

Clinical Studies DeNovo Philip's Intellisite Pathology System

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Conflicts and Disclosures

- SAB + Consultant Inspirata - \$/Stock
- Consultant and SAB Philips - \$
- SAB XiFin - \$

Two studies performed in clinic

- Pivotal study:
 - assessing accuracy

- Instrument precision:
 - assessing repeatability and reproducibility

Study design

Primary Objective

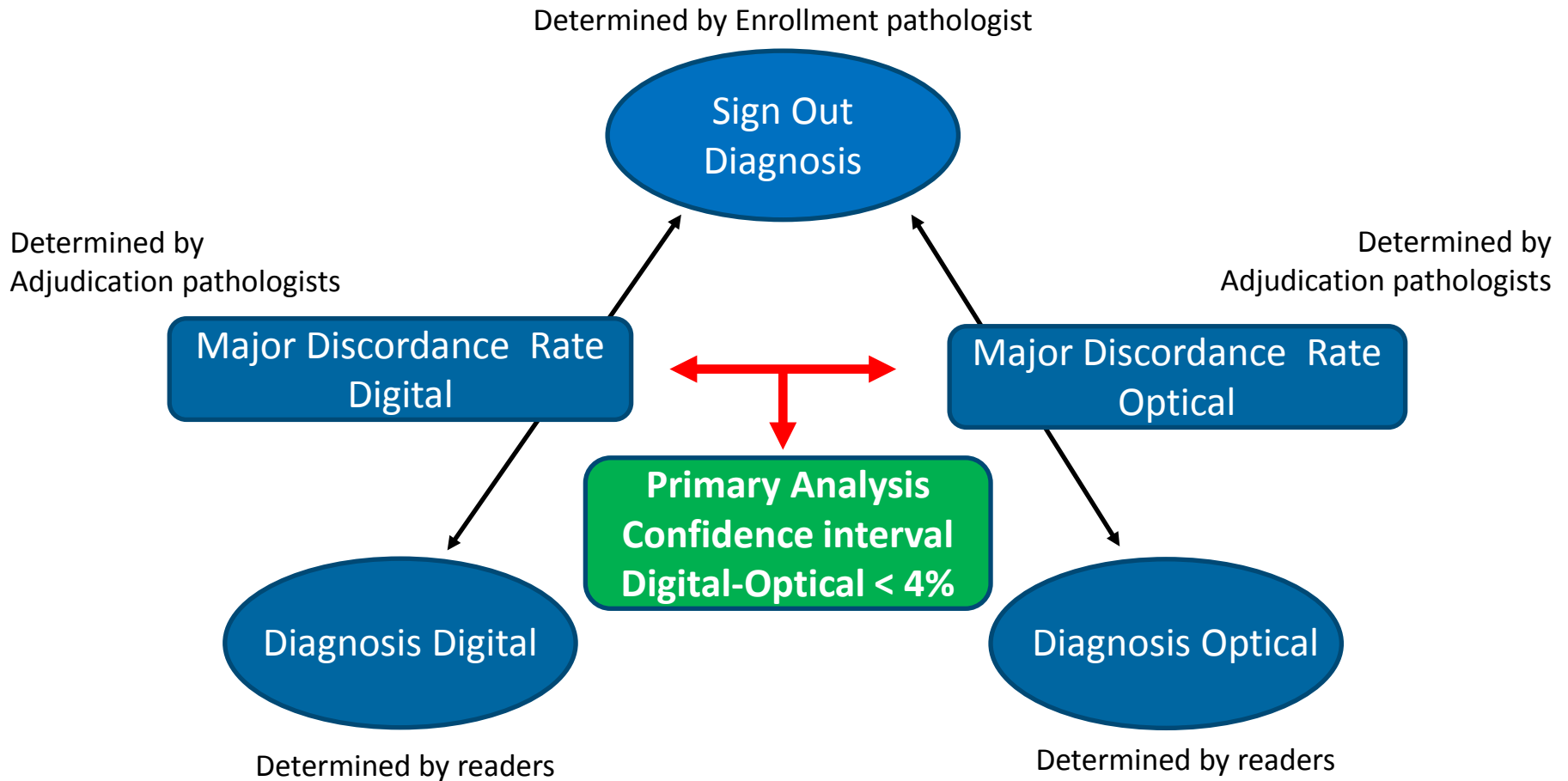
The primary objective is to demonstrate that viewing, reviewing and diagnosing surgical pathology tissue slides by using PDx is non-inferior to using optical microscope.

