AISight | Clinical Trials

AIM-NASH Algorithm for Artificial Intelligence-Based Measurement of Non-Alcoholic Steatohepatitis Histology

Version 1.5

REF 2012200001

User Manual

RUO

NOTE: The AISight Clinical Trials Platform and the AIM-NASH Algorithm are intended for Research Use Only. Not for use in diagnostic procedures. Access is intended for authorized users only, contact your institution for access approval.

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Supported Software

This document applies to AIM-NASH Algorithm for Artificial Intelligence-Based Measurement of Non-Alcoholic Steatohepatitis Histology Version 1.5.x.

Cybersecurity Disclaimer

The maintenance and security of the local infrastructure — including the site's network, systems access, physical and other logical responsibility – are all outside the scope of PathAI Inc.'s responsibility and are the responsibility of the site.

Contents

Chapter 1: Important Information

This chapter includes:

About This Manual

This manual describes information and functionalities pertaining to the AIM-NASH Algorithm. For instructions on using functionalities of the AISight Clinical Trials Platform (the platform that houses this algorithm), see the *AISight Clinical Trials User Manual (CD-224).*

Symbol Definitions

The following table defines symbols that appear in this user manual:

Symbol	Definition
	Indicates the product is *"For Research Use Only. Not for use in diagnostic procedures."*
	Indicates the manufacturer's catalog number so the product can be identified.
	Indicates the need for the user to consult the Instructions for Use.
	Indicates the manufacturer of the product.

List of Abbreviations

The following table defines abbreviations used in the product or user manual:

Abbreviation	Definition
AI	Artificial Intelligence
AIM-NASH	AI-based Measurement of NASH Histology
CRN	Clinical Research Network
FFPE	Formalin-Fixed Paraffin-Embedded
H&E	Hematoxylin and Eosin
ID	Identifier
MPP	Microns Per-Pixel
MT	Masson's Trichrome Blue
NAFLD	Non-Alcoholic Fatty Liver Disease
NAS	NAFLD Activity Score
NASH	Non-Alcoholic Steatohepatitis
RUO	Research Use Only
WSI	Whole Slide Image

List of Terms

The following table defines terms used in the product or user manual:

Term	Definition
Algorithm	The algorithm comprises the specific combination of AI models that produce the outputs the user(s) interact with on the platform.
Platform	The platform comprises the infrastructure that houses the algorithm, and enables various configurations of algorithm outputs per clinical trial.
Product	The product comprises the specific combination of the algorithm and the platform.
Primary Pathologist	The Primary Pathologist is the first pathologist that reviews the AIM-NASH-derived outputs.
Secondary Pathologist	The Secondary Pathologist is the pathologist who reviews AIM-NASH scores that are rejected by the Primary Pathologist.

Configurable Software Labels for Trial Information

During onboarding with PathAI, the PathAI team works with your site to determine how specific trial-relevant labels appear in the software to identify trial information:

- Subject ID or Participant ID; and
- Accession ID or Sample ID

NOTE: References to software labels in this document may differ from your software due to the platform configurations selected for your trial.

Accessing Help and Determining Software Version

Within the platform you can click **Help** on the top navigation bar to access algorithm and platform related information, including Instructions for Use, software version (algorithm and platform), and the current terms of use. The **Help** screen also includes a link for contacting technical support.

Contacting PathAI Technical Support

If you have questions about the software, contact technical support at cta-support@pathai.com.

Chapter 2: Introduction

This chapter includes:

Product Description

The AIM-NASH Algorithm assists pathologists in grading and staging the cardinal histologic features of NASH from digitized slides containing H&E- and MT-stained liver biopsy tissue in a clinical trial setting. Specifically, the AIM-NASH Algorithm delivers AI-derived NASH CRN Steatosis, Ballooning, and Lobular Inflammation Grades in addition to Fibrosis Stages per case, while also producing colorized heatmap overlays that spotlight these features in paired H&E and MT WSIs per case. In addition to detecting and visualizing histologic features of NASH, AIM-NASH also detects and visualizes areas of Artifacts, including artifacts that arise from abnormal tissue processing, staining, and/or scanning, and Slide Background. The AIM-NASH Algorithm is accessed via the AISight Clinical Trials Platform.

