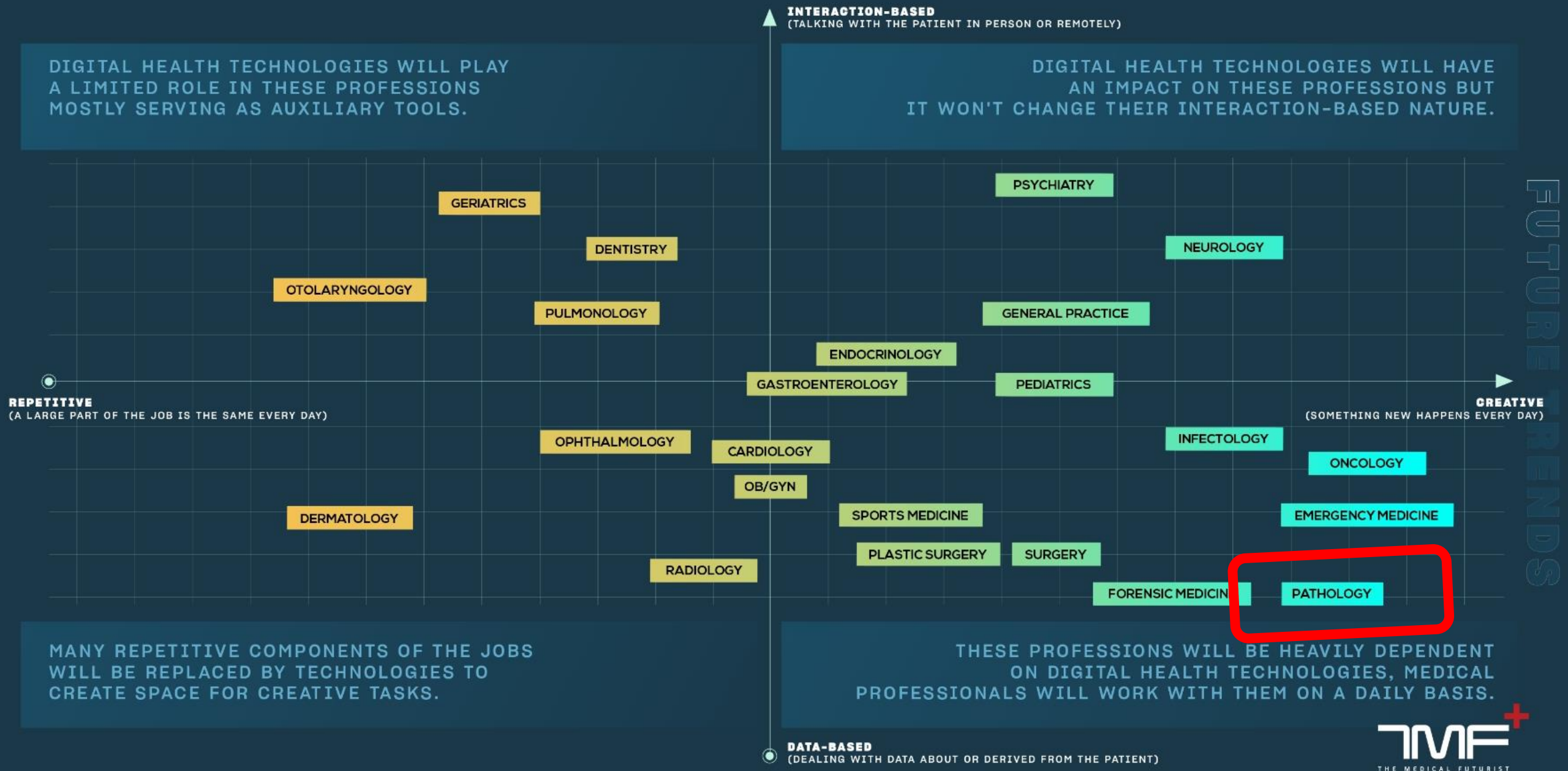
The rise of *artificial intelligence* and its impact on histopathology

Jeroen van der Laak

WILL DIGITAL HEALTH TECHNOLOGY REPLACE PHYSICIANS?



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The rise of *artificial intelligence* and its impact on histopathology

Jeroen van der Laak

Notice of financial disclosure

Philips	SAB	Honorarium
Philips	Research collab.	Remuneration
ContextVision	SAB	Honorarium
Sectra	Research collab.	Grant

柯洁 KE JIE

2018 삼성화재배
월드바둑마스터스
안 국 현 八단
커 제
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GAME OVER
KASPAROV AND THE MACHINE

中国乌镇 围棋峰会
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中国围棋协会

柯洁 KE JIE
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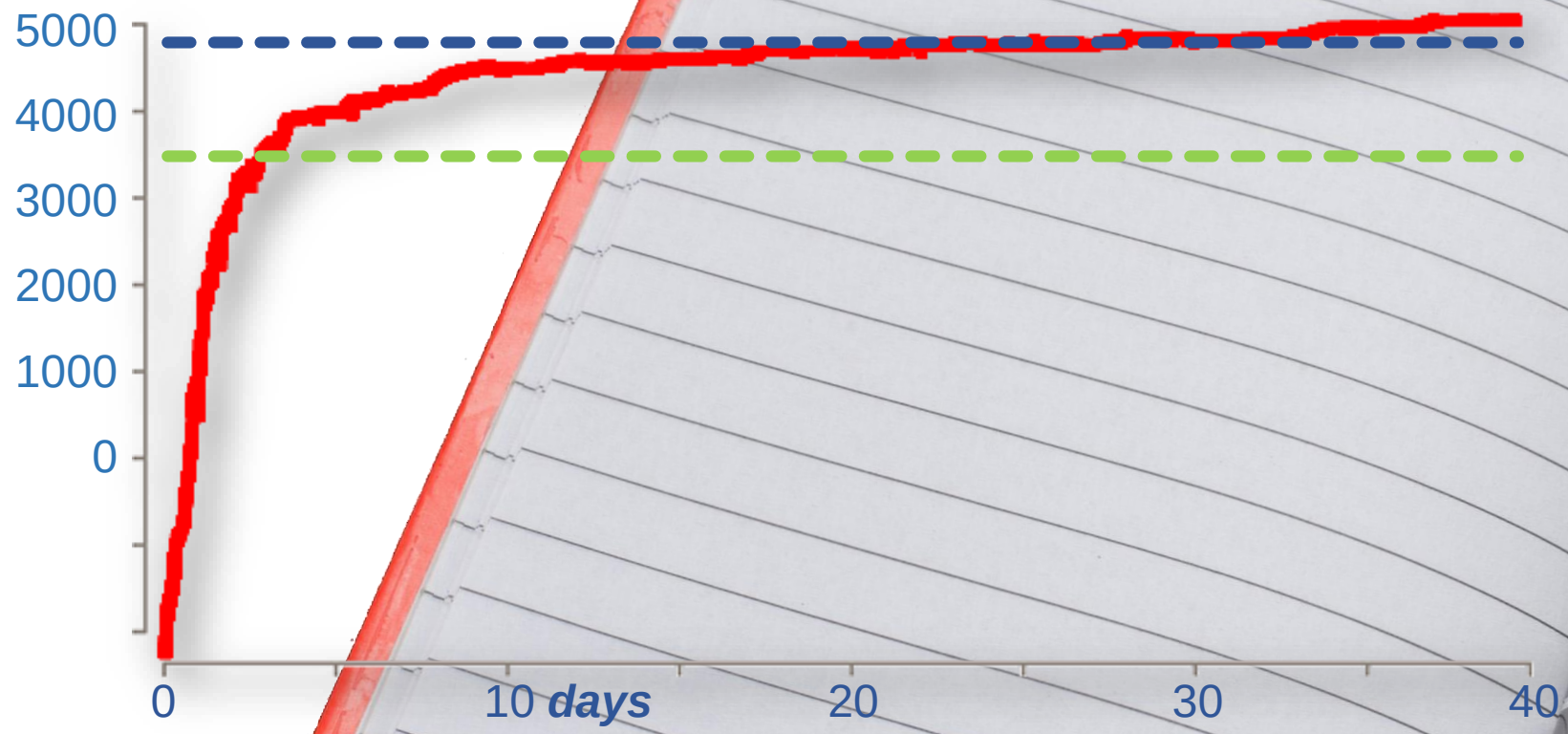
Reuters

