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QONM: PathAI AIM-NASH Drug Development Tool Experience

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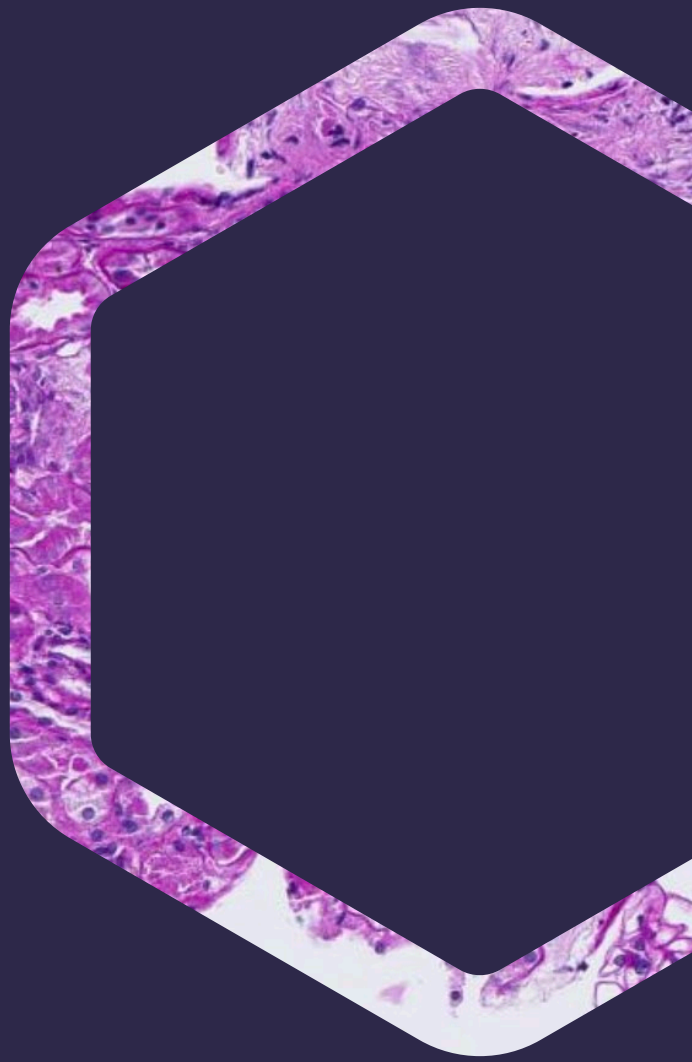
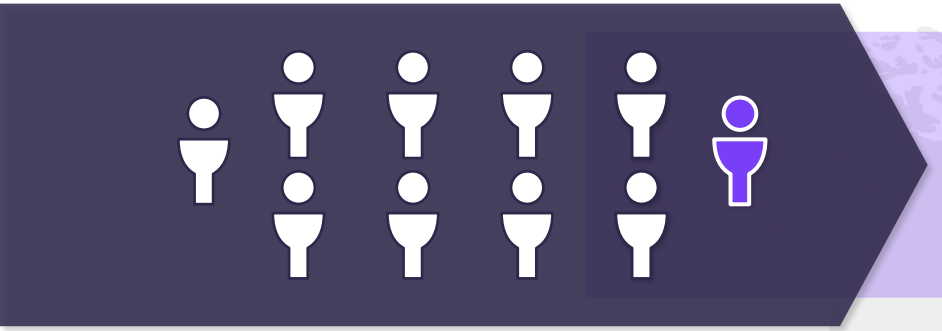
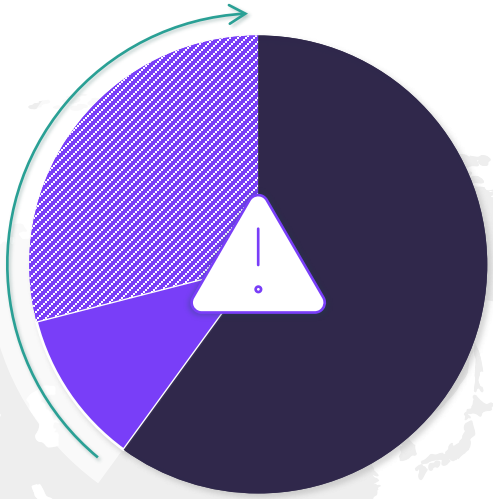