The Digital modality (MD) will be declared non-inferior to the Optical modality (MO) if the upper bound of the 95% two-sided confidence interval for the MD – MO difference in Major Discordance Rate is less than 4%.

Definitions

- Major discordance rate:
 - Proportion of major discordances between
 - » the optical diagnoses and the sign out diagnosis
 - » the digital diagnoses and the sign out diagnosis
- Major Discordance
 - A difference in diagnosis that would be associated with a significant difference in patient management.

Study Design: non-inferiority



Overall Clinical Study Design

- 2 000 cases to be included from pre-defined list.
- Four sites
 - Mixed profile to reflect clinical practice
 - 2000 cases will be divided over sites
- Per site:
 - One enrollment pathologist for selection of main diagnosis and case/slide selection
 - One validation pathologist for validation of slide selection
 - Four reading pathologists for case reading
 - Read both MO and MD
 - Four week washout between MO and MD reads
 - Read all cases at site
- Central adjudication panel (n=3) to determine concordance
 - Sign-out diagnosis is clinical reference to determine concordance.
 - Adjudication panel (3 members) will review all cases from all sites independently.
 - Majority vote.
 - Three step approach
 - Step 1: two adjudicators
 - Step 2: third adjudicator
 - Step 3: panel review

Adjudication example - Adrenal

A - Benign

Adrenal cortical adenoma

Nodular cortical hyperplasia with dominant nodule

Benign adrenal tissue with multiple micronodules

Macronodular adrenal tissue with a dominant nodule

B - Pheochromocytoma

C - Malignant Carcinoma

Metastatic poorly differentiated carcinoma, consistent with prostatic origin

Concordant	Major Discordant
within A	between A and B
within C	between B and C
	Margins +/-
	Lymph nodes +/-

Adjudication data structure

Case	Pathologist															
	A								B							
	Method								Method							
	MD				MO				MD				MO			
	AR 1	AR 2	AR 3	final score	AR 1	AR 2	AR 3	final score	AR 1	AR 2	AR 3	final score	AR 1	AR 2	AR 3	final score
1	1	1	.	1	2	2	.	2	3	3	.	3	1	1	.	1
2	2	1	2	2	2	1	2	2	1	1	.	1	1	1	.	1
3	1	1	.	1	1	1	.	1	1	1	.	1	1	1	.	1
4	1	1	.	1	1	3	2	2	1	1	.	1	2	3	3	3
5	2	2	.	2	2	2	.	2	1	1	.	1	2	2	.	2
6	1	1	.	1	1	1	.	1	1	1	.	1	1	1	.	1
7	1	1	.	1	1	1	.	1	1	1	.	1	1	1	.	1
8	1	2	2	2	1	1	.	1	1	3	2	2	1	1	.	1
9	1	1	.	1	1	1	.	1	1	1	.	1	1	1	.	1
10	1	2	2	2	1	2	2	2	2	2	.	2	1	1	.	1

1 = Concordance
 2 = Minor Discordance
 3 = Major Discordance

Number of Cases needing 3rd Adjudication

- MD: 772 out of 7964 readings = 9.7%
- MO: 760 out of 7961 readings = 9.5%

Needing 3rd adjudication involving a major discordance:

- MD: 325 out of 7964 readings = 4.1%
- MO: 333 out of 7961 readings = 4.2%

Overall Clinical Study Design

	Philips	CAP guidelines	Bauer paper
Number of cases	2,000	60 per application	607
Number of reads	16,000	120 per application	607
Number of reading pathologists	16	1	2
Number of sites	4	1	1
Enriched sample set	Yes	No	No

