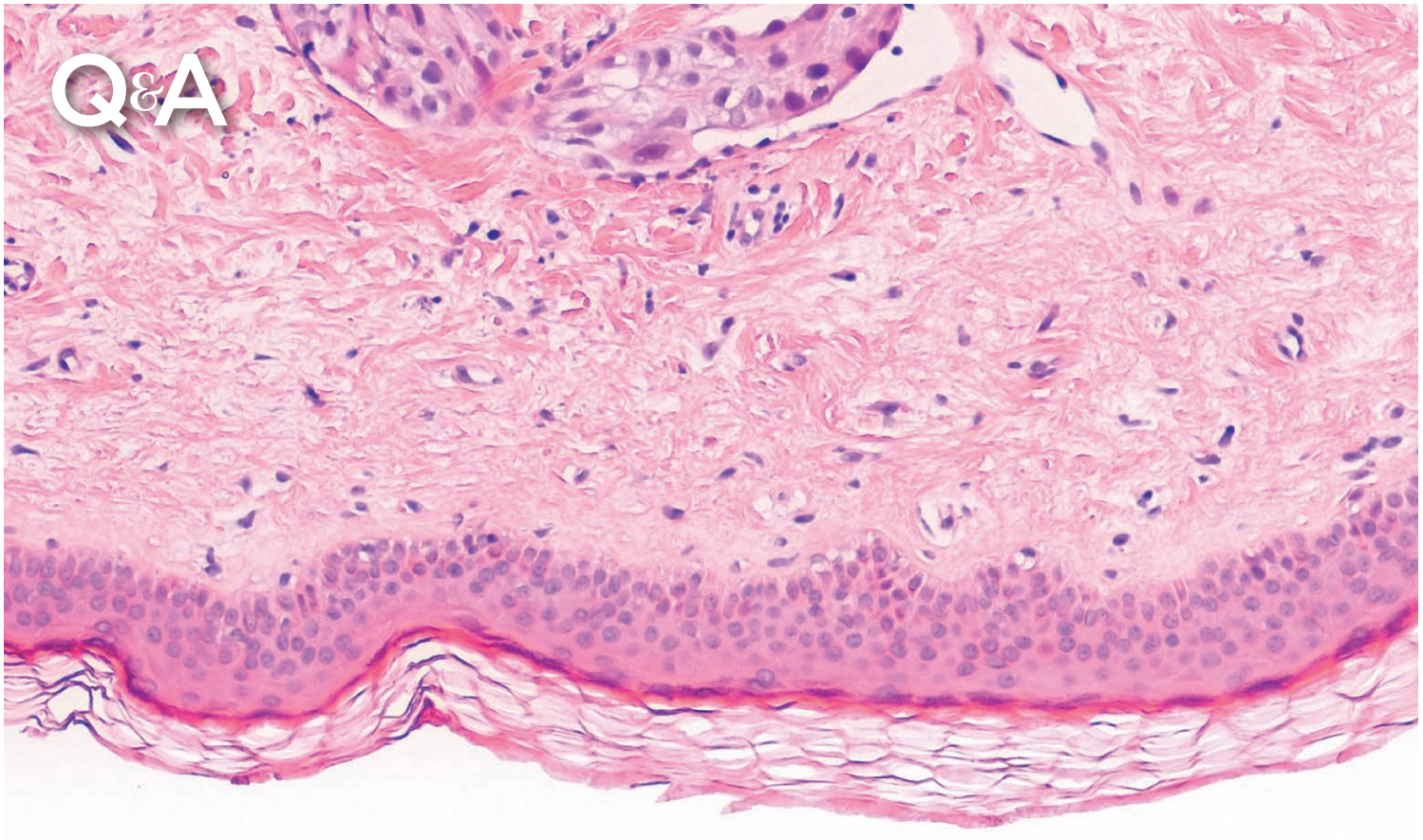

A Clinical AI Application to Enable Accurate and Efficient Detection of Breast Cancer Metastases in Lymph Nodes