AlphaGo Zero



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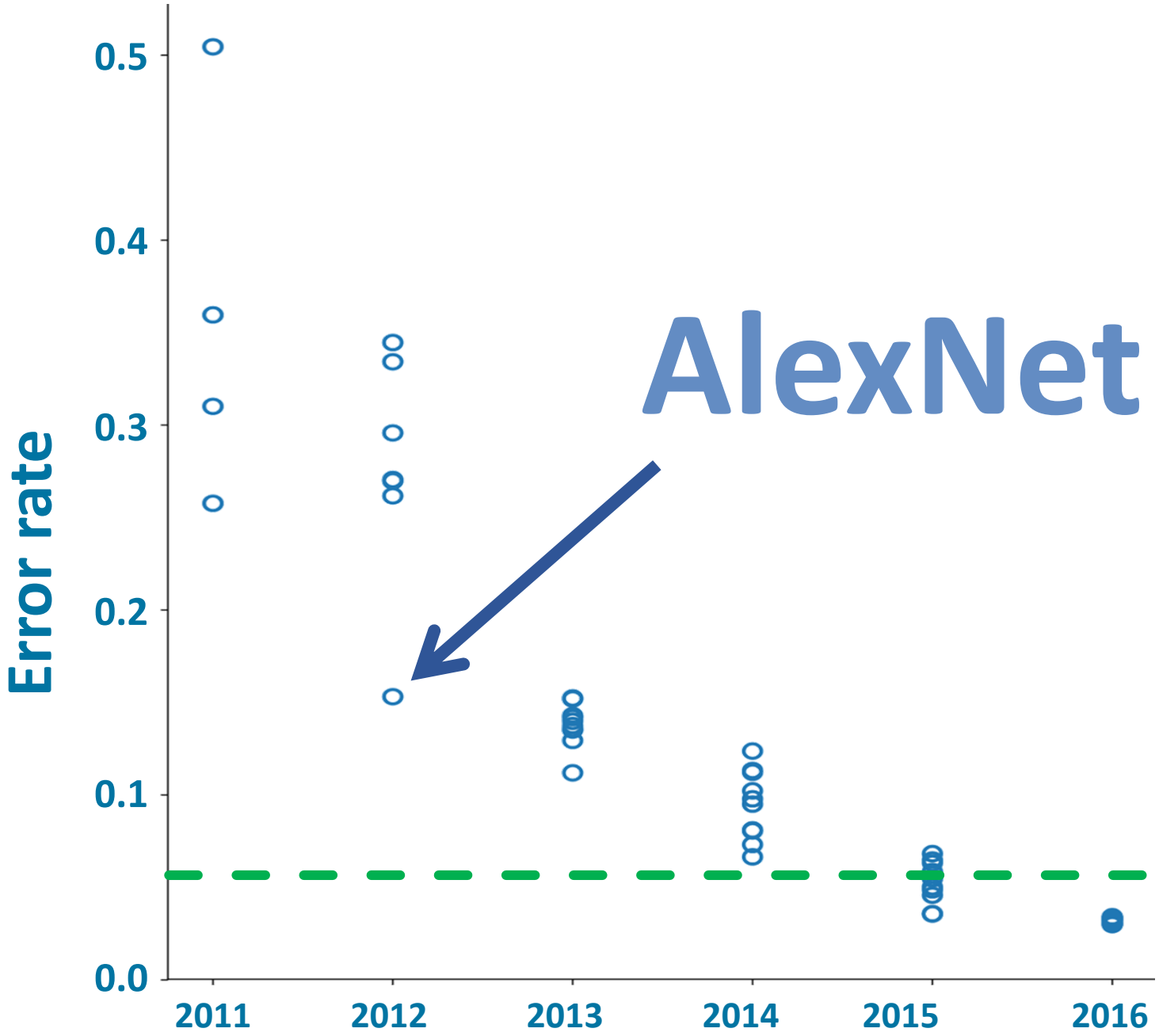
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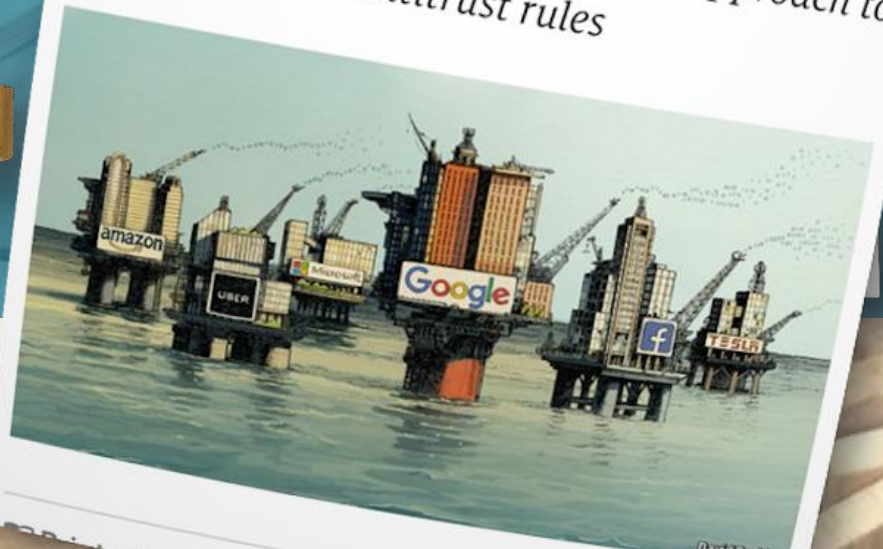

