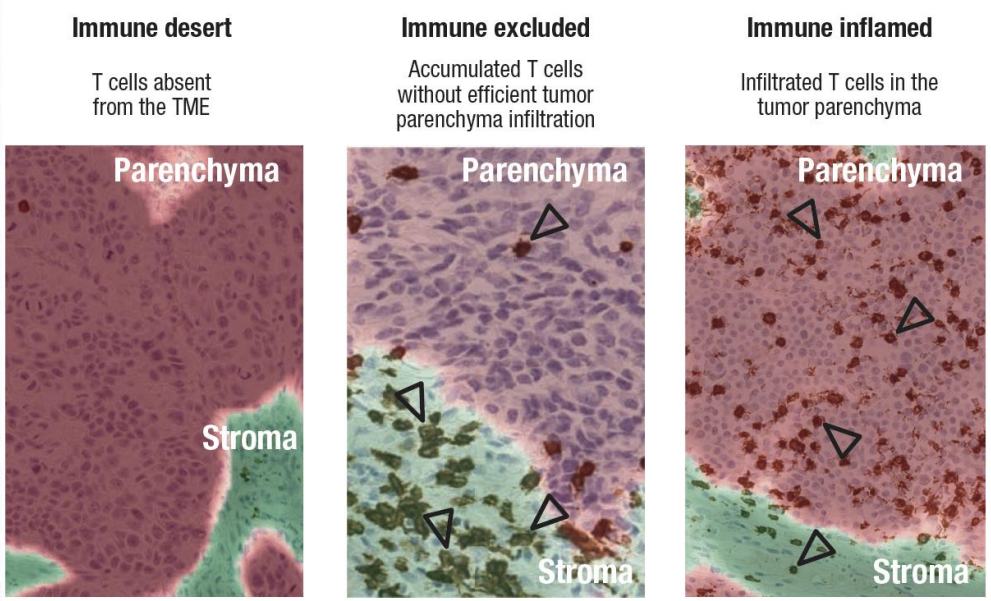
cIHC With AI-Based Digital Image Analysis and Gene Expression Profiling – novel topology-based signatures[11]





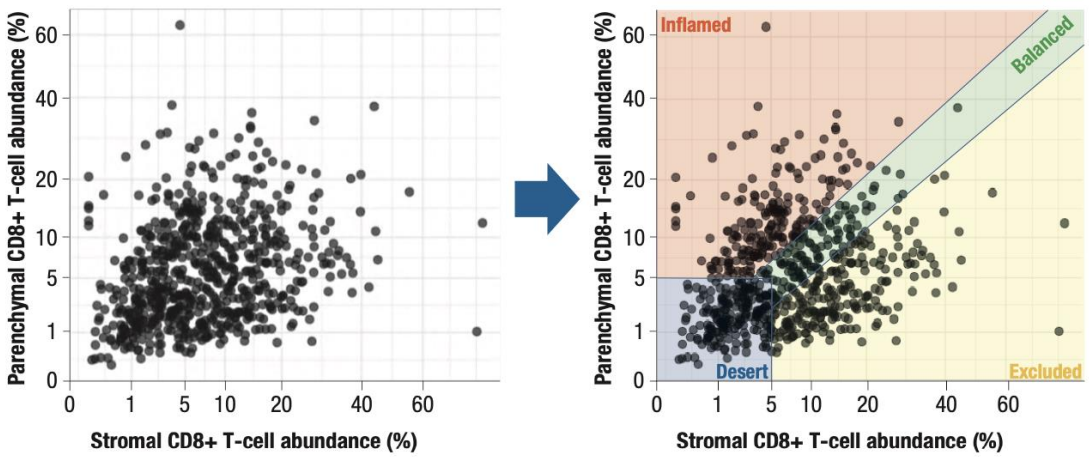


11. Szabo et al., CD8+ T Cells in Tumor Parenchyma and Stroma by Image Analysis and Gene Expression Profiling: Potential Biomarkers for Immuno-oncology Therapy. Poster presented at ASCO 2019.

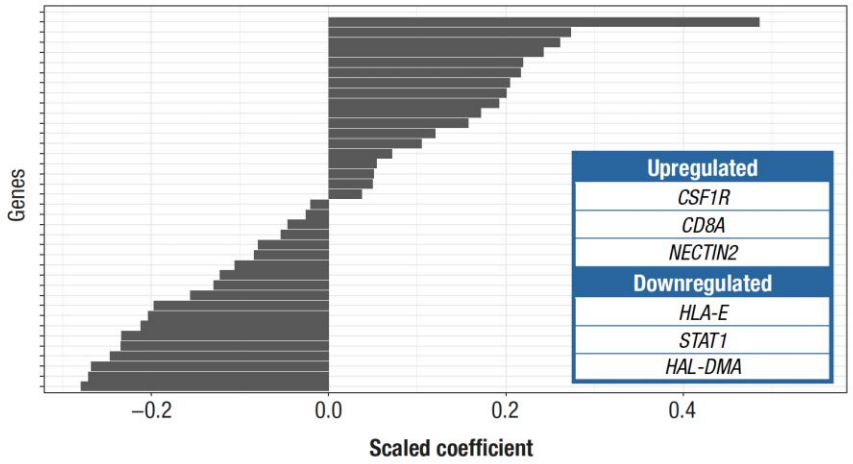
cIHC With AI-Based Digital Image Analysis and Gene Expression Profiling – novel topology-based signatures[11]

Figure 3. Phenotypes characterizing immune activity in tumors by CD8 IHC

A. Parenchymal vs stromal T-cell abundance used to define immune phenotypes

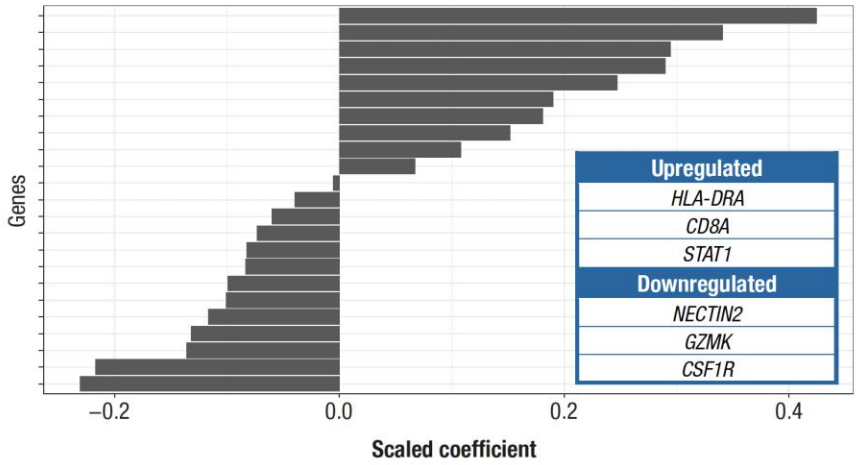


Stromal CD8 Abundance



Samples with matched RNAseq analysis (HTG panel)

