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Latest Development in Pathology AI

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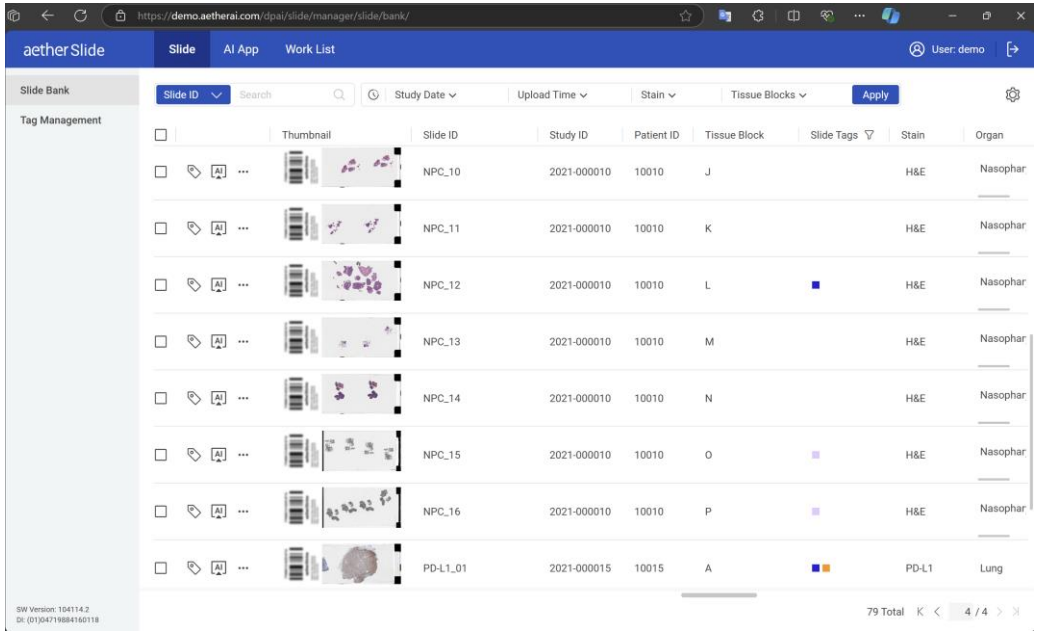
Outlines

- Digital Pathology System
- Pathology AI Diagnostic Support
  - IHC Quantification
  - Gastric Biopsy Triage
  - Lymph node metastasis detection
  - Cancer detection on frozen section

Digital Transformation for Pathology

- From chaos to order?



- Order doesn’t necessarily mean efficiency !
- AI provides the long-awaited help for pathologists.

IHC Quantification

- Background:
  - Pathologists have to report on the percentage of cells stained positive for many biomarkers (e.g. Ki-67, ER, PR, HER2, PD-L1, etc.) on a daily basis.
  - Traditionally, pathologists make their diagnosis by looking at the specimen through eyepieces of a microscope and making mental notes
  - The traditional method yields highly variable results between different pathologists