NASH is a growing public health issue



NAFLD progresses to **NASH, the more advanced form of disease, in 20-30% of cases.**[2]



Nearly a quarter of adults worldwide suffer from **non-alcoholic fatty liver disease** (NAFLD)[1], and prevalence is projected to **increase by up to 21% between 2015 and 2030**.[3]

NASH cases are projected to **increase by 63% (16.5 million to 27 million cases) between 2015 and 2030**[3]

- No current medication options
- Expected to be lead cause of liver transplants[3]
- Major economic and health issue

1. Younossi Z, et al Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018; 15: 11-20.
2. Fernando, et al. Development and progression of Non-Alcoholic Fatty Liver Disease: The Role of Advacnced Glycation End Prodcuts. Int J Mol Sci. 2019 Oct; 20(20): 5037
3. Estes C, et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates and exponential increase in burdeb of disease. Hepatol 2017

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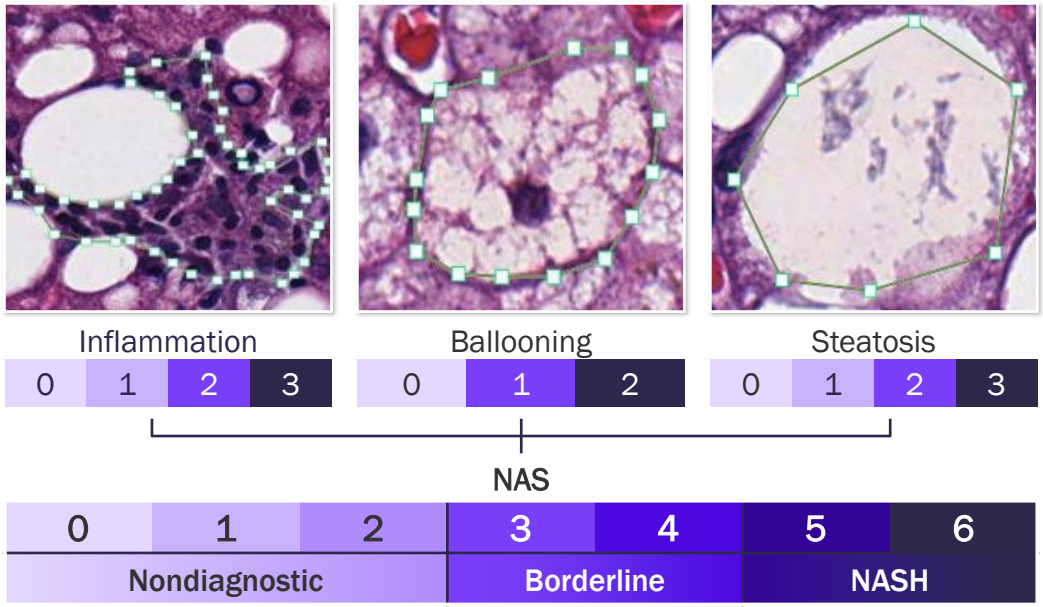
FDA and EMA guidance recommend histologic endpoints for drug approval

Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment
Guidance for Industry

"Because of the slow progression of NASH, the FDA recommends liver histological improvements as endpoints reasonably likely to predict clinical benefit to support accelerated approval."[1]