Parenchymal CD8 Abundance



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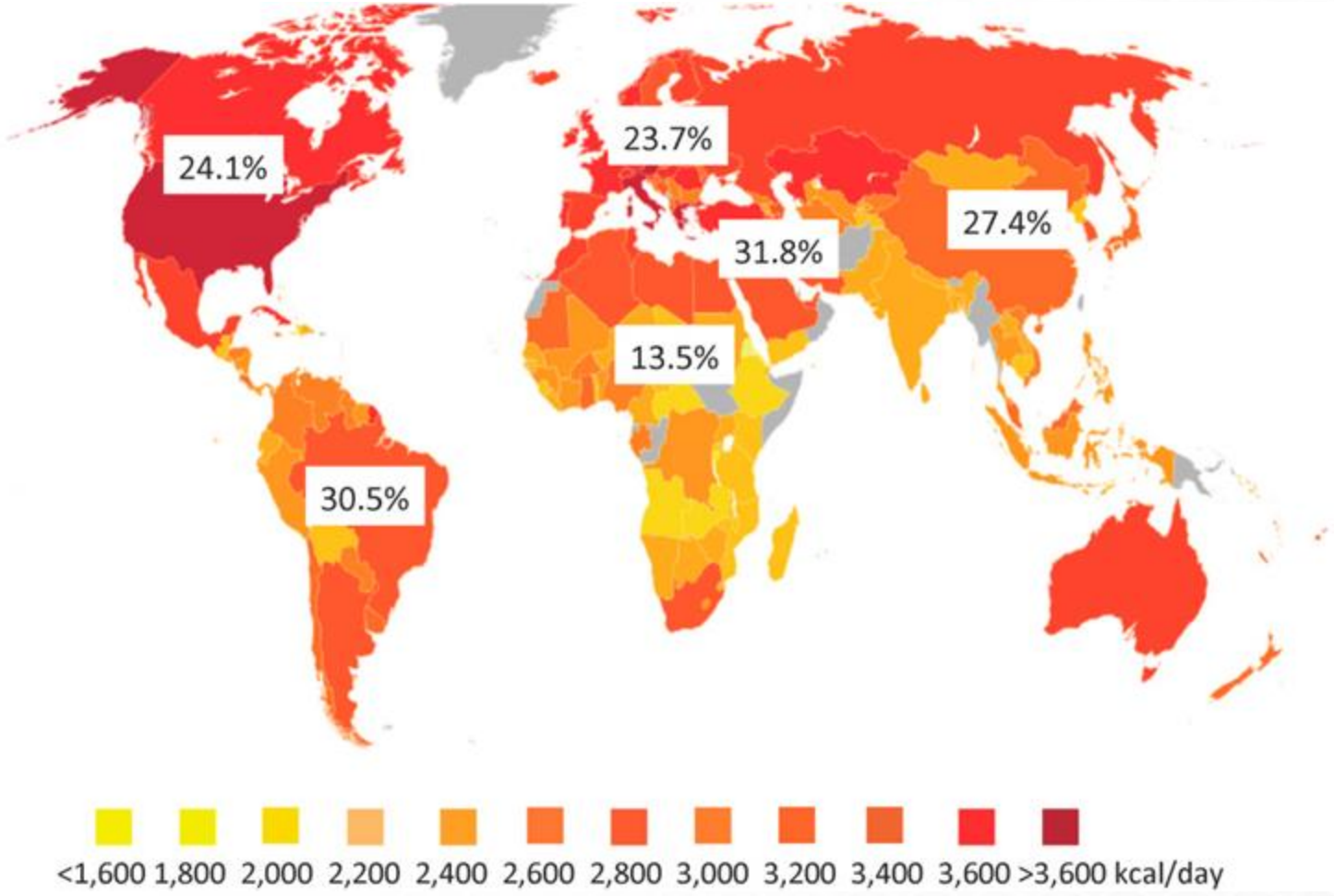
The Global Non-alcoholic fatty liver disease (NAFLD) Burden



- Prevalence linked to increased incidence of obesity
- Correlated with other metabolic diseases, increasing prevalence of Type II Diabetes
- NAFLD may progress to NASH, which may progress to fibrotic liver disease and death

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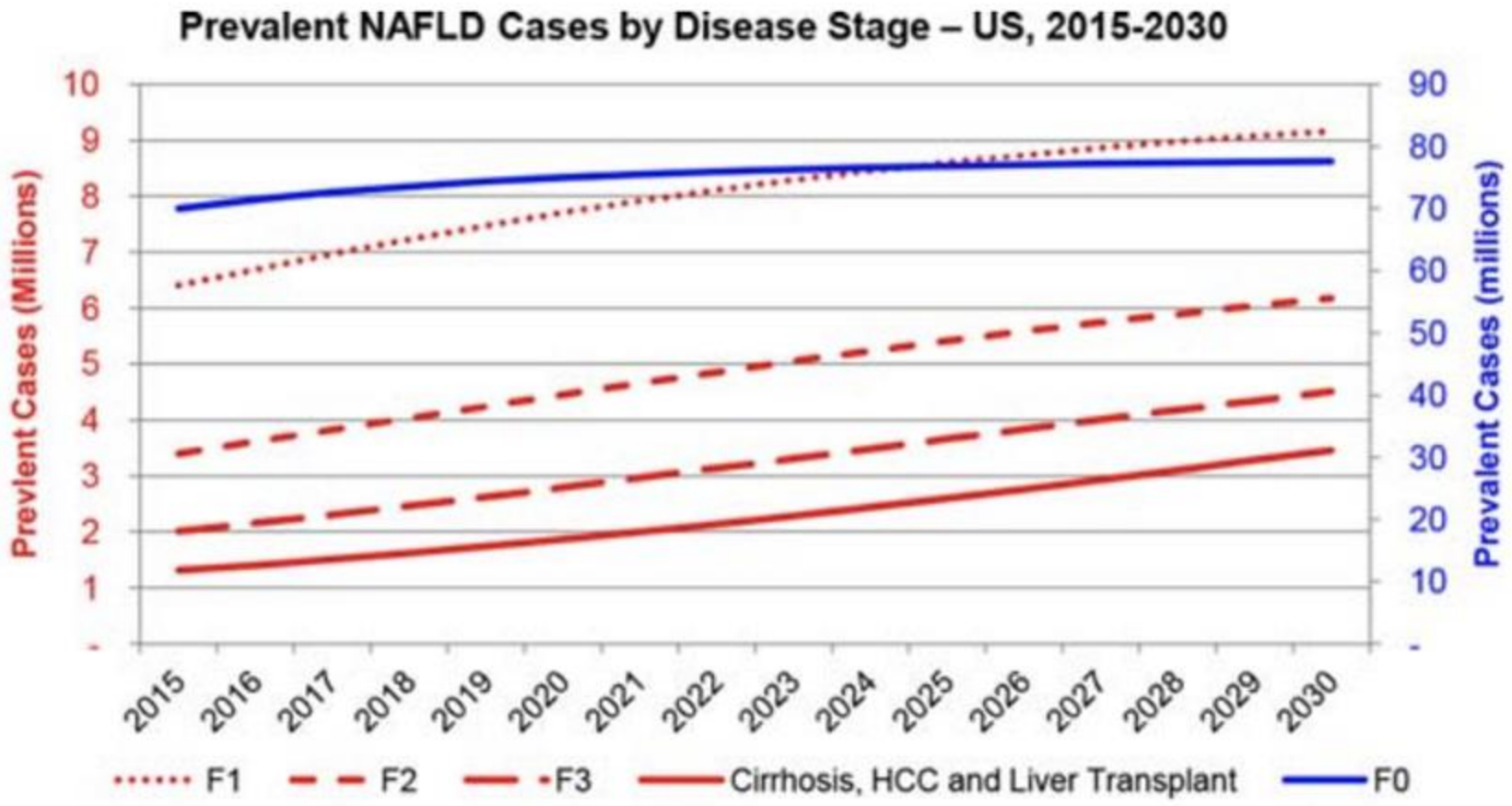
Mary Rinella, Michael Charlton . The globalization of nonalcoholic fatty liver disease: Prevalence and impact on world health. Hepatology (2016)

NAFLD, NASH and Deaths due to Liver Disease are Projected to Continue to Increase



- Burden of serious outcomes projected to increase 100 – 200% in next decade
- During 2015-2030, there are projected to be nearly 800,000 excess liver deaths
- Therapeutic options are necessary to mitigate disease burden.

