

FDA Cytology Update

Marina Kondratovich, Ph.D.,
Associate Director for Clinical Studies,
OIVD, CDRH, FDA

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The Clinical Laboratory Improvement Act of 1988 (CLIA 88) provides that

- ❑ “individual workload limits must be established by the technical supervisor and based on individual capabilities/performance” and
- ❑ maximum workload limit for manual screening is 100 slides in no less than an 8-hour day

FDA approved two semi-automated screening devices:

- ❑ Hologic's ThinPrep Imaging System (TIS) for ThinPrep Pap slides and
- ❑ Becton Dickinson Focal Point Guided Screening System (BD) for SurePath Pap slides.

- For a Pap slide, TIS imaging algorithm identifies Field of View (FOV) (field of diagnostic interest).
- Cytotechnologist (CT) reviews the FOV.
 - If no abnormality is identified during FOV review and there are no specimen adequacy limitations, then slide is Negative.
 - If abnormal cells or specimen adequacy limitations are identified during FOV review, the CT performs a Full Manual Review (FMR).

Each device has its own maximum workload limit (200 slides for TIS and 170 slides for BD) that was determined during the course of clinical studies for evaluation of diagnostic accuracy and workload limits.

It was brought to FDA attention that the current product labeling regarding workload for these two devices has been difficult to interpret resulting in variability and lack of standardization in counting methods.

FDA together with CMS investigated this issue and determined that the following method for calculation of workload should be used

(Lab Tips is published on the FDA website on July 27, 2010) .

- ❑ All slides with full manual review (FMR) count as 1 slide (as mandated by CLIA'88 for manual screening)
- ❑ All slides with field of view (FOV) only review count as 0.5 or ½ slide
- ❑ Then, slides with **both** FMR and FOV count as 1.5 or 1½ slides
- ❑ Use these values to count workload, not exceeding the CLIA maximum limit of 100 slides in no less than an 8-hour day.

FMR = 1 slide
FOV = 0.5 slide
Both FMR + FOV = 1.5 slides
Upper Limit = 100 slides

- ❑ Why there were difficulties in interpretation of labeling;
- ❑ Why approach with counting of slides with weights of 0.5 and 1.5 is safe.

Design of Pivotal Clinical Study

TIS

Basic Characteristics of Clinical Pivotal Study:

- ❑ 4 cytology laboratories in the US
(two CTs at each site)
- ❑ Accuracy of “Manual” screening was compared to accuracy of screening with TIS;

- ❑ 9,544 slides were reviewed manually
- ❑ Then wash-out period (at least 8 weeks)
- ❑ Then 9,544 slides were reviewed with TIS by the same CT and pathologists

		Manual		
		Abnormal	Negative	
TIS	Abnormal	513	254	767
	Negative	227	8,550	8,777
		740	8,804	9,544

		Manual		
		Abnormal	Negative	
TIS	Abnormal	513	254	767
	Negative	227	8,550	8,777
		740	8,804	9,544

513 slides (abn-abn)
 254 slides (neg-abn)
 227 slides (abn-neg)
 5% of 8,550 (neg-neg)=
 428 slides



3 Independent
 Pathologists
 (majority rule)

Adjudicated result = “Gold” Standard

Diagnostic accuracies of “Manual” and “TIS” were estimated and compared

For Manual arm and for TIS arm:

- Each day number of slides and number of hours were recorded; a slide was counted as **one** slide regardless whether FOV only or in addition FMR
- Data for days with number of hours < 4 were deleted from calculations of workload data;
- If CT showed a decrease in accuracy, the CT data should be deleted from calculation of the workload data.

❑ In the TIS arm of the study, **22%** of slides in average were reviewed manually after FOV review

Prevalence of ASC-US+ (by Gold standard)=7.3%

Prevalence of LSIL =2.4%;Prevalence of HSIL=1.5%

In the study,

- CT reviews only FOV (it does NOT allow to do even a quick check outside of FOVs);
- if FOV does not have abnormal findings, CT is NOT allowed to do a full review.