An interview with Paige.AI with David Klimstra and Juan Antonio Retamero

Introduction

Paige's stated mission is to use the power of tissue-based AI to develop and deliver globally, a new generation of digital diagnostics and predictive tests, empowering pathologists and transforming oncology. A team of Paige's experts have brought their collective experience to bear on building an AI-driven tool that gleans and assesses information from slides of digitized tumor images.* Paige achieves this result by combining proprietary scalable, flexible computational pathology technology with data from millions of digitized slides and corresponding pathology reports to identify subtle or hard to recognize tissue patterns. Key to this approach is being able to process a large volume of images while drawing on the system's processing power in a manner sufficiently fast to provide actionable guidance to clinicians.

To learn more about this platform and its applications, we connected with Drs Klimstra and Retamero to pose the following questions to them.

Technical considerations

Q. What details can you provide on Paige.AI's machine learning and deep learning methods?

A. The method Paige uses for training its algorithms is called multiple instance learning, a weakly supervised deep learning approach that pairs the pathology whole slide image (WSI) with the corresponding pathology report.

Other deep learning approaches rely on images annotated by pathologists, which has the disadvantages of being time-consuming, inexact, and difficult to scale. However, multiple instance learning permits the use of large training datasets that, by exposing the algorithms to more WSI variability, make the resulting algorithms more robust to image variations related to pre-analytical variables related to how the pathology sample has been processed.

Q. What can you tell us about the training set used to develop the application?

A. Paige Prostate was trained using 44,000 WSIs from 15,000 patients coming from over 800 institutions worldwide. Paige Breast Lymph Node was trained using more than 20,000 WSIs. The use of multiple instance learning makes training our models possible with very large training datasets, which result in algorithms that are very robust to image variations.

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Q. How is this application different from other efforts in this space?

A. Other commercial AI algorithms available are trained using a different approach, based on supervised learning, as opposed to Paige's **weakly** supervised learning. Supervised learning requires pathologists drawing annotations on WSIs to segment (i.e., delineate boundaries) around areas of interest (for example, tumor). This has disadvantages, like being laborious, inexact, time consuming and difficult to scale. For example, one of the largest annotated datasets publicly available (Camelyon16) comprises less than 300 slides. Other commercially available algorithms were trained using a few hundred annotated slides, instead of the tens of thousands used by Paige.

The clinical relevance of this is that algorithms trained with smaller datasets do not generalize very well to WSIs different to those in which they were trained, and are vulnerable to changes in stain quality, tissue thickness, etc. This results in variable AI outputs that may limit their clinical use. However, given the exposure to larger datasets and image variations possible using multiple instance learning, Paige algorithms generalize to any clinical setting. This was the basis for the authorization by the FDA of Paige Prostate for diagnostic use.

Q. What are the technical requirements (resolution? other metrics?) for images to be evaluated by the Paige Breast Lymph Node AI module? Could you please site preferred image vendors for the platform?

A. The training dataset consisted of images scanned at 20x with a resolution of 0.5 microns per pixel. The models have been validated using different resolutions (20-40x, 0.5-0.25 microns/pixel) and image formats from FDA-approved scanners (iSyntax, SVS), although Paige algorithms work with most image files (i.e., scanner agnostic)

Q. Can the AI module be used to assess tissue slides from biopsies (histology, pathology)?

A. The intended use for Paige Prostate is FFPE prostatic core needle biopsy samples. For Paige Breast Lymph Node (LN) it is LN resection specimens. However, we have some evidence that both algorithms perform well in other use cases (like prostatic resections, TURP specimens, LN frozen sections), although these are beyond their current intended use.

Q. Has Paige.AI evaluated adjuvant assays to be used in conjunction with this imaging assay? For example, are liquid± or solid biopsies profiled for markers to go along with the image analysis?

A. In addition to the development of algorithms designed to aid pathologists in their routine diagnosis, Paige is also developing digital essays that attempt to predict a certain biomarker status based on H&E stain only.

