



THE FORUM
For Collaborative ResearchSM

Digital Histology Working Group Update

Bethesda, MD

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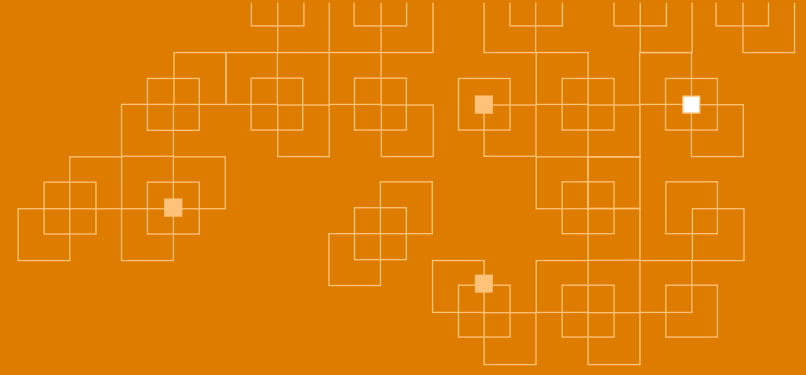
Berkeley Public
Health

Digital Histology Working Group Aims



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- The objective of this Working Group is to help inform the field on how to incorporate AI digital assessment of liver histology in clinical trials and for liver research.
- Focus will be on:
 - technical issues from the perspective of end-to-end tissue assays, with emphasis on quality control.
- This group also aims to:
 - Address the knowledge gap regarding digital and AI/ML histology amongst Liver Forum stakeholders.



Key Themes and Questions

Main Themes



- Demystify Digital AI/ML Histology and its contribution to NASH drug development
- Apply end-to-end assay development perspective to Digital AI/ML Histology
 - Develop recommendations for quality assessment and quality control
- Identify opportunities for collaboration and learning across three companies



What are key performance indicators (KPI) for biopsy adequacy and availability?

Digital Biopsy Adequacy Scores as Industry Benchmark

Delivered Worldwide via the cloud

The Digital Biopsy Adequacy (DBA) Score quantifies the overall quality and adequacy of the digital Images.

Context of Use

- 1- Generate a Biopsy Adequacy score
- 2- Assign a confidence level to FibroNest's Scores
- 3- Manage the performance of the histology CRO

It is compliant to novel FDA specifications for NASH Trials

- Biospecimen Finding (BS) Domain
- Supplemental Microscopic Findings (SUPPMI) Domain