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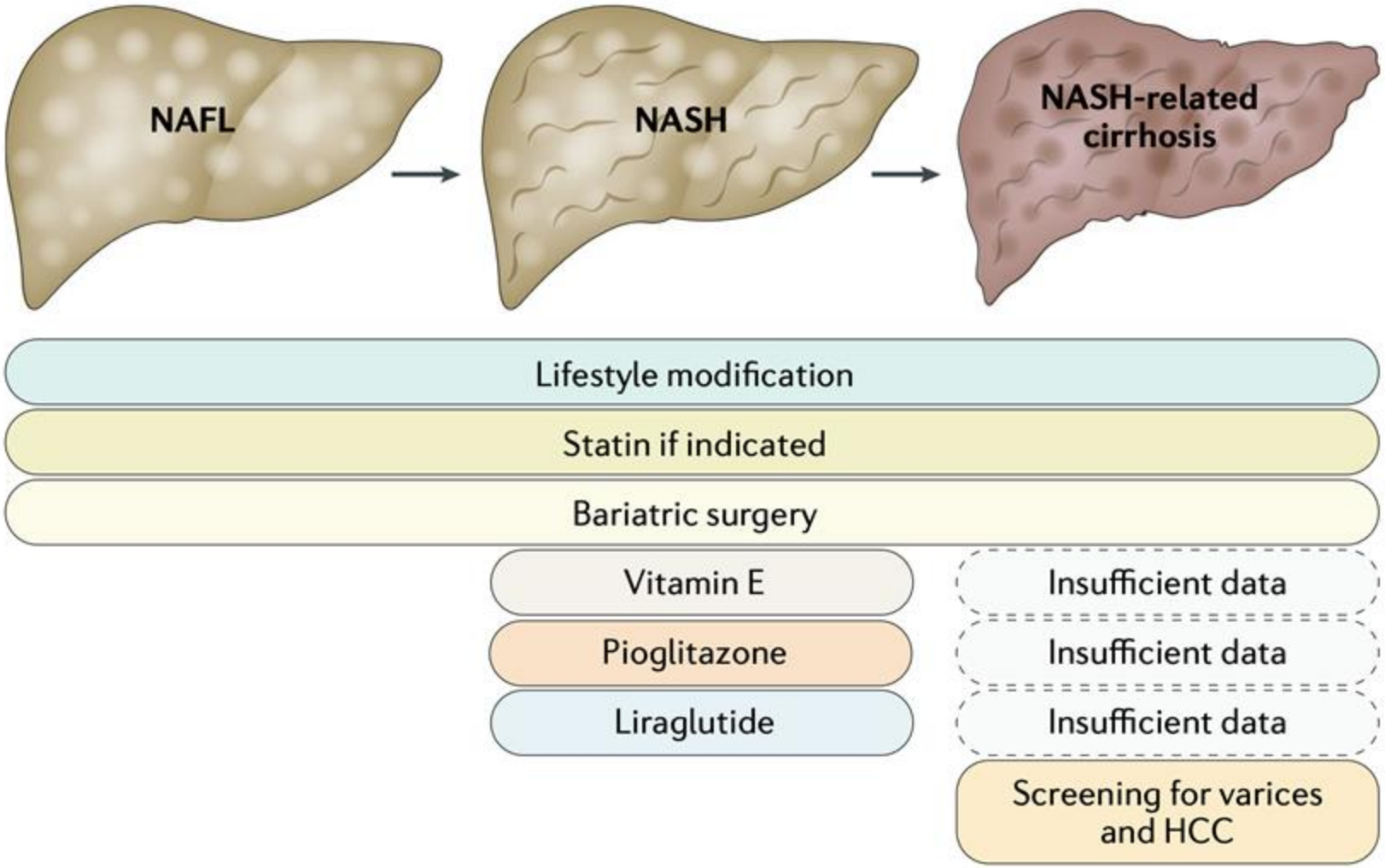
Estes…Sanyal. “Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease.” Hepatology. 2018 Jan; 67(1): 123–133.

No treatments currently available to reverse fibrosis in NASH-related cirrhosis



Wong et al. (Nat Rev Gasro & Hepatol August 2018)

FDA guidance on histological endpoints for NASH

"Because of the slow progression of NASH, liver histological improvements as endpoints reasonably likely to predict clinical benefit to support accelerated approval."

"Resolution of steatohepatitis on overall histopathological reading **and** no worsening of liver fibrosis on NASH CRN fibrosis score;

OR

Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) **and** no worsening of steatohepatitis;

OR

Both resolution of steatohepatitis and improvement in fibrosis"

Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact Evangela Covert 301-796-4075.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2018
Clinical/Medical

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11/29/2018

https://www.fda.gov/media/119044/download

Complexities of NASH Clinical Trials

High Variability in Scoring Endpoints, Even by Experienced Pathologists

Published literature has **shown only moderate levels of inter- and intra-observer concordance** in the assessment of inflammation, ballooning, steatosis and fibrosis in NASH

- Inter-reader kappas were 0.61, 0.48, 0.33, and 0.52 for steatosis, fibrosis, lobular inflammation, and ballooning, respectively[1]
- Inter-reader unweighted kappas were 0.40 for the diagnosis of NASH, 0.40 for NASH resolution without worsening fibrosis, and 0.37 for fibrosis improvement without worsening NASH[1]

Intra-observer discordance for NAS grading is high[2]

(Particularly for lobular inflammation and ballooning, 22–47% of cases)

	Steatosis		Lobular Inflammation		Ballooning	
Number of Biopsies	**Kappa**	**Cases with Discordance**	**Kappa**	**Cases with Discordance**	**Kappa**	**Cases with Discordance**
166	0.69	22%	0.38	42%	0.66	22%
162	0.50	29%	0.29	43%	0.43	36%
149	0.59	26%	0.42	39%	0.29	47%

High-range of reader variability may have contributed to recent challenges in NASH trials by misclassifying fibrosis stage and reducing drug treatment effects

PathAI

1 Beth A. Davison, PhD et al. "Liver biopsies in nonalcoholic steatohepatitis (NASH) clinical trials." *Hepatology 2020*
2 PathAI Analysis: AASLD 2019, median interval between biopsy re-reads, 16 weeks (range 9, 20).

Complexities of NASH Clinical Trials

Scoring variability and inaccuracy impacts trial success probability

Results for 10,000 simulated trials for each scenario showing effect of endpoint misclassification

- True response rate is 20% with active compound
- True response rate is 10% with placebo

	Probability of p<.05 for drug effect vs placebo	Mean OR
With perfect agreement and accuracy	93.61%	2.34
With kappa=0.43, sensitivity=0.9, specificity=0.9	61.78%	1.61

If drug has a true effect (OR = 2.25), perfect agreement and accuracy increases chance of success by 50% compared with real world levels of variability in manual scoring of the histologic endpoint.

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PathAI

Davison BA, et al. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials, (Journal of Hepatology, 2020).

Manual scoring approaches may have contributed to recent late-stage NASH failures

FIERCE Pharma

Intercept's NASH hopeful spurned by FDA, raising questions for other companies in the race

- Study hit 1 of 2 of the recommended histological end-points
- Expectation was this efficacy data would be enough for accelerated approval

"The FDA has progressively increased the complexity of the histologic endpoints, creating a very high bar ."

Mark Pruzanski, Intercept CEO

ENDPOINTS NEWS

Genfit's NASH drug fails a closely-watched PhIII showdown, adding one more setback to a plagued field

- 19% positive response to drug, 15% placebo had improved response

" Although the response rates observed with elafibranor treatment were broadly aligned with our initial expectations, the placebo response rate was significantly higher than we anticipated."

Dean Hum, Genfit COO

BIOPHARMA DIVE

Cirius withdraws $86M IPO as vaunted 'Year of NASH' draws to brutal close

- Inter-reader unweighted kappas were 0.400 for the diagnosis of NASH, 0.396 for NASH resolution without worsening fibrosis, and 0.366 for fibrosis improvement without worsening NASH.