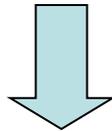
OTHERWISE estimation of TIS accuracy will be BIASED (overestimated).

200 slides per 8 hours is

1) An upper limit of workload
(it is NOT a productivity level);

Productivity is a different concept (a worker can work in an optimal way for a very long period of time).

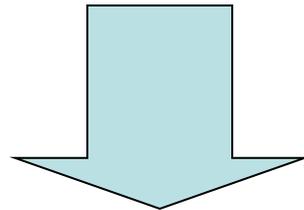
2) It is an upper limit only if 22% of slides in average were manually reviewed after FOV review.



Percent of slides with FMR depends on

- Prevalence of abnormal slides;
- Prevalence of UNSAT
- Lab Policy for full review of slides
(as high risk slides);
- Skills of CT,
- Other

The upper workload limit can be easily calculated if the percent of slides which require full review is higher than 22%.



□ There is an upper limit of 100 slides for manual review during 8 hours; it means that 100 slides with manual review require at least 480 minutes ($60 \text{ min} * 8 \text{ hours}$). So, each slide with only manual review requires 4.8 min ($480/100=4.8$).

□ In the study, 22% of slides in average required manual review. It means that 44 slides in average among 200 slides required manual review.

211.2 minutes ($4.8 * 44$) were spent for these slides.

□ For 200 FOV, CT has 268.8 minutes ($480-211.2$)

❑ Slide with FOV review only requires not less than 1.4 minutes ($268.8/200=1.344$)

❑ In the study, slide with FOV review and then full manual review requires not less than 6.2 minutes ($4.8+1.35=6.15$)

Let **X** be a number of slides with full review with FOV and **Y** be a number of slides with FOV review only, then for 8 hours:

$$6.15 * X + 1.35 * Y = 480 \text{ minutes}$$

or

$$1.28 * X + 0.28 * Y = 100 \text{ slides}$$

Upper limit for the total number of slides is **X+Y**

Example:

X=60 - number of slides with manual review with FOV;

$$60 * 6.15 + 1.35 * Y = 480 \Rightarrow Y = 82$$

Y=82 – number of slides with FOV review only.

Total number of slides 142 (=60+82)

**Upper limit of the total number of slides =
142 (not 200)**

Normal flow of slides:

- Total number=142;
- Among them, 42.3% (60/142) are slides with manual review with FOV (not 22%).

BD FocalPoint GS Imaging System

- ❑ Similar study design

Differences

- ❑ Prevalence of ASC-US+ was 14.8%
- ❑ In the study, 31% of slides in average required manual review.
- ❑ Upper limit of workload is 170 slides per 8 hours

Similar calculations for BD:

Let **X** be a number of slides with full review with FOV and
 Y be a number of slides with FOV only review,
then for 8 hours:

$$6.15 * X + 1.35 * Y = 480 \text{ minutes}$$

or

$$1.28 * X + 0.28 * Y = 100 \text{ slides}$$

Note: same formula for two independent clinical studies

Lab X Workload Recording SOP

□ Lab X Workload Recording SOP counts a TIS slide once, whether FOV review only was or the slide was screened manually after FOV review.