Case selection

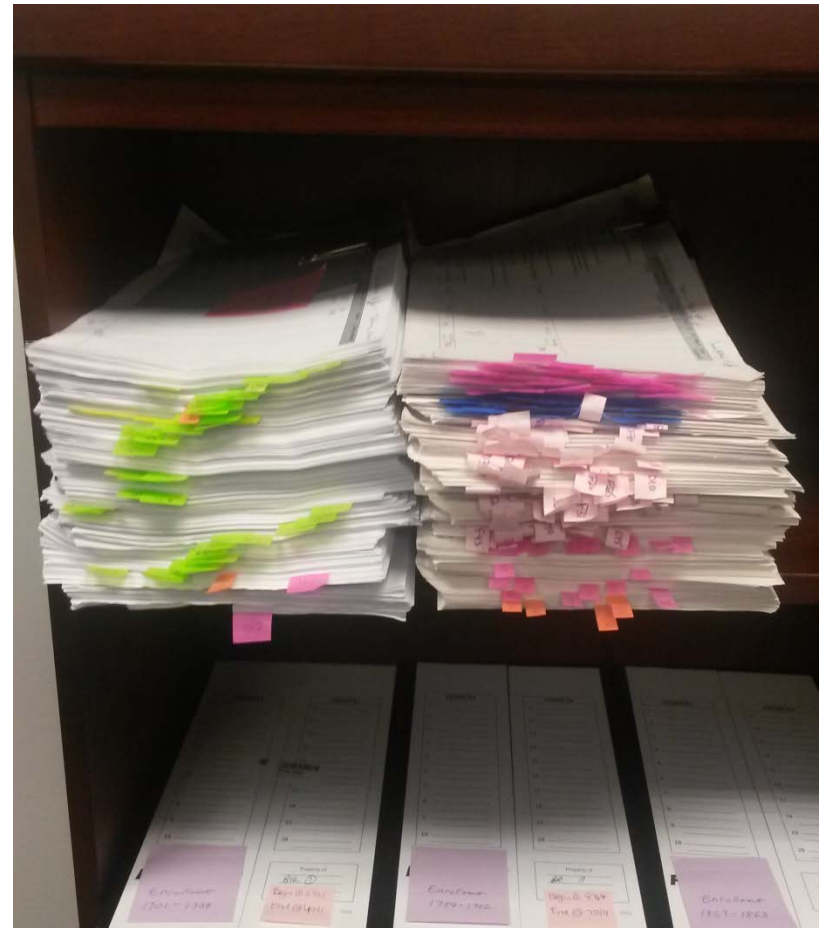
ORGAN TYPE	# OF CASES	SUBTYPES (procedures)	
		#	
BREAST	300	50	Benign/Atypical CNB
		50	Benign/Atypical Lumpectomy
		50	In-Situ Carcinoma CNB
		50	In-Situ Carcinoma Lumpectomy
		50	Invasive Carcinoma CNB
PROSTATE	300	50	Invasive Carcinoma Lumpectomy
		120	Benign Core Bx
		30	Benign Resection
		120	Adenocarcinoma Bx
		30	Adenocarcinoma Resection

ORGAN TYPE	# OF CASES	SUBTYPES (procedures)	
		#	
BREAST	300	50	Benign/Atypical CNB
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		50	Invasive Carcinoma CNB
PROSTATE	300	50	Invasive Carcinoma Lumpectomy
		120	Benign Core Bx
		30	Benign Resection
		120	Adenocarcinoma Bx
		30	Adenocarcinoma Resection