The AIM-NASH Algorithm results must be reviewed by a pathologist (Primary Pathologist) before final reporting. The Primary Pathologist reviews the tissue quality and WSI quality, including stain and scan quality, before deciding whether to accept or reject the AI-derived scores. If the Primary Pathologist disagrees with the AI-derived score by at least two (2) grades/stages for any histologic component, the respective WSI is sent to another pathologist (Secondary Pathologist) for a second review of the histologic component with the rejected score. If the Secondary Pathologist's score agrees with the Primary Pathologist’s score, this is the final score. If the Secondary Pathologist's score does not agree with the Primary Pathologist’s score, the Primary and Secondary Pathologists convene to discuss the case and decide on a final score. In the event that the pathologists cannot come to an agreement, the Primary Pathologist’s score will be entered as the final score.

NOTE: For details about user roles and instructions for performing the workflow steps within the AISight Clinical Trials Platform, refer to the AI + Consensus Pathologist Review Workflow section of the *AISight Clinical Trials Platform User Manual (CD-224).*

This product is intended for Research Use Only. Not for use in diagnostic procedures.

About Algorithm Limitations

The AIM-NASH Algorithm analyzes WSIs of liver biopsy tissue stained with H&E or MT.

Guidelines for Ensuring Optimal Stain Quality

To optimize stain quality, follow the manufacturer's recommendations for each applicable assay using all the positive and negative quality control materials.

Guidelines for Understanding Algorithm Limitations

When reviewing AIM-NASH Algorithm results, note the following limitations:

- The AIM-NASH Algorithm results are only as good as the quality of the stain and the quality of the subsequent WSI that is evaluated by the algorithm.
- The AIM-NASH Algorithm may generate incorrect scores if the slide was improperly scanned or has significant artifacts obscuring relevant tissue areas; or abnormal staining.

These factors may result in the algorithm misidentifying liver tissue features that are relevant to NASH CRN grading and staging.

Criteria for Images and Scanner

The AIM-NASH Algorithm requires one H&E-stained WSI and one MT- stained WSI as inputs per algorithm run. The AIM-NASH Algorithm has been validated for WSIs in .SVS file format, created by the Leica Aperio AT2 scanner at 40X magnification.

Quality Assurance Checks for Images and Scanner

WARNING: Always inspect the quality of the WSI generated by the appropriate scanner to ensure adequate image quality in accordance with your local laboratory procedures.

NOTE: Results are optimized for slides scanned on the Leica Aperio AT2 scanner.

NOTE: The AIM-NASH Algorithm has only been validated on WSIs generated from 40X magnification scans.

For quality assurance, the AIM-NASH Algorithm verifies that each WSI within a sample meets specific criteria for File Format, Scanner Vendor, Scanner Type, and range in MPP . If the software detects incompatibilities, the following actions occur:

Incompatibility	Consequence	Error Message
File Format	Product run is blocked	"This slide does not meet the file format requirements for the algorithm. Only slides in .svs format are accepted."
Scanner Vendor	Product run is blocked	"The vendor and/or scanner type for this slide may be incompatible. The algorithm results and overlays have been optimized for slides scanned on the Aperio AT2."
Scanner Type	Product run proceeds	"The scanner type for this slide may be incompatible. The algorithm results and overlays have been optimized for slides scanned on the Aperio AT2."
MPP	Product run is blocked	"This slide does not meet the Microns Per-Pixel (MPP) requirements for the algorithm. Only slides scanned in the range of 0.2358 - 0.2659 or 0.4716 - 0.5319 MPP are accepted."

Chapter 3: Algorithm Results Overview

This chapter includes:

Viewing Algorithm Overlays

After an algorithm run is completed, it produces colorized overlays on the WSIs that appear in the slide viewer window. These overlays (**1**) highlight specific tissue regions detected by the algorithm (Figure 1). Each overlay is represented by a different color.

Special tools are provided in the **Overlays** panel for controlling the opacity and visibility of the colors:

- To control opacity, click the opacity icon (**2**) and drag the slider (Figure 1).
- To control visibility, click any of the toggle icons (**3**) to toggle the overlays on and off (Figure 1).