Ki-67 Immunohistochemistry(IHC) Image

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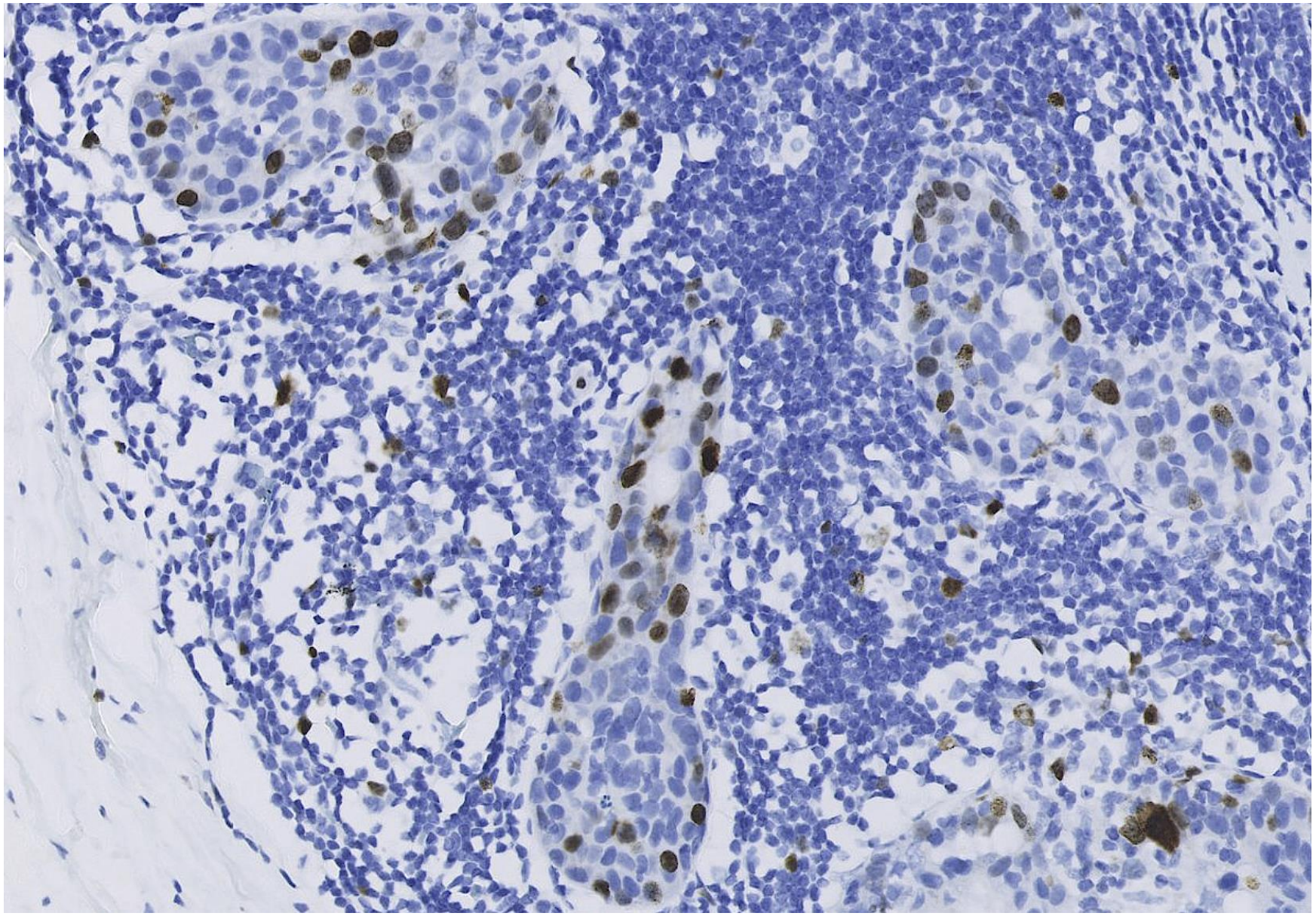
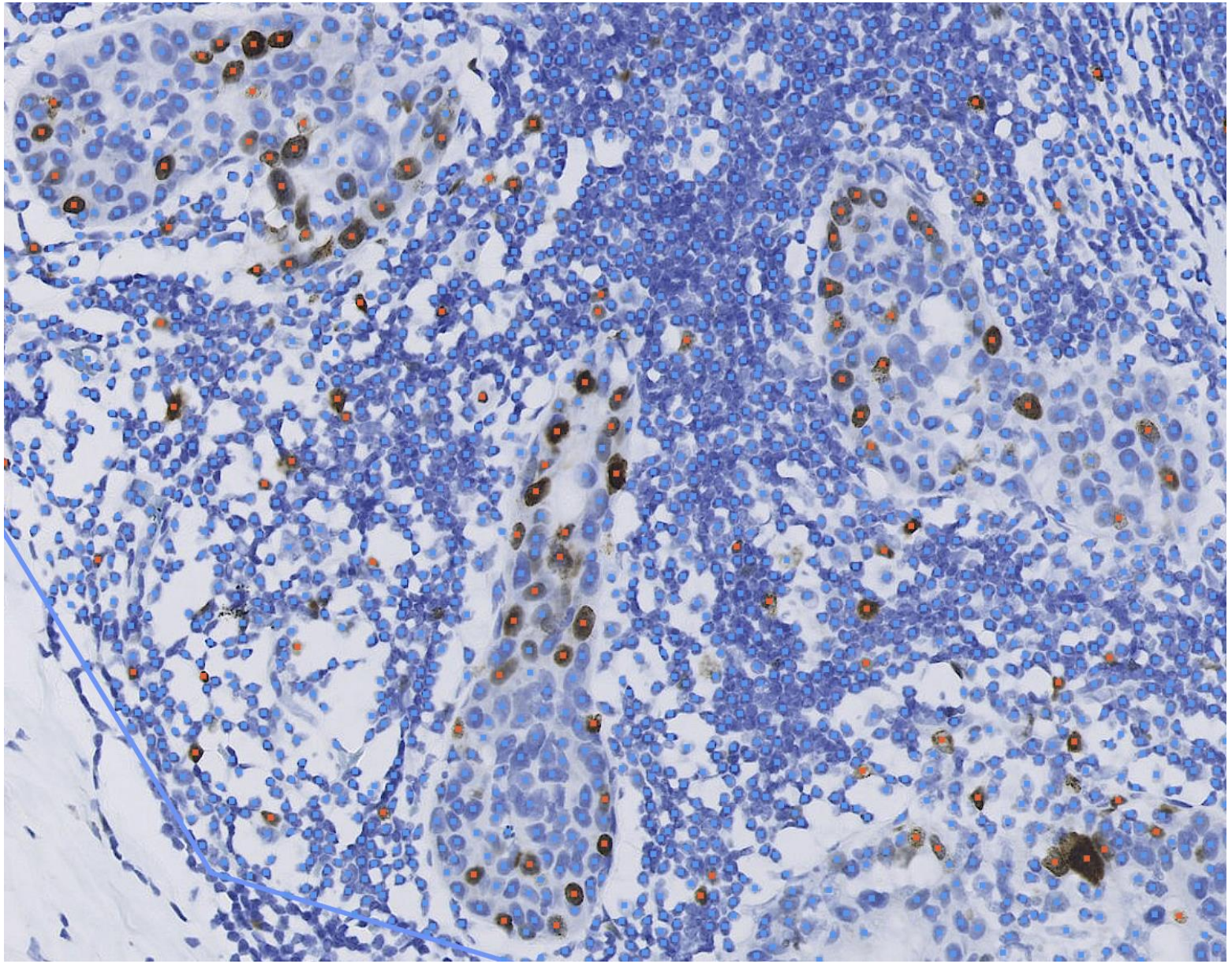