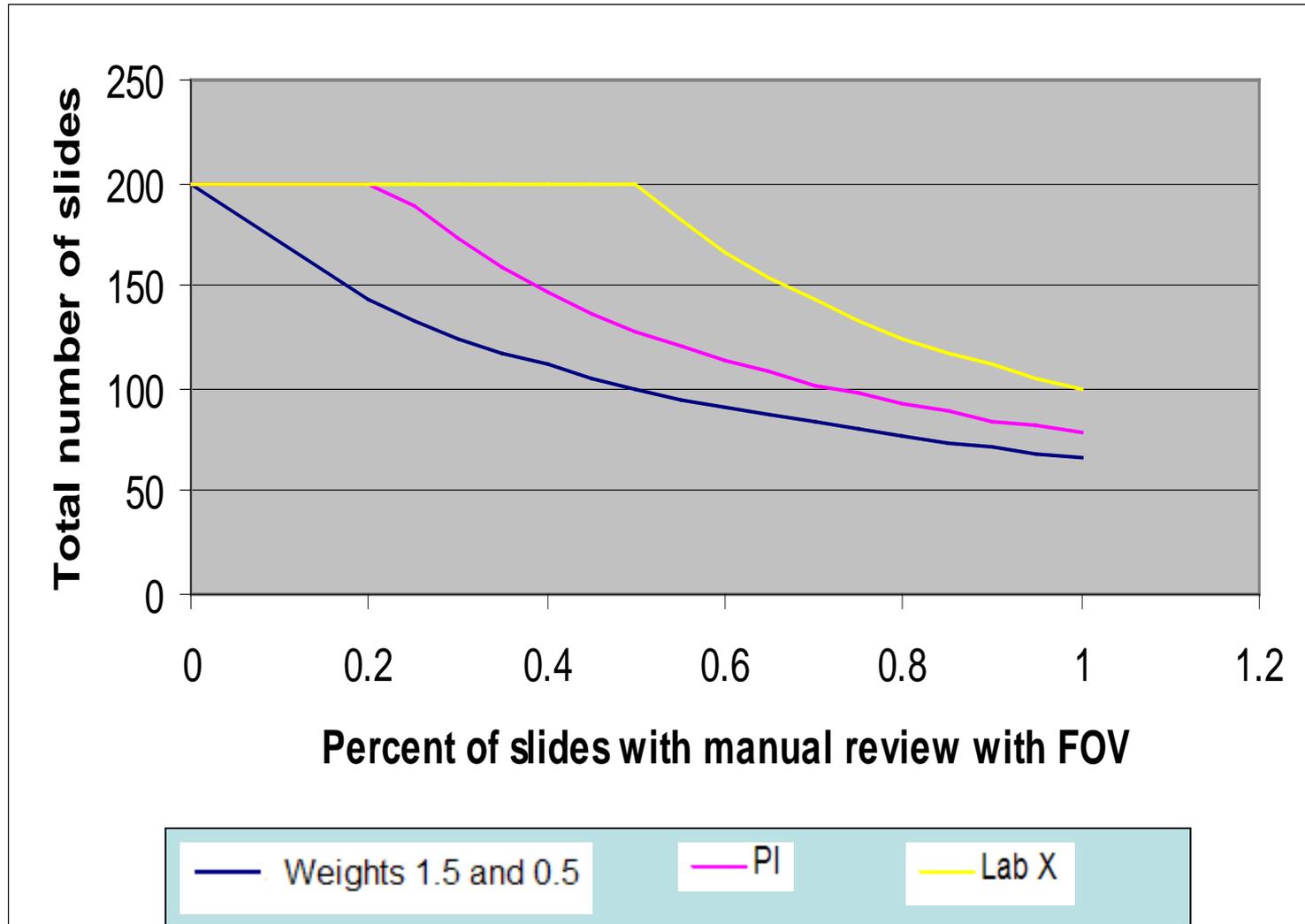
Let X be a number of slides with manual review with FOV and Y be a number of slides with FOV review only, then for 8 hours:

$$X + Y \leq 200 \text{ and } X \leq 100$$

This formula is correct ONLY if the percent of manual review slides with FOV is less than 22% (as in the clinical study).

It is WRONG to use this formula for percents larger than 22%.