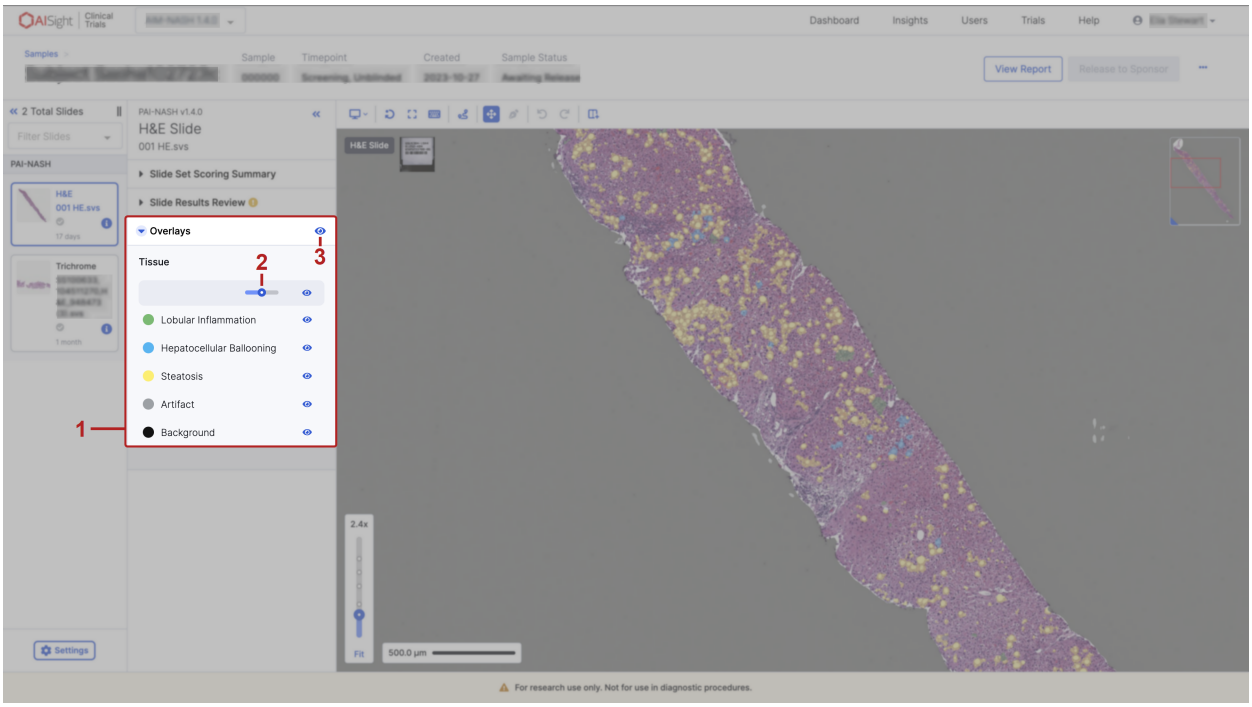

Figure 1 – Overlays Panel

Color Legend

The overlays that appear on analyzed WSIs highlight specific tissue and cell regions detected by the algorithm. The following tables define each color:

Artifact and Background (H&E and MT WSIs)

Color		Definition
	Grey	Artifact Region
	Black	Background Region

H&E Tissue Overlays

Color		Definition
	Yellow	Steatosis
	Light blue	Hepatocellular Ballooning
	Green	Lobular Inflammation

MT Tissue Overlays

Color		Definition
	Orange	Fibrosis

Viewing Results

After the PathAI software completes the NASH algorithm analysis, you can view the algorithm score in the Results panel (**1**) of the Slide Viewer screen (Figure 2).