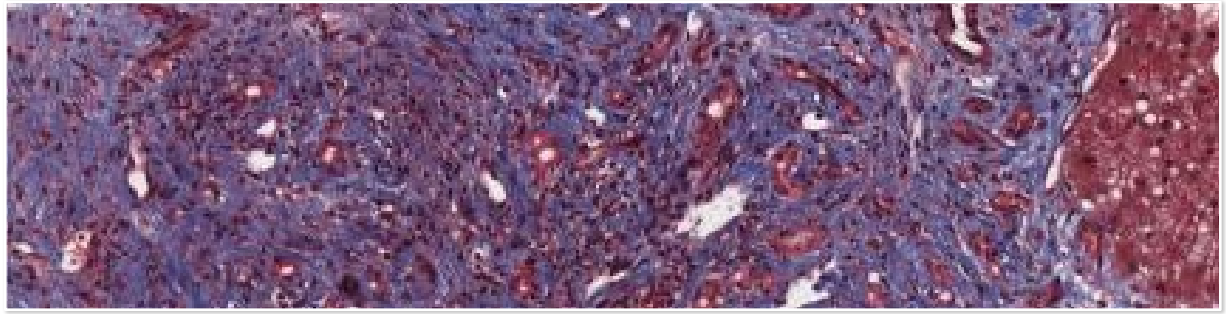
NAFLD Activity Score (NAS)

(H&E stain)



Fibrosis Staging

(trichrome stain)



0	1	2	3	4
No fibrosis	Perisinusoidal or periportal	Perisinusoidal and periportal	Bridging fibrosis	Cirrhosis

1. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment. Guidance for Industry. US Dept of Health and Human Services Food and Drug Administration and CDER. Dec 2018: https://www.fda.gov/media/119044/download

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The accepted NASH scoring system is prone to inter- and intra-reader variability…

NAFLD Activity Score[1]

Inflammation

No foci	<2 foci per 20x field	2-4 foci per 20x field	>4 foci per 20x field

Ballooning

None	**Few** balloon cells	**Many** cells/ prominent ballooning

Steatosis

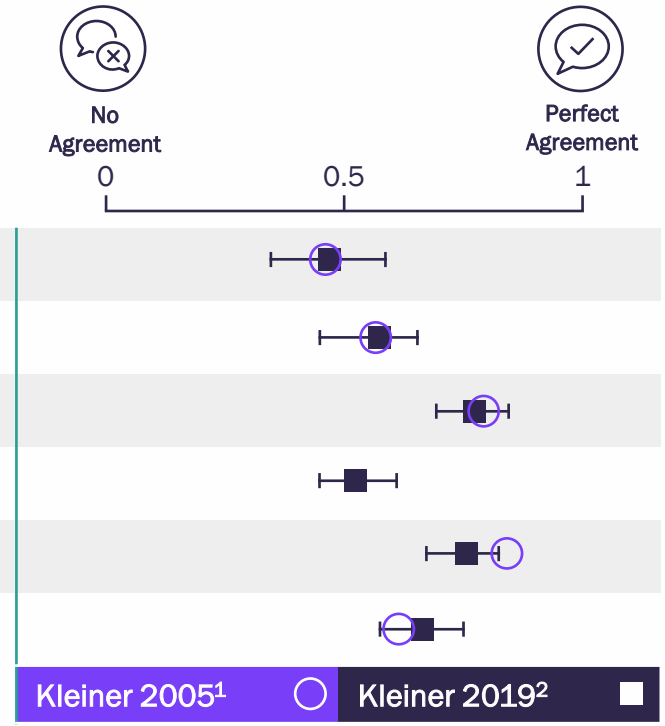
<5%	5-33%	>33-66%	>66%

Variable and subjective approaches to counting foci

Subjective interpretation

Arbitrary category boundaries

Kappa statistic (95% CI)



Results in inter-reader variability among pathologists

1. Kleiner DE, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005 Jun; 41(6):1313-21.
2. Kleiner DE, et al. Association of Histologic Disease Activity with Progression of Nonalcoholic Fatty Liver Disease. JAMA Network Open 2019; 2:31912565