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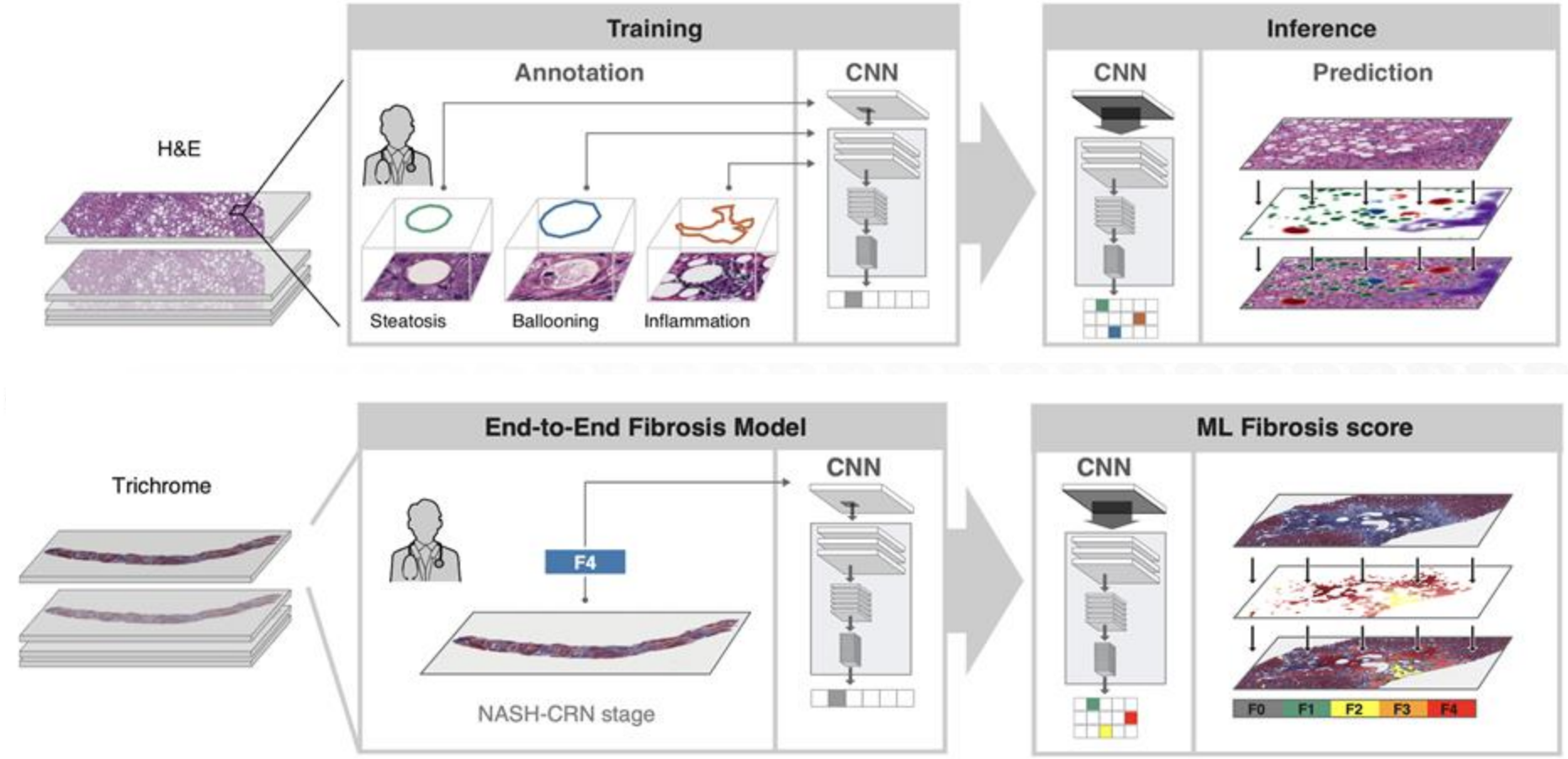
"Poor reliability [of biopsy reading] allows improper entry, misclassification, and diminishes treatment effect."

Beth Davidson, et al

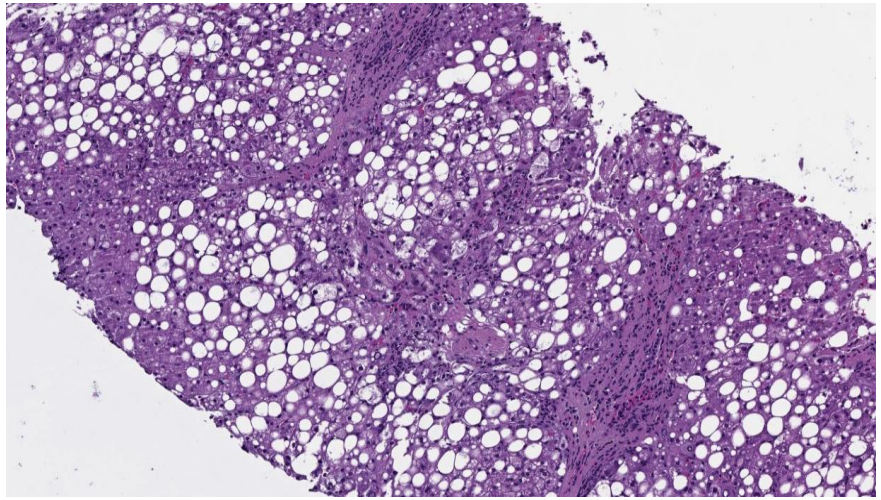
Development of ML-models for NAS and Fibrosis

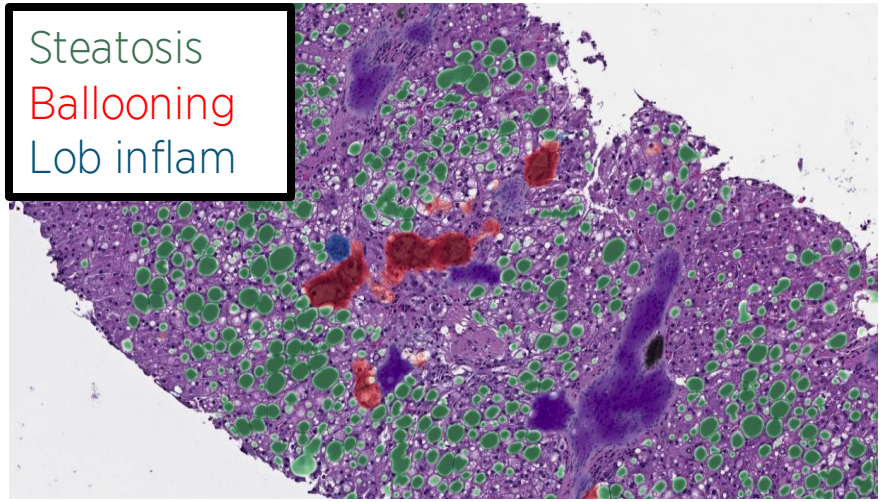
Analysis of the STELLAR clinical trials

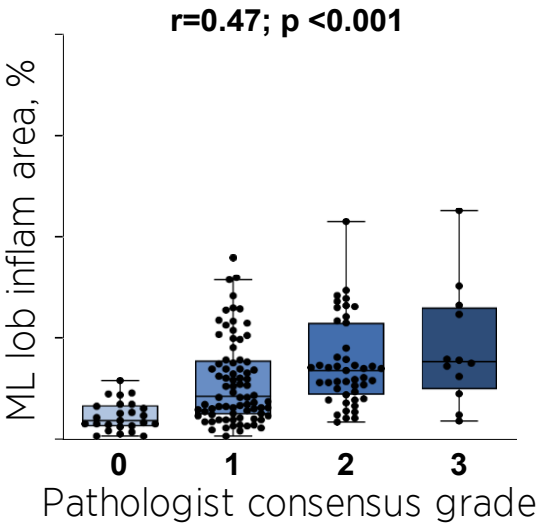


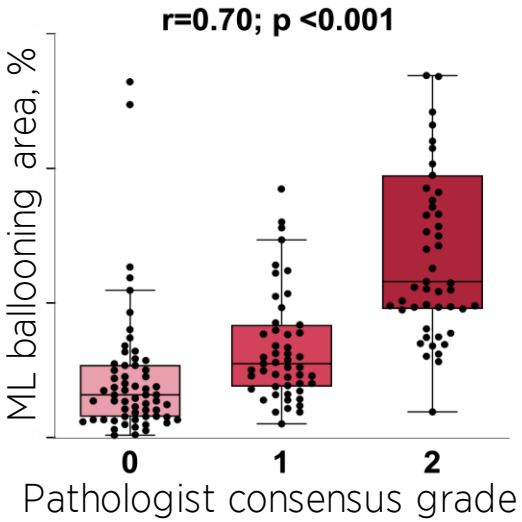
Pokkalla H, et al., Oral presentation #187, AASLD 2019