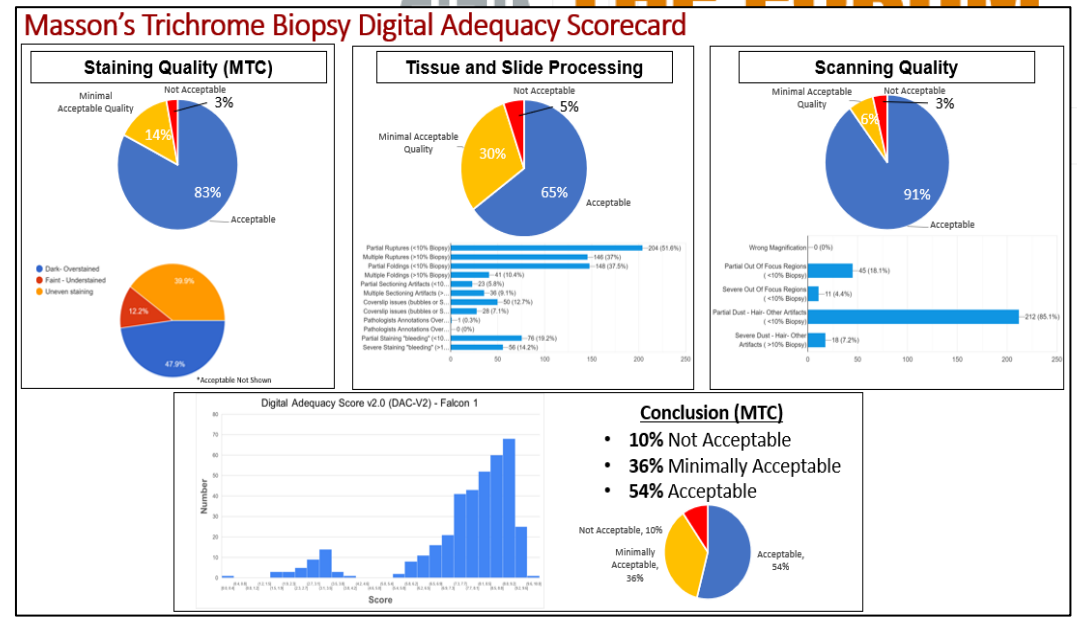
Manual (for now) and Robust

ANOVA - 2 operators - N=99- MTC FALCON 1

Source of Variation	SS	df	MS	F	P-value	F crit
Rows	705.5443	98	7.199432	17.02127	2.55E-35	1.396443
Columns	5.720108	1	5.720108	13.52377	0.000385	3.938111
Error	41.45075	98	0.422967			
Total	752.7152	197				

Intra-Class Correlation **0.87671** "Excellent" Cicchetti (1994)
 Linear Correlation **0.88574** "Good" (Koo and Li (2016))

Operator 1: 385 images (Falcon 1)
 Operator 2: Random subset of 99 images



Biospecimen Findings (BS) domain: This findings domain contains information related to observations of specimen quality and characteristics of collected biospecimens. This information is collected to assess the adequacy of the biopsies that are used for analysis and is structured as one record per measurement per biospecimen identifier per subject.

Supplemental Microscopic Findings (SUPPMI) domain: This domain contains supplemental information related to the biopsies, specifically the sponsors' assessment of slide adequacy. Justification should be provided in this domain for specimens deemed inadequate.

Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Nonalcoholic Steatohepatitis (NASH) – Guidance to Industry, August 2021
[WEBLINK](#)