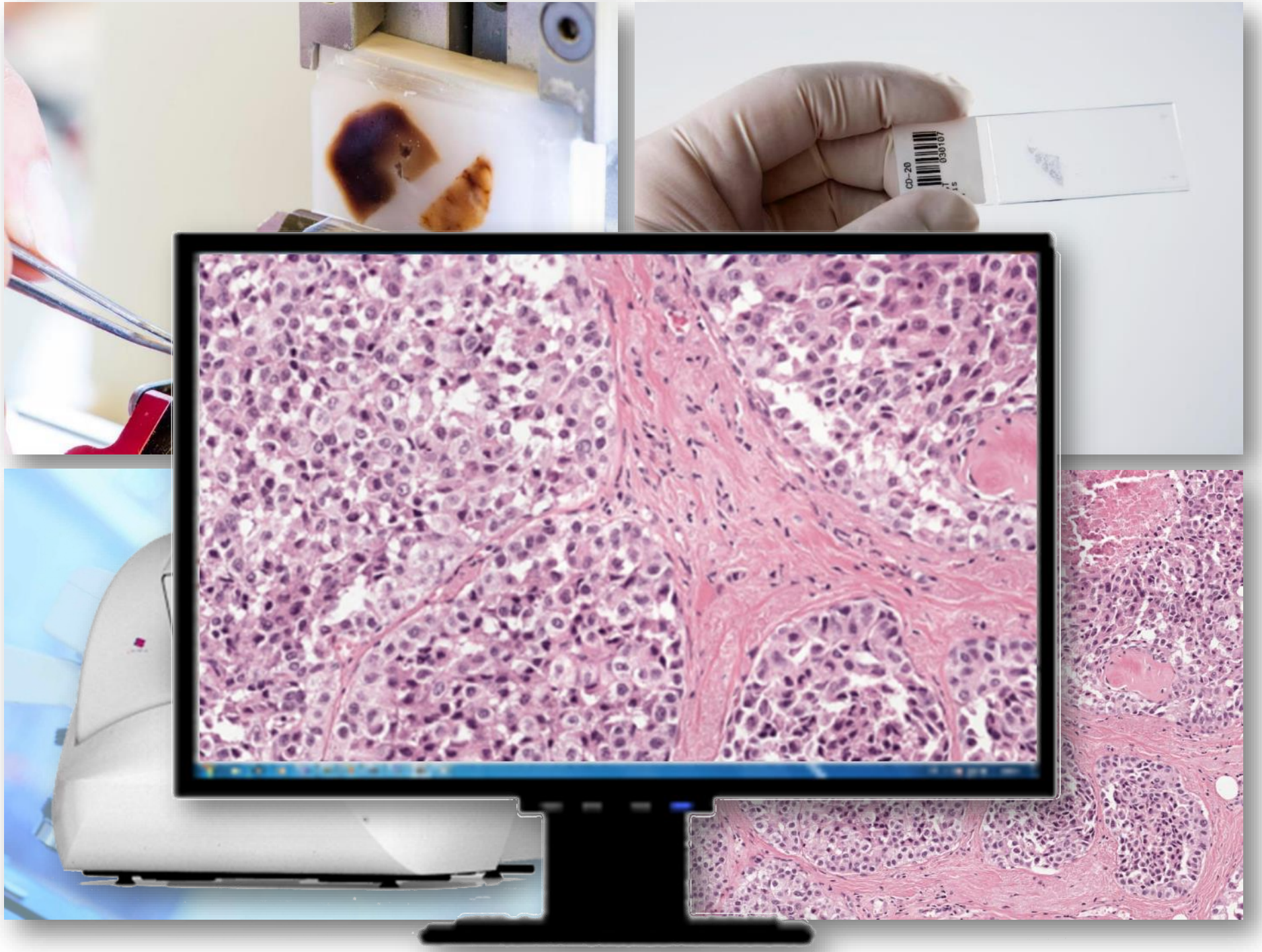

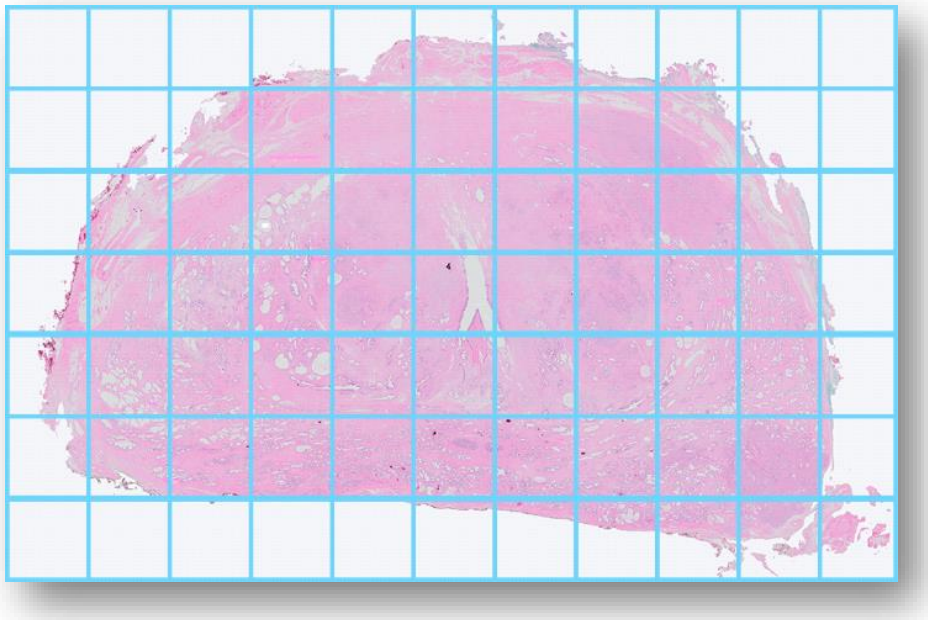

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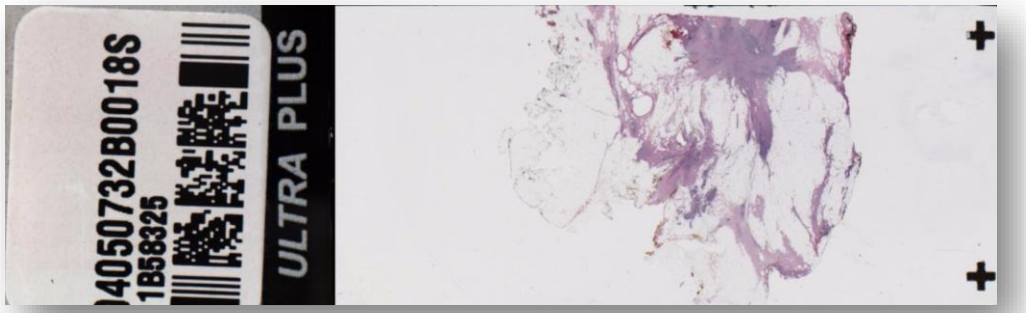

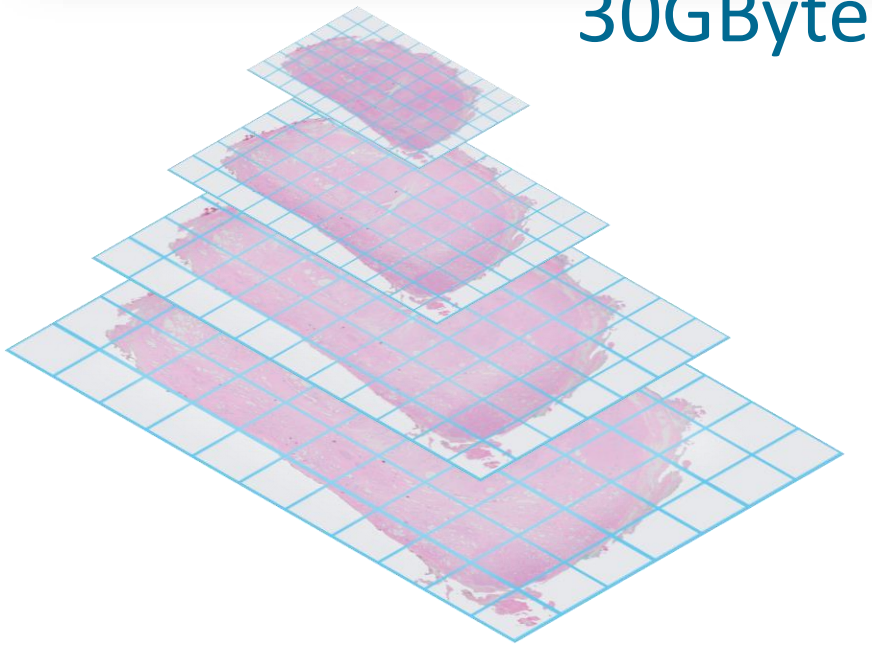

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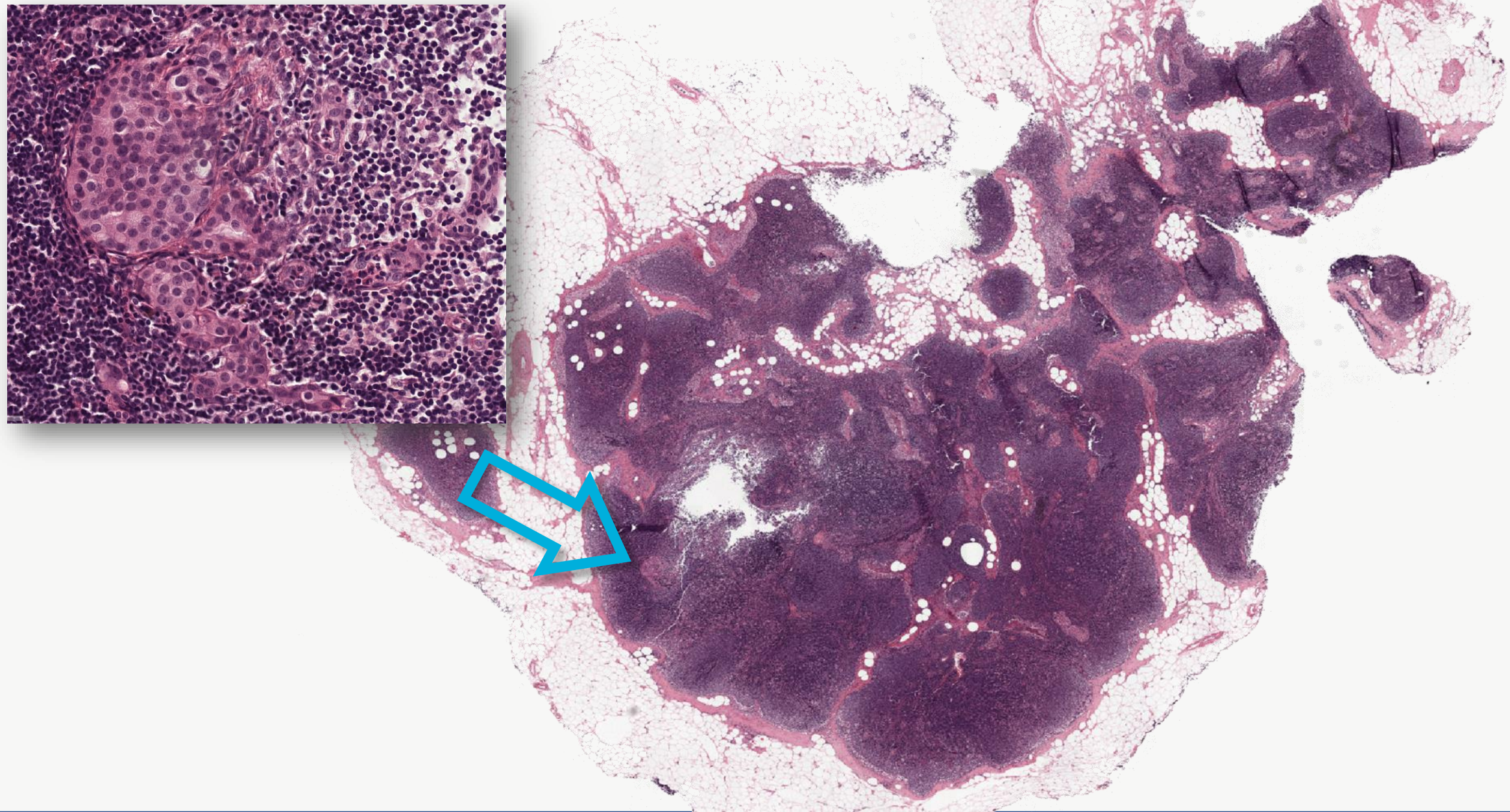