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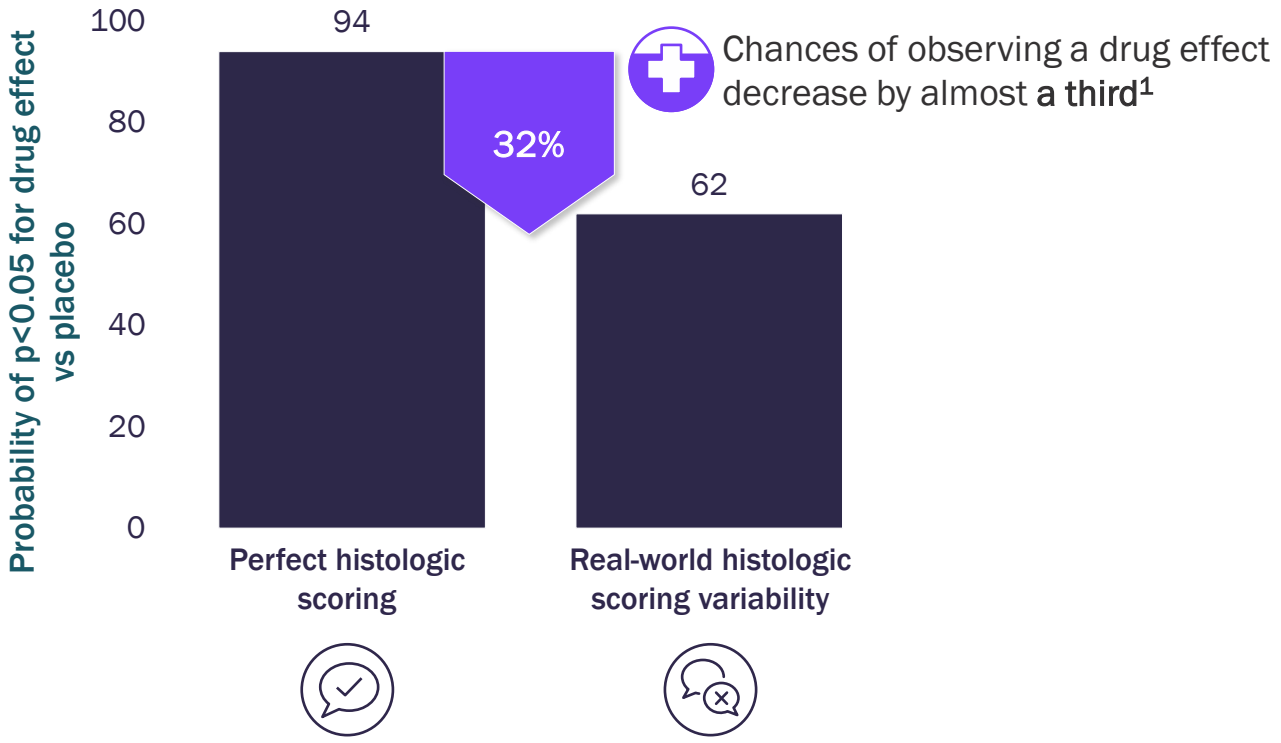
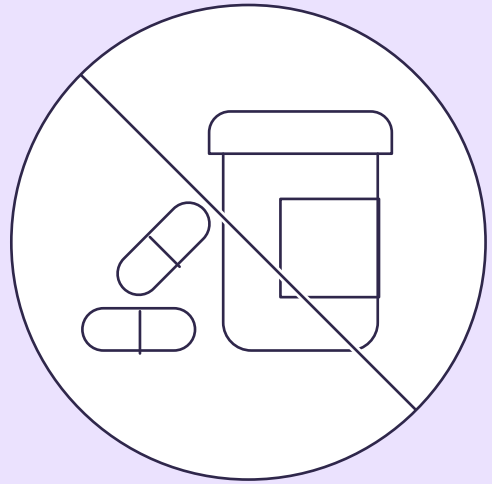
And this variability in scoring increases the risk to trial success