Metrics and scoring of images

Q. What tumor characteristics are measured – e.g., tumor volume, morphology, etc? Can the AI module differentiate between cancerous and benign masses? If so, how is this differentiation determined?

A. The algorithm "learns" to recognize the morphologic features of cancer, compared with non-cancerous tissue. Paige Prostate is composed of three different modules: Paige Prostate Cancer Detect, Paige Prostate Cancer Grading and Quantification and Paige Prostate PNI Detect. Paige Prostate Cancer Detect offers a binary result at the slide level (i.e., "Benign" or "Suspicious"). If a concerning morphology is detected, it draws the pathologist's attention to the areas suspicious for cancer. Paige Prostate Cancer Grading and Quantification identifies the primary and secondary Gleason grades and quantifies tumor burden. If cancer is present, it will identify the primary and secondary Gleason grade for the slide, estimate the percentage and linear extent measurement (in mm) of total tumor burden, generate additional slide overlays containing the predicted locations for total tumor and each Gleason pattern for the user's review. Finally, Paige Prostate Perineural Invasion Detection identifies perineural invasion and it will also produce an output indicating whether Perineural Invasion is present at the slide level, as well as highlighting these suspicious regions on the WSI.

"Paige Prostate Perineural Invasion Detection identifies perineural invasion and it will also produce an output indicating whether Perineural Invasion is present at the slide level, as well as highlighting these suspicious regions on the WSI."

Q. As noted on a Paige.AI website, "AI technology is not designed to replace pathologist assessment, but instead to allow pathologists to work much more efficiently and could help draw their attention to cancers they might have missed." Are these images scored on a scale to assist the pathologist in triaging images for review? Or are images sorted as, say, indeterminate – positive (cancerous) – negative (benign) for pathologist follow-up?

A. The AI output is binary (either "Benign" or "Suspicious"). If a slide is suspicious, the relevant areas will be highlighted. In benign slides, the message "No suspicious tissue detected" is displayed, but no additional output is offered. There is a capability to indicate the status (benign or suspicious) on the pathologist's worklist, which contains all of the images the pathologist is assigned to review. This allows the pathologist to triage their work (e.g., review all of the suspicious cases first).

Q. How are indeterminate cases handled? What percentage of indeterminate images might a pathologist expect to encounter in a clinical setting?

A. Given the binary nature of the AI output, there are no indeterminate cases. An indication of "suspicious" will direct the pathologist's attention to the focus on the slide of greatest concern, but the final diagnosis (benign, suspicious, or cancer) remains the judgment of the pathologist.

Q. A sensitivity of over 98% in detecting [breast cancer] metastases is cited in Paige. AI literature. Could you please explain how this figure of sensitivity was calculated?

A. This was calculated by measuring the performance of Paige LN on a dataset that comprised WSIs harboring macro-metastases (n=229), micro-metastases (n=148), isolated tumor cells (n=57) and benign slides (n=217). The average sensitivity was 0.98 across these diagnostic categories. The slides comprising this dataset were not used for training the algorithm.

Q. Other assay metrics might include accuracy and specificity; can you cite a figure of merit for specificity and accuracy (false positive/negative rates), respectively? How are those figures determined?

A. These metrics were also calculated using the dataset described above. Overall accuracy was 0.92 and specificity 0.85.

Applications to therapeutic guidance

Q. Beyond aiding pathologists, to what extent can the Paige.AI module be used to guide a physician in prescribing a therapy for breast cancers?

A. In addition to its role in assessing nodal stage, Paige will soon incorporate AI tools to quantify ER, PR, Ki 67 and Her2 status on IHC stains. Furthermore, there is evidence that an experimental AI model can help identify certain genomic profiles on a H&E slide in early breast cancer. Therefore, patients with a high risk MammaPrint profile can be flagged using just tumor morphology, obviating the need for molecular testing.

Q. How would the Paige.AI module be used to assess the response to a therapy – e.g., tumor size, tumor volume, tumor morphology?