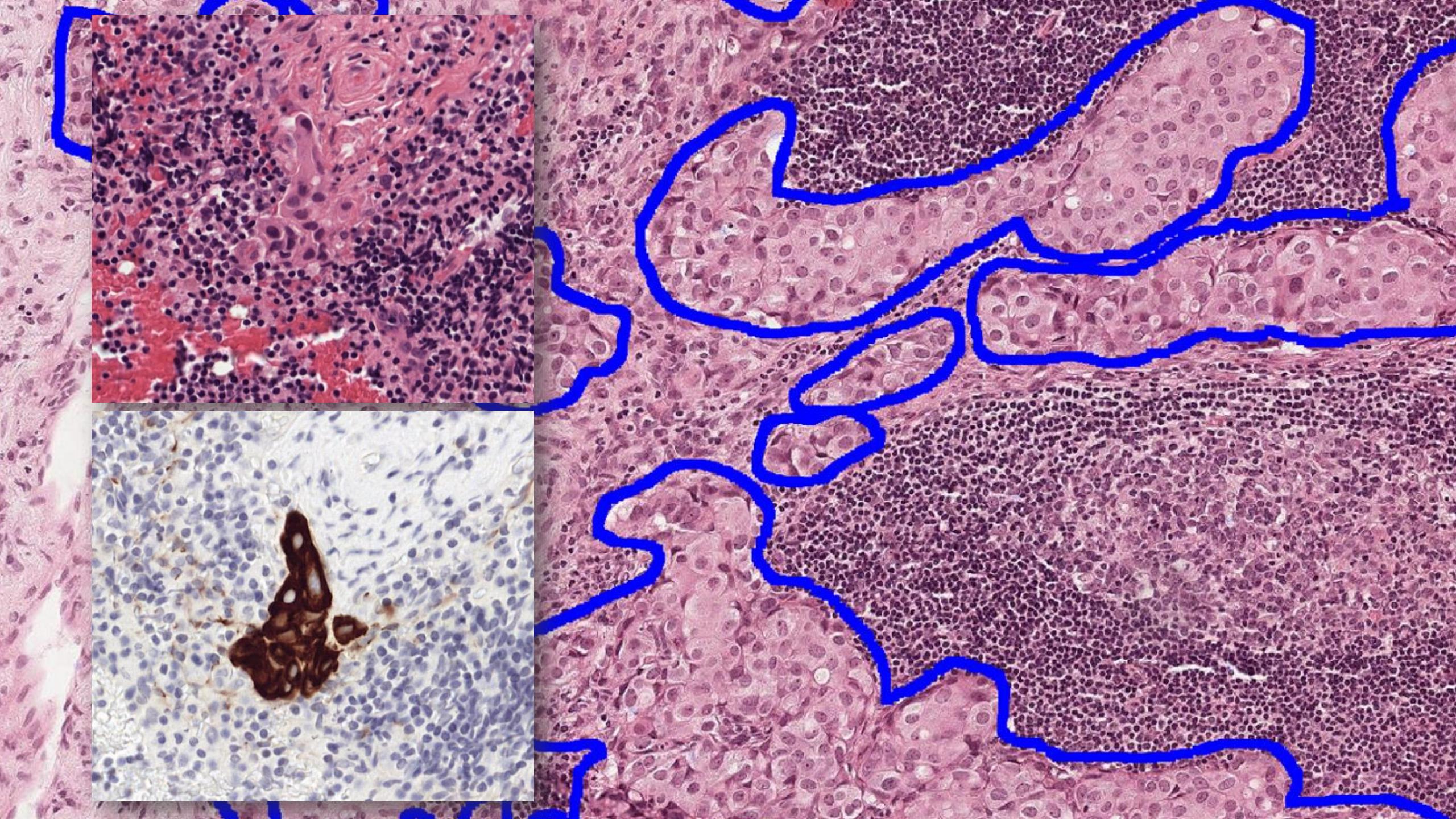

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SCIENTIFIC REPORTS

OPEN

Deep learning as a tool for increased accuracy and efficiency of histopathological diagnosis

Received: 28 January 2016
Accepted: 27 April 2016
Published: 23 May 2016

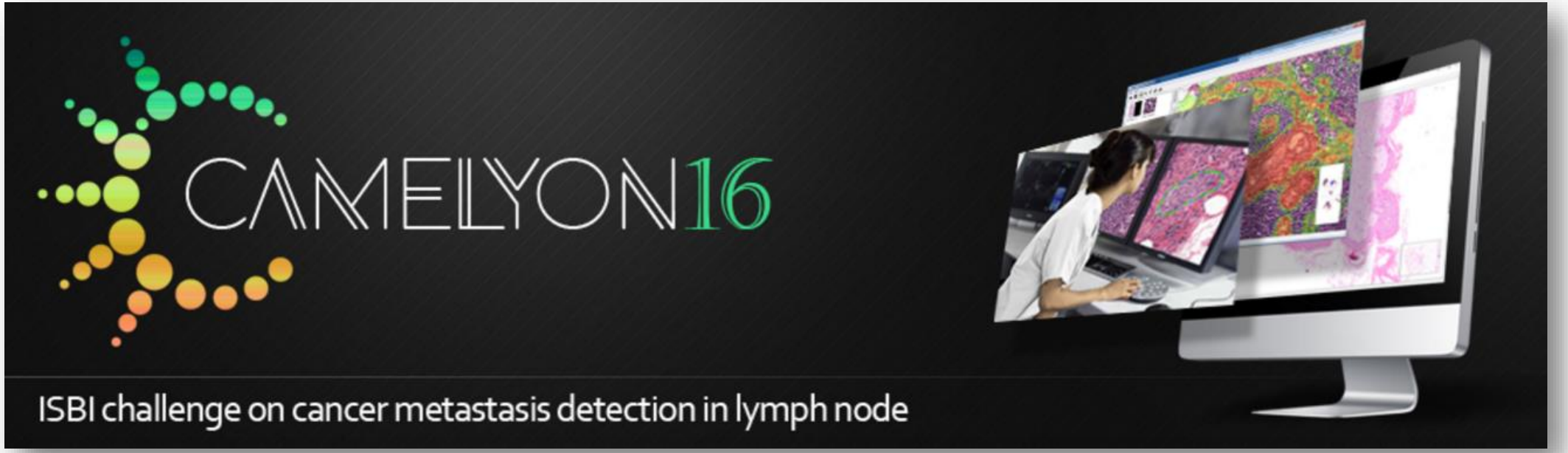
Geert Litjens[1], Clara I. Sánchez[2], Nadya Timofeeva[1], Meyke Hermsen[1], Iris Nagtegaal[1], Iringo Kovacs[3], Christina Hulsbergen - van de Kaa[1], Peter Bult[1], Bram van Ginneken[2] & Jeroen van der Laak[1]

Pathologists face a substantial increase in workload and complexity of histopathologic cancer diagnosis due to the advent of personalized medicine. Therefore, diagnostic protocols have to focus equally on efficiency and accuracy. In this paper we introduce 'deep learning' as a technique to improve the objectivity and efficiency of histopathologic slide analysis. Through two examples, prostate cancer identification in biopsy specimens and breast cancer metastasis detection in sentinel lymph nodes, we show the potential of this new methodology to reduce the workload for pathologists, while at the same time increasing objectivity of diagnoses. We found that all slides containing prostate cancer and micro- and macro-metastases of breast cancer could be identified automatically while 30–40% of the slides containing benign and normal tissue could be excluded without the use of any additional immunohistochemical markers or human intervention. We conclude that 'deep learning' holds great promise to improve the efficacy of prostate cancer diagnosis and breast cancer staging.