LUNG/BRONCHUS/Larynx/oral cavity/nasopharynx	100	25	Benign/Inflammatory Bx Only
		25	Dysplasia Bx Only
		30	Carcinoma Bx
		20	Carcinoma Resection
COLORECTAL	150	50	Benign/Inflammatory Bx
		50	Adenomas Including Severe Dysplasia Bx
		40	Adenocarcinoma Endoscopic Bx
		10	Adenocarcinoma Resection
GE Junction	100	50	R/O Barrett's/Dysplasia Bx
		50	Non-Neoplastic/Inflammatory Bx
Stomach	100	50	Inflammatory Including R/O H. Pylori Bx
		40	Polyps/ Neoplastic Bx
		10	Polyps/ Neoplastic Resection
SKIN	175	50	Non-Neoplastic/Inflammatory Bx
		50	Squamous/Basal Cell Neoplasms Bx
		75	Melanocytic Lesions Bx
LYMPH NODE	100	75	For Presence/Absence Of Metastasis
		25	Non-Neoplastic
(no micrometastases smaller than 0.5 mm)			
BLADDER	100	25	Benign/Inflammatory/Non-Neo Bx
		25	Dysplasia Bx
		25	Noninvasive Carcinoma (TUR Or Bx)
		15	Carcinoma TUR/Bx
		10	Carcinoma Resection
		5	
Gyn	150	50	Endometrial Bx/Curetting
		25	Cervix Bx/Curetting (Bx, ECC)
		25	Cervix Bx/Curetting (Cone/LEEP)
		20	Ovary Benign Neoplastic/Non-Neoplastic
		30	Ovary Malignant Neoplastic
LIVER/BD, NEO	50	40	Core Bx
		10	Wedge Bx or Resection
Endocrine	100	50	Pancreas
		30	Thyroid
		10	Parathyroid
		10	Adrenal
BRAIN/NEURO	60	10	Non-Neoplastic
		25	Neoplastic Bx
		25	Neoplastic Resection
KIDNEY, NEOPLASTIC	50	50	All Comers (Consecutive Cases)
		50	All Comers (Consecutive Cases)
		10	All Comers (Consecutive Cases)
		10	All Comers (Consecutive Cases)
		10	All Comers (Consecutive Cases)
		10	All Comers (Consecutive Cases)
		20	All Comers (Consecutive Cases)
		50	Bx
		15	All Comers (Consecutive Cases)
Miscellaneous to reach 2000		15	All Comers (Consecutive Cases)

The Great Wall of Project PDx:

4 sites – 27 pathologists - 16.000 Reads – 33.000 adjudications



Familiarization for reader

Familiarization program for readers

The recommended familiarization in the pivotal study was:

1. Review the Instructions for Use for PIPS
2. Selection of slides
3. Practice: Complete Practice set of cases
4. Self assessment: Upon completion of the practice session and preferably after a day washout period, complete the Self-Assessment set of cases
5. As needed, pull in cases from the Reserve set