A. Based on preliminary evidence, AI can be used to predict response to therapy as well as prognosis based on morphology alone. It can also help pathologists find minimal residual disease after neoadjuvant therapy, the presence and extent of which is a reflection of the degree of treatment response.

"Based on preliminary evidence, AI can be used to predict response to therapy as well as prognosis based on morphology alone."

Q. Do you have any concluding comments regarding the long-term utility of this platform? Does Paige.AI have plans for other applications of this platform – beyond cancer to other therapeutic areas?

A. Based on the existing evidence, pathologists improve their efficiency and diagnostic accuracy when aided by Paige. In addition, surveyed pathologists prefer to work with the aid of Paige to working unaided. For these reasons, we believe that the practice of the profession will change to adopt this technology. Paige is working to develop algorithms in other areas, not just prostate and breast, but also colon, skin, lung, etc. Although cancer is our current focus, there are applications in non-neoplastic disease that could be pursued. Additionally, multimodal predictive models that incorporate data from other technologies can be developed to enhance the predictive power over any of the individual technologies alone.

Thank you both for your informative replies. JoPM

David Klimstra, M.D

David is Founder and Chief Medical Officer at Paige, the first company to receive FDA approval for an AI product in digital pathology, Paige Prostate. An internationally recognized expert on the pathology of tumors of the digestive system, pancreas, liver, and neuroendocrine system, he has published over 425 primary articles and his research focuses on the correlation of morphological and immunohistochemical features of tumors of the gastrointestinal tract, liver, biliary tree, and (most notably) pancreas with their clinical and molecular characteristics. Dr. Klimstra received his M.D. and completed a residency in anatomic pathology at Yale University, and he completed fellowship training in oncologic surgical pathology at Memorial Sloan Kettering Cancer Center. He practiced surgical pathology at Memorial Sloan Kettering for 30 years prior to joining Paige, and served a the Chairman of the Department there for the past 10 years.

Dr. Juan Antonio Retamero

Juan is an anatomical pathologist with extensive experience in the implementation and use of digital pathology and artificial intelligence in clinical use. He played a key role in the adoption of digital pathology for routine diagnosis in a pioneering group of hospitals in 2016. Since then, he has shared his experiences worldwide and has supported many centers in the adoption of digital pathology, including labs in the United States and many countries in Europe and Asia. He is a regular speaker at different digital and computational events globally and is an ardent advocate for the modernization of the profession.

About Paige

Paige was founded in 2017 by Thomas Fuchs, Dr.Sc., David Klimstra, M.D., and colleagues from Memorial Sloan Kettering Cancer Center (MSK). The company builds computational pathology products designed so patients and their care teams can make effective, more informed treatment decisions. With this new class of AI-based technologies positioned to drive the future of diagnostics, Paige created a platform to deliver this novel technology to pathologists to transform their workflow and increase diagnostic confidence and productivity. Paige's products deliver insights to pathologists and oncologists so they can arrive efficiently at more precise diagnoses for patients. Paige is the first company to receive FDA approval for an AI-based digital pathology product.

For more background, see also:

- https://www.paige.ai/resources/paige-announces-new-uk-study-to-evaluate-ai-tools-that/.
- An online accessible article on an evaluation of Paige's platform Is available at *"An independent assessment of an artificial intelligence system for prostate cancer detection shows strong diagnostic accuracy,* Sudhir Perincher *et al*., Mod Pathol. 2021; 34(8): 1588–1595. Published online 2021 Mar 29. doi: 10.1038/s41379-021-00794-x"

Notes

* An artificial intelligence primer can be viewed at HPI Lecture Series – #4 – Thomas J Fuchs, DSc: AI in Healthcare: From Terminators to Virtual Doctors, https://www.youtube.com/watch?v=85yO68f6By4 (Introduction in German, lecture in English starts about 95 seconds into the video.)

± In this instance, liquid biopsies may include circulating tumor cells, RNA, DNA or protein markers that indicate the presence of a tumor.