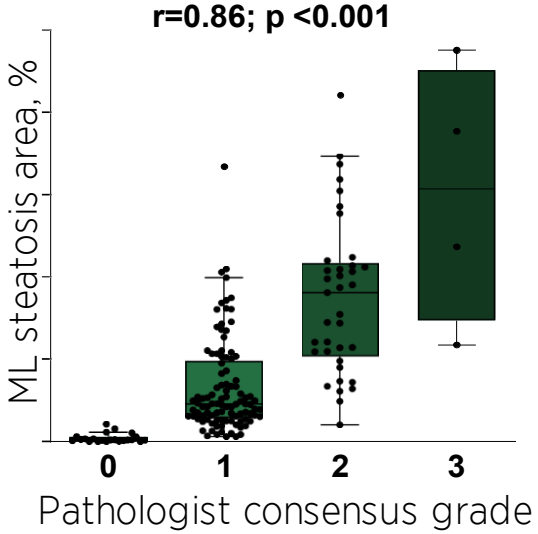
NAFLD Activity Score (NAS)





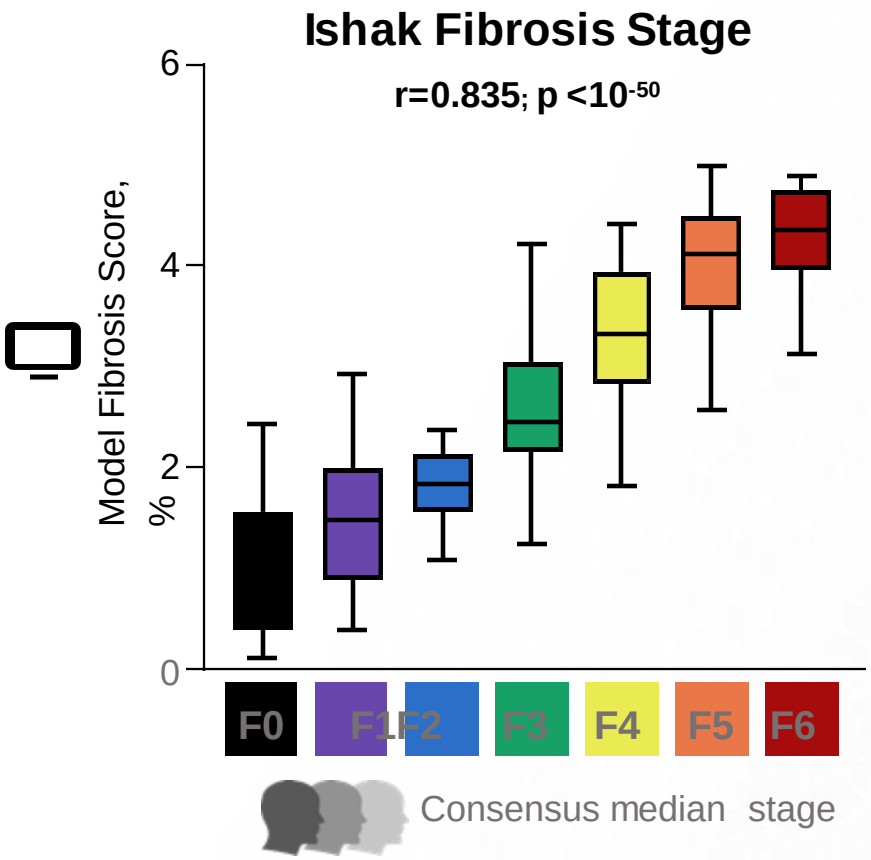




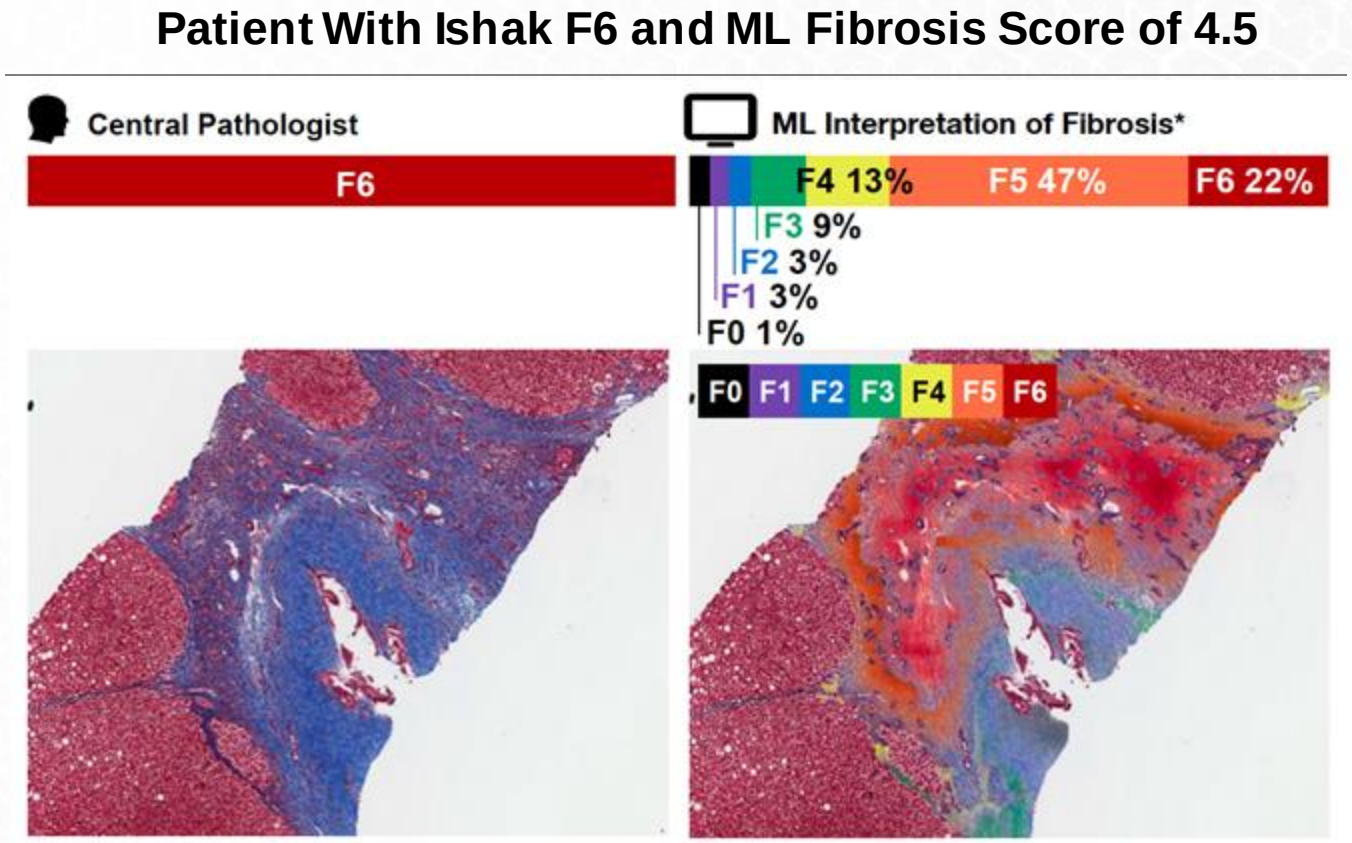


Pokkalla H, et al., Oral presentation #187, AASLD 2019

Fibrosis Staging



Younossi Z, et al. AASLD 2019 (Poster #1718).