Digital Biopsy Adequacy Scores as Industry Benchmark

Examples

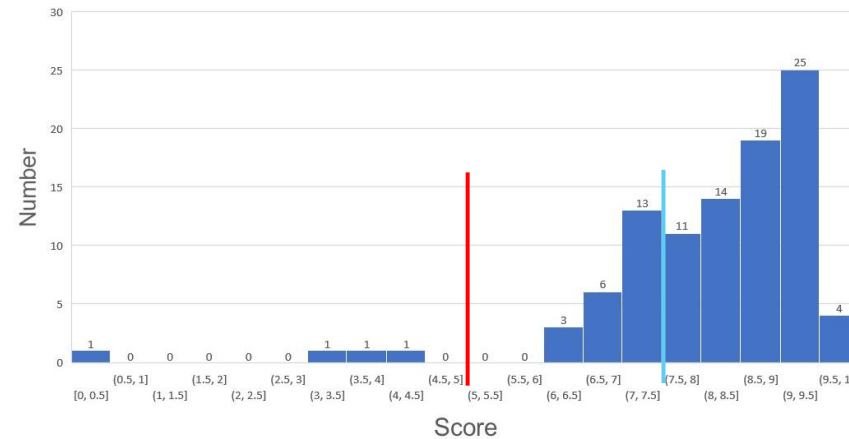


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Context of Use

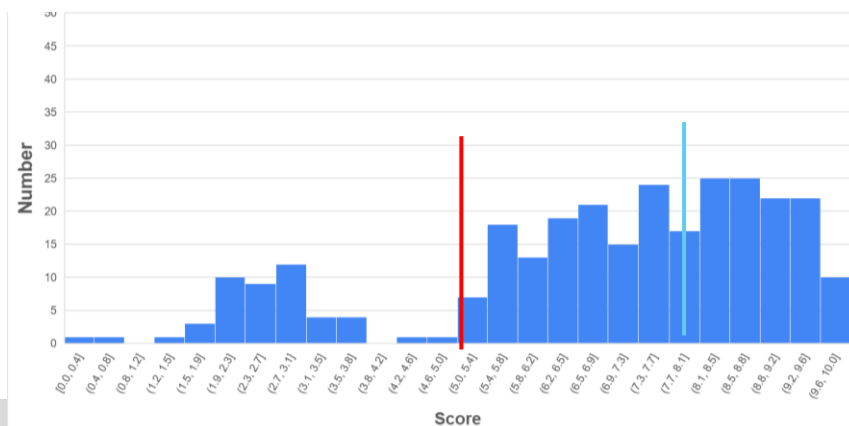
NASH Phase 2b F2/F3 N>>100



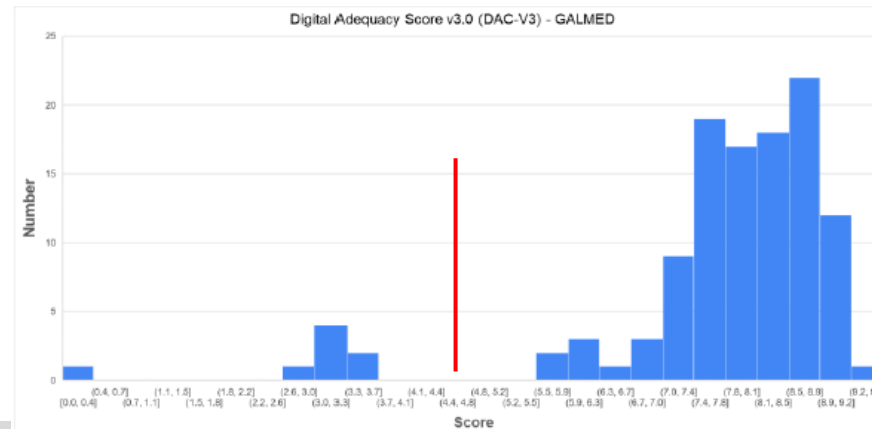
NASH Phase 2b F2 | F3 N~100



NASH Phase 2b F4 N >>100



NASH Phase 2b F2 | F3 N~120



- CRO quality KPI
- Confidence-enhanced Data Analysis



FibroNest Digital Biopsy Adequacy industry Benchmark

Agregated data from 13 Phase 2/3 NASH Studies

(MTC-H&E treated as separate studies)

N=4396 digital images

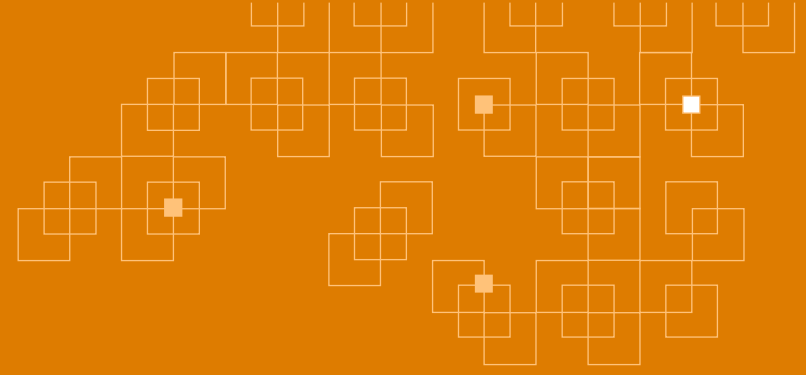
	Not Acceptable	Minimally Acceptable	Acceptable
Min	0%	8%	15%
Mean	12%	23%	65%
Median	6%	16%	75%
STD	14%	16%	25%
Max	44%	59%	87%

- **10% defects might result in ~20% lost opportunities of paired-biopsy analysis !!**
- **Each DP companies has strategies to “compensate”, but comes at a cost and waist of talent & Resources**
- **0% - 3% defects is achievable : choose your histology CRO wisely, create KPIs, incentivize performance**
- **Six-Sigma Sensei says: “if you don’t measure, don’t whine about it”**

Outputs from this Working Group



- A series of short and concise papers to address key themes.



Thank you!