Results

Primary analysis

Primary analysis

Difference in Major Discordance Rate = digital-optical

Left CI (95%)	Average	Right CI (95%)
-0.31%	0.35%	1.00%

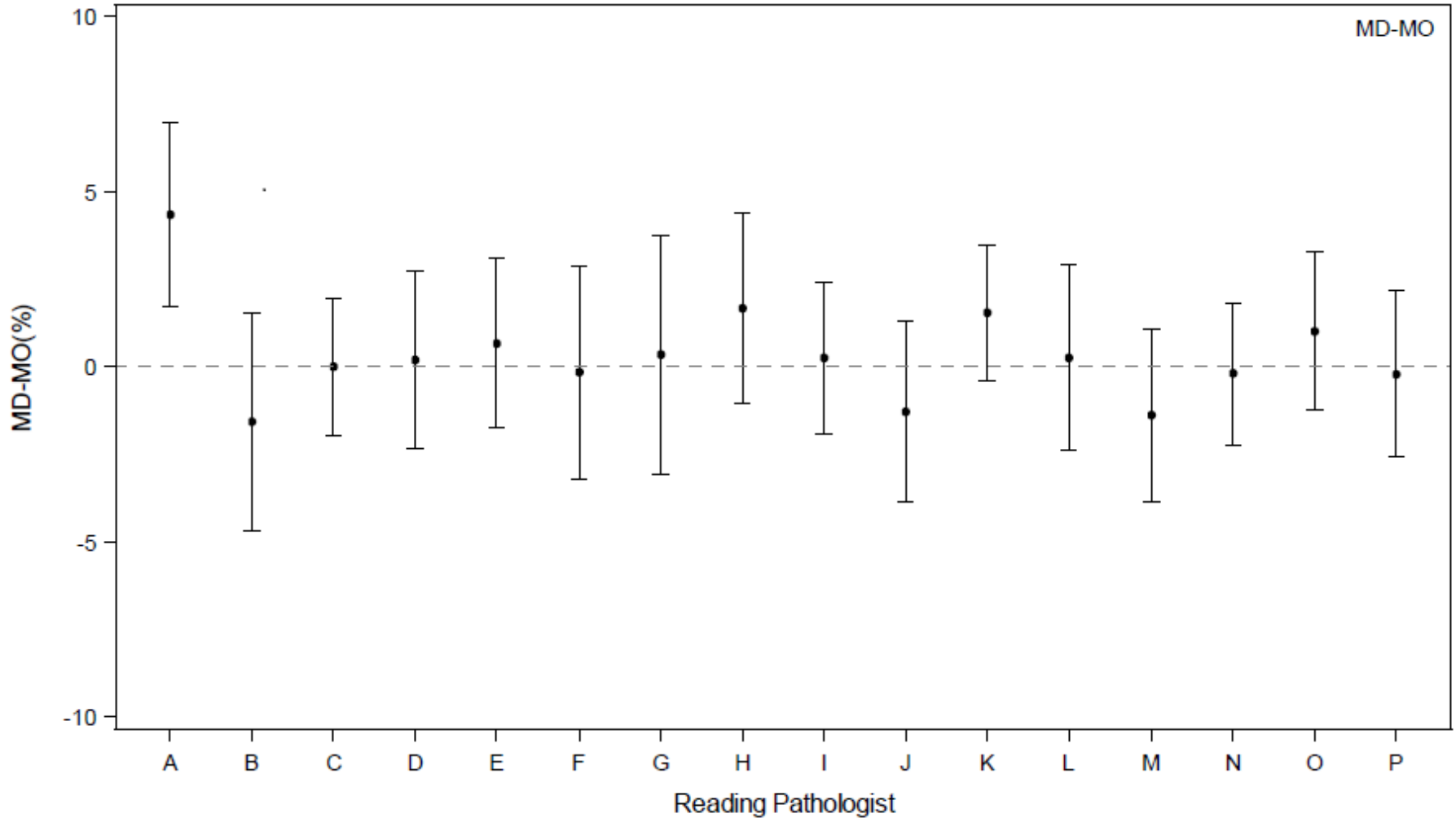
**Acceptance
criterion <4%**

Major Discordance rate

Digital n=7964		Optical n=7961	
Major discordance rate (%)	95% CI	Major discordance rate (%)	95% CI
4.7%	(3.3; 6.8)	4.4%	(3.0; 6.3)