ML fibrosis score associated with time to first clinical event (HR=3.2 [1.4, 7.1]; p=0.005) and c-statistic = 0.67 [0.53-0.80]

Machine Learning Models Identify Novel Histologic Features Predictive of Clinical Disease Progression in Patients With Advanced Fibrosis Due to Nonalcoholic Steatohepatitis

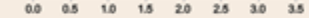
Harsha Pokkalla, Kishalve Pethia, Amaro Taylor-Weiner, Benjamin Glass, Hunter Elliott, Ling Han, Catherine Jia, Ryan S. Huss, Chuhan Chung, G. Mani Subramanian, Robert P. Myers, Stephen A. Harrison, Zachary Goodman, Murray Resnick, Aditya Khosla, Andrew Beck, Ilan Wapinksi, Arun J. Sanyal, Zobair M. Younossi

Presented at The Digital International Liver Congress, 27–29 August 2020

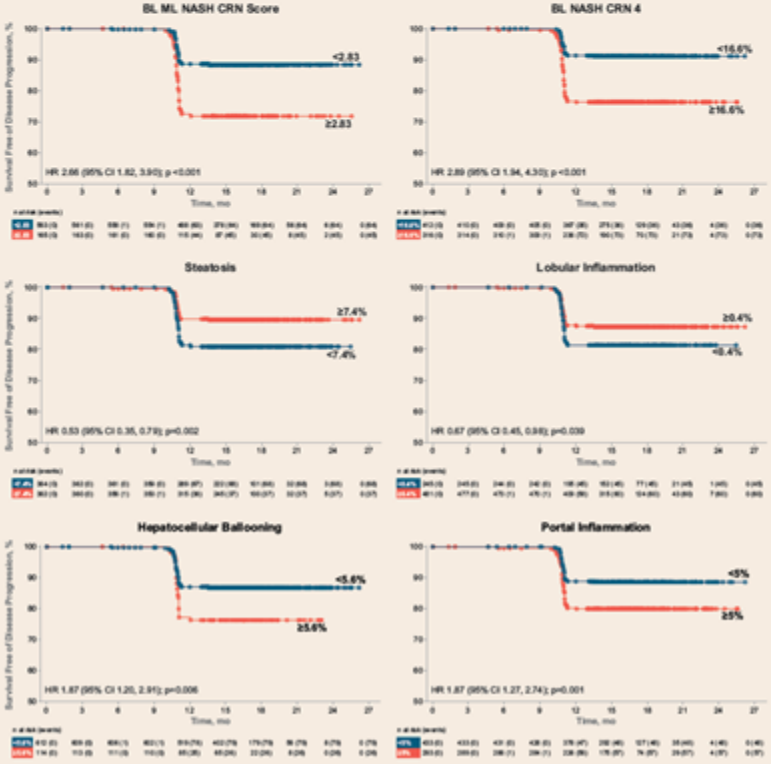
ML-Based Histologic Features Predicted Disease Progression in Patients With Bridging Fibrosis (F3)

- During median follow-up of 16.5 mo, 15% of patients with F3 fibrosis progressed to cirrhosis (n=112) or experienced a liver decompensation event (n=1)

	Bridging Fibrosis (clinical disease progression; n=113/755)		
	HR	95% CI	p-Value
ML NASH CRN fibrosis score*			
Average score, per 1 unit	2.18	1.56, 3.06	<0.001
NASH CRN F4 area	1.33	1.21, 1.45	<0.001
NASH CRN ≤F2 area	0.83	0.76, 0.90	<0.001
NASH CRN F1 area	0.77	0.65, 0.91	0.002
ML Ishak fibrosis score*			
Average score, per 1 unit	1.78	1.39, 2.26	<0.001
Ishak 6 area	1.49	1.22, 1.82	<0.001
Ishak ≤4 area	0.79	0.73, 0.87	<0.001
Ishak ≤2 area	0.83	0.75, 0.91	0.001
Ishak 1 area	0.77	0.64, 0.93	0.006
NAS-related and other parameters†			
Steatosis area	0.98	0.95, 1.01	0.13
Lobular inflammation area	0.82	0.57, 1.19	0.30
Hepatocellular ballooning area	1.06	1.00, 1.12	0.051
Portal inflammation area	1.11	1.06, 1.16	<0.001
Bile duct area, per mm²	0.94	0.60, 1.47	0.78



- Progression to cirrhosis was associated with higher ML NASH CRN and Ishak fibrosis scores, higher proportionate areas of NASH CRN F4 and Ishak stage 6 fibrosis, and lower proportionate areas of mild fibrosis (all p <0.05)
- Among nonfibrosis-related parameters, higher proportionate areas of hepatocellular ballooning and portal inflammation were associated with progression to cirrhosis

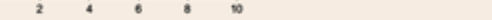


*Unless otherwise specified, hazard ratio (HR) reflects per 10% difference in parameter; †Unless otherwise specified, HR reflects per 1% difference in parameter. CI, confidence interval.

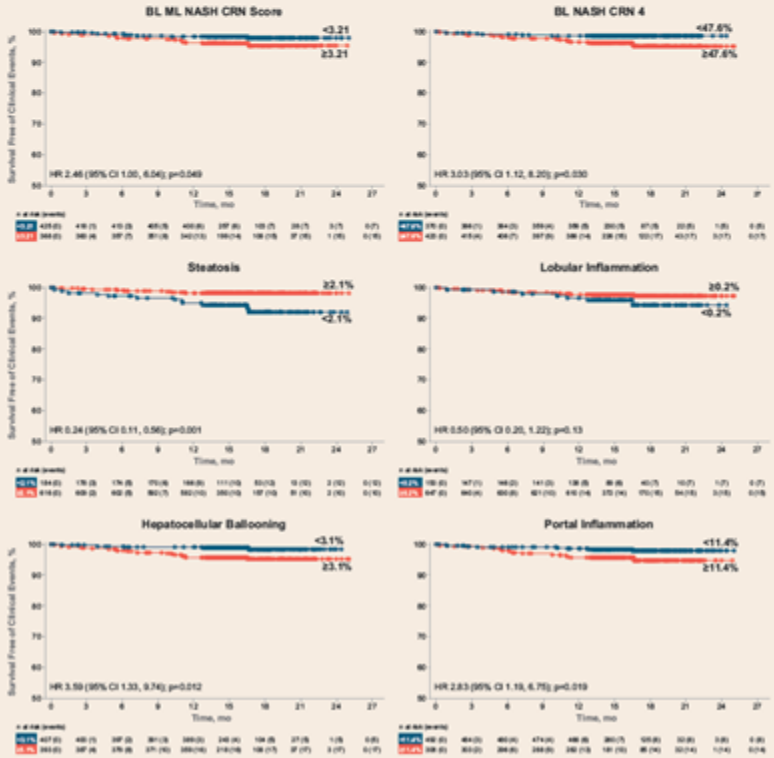
ML-Based Histologic Features Predicted Disease Progression in Patients With Cirrhosis (F4)

- During median follow-up of 15.8 mo, 3% (22/838) of F4 patients had liver-related clinical events