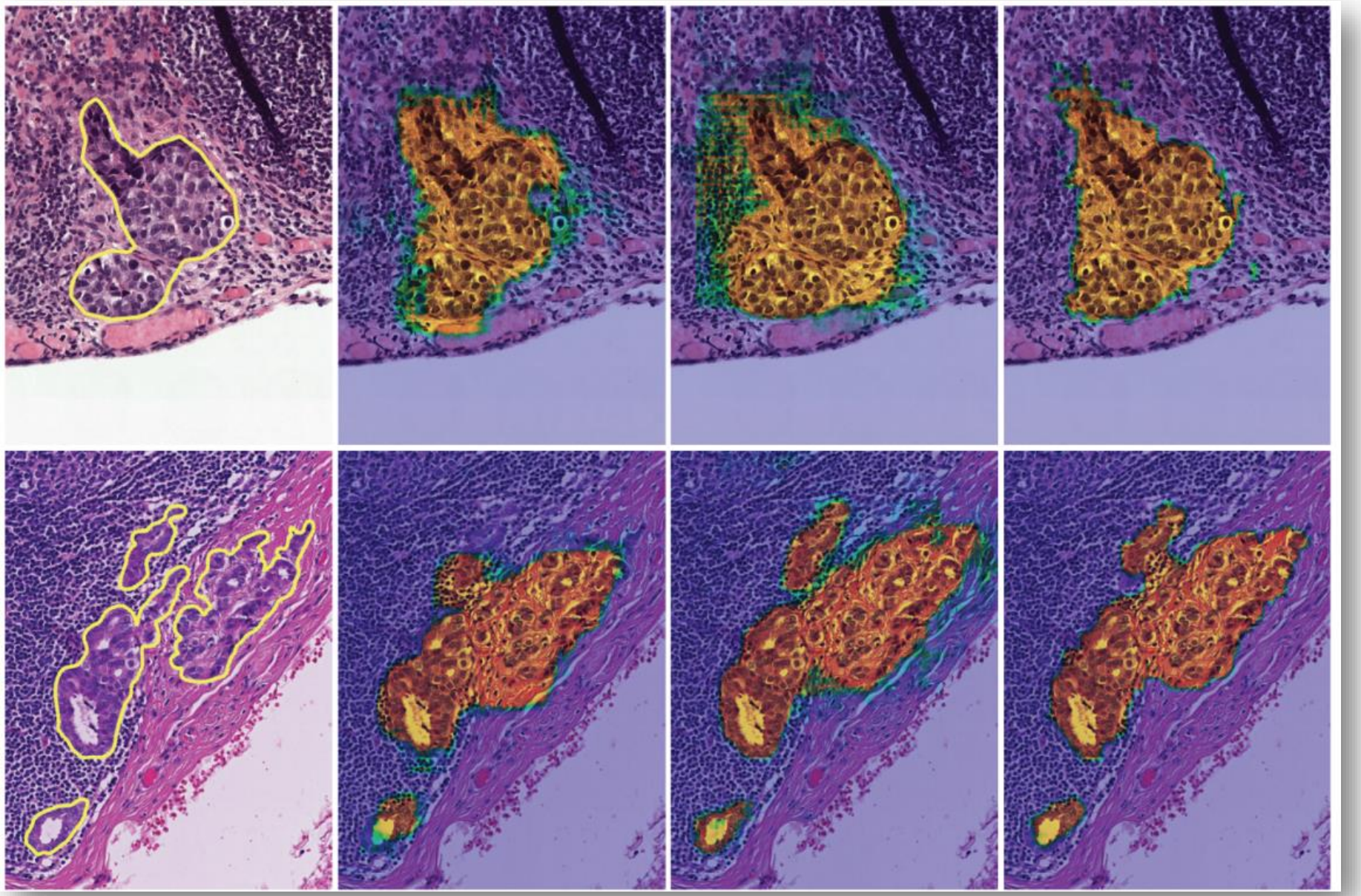
Microscopic analysis of hematoxylin and eosin (H&E) stained sections has been the basis for cancer diagnosis and grading for the past century[1]. Protocols for the complete workup of biopsies or resected tissue specimens, including microscopic analysis, exist for many of the most common cancer types (e.g. lung, breast, prostate). Use of these protocols has led to strong prognostic and widely used grading strategies (e.g. the Gleason grading system)[2].

Due to the rise in cancer incidence and patient-specific treatment options, diagnosis and grading of cancer has become increasingly complex. Pathologists nowadays have to go over a large number of slides, often including additional immunohistochemical stains, to come to a complete diagnosis. Moreover, there is an increase in the amount of quantitative parameters pathologists have to extract for commonly used grading systems (e.g. lengths,

Litjens G, et al. Scientific Reports 6: 26286, 2016.



Litjens G, et al. GigaScience 7, 2018.