AI-Assisted IHC Quantification

- Two approaches
  - AI detects and classifies individual nucleus as being positive or negative for staining (the end-to-end black-box approach)
  - 1) AI detects individual nucleus, 2) nuclei are sorted according to color composition from brown to blue using traditional image processing methods, 3) a threshold is set by human expert to differentiate between positive and negative staining

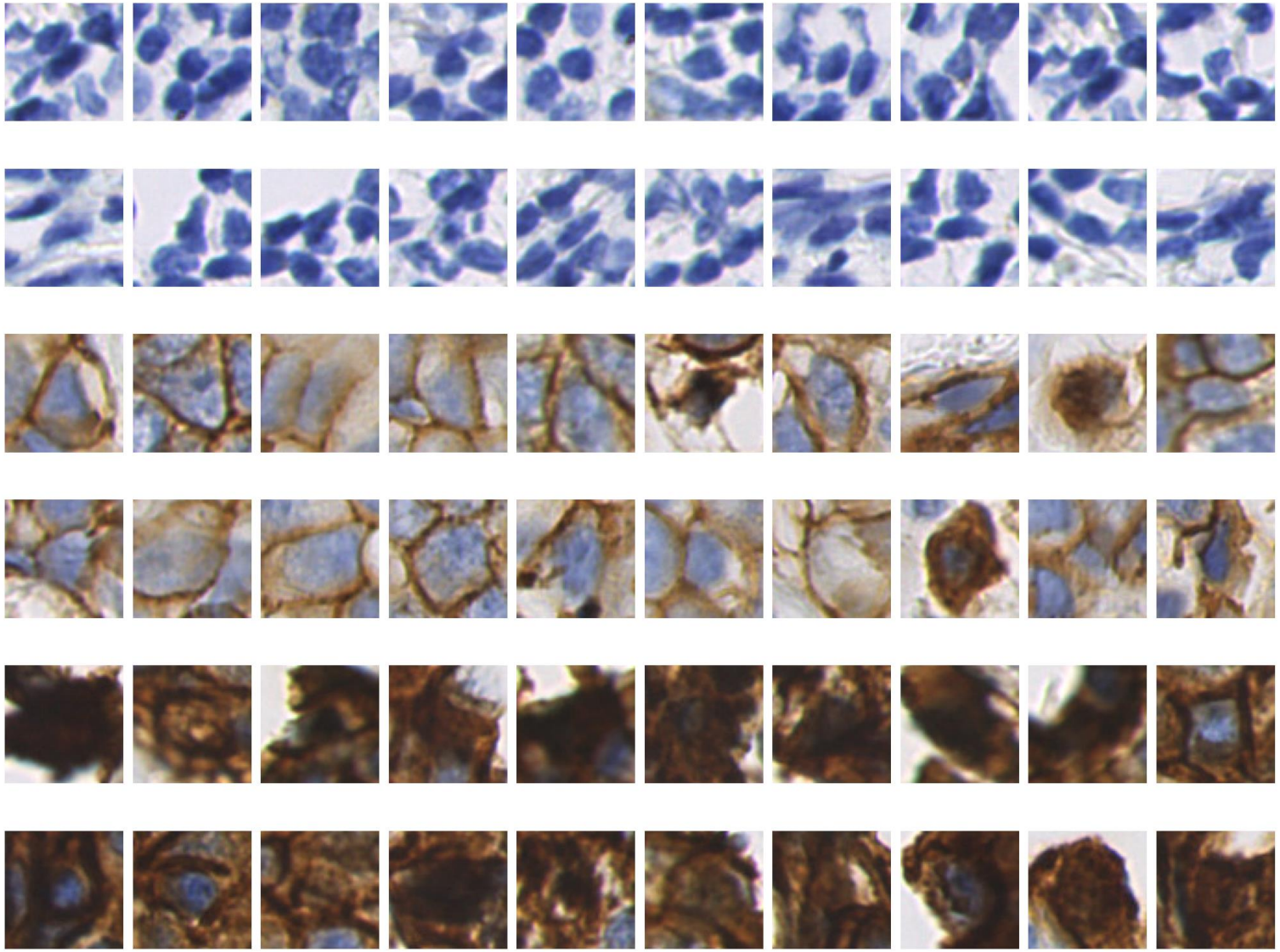
AI-Assisted Ki-67 Quantification

Black-box approach for nucleus detection and classification



Traditional image processing methods for color pattern ranking

Algorithm for color separation and ranking



Issues:

- With the end-to-end black-box approach, how should the AI be regulated? What gold standard should be used when validating AI's performance? Can the traditional method be used as gold standard even if it's known to be not accurate?
- Should traditional image processing methods be regulated if it is a well-known process and generates predictable and understandable results?

Gastric Biopsy Screening

- Background:
  - Pathologists have to review a large quantity of gastric biopsies
  - Most gastric biopsies are negative (Positive rate ~1%)
  - Small lesions (e.g. Signet ring cells) can be easily missed

AI-Assisted Biopsy Screening(Triage)

- AI Model:
  - Deep neural network trained on ~10,000 whole slide images at 20billion pixel resolution to perform classification
  - AUROC for cancer classification is 0.9971
- AI-assisted biopsy review workflow
  - We choose a threshold for the AI so its negative predictive value is 1.00, and its positive predictive value is 0.315
  - AI performs first reads, pathologists review only cases identified as positive by AI

Performance of AI vs Human in gastric biopsy screening

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- Test set: 2957 cases, 60 positive, 2897 negative
- Human performance (double review):
  - sensitivity: 96.7%, specificity: 100%, PPV: 100%, NPV: 99.9%

	Criteria / Thres.	Sensitivity	Specificity	PPV	NPV
Bag of MLPs 20x	SE >= .9 thres. = .01584	.9138	.9952	**.7910**	.9983
	PPV >= 0.6 thres. = 2.662e-3	**.9310**	.9879	**.6067**	.9986
	SE = 1 NPV = 1 thres. = 8.740e-5	1.0000	**.9565**	.3152	1.0000

- Double AI reading? High specificity review followed by high sensitivity review

The Best Way to Use AI for Gastric Biopsy Screening?