	Cirrhosis (clinical disease progression; n=22/838)		
	HR	95% CI	p-Value
ML NASH CRN fibrosis score*			
Average score, per 1 unit	2.94	1.04, 8.33	0.043
NASH CRN F4 area	1.23	1.00, 1.51	0.050
NASH CRN ≤F2 area	0.69	0.49, 0.97	0.034
NASH CRN F1 area	0.46	0.20, 1.08	0.08
ML Ishak fibrosis score*			
Average score, per 1 unit	3.36	1.61, 7.02	0.001
Ishak 6 area	1.31	1.10, 1.55	0.002
Ishak ≤4 area	0.64	0.49, 0.82	<0.001
Ishak ≤2 area	0.55	0.32, 0.94	0.029
Ishak 1 area	0.39	0.15, 1.02	0.06
NAS-related and other parameters†			
Steatosis area	0.84	0.73, 0.97	0.017
Lobular inflammation area	0.56	0.15, 2.16	0.40
Hepatocellular ballooning area	1.11	1.02, 1.21	0.016
Portal inflammation area	1.10	1.04, 1.17	<0.001
Bile duct area, per mm²	1.98	1.15, 3.41	0.014



- Liver-related events were associated with higher ML NASH CRN and Ishak fibrosis scores, higher proportionate areas of NASH CRN F4 and Ishak stage 6 fibrosis, and lower proportionate areas of mild fibrosis
- Among nonfibrosis-related parameters, higher proportionate areas of hepatocellular ballooning and portal inflammation, higher bile duct area, and a lower proportionate area of steatosis were associated with liver-related events (all p <0.05)



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Safety and Efficacy of Combination Therapies Including Cilofexor/Firsocostat in Patients With Bridging Fibrosis and Cirrhosis Due to NASH: Results of the Phase 2b ATLAS Trial

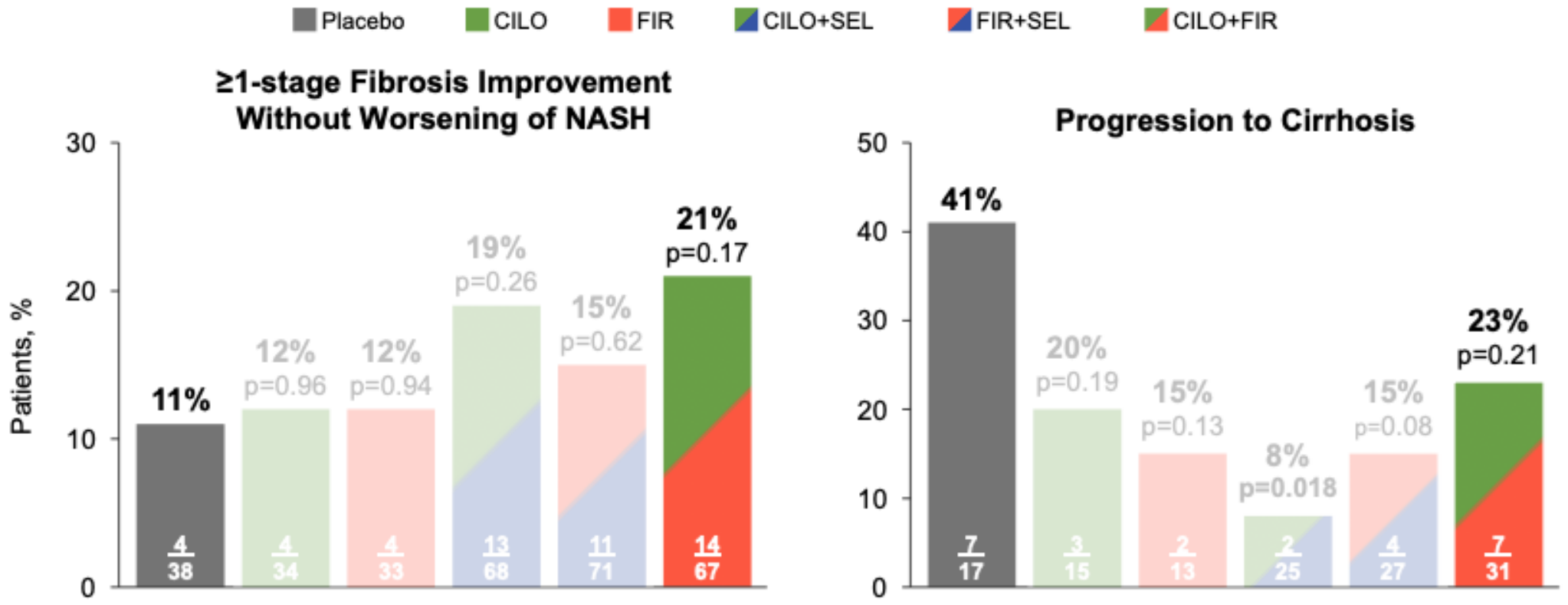
Rohit Loomba,[1] Mazen Noureddin,[2] Kris V. Kowdley,[3] Anita Kohli,[4] Aasim Sheikh,[5] Guy Neff,[6] Bal Raj Bhandari,[7] Nadege Gunn,[8] Stephen H. Caldwell,[9] Zachary Goodman,[10] Ilan Wapinski,[11] Murray Resnick,[11] Andrew H. Beck,[11] Dora Ding,[12] Catherine Jia,[12] Ryan S. Huss,[12] Chuhan Chung,[12] G. Mani Subramanian,[12] Robert P. Myers,[12] Keyur Patel,[13] Brian B. Borg,[14] Reem Ghalib,[15] Heidi Kabler,[16] John Poulos,[17] Ziad Younes,[18] Magdy Elkhashab,[19] Tarek Hassanein,[20] Rajalakshmi Iyer,[21] Peter J Ruane,[22] Mitchell L. Shiffman,[23] Simone Strasser,[24] Vincent Wai-Sun Wong,[25] Naim Alkhouri,[26] for the ATLAS Investigators

[1]University of California at San Diego, La Jolla, CA, USA; [2]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [3]Liver Institute Northwest, Washington State University, Seattle, WA, USA; [4]Arizona Liver Health, Chandler, AZ, USA; [5]Gastrointestinal Associates of Georgia, Marietta, GA, USA; [6]Covenant Research, Sarasota, FL, USA; [7]Delta Research Partners, Monroe, LA, USA; [8]Pinnacle Clinical Research, San Antonio, TX, USA; [9]University of Virginia, Charlottesville, VA, USA; [10]Inova Fairfax Hospital, Falls Church, VA, USA; [11]PathAI, Boston, MA, USA; [12]Gilead Sciences, Inc., Foster City, CA, USA; [13]University of Toronto, Toronto, ON, Canada; [14]Southern Therapy and Advance Research, Jackson, MS, USA; [15]Texas Clinical Research, Arlington, TX, USA; [16]Jubilee Clinical Research, Las Vegas, NV, USA; [17]Cumberland Research Associates, Fayetteville, NC, USA; [18]Gastro One, Germantown, TN, USA; [19]Toronto Liver Centre, Toronto, ON, Canada; [20]Southern California Liver Centers, Coronado, CA, USA; [21]Iowa Digestive Disease Center, Clive, IA, USA; [22]Ruane Medical and Liver Health Institute, Los Angeles, CA, USA; [23]Bon Secours Mercy Health, Richmond, VA, USA; [24]Royal Prince Alfred Hospital, AW Morrow Gastroenterology and Liver Centre, University of Sydney, NSW, Australia; [25]The Chinese University of Hong Kong, Hong Kong; [26]Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, USA