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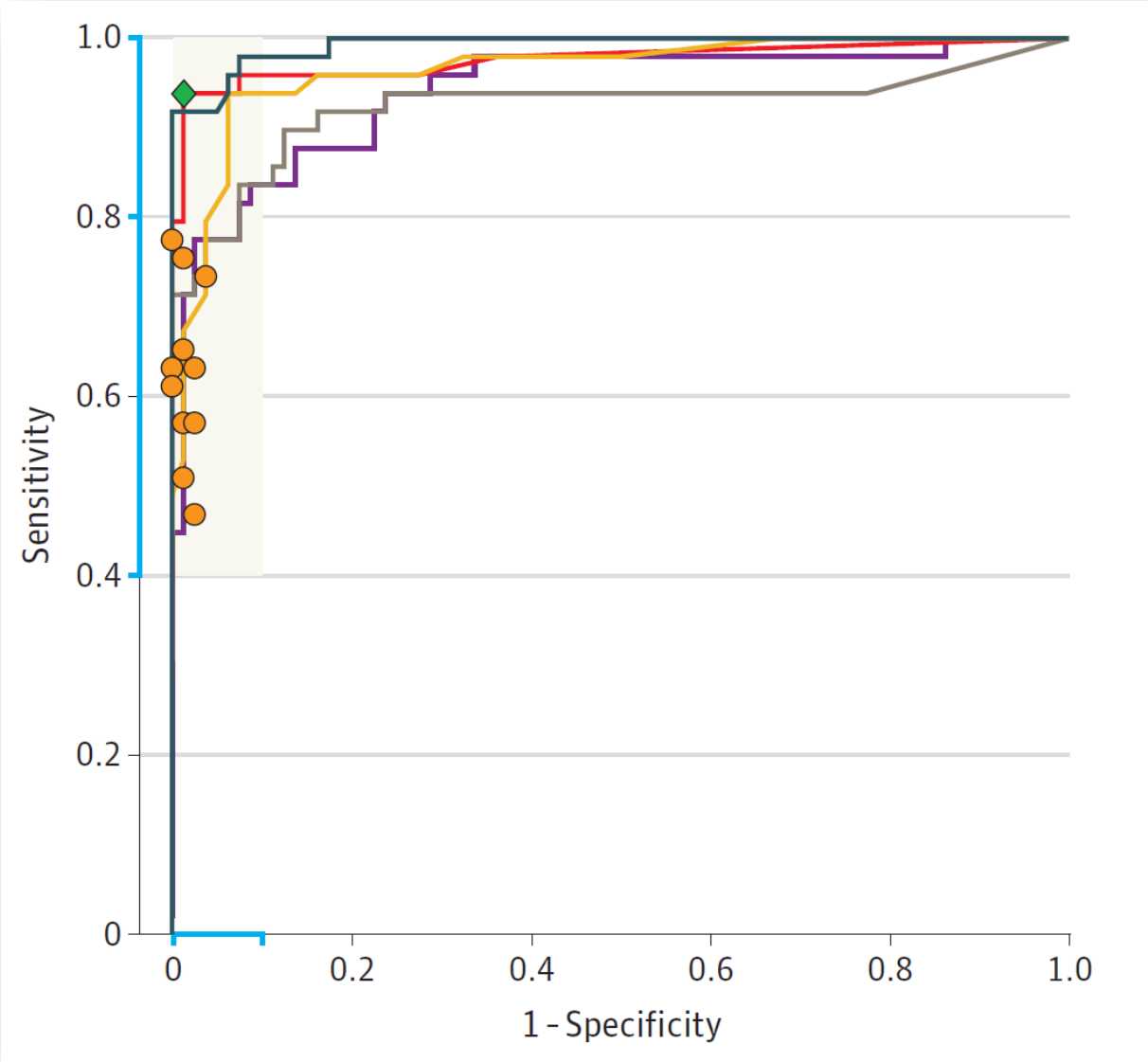
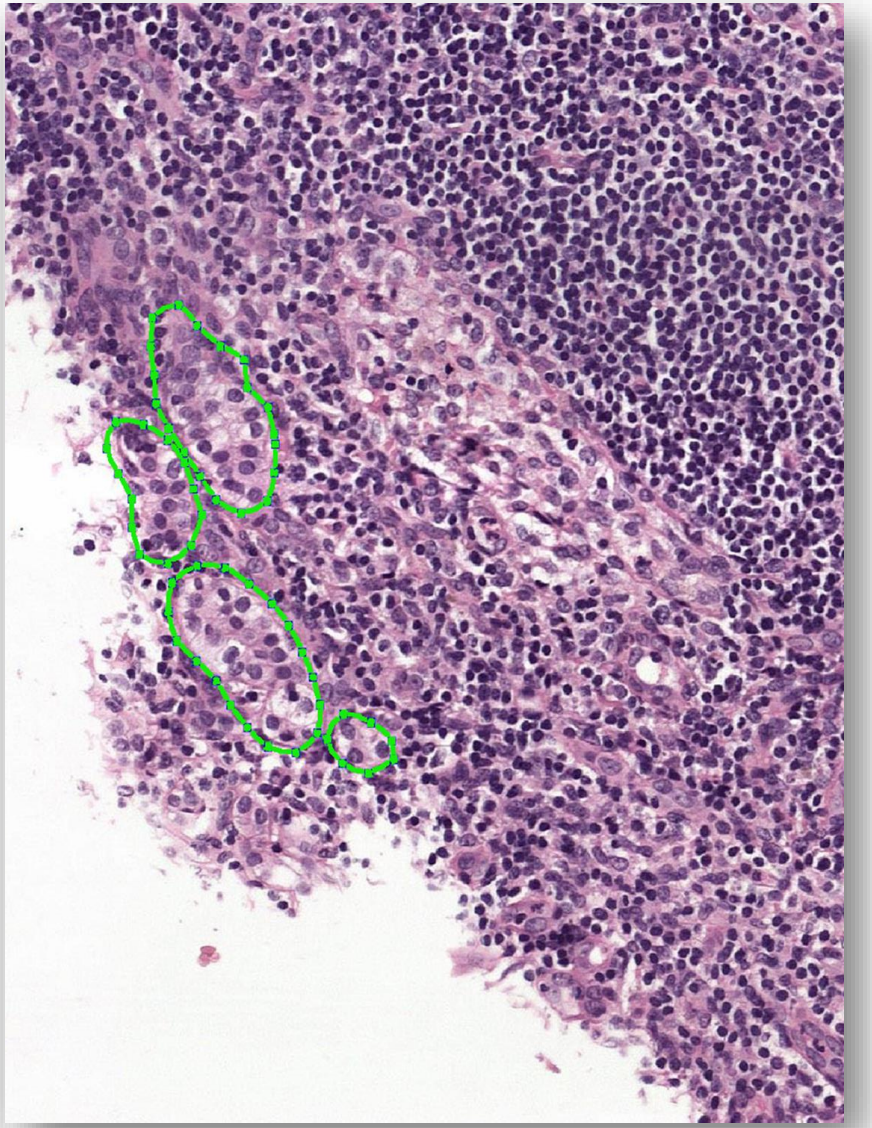




Ehteshami Bejnordi B, et al. JAMA 318: 2199-2210, 2017.

Steiner DF, et al. Am J Surg Pathol 42(12):1636-1646, 2018.

ORIGINAL ARTICLE

OPEN

Impact of Deep Learning Assistance on the Histopathologic Review of Lymph Nodes for Metastatic Breast Cancer

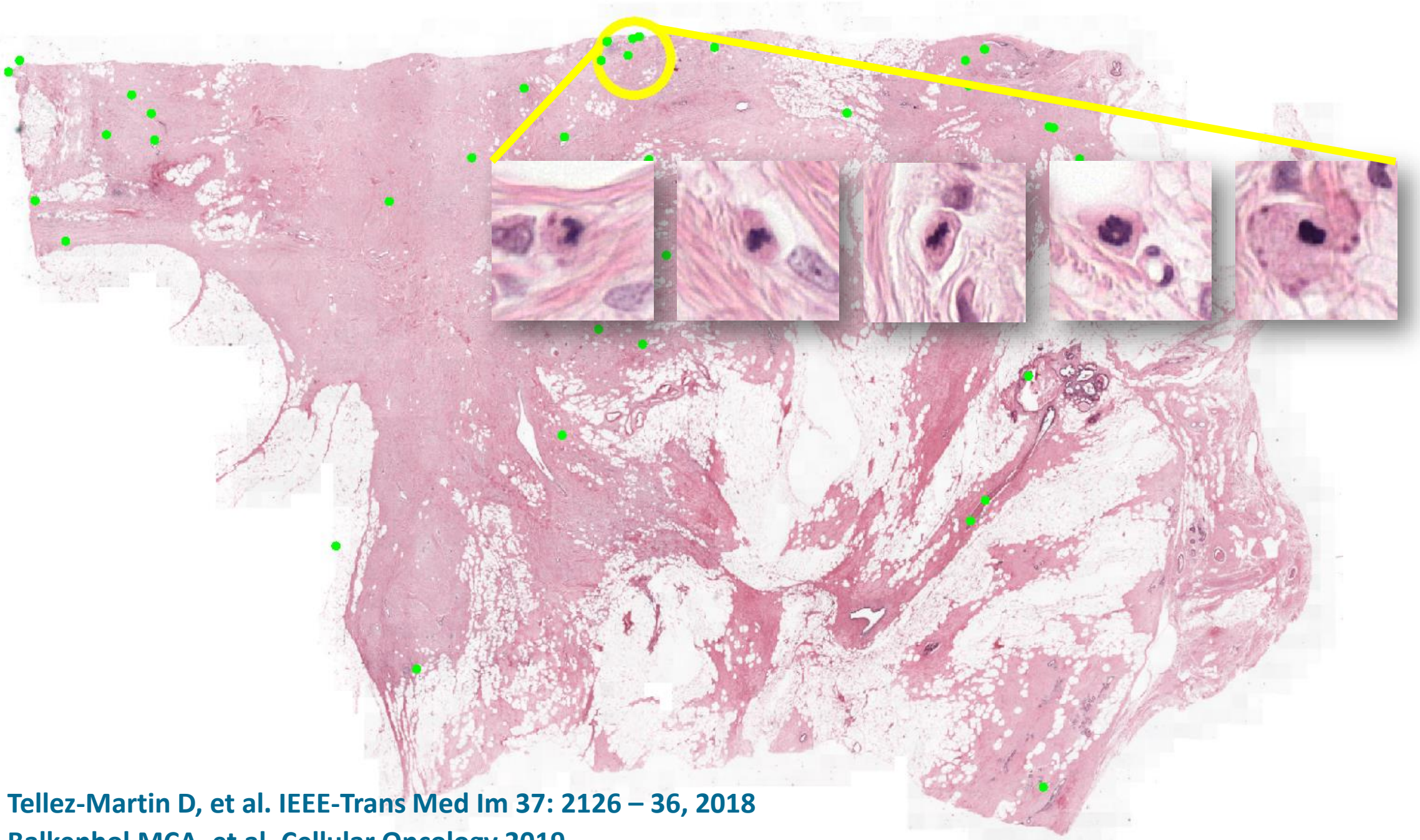
David F. Steiner, MD, PhD, Robert MacDonald, PhD,* Yun Liu, PhD,* Peter Truszkowski, MD,* Jason D. Hipp, MD, PhD, FCAP,* Christopher Gammage, MS,* Florence Thng, MS,† Lily Peng, MD, PhD,* and Martin C. Stumpe, PhD**