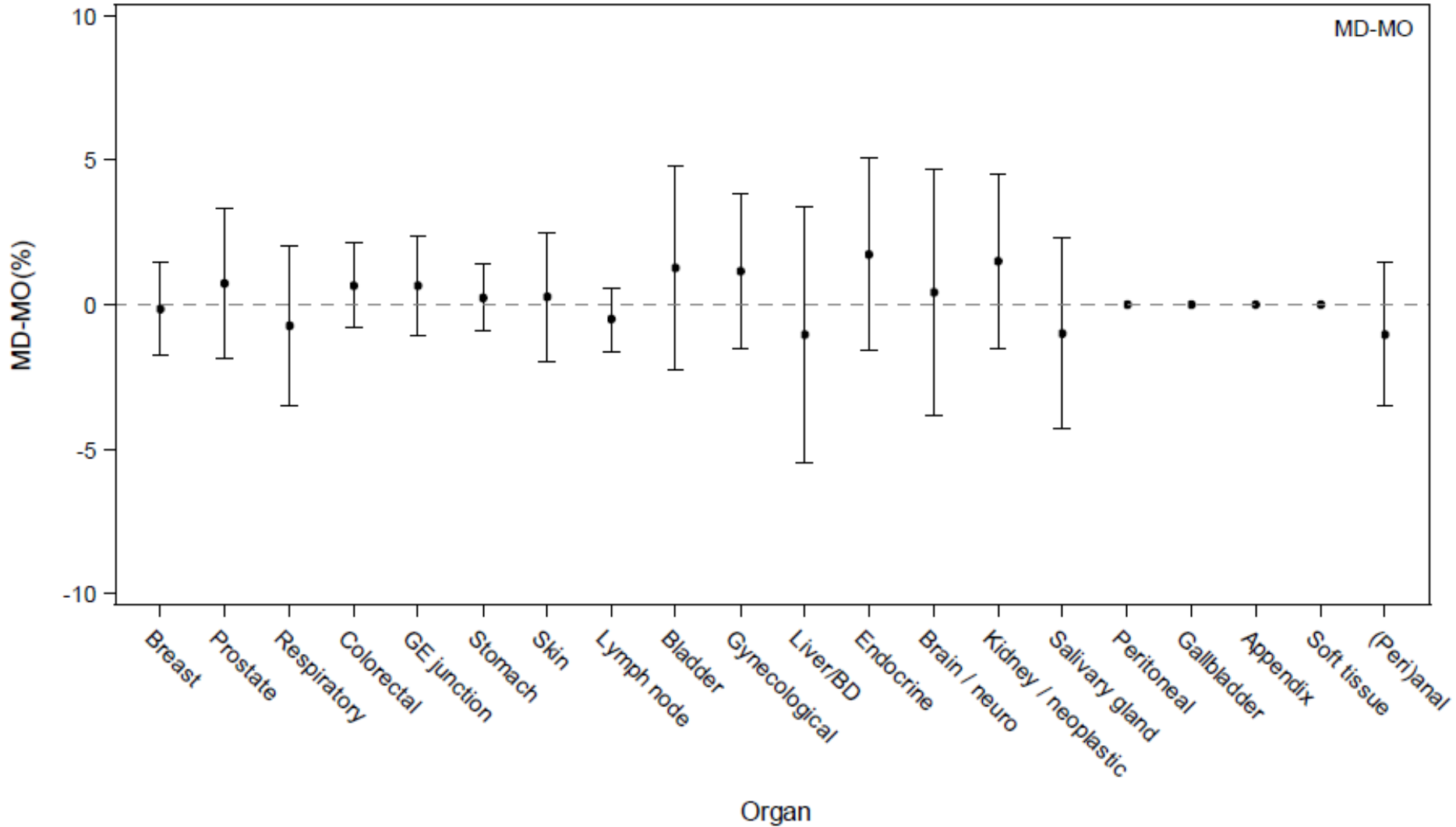
Results Per Reader

Difference Major discordance rates by reader



Results Per Organ

Difference Major discordance rates by organ



Timing of reads

Reading time (minutes) *	n	Mean	Median	Minimum	Maximum	Standard Deviation	Lower 95 % Confidence Limit for Mean	Upper 95 % Confidence Limit for Mean
Optical	7459	1.3	0.7	0.1	27.9	1.84	1.276	1.359
Digital	7459	1.4	0.8	0.1	27.2	1.74	1.355	1.434
Difference Digital - Optical	7459	0.1	0.0	-25.7	26.7	1.97	0.032	0.121

Conclusion:

**PIPS is comparable to
microscope**

Instrument Precision study

Assessing repeatability and reproducibility

Objectives

- This study was a feature study, meaning that it is about detecting features repeatedly and not about providing a diagnosis.

	Magnification		
	40 X	20 X	10 X
Study Features	Nucleolus	Reed Sternberg	Small artery
	Eosinophil granules	Polymorph neutrophil	Psammoma body
	Mitosis	Plasma cell	Keratin pearl
	Nuclear membrane	Goblet cell	Granuloma
	Cilia	Tingible body macrophage	Adipose Cell
	Prickles desmosomes	Foreign Body giant cell	Glandular formation
	Pigment laden macrophages	Lymphocyte	Necrosis

- The precision is based on the proportion of agreement of 3 repeated readings (agreement rate)

Design

Precision was assessed in three sub-studies:

1. Intra-System Precision Study
2. Inter-System Precision Study
3. Inter-Site Precision Study

- Per sub-study:

Acceptance criterion is 85% on the left hand limit of the 95% confidence interval of the overall agreement rate

Intra System Precision

- Each slide is scanned three times, each time on the same system
- Intra system precision is studied on three different systems
- Three reading pathologists, one site, 3591 reads, only digital

Results intra system precision

Left CI (95%)	Average	Right CI (95%)
90.6%	92.0%	93,3%

**Acceptance
criterion >85%**

Inter System Precision

- Slides are scanned three times, each time on a different system
- Inter system precision is studied on three different systems
- Three reading pathologists, one site, 3591 reads, only digital

Results inter system precision

Left CI (95%)	Average	Right CI (95%)
92.6%	93.8%	95.0%

**Acceptance
criterion >85%**

Inter Site Precision

- Slides are scanned three times, each time on a different site and system
- At each site there is a different system and a different reading pathologist
- Three reading pathologists, three sites, 1197 reads
- Review criterion

Results inter site precision

Left CI (95%)	Average	Right CI (95%)
87.9%	90.2%	92.4%

**Acceptance
criterion >85%**

Conclusion:

**Passed acceptance
criterion with a
substantial margin**

It takes a village!

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