The Digital International Liver Congress, 27–29 August 2020: Abstr 4479

Topline ATLAS trial results

Fibrosis Regression and Progression to Cirrhosis

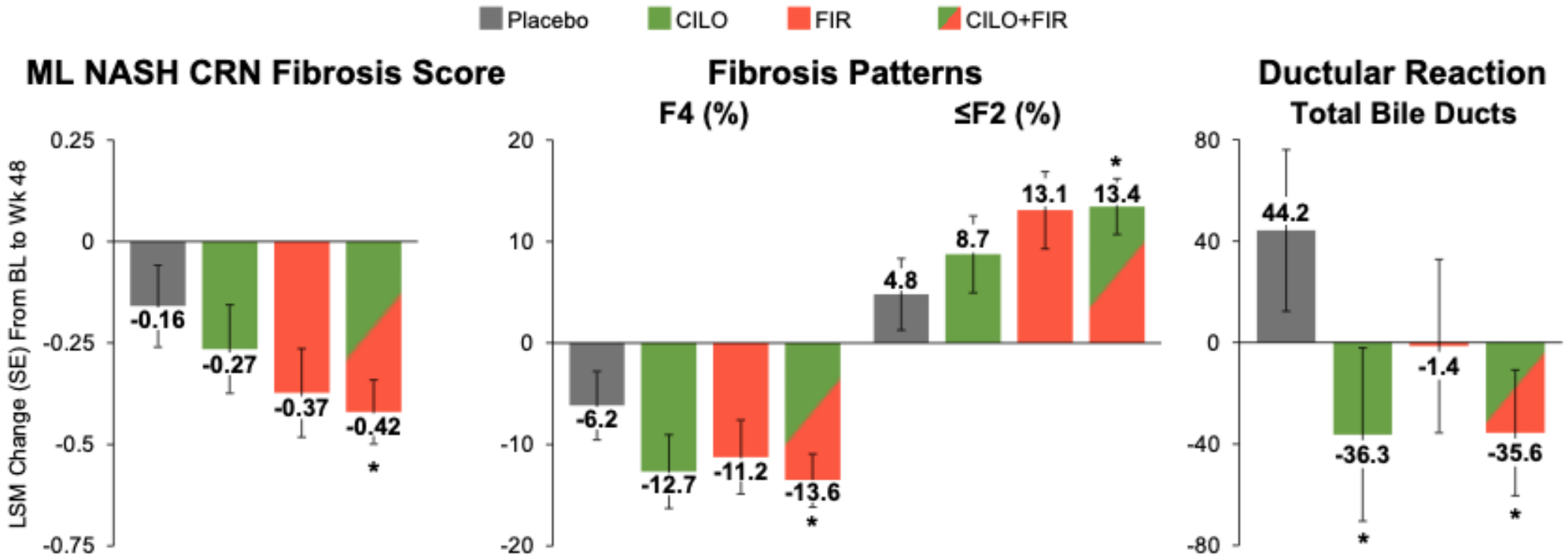


- CILO+FIR led to highest rate of fibrosis regression, but not statistically significant vs placebo
- Reduced progression to cirrhosis vs placebo in all groups, significant for CILO+SEL

All p-values vs placebo adjusted for baseline (BL) diabetes and cirrhosis status.

Topline ATLAS trial results

CILO+FIR Improved Fibrosis and Ductular Reaction Based on Machine Learning Assessment



- CILO+FIR led to a significant reduction in ML NASH CRN fibrosis score
- CILO+FIR led to a significant decrease in F4 and increase in ≤F2 proportionate area
- Reduced ductular reaction observed in CILO-treated patients

*p <0.05 vs placebo after adjustment for BL diabetes and cirrhosis status. LSM, least-squares mean; SE, standard error.
Pokkalla H. AASLD 2019, abstr 0187; Younossi ZM. AASLD 2019, abstr 1718; Pokkalla H. EASL 2020, abstr 2947.

Agenda

1. Intro: AI-based pathology in drug development
2. Examples of utility in drug development
   - Oncology PD-L1
   - Oncology CD8 topology
   - Liver Disease (NASH)
4. Regulatory environment

PathAI

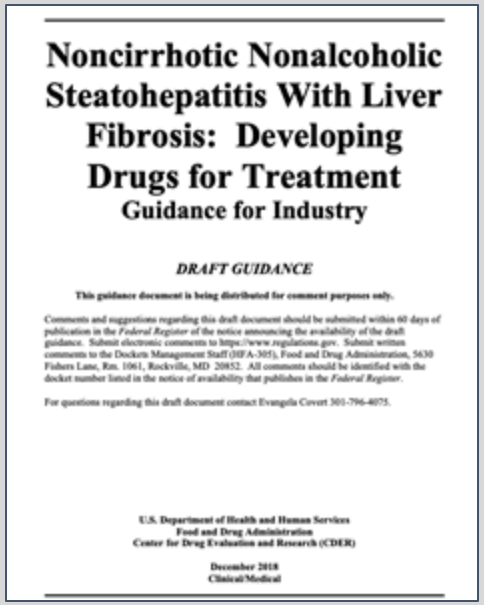
FDA has progressed thinking on digital pathology for clinical use… next frontier: Drug Development Endpoints

FDA

Progress in FDA's thinking regarding Digital Pathology for Diagnostic Use

- >30 510(k) clearances for product codes NOT, NQN, OEO, QKQ, PVV (image analysis for IHC)
- 4x 510(k) clearances for WSI Primary Diagnosis on Digital Pathology Devices
- FDA Draft Guidance for WSI: Technical Performance Assessment Guidance Document
- Proposed Framework Modifications to AI/ML SAMM

Several FDA Guidance docs for histological-based endpoints in drug development



Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment

Guidance for Industry

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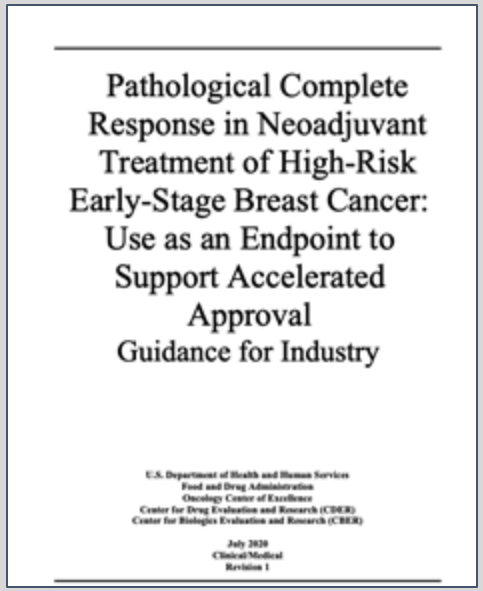
For questions regarding this draft document contact Evangelia Covert 301-796-4075.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2018
Clinical/Medical

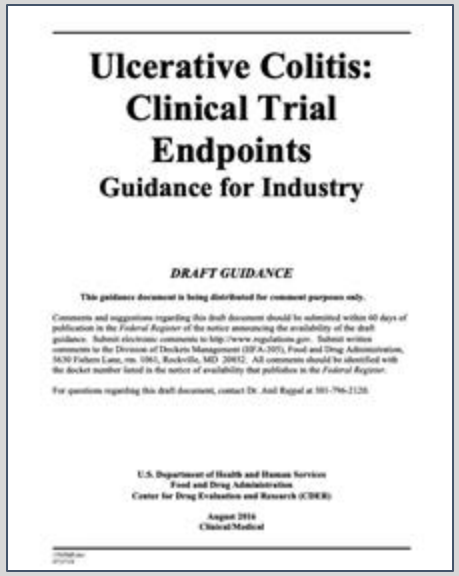


Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2020
Clinical/Medical
Revision 1



Ulcerative Colitis: Clinical Trial Endpoints

Guidance for Industry

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For questions regarding this draft document, contact Dr. Anil Rajpal at 301-796-2126.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2016
Clinical/Medical

PathAI

Thank You

We thank our investigator colleagues, the patients and their families who participated in the Bristol Myers Squibb and Gilead clinical trials