Abstract: Advances in the quality of whole-slide images have set the stage for the clinical use of digital images in anatomic pathology. Along with advances in computer image analysis, this raises the possibility for computer-assisted diagnostics in pathology to improve histopathologic interpretation and clinical care. To evaluate the potential impact of digital assistance on interpretation of digitized slides, we conducted a multireader multicase study utilizing our deep learning algorithm for the detection of breast cancer metastasis in lymph nodes. Six pathologists reviewed 70 digitized slides from lymph node sections in 2 reader modes, unassisted and assisted, with a washout period between sessions. In the assisted mode, the deep learning algorithm was used to identify and outline regions with high likelihood of containing tumor. Algorithm-assisted pathologists demonstrated higher accuracy than either the algorithm or the pathologist alone. In particular, algorithm assistance significantly increased the sensitivity of detection for micrometastases (91% vs. 83%, $P = 0.02$). In addition, average review time per image was significantly shorter with assistance than without assistance for both micrometastases (61 potential of a deep learning algorithm to improve pathologist accuracy and efficiency in a digital pathology workflow.

Key Words: artificial intelligence, machine learning, digital pathology, breast cancer, computer aided detection

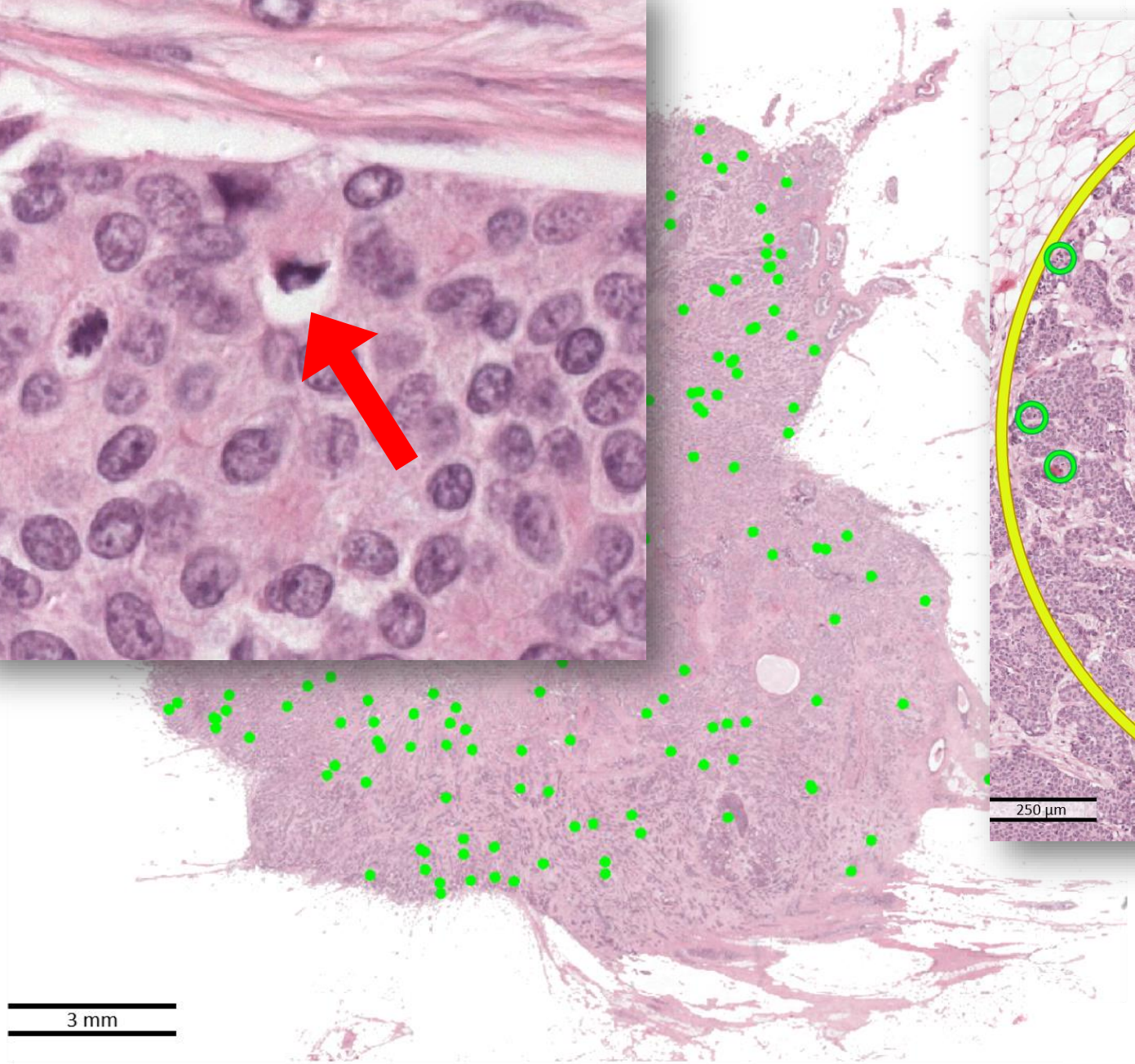
(*Am J Surg Pathol* 2018;00:000–000)

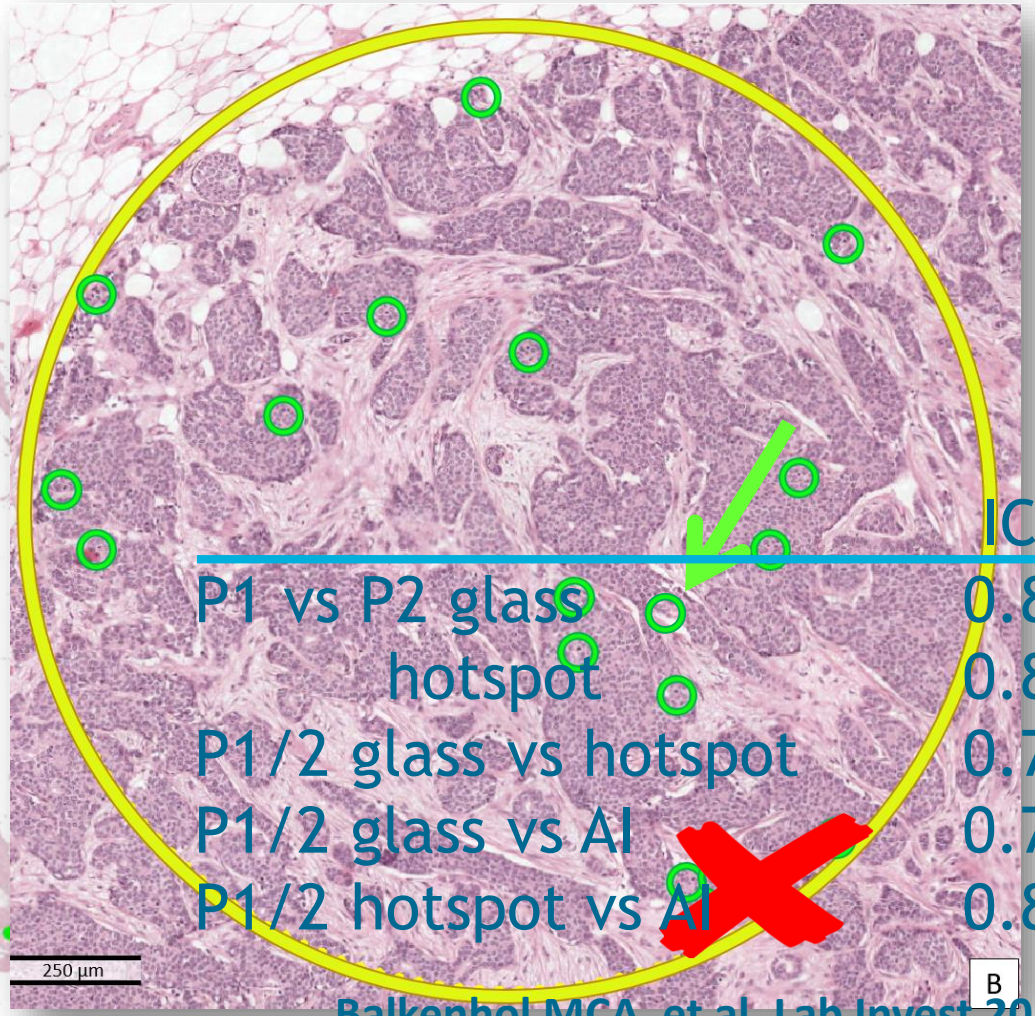
The regulatory approval and gradual implementation of whole-slide scanners has enabled the digitization of glass slides for remote consults and archival purposes.[1] Digitization alone, however, does not necessarily improve the consistency or efficiency of a pathologist's primary workflow. In fact, image review on a digital medium can be slightly slower than on glass, especially for pathologists with limited digital pathology experience.[2] However, digital pathology and image analysis tools have already demonstrated potential benefits, including the potential to reduce inter-reader