Chances of observing a drug effect decrease by almost **a third**[1]



May result in effective treatments not being approved for patients

1. Davison BA, et al. Journal of Hepatology 2020; 73: 1322-32

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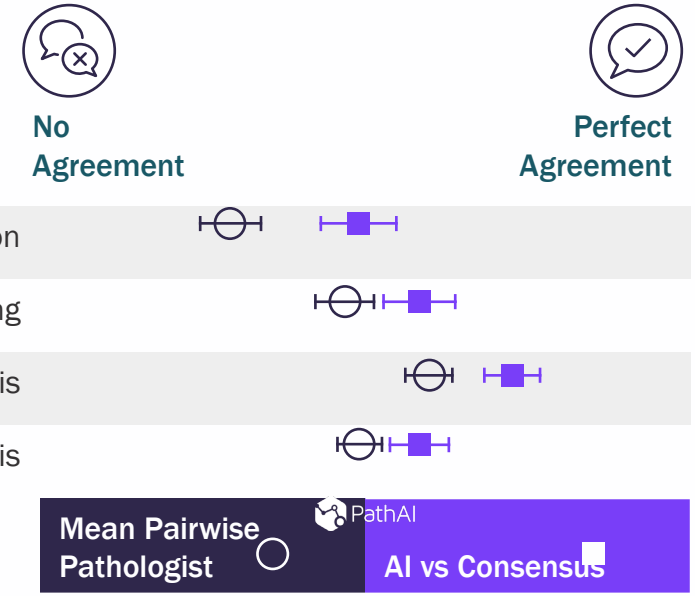
AI-powered pathology reduces scoring variability