- AI performs first reads and pathologists review only cases that are classified by AI as positive
  - Considering average positive rate for gastric biopsy is 1%
  - For the AI that has a PPV of 0.315, pathologists will only have to review <4% of total cases because the AI has a total false positive to true positive ratio of 2.17 (for every true positive case, it will report additional 2.17 positive cases)

$$\frac{1}{PPV} = \frac{True\ Positive\ +\ False\ Positive}{True\ Positive}$$

  - Of the cases classified by AI as negative, there is only a very small chance (0.1%) to miss cancer.

Issues:

- Can AI be trusted to perform reading alone?
- If AI is more accurate than humans in terms of identifying negative cases, why can’t we trust AI to perform the reading alone?
- If we cannot trust AI to perform readings along, how can AI be useful and re-imbursed?
- Under what circumstances can AI be trusted to perform readings alone?

Lymph node metastasis detection

- Background:
  - Diagnosis of lymph node metastasis is a crucial task in cancer staging and constitutes a significant workload
  - Diagnosis of micro-metastasis(<2mm) and isolated tumor cells(<0.2mm) are challenging
  - Diagnostic sensitivity of lymph node metastasis is between 30% and 80% for pathologists

Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women with Breast Cancer

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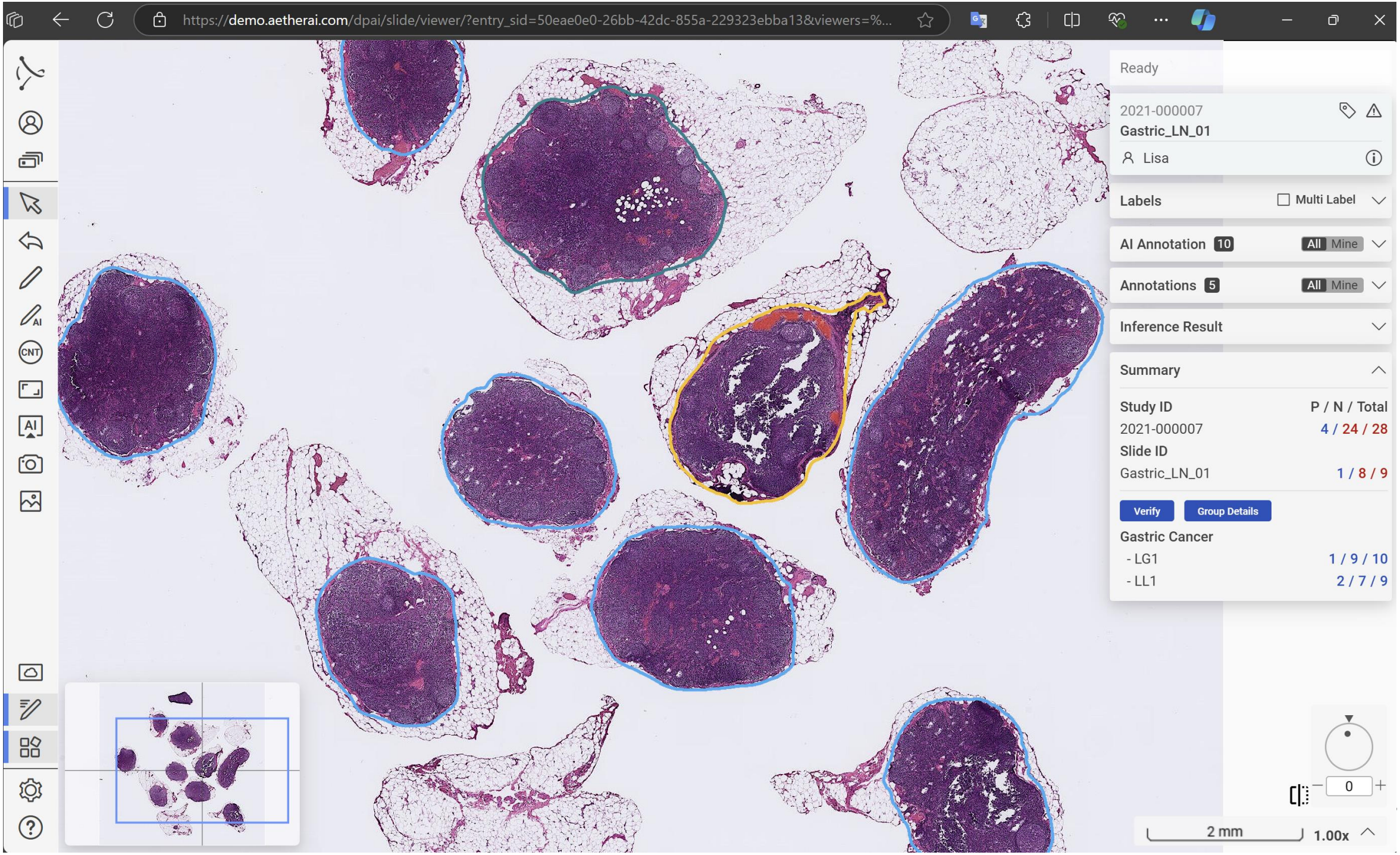
- JAMA. 2017;318(22):2199-2210
- 11 pathologists participated in the test with time constraint on 129 test slides using traditional microscope
  - 1 3rd-yr resident pathologist and 10 practicing pathologists (mean yrs in practice:16.4)
  - Ground truth of the test set is established by expert opinion and immunohistochemistry
  - Participants asked to finish the task within 120 minutes (range: 72-180min)
- Results
  - **Human:**
    - Macro-metastases: mean sensitivity: 92% (95%CI: 90.5%-98.5%)
    - Micro-metastases: mean sensitivity: 38.3% (95%CI: 32.6%-52.9%, best: 62.9%)
    - **Average: Area under curve: 0.810**
  - (**Human without time constraint: average AUC: 0.966**, 1 pathologist, 30 hours)
  - **AI: Average: Area under curve: 0.994**