Relationships of the total number of slides vs percent of slides with manual review with FOV for 8 hours



Relationships of the total number of slides vs percent of slides with manual review with FOV for 8 hours

Percent of slides which require manual review with FOV in average	Upper limit for total number of slides based on Clinical Study	Upper limit for total number of slides with weights 0.5 and 1.5	Upper limit for total number of slides Lab X
20%	200	142	200
25%	188	133	200
30%	172	125	200
40%	147	111	200
50%	128	100	200
60%	113	90	166
70%	102	83	142
80%	92	76	125
90%	84	71	111
100%	78	66	100

Diagnostic Accuracy

Diagnostic accuracy

Results of the pivotal clinical study for TIS

	Sensitivity (ASC-US+)	Specificity (Neg)
Manual	75.6%	97.6%
TIS	82.0%	97.8%

	Frequency of ASC-US/AGUS for “Negative” result	Frequency of LSIL+ for “Negative” result
Manual	1.62%	0.30%
TIS	1.20%	0.22%



Statistically significant improvement

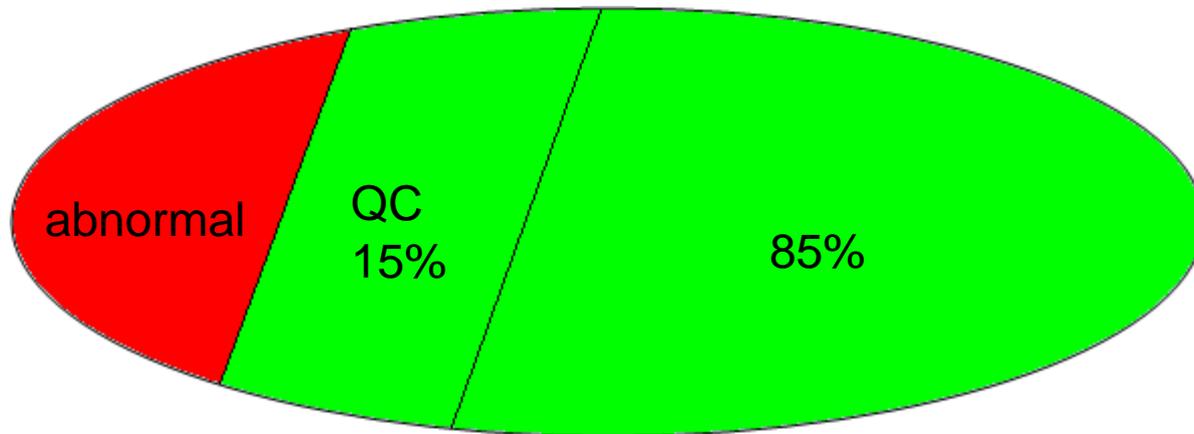


Not statistically significant difference

Discrepancies among QC slides

Source of data: CMS

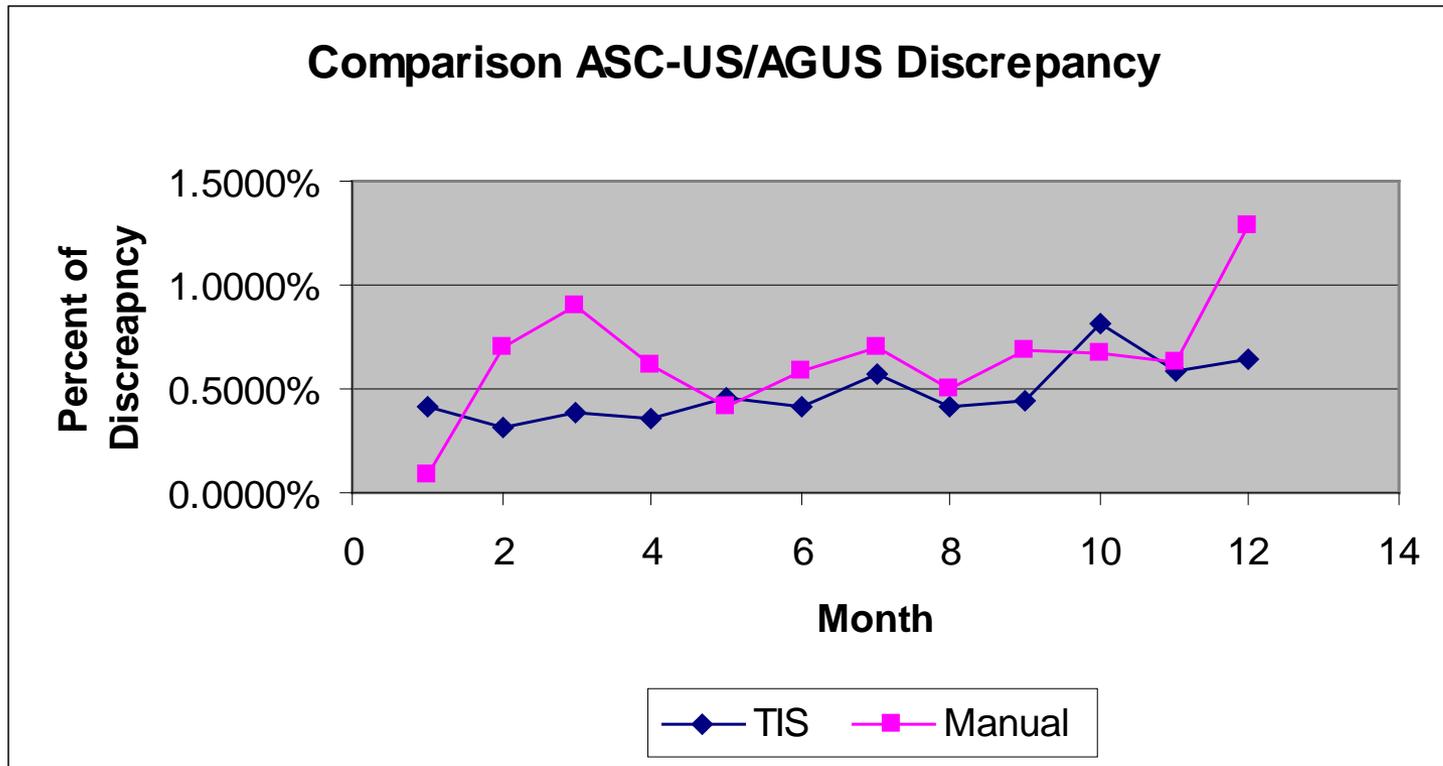
Data for 2009, January-December



Description of QC Data

	TIS	Manual	Total
Total number of slides	454,819	378,904	833,723
Total number of QC slides	72,925	51,748	124,673
Percent of QC slides	16.03%	13.66%	14.95%
Number of ASC-US/ AGUS Discrepancy	356	320	676
Number of LSIL+ Discrepancy	96	77	173

ASC-US/AGUS Discrepancies



Percent of Discrepancy in Average	TIS	Manual Method
ASC-US/AGUS	0.4882% (356/72925)	0.6184% (320/51748)

ASC-US/AGUS Discrepancies

Manual: 0.618% (320/51,748)

TIS: 0.488% (356/72,925)