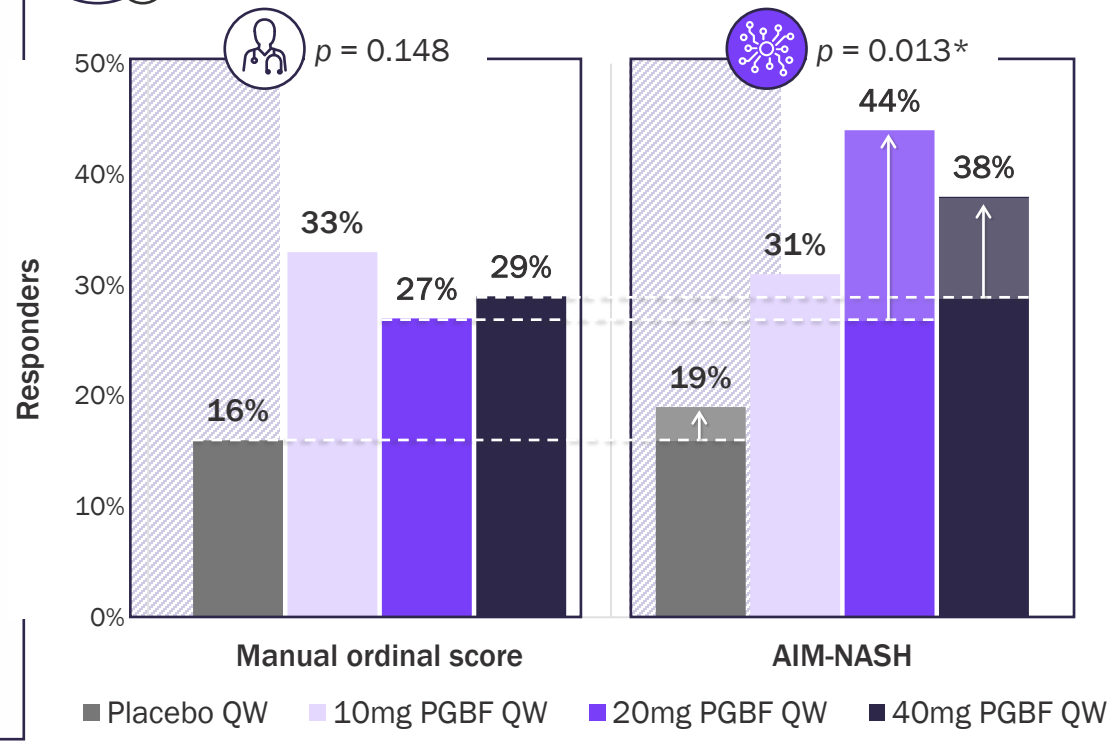
Kappa statistics

AIM-NASH vs. manual consensus compared to mean pairwise pathologist



Agreement was **higher between AI and gold-standard pathologist** consensus than between pathologists[1]