AI-Assisted Diagnosis of Lymph Node Metastasis

- AI Model:
  - 1st deep neural network trained to segment individual lymph nodes within a whole slide image
  - 2nd deep neural network, trained on ~6000 lymph node images, classifies individual lymph node into being positive or negative for metastasis. AUROC: 0.99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Ready
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Summary
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Verify
Group Details
Gastric Cancer
- LG1
1 / 9 / 10
- LL1
2 / 7 / 9
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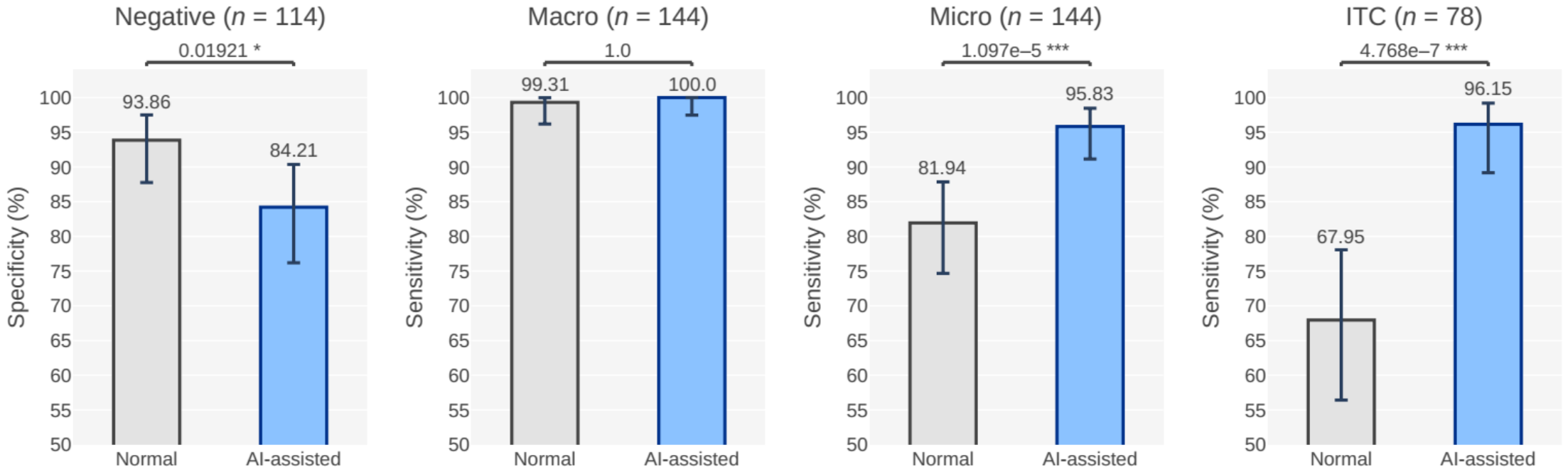
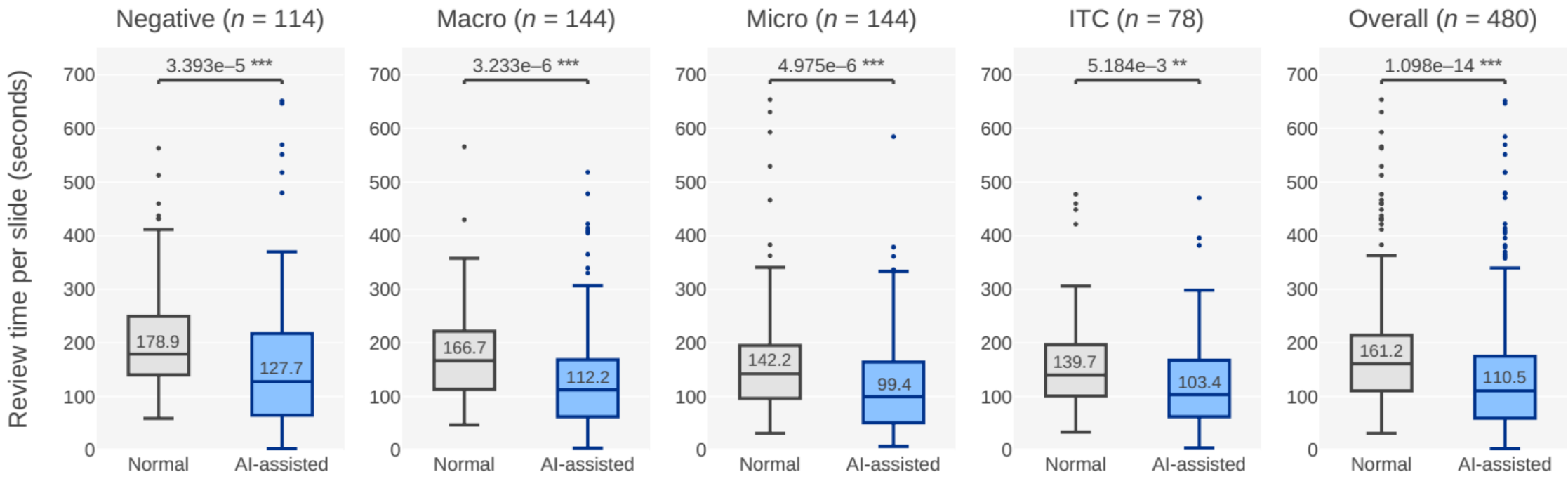
AI-Assisted Diagnosis of Lymph Node Metastasis

- Benefit of AI-Assisted Workflow for Diagnosis of Lymph Node Metastasis

  For gastric cancer, AI **Improved diagnostic sensitivity** of **micro-metastasis** (lesion<2mm) in lymph nodes **from 82% to 96%,** and that of **isolated tumor cells** (lesion<0.2mm) in lymph nodes **from 68% to 96%**



For gastric cancer, AI **reduced review time** of **micro-metastasis** (lesion<2mm) in lymph nodes **by 30%**, and that of **isolated tumor cells** (lesion<0.2mm) in lymph nodes **by 25%**



Cancer Detection on Frozen Section

- Background:
  - Frozen section of surgical specimen is an important method to determine whether the surgical margin is clean during a cancer surgery.
  - Many hospitals don’t have enough pathologists to support the frozen section service and are forced to forgo the practice.

AI-Assisted Cancer Detection on Frozen Section

- Setup:
  - Digital camera mounted on the microscope to capture real-time images
  - Real-time images processed by AI to segment cancer regions
  - AI prediction results overlaid on original image displayed on computer screen

AI-Assisted Cancer Detection on Frozen Section

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- Issues:
  - Scope of regulation?
  - Microscope is not a medical device
  - Digital camera is not a medical device
  - Computer screen can be a medical device
  - AI is often considered a medical device (which class?)

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