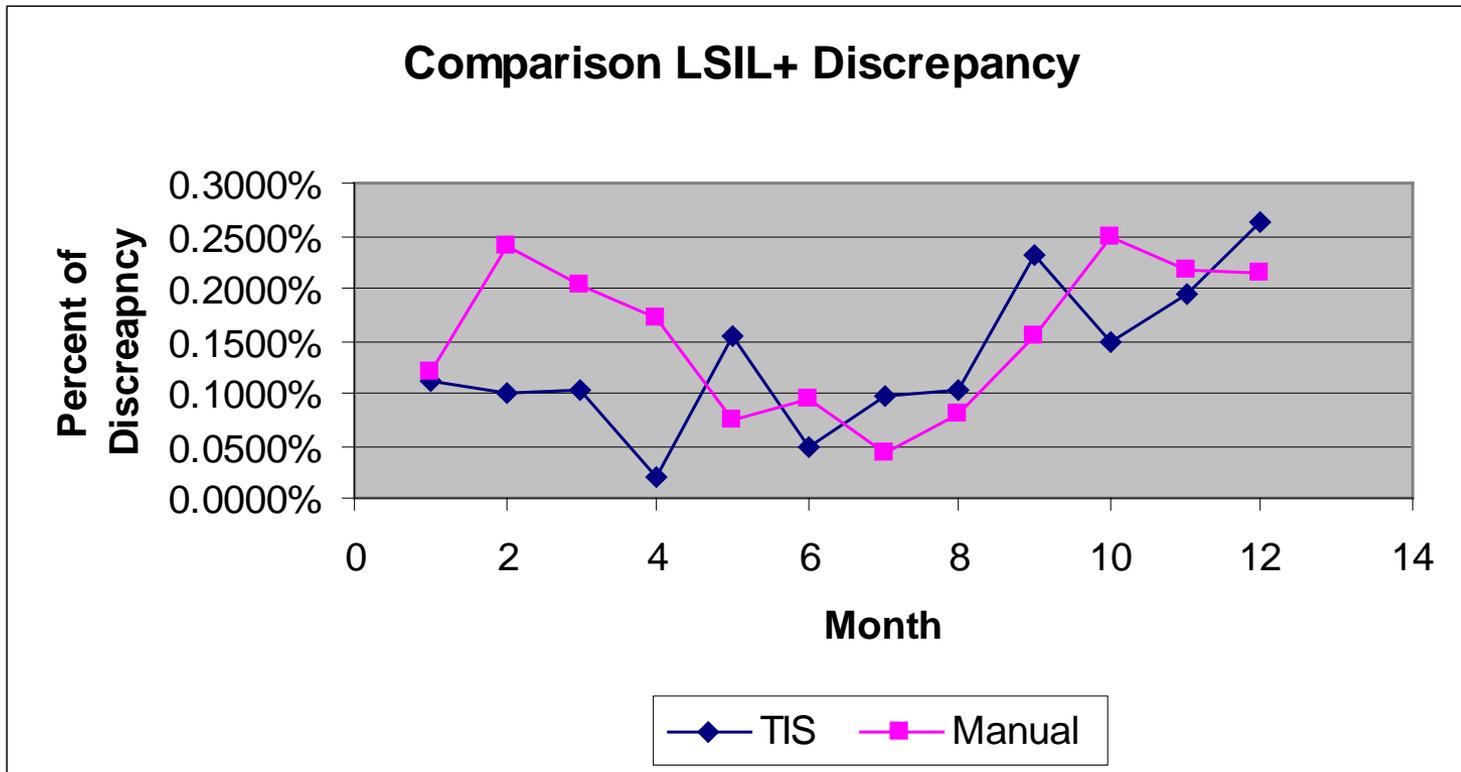
Difference: 0.130%

95% CI: 0.047% to 0.216%

Statistically significant

- TIS was better than Manual method in average
- TIS was better than Manual method for 9 out of 12 months

LSIL+ Discrepancies



Percent of Discrepancy in Average	TIS	Manual Method
LSIL+	0.1316% (96/72925)	0.1488% (77/51748)

LSIL+ Discrepancies

Manual: 0.149% (77/51,748)

TIS: 0.132% (96/72,925)