Translates into **stronger demonstration of treatment effect**

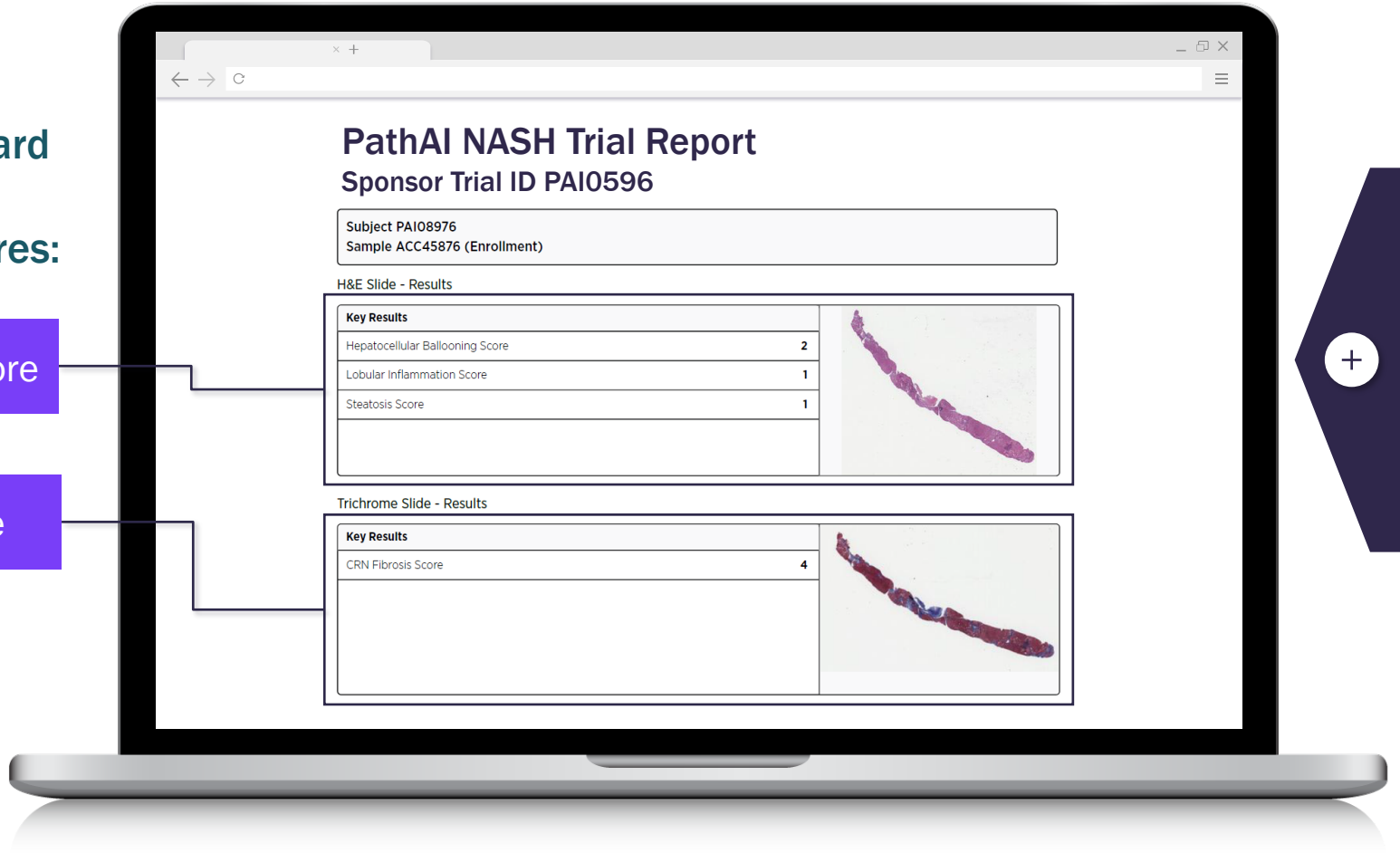


1. Carrasco-Zevallos et al., AI-based histologic measurement of NASH (AIM-NASH): A drug development tool for assessing clinical trial endpoints, EASL 2021 abstr 1611
2. Shevell et al. Comparison of manual vs machine learning approaches to liver biopsy scoring for NASH and fibrosis: a post hoc analysis of the FALCON 1 study. AASLD poster 2021

AIM-NASH Drug Development Tool Example Report

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

- NAFLD activity score
- CRN fibrosis score



Plus, AISight, a **validated** whole slide image viewer for Pathologist evaluation and data capture (GCP compliant).

Types of Validation Evidence Needed to Support Proposed Context of Use in NASH Trials

Relevant Considerations: A Whole Slide Image (WSI) is the direct input to the version-controlled algorithm. The algorithm should generate accurate and consistent scores for the pathologist to QC. Pathologist ultimately in control and is making other histopathological evaluations during a study (in addition to scoring) utilizing the WSI viewer:

A. Analytical Validation: all non-clinical studies demonstrating performance characteristics of algorithm outputs.
1. Validation of WSI viewing platform
2. Overlay Validation on the "frames" level
3. Accuracy (compared to current gold standard consensus), repeatability and reproducibility of algorithm

B. Clinical Validation: Prospectively read cases, where Pathologists utilize AIM-NASH and the validated WSI platform to score biopsies from Retrospective Trial Datasets to cover proposed context of use, compare to current gold standard.
1. Representative Trial Populations: multiple trials (ph2, ph3) with different drug candidates, enrolled and screen failures represented, baseline and follow-up timepoints
2. Demonstrate high accuracy per histologic component compared to gold standard consensus, with pathologist QC of algorithm.

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EMA and FDA qualification processes

FDA

LETTER OF INTENT (LOI)

- Identification of drug development need
- Information to support that the proposed DDT and its COU would address that need
- Feasibility assessment of proposal will include information to support that measurement of the novel DDT is, in fact, possible

QUALIFICATION PLAN

- Define DDT development project plan to support the COU
- Reach agreement on the interpretation and significance of existing information
- Identify knowledge gaps and align on mitigation plan or additional data to address those gaps

FULL QUALIFICATION PACKAGE

- Data and analyses to support the DDT's COU

Parallel reviews are no longer performed, but EMA will communicate with FDA during process

EMA

DRAFT BRIEFING DOCUMENT

FINAL BRIEFING DOCUMENT for Qualification Advice

FINAL BRIEFING DOCUMENT for Qualification Opinon (including validation results)

FDA and EMA General Qualification History, AIM-NASH

EMA Review Times, Based on Rolling Meeting Schedule for Qual Advice & Qual Opinions:

-Draft Briefing Doc Review: 45 days (w/ preparatory meeting held)

-Final Review of BD and List of Questions Prepared Sent-: 30 days

-Discussion meeting w/ response to LOI held and Qualification Advice Adopted/Issued on Final BD (QP): 40 days