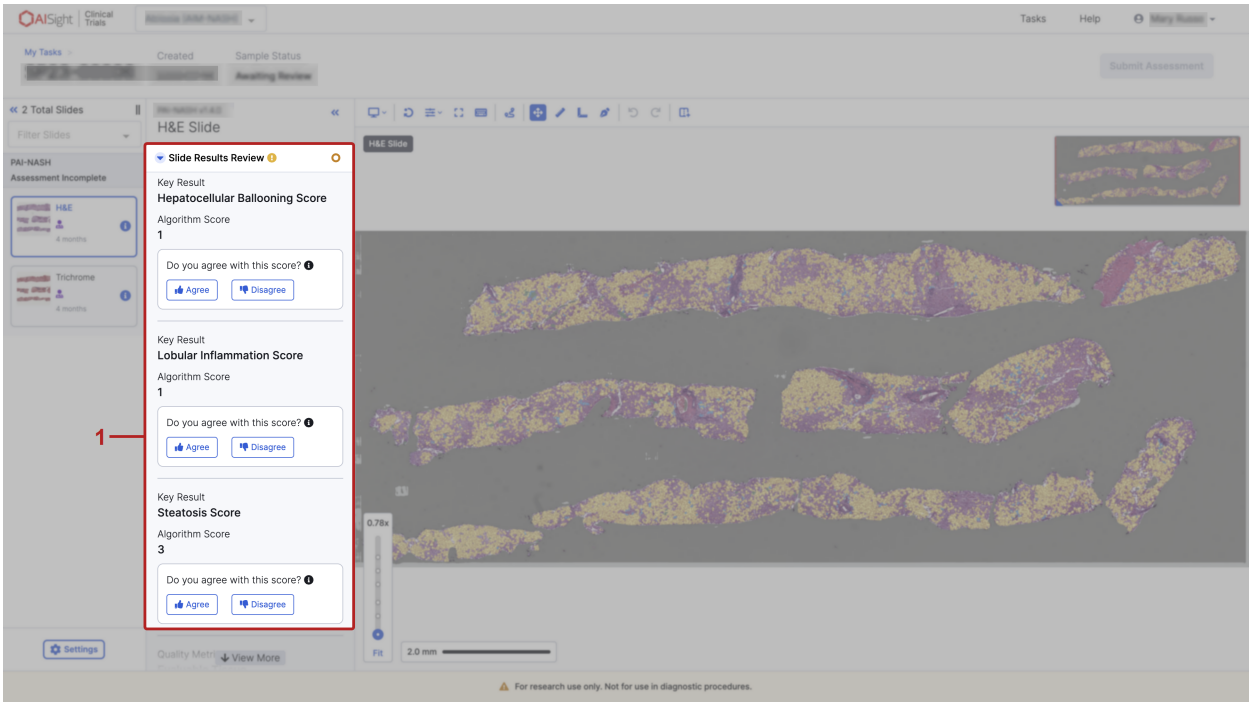

Figure 2 – Example H&E Slide Results Panel

H&E Results

Results	Description
Steatosis Score	The AI-derived NASH CRN Steatosis Grade computed from tissue in non-Artifact regions of the WSI. The value will be a whole number ranging from 0-3.
Lobular Inflammation Score	The AI-derived NASH CRN Lobular Inflammation Grade computed from tissue in non-Artifact regions of the WSI. The value will be a whole number ranging from 0-3.
Hepatocellular Ballooning Score	The AI-derived NASH CRN Hepatocellular Ballooning Grade computed from tissue in non-Artifact regions of the WSI. The value will be a whole number ranging from 0-2.

MT Results

Results	Description
Fibrosis	The AI-derived NASH CRN Fibrosis Stage computed from tissue in non-Artifact regions of the WSI. The value will be a whole number ranging from 0-4.

Quality Metrics (H&E and MT)

Results	Description
Evaluable Tissue	The area (mm^2) of tissue determined to be evaluable by the algorithm. Evaluable tissue excludes regions of artifact.
Percentage Artifact	The percentage (%) of the slide, including non-tissue area, determined to have artifacts from the pre-analytic, analytic, or post-analytic process such as slide preparation, staining and scanning by the algorithm.

About NASH CRN Grades and Stages

The NASH CRN recommends assessing NASH disease activity and fibrosis through grading of Steatosis, Ballooning, and Lobular Inflammation, and staging of Fibrosis. The sum of the Steatosis, Ballooning, and Lobular Inflammation grades is also referred to as the NASH CRN NAS. The NASH CRN designed and validated these scales[1] to serve as semi-quantitative systems that could be used to assess NASH disease severity at a single time point. The grading/staging system they proposed is described in the table below:

Assessment	Definition	Score
Steatosis	< 5%	0
	5%-33%	1
	> 33%-66%	2
	>66%	3
Lobular Inflammation	No foci	0
	< 2 foci per 200X field	1
	2-4 foci per 200X field	2
	> 4 foci per 200X field	3
Hepatocyte Ballooning	None	0
	Few balloon cells	1
	Many cells / prominent ballooning	2
Fibrosis	None	0
	Mild to Moderate, zone 3 perisinusoidal or periportal sinusoidal without accompanying zone 3	1
	Zone 3 perisinusoidal and portal/periportal	2
	Bridging fibrosis	3
	Cirrhosis	4

1: Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41(6):1313-1321. doi:10.1002/hep1ajssessment

Chapter 4: Generating Reports

This chapter includes:

About Generating Reports

The following reports are restricted to specific User roles. The following reports are generated by the platform for samples analyzed by the AIM-NASH Algorithm and reviewing pathologist(s). The availability and design of PDF reports are configurable per trial on the platform.

Reports	Description
Cumulative Report	Download WSI-level notifications regarding whether or not the reviewing pathologist produced exclusion annotations over non-liver tissue. **To download this report:** From the **Insights** screen, navigate to the **Cumulative Report** tile and click **Download CSV**.
PDF Report	Summarizes details about the sample and results. In the **Slide Viewer**, click **View Report**.

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