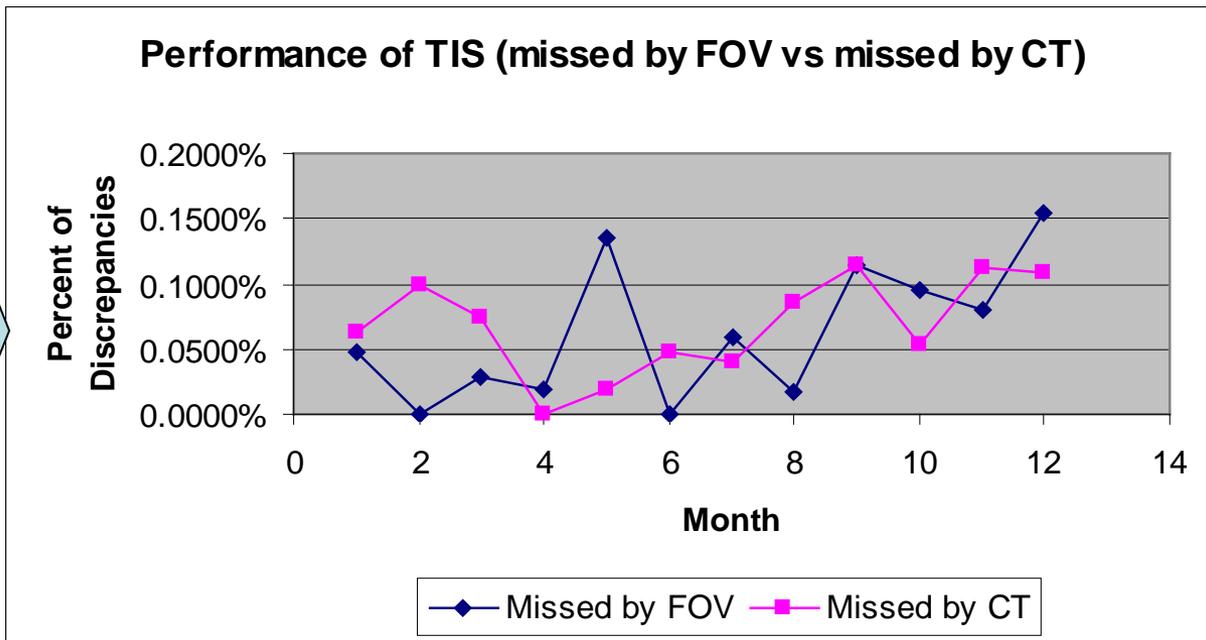
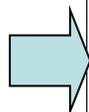
Difference: 0.017%

95% CI: -0.024% to 0.061%

Not statistically significant

- It was observed that TIS was better than Manual method in average but this difference can be explained by chance alone (not stat. sign.)
- It was observed that TIS was better than Manual method for 7 out of 12 months

**TIS:
LSIL+
Discrepancies
– More
Detailed
Presentation**



Percent of Discrepancy in Average	TIS		Manual
LSIL+	0.1316% (96/72925)		0.1488% (77/51748)
	Missed by FOV	Missed by CT	
	0.0617% (45/72925)	0.0699% (51/72925)	
	46.9%	53.1%	

Summary About Diagnostic Accuracy

Hologic ThinPrep Imaging System Discrepancies

	LSIL+		ASC-US/AGUS	
	TP- Imaging	TP- Manual	TP- Imaging	TP- Manual
Clinical Study (4 sites)	0.22%	0.30%	1.20%	1.62%
	Not stat. significant		Stat. significant improvement	
QC data	0.13%	0.15%	0.49%	0.62%
	Not stat. significant		Stat. significant improvement	

Summary

- ❑ Upper limit of 200 provided in the PI is estimated based on the clinical study with 22% of manual review with FOV in average (170 slides with 31%);

Laboratories have different percents of manual review (because of different prevalence, lab policy, CT skills and so on); therefore, the upper limit of 200 cannot be applied directly to laboratories.

- ❑ Recommended counting approach for the two FDA-approved devices with weights of 0.5 for FOV only review slide and 1.5 for slide for FOV+FMR slide is a safe approach;

Summary

- ❑ Upper limit of workload is NOT productivity/norm; productivity for each individual should be established by technical supervisor;
- ❑ Additional post-market data did not demonstrate a different performance compared to the clinical study performance;
- ❑ FDA will work on labeling changes with Hologic and BD.

Counting Approach for two FDA approved devices:

- ❑ All slides with full manual review (FMR) count as 1 slide (as mandated by CLIA'88 for manual screening)
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Upper Limit = 100 slides

X - number slides with FMR+FOV,
Y - number slides with FOV
Z - number slides with FMR

$$1.5 X + 0.5 Y + Z \leq 100$$

Thank you!

Questions?