-Draft Qualification Package review (w/ validation results): 45 days (w/ preparatory meeting held)

-Final Review of BD and List of Questions Prepared Sent-: 30 days

-Discussion meeting if needed, held and Qualification Opinion Adopted: 40 days

-Public Consultation Period: 45 days

Estimated FDA Review Timelines (FDA Guidance, Qualification Process for Drug Development Tools); AIM-NASH timeline

-LOI Review: ~3 months (AIM-NASH ~3 months); ~ 3 months

-QP Review: ~6 months (AIM-NASH); ~2.5 yrs

-FQP Review: ~10 months; TBD

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Thoughts on going FDA, EMA route and trying to keep in parallel

Parallel review is largely out of the hands of the submitter

- EMA process seems to be more predictable with a rolling schedule, and thus far, more efficient
- FDA review is not tied to PDUFA / MDUFA (or other UFA) timelines or expectations

Discuss EMA and FDA willingness to establish inter-agency collaborative review teams

- Greater consistency to tool developers, drug developers, and therefore patients in an area where this a significant unmet need
- Submission expectations for these programs are already well aligned
- Relevant consensus standards and practices are recognized by both bodies

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Thoughts around efficient change control to allow for updates/improvements of technology-based drug development tools

There are unique challenges and opportunities when evaluating changes to soft-ware based drug development tools, particularly AI/ML-derived, novel drug development methods as compared to more traditional tools such as biomarkers.

- Continual updates to infrastructure - software and platform - to ensure continued trial data security and integrity
- Even with locked algorithms, additional data allows for refinement and algorithm updates to improve tool, and therefore outcomes of the drug study (not sure we are here yet, but it seems like a logical next step)

Mechanisms for modifications under a quality system, following recognized consensus standards ISO 14971, ISO 13485 21CFR820), would allow developers to make necessary and impactful updates without impacting patients or overall risk profile.

- Pre-determined and agreed-upon change classes: performance improvement, data security, SW EOL, cybersecurity, etc. (See FDA's Draft Guidance)
- Expedited review of proposed changes implemented according to appropriate risk management processes

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Suggested Processes to Evaluate Changes to Software-based Drug Development Tools

1. Changes will be evaluated from a risk-based approach and determined if they:
   - Introduce a new risk or modify an existing risk, or
   - Create or necessitate a new risk control measure or a modification of an existing risk control measure for a hazardous situation that could result in significant harm
2. If these changes do not significantly impact risk, then they will be assessed to determine if they significantly affect clinical functionality or performance specifications directly associated with the COU.

If changes are insignificant after evaluating (1) and (2), then they will be deemed insignificant and implemented per PathAI's QMS.

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Examples of Anticipated Changes Post Qualification

- As the clinical trial populations evolve and expand and technologies improve, some changes are anticipated.
- Anticipated changes are evaluated from a risk-based approach and significant impact to clinical functionality or performance specifications will be determined.
- Validation of WSI viewing platform, the user interface (UI), will be performed if there are significant changes to digital images or UI functionality for manual review.
- Analytical validation will be performed for the anticipated algorithm changes where algorithm outputs are not significantly changed. A portion of the same validation set will be used where feasible in order to demonstrate substantial equivalence or improvement, and to assure no temporal degradation
  - Example 1: Training for robustness; Analytical validation on other scanners and some subset confirmatory accuracy and precision on images from the existing scanner, if relevant.
  - Example 2: Supplementing training set with additional data; Analytical validation (accuracy, precision (R&R)) focused on broader data from intended population with additional images broadening the entire measuring range as confirmation of continued acceptable or improved performance.
- Clinical Validation with representative subset will be performed where outputs of algorithm that pathologist is interacting with and/or the algorithm review workflow significantly changes.
- We propose including this information and proposals for bridging/validation studies where applicable in final qualification document to allow for incorporation of improvements without the need for a new qualification procedure, where appropriate.

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Thank You!

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