Tellez-Martin D, et al. IEEE-Trans Med Im 37: 2126 – 36, 2018

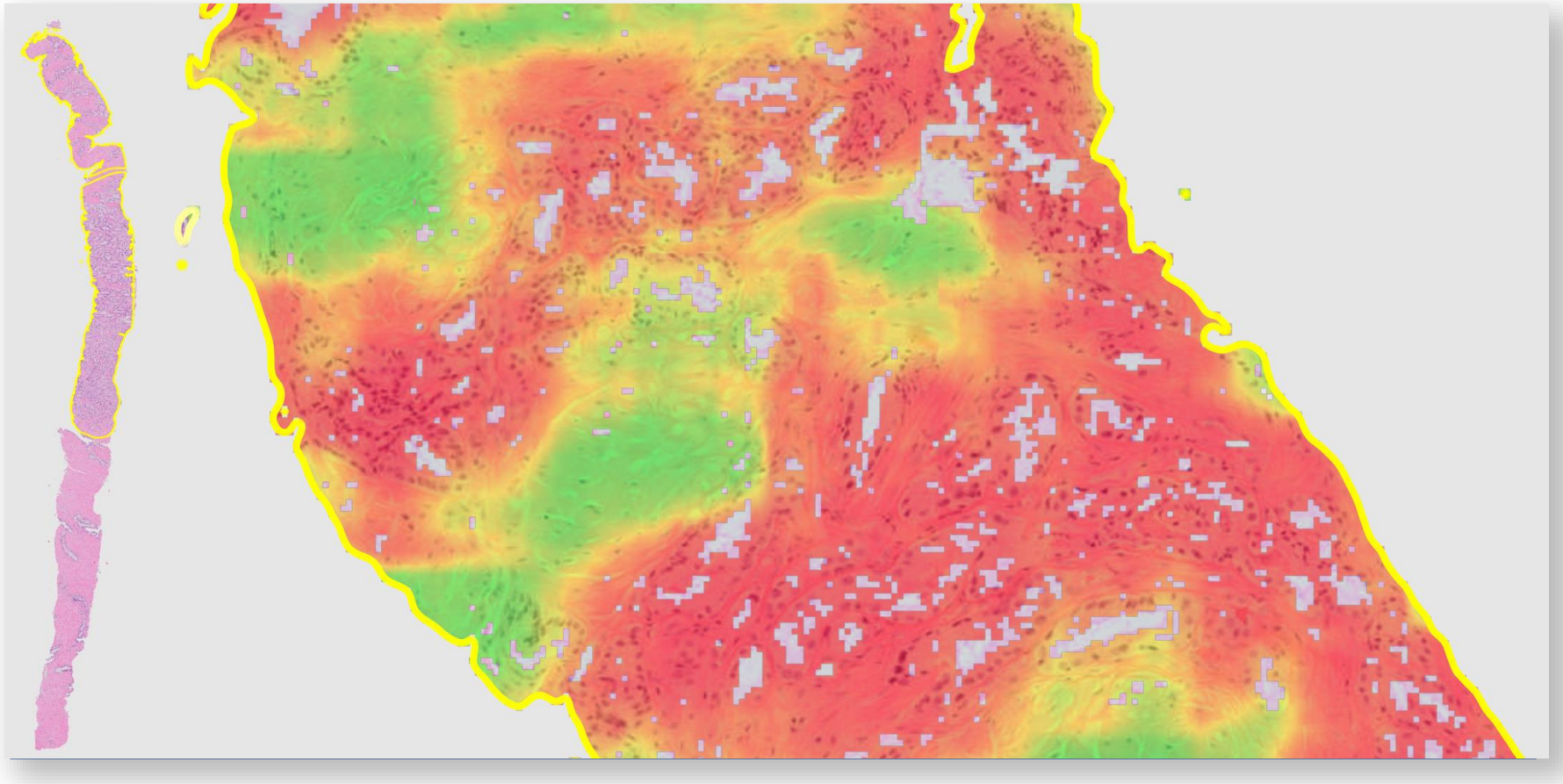
Balkenhol MCA, et al. Cellular Oncology 2019.



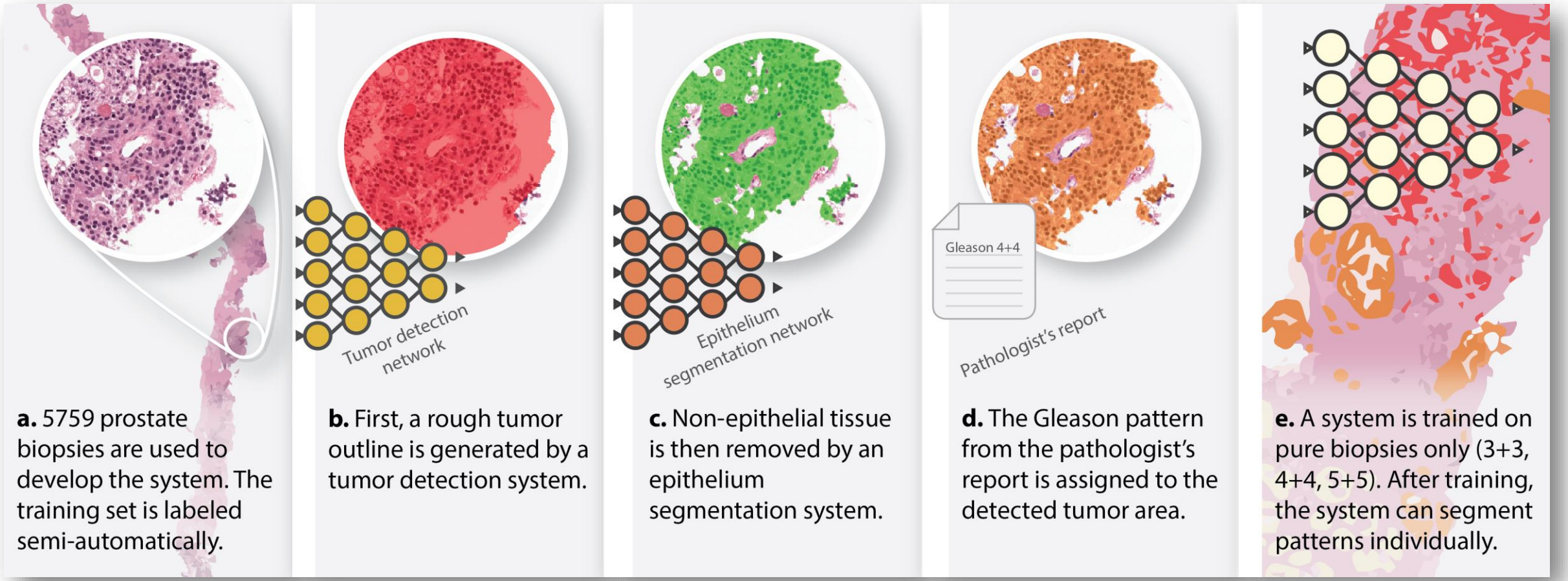


	ICC
P1 vs P2 glass	0.84
hotspot	0.85
P1/2 glass vs hotspot	0.79
P1/2 glass vs AI	0.79
P1/2 hotspot vs AI	0.89

Balkenhol MCA, et al. Lab Invest 2019



Litjens G, et al. Scientific Reports 6: 26286, 2016.



a. 5759 prostate biopsies are used to develop the system. The training set is labeled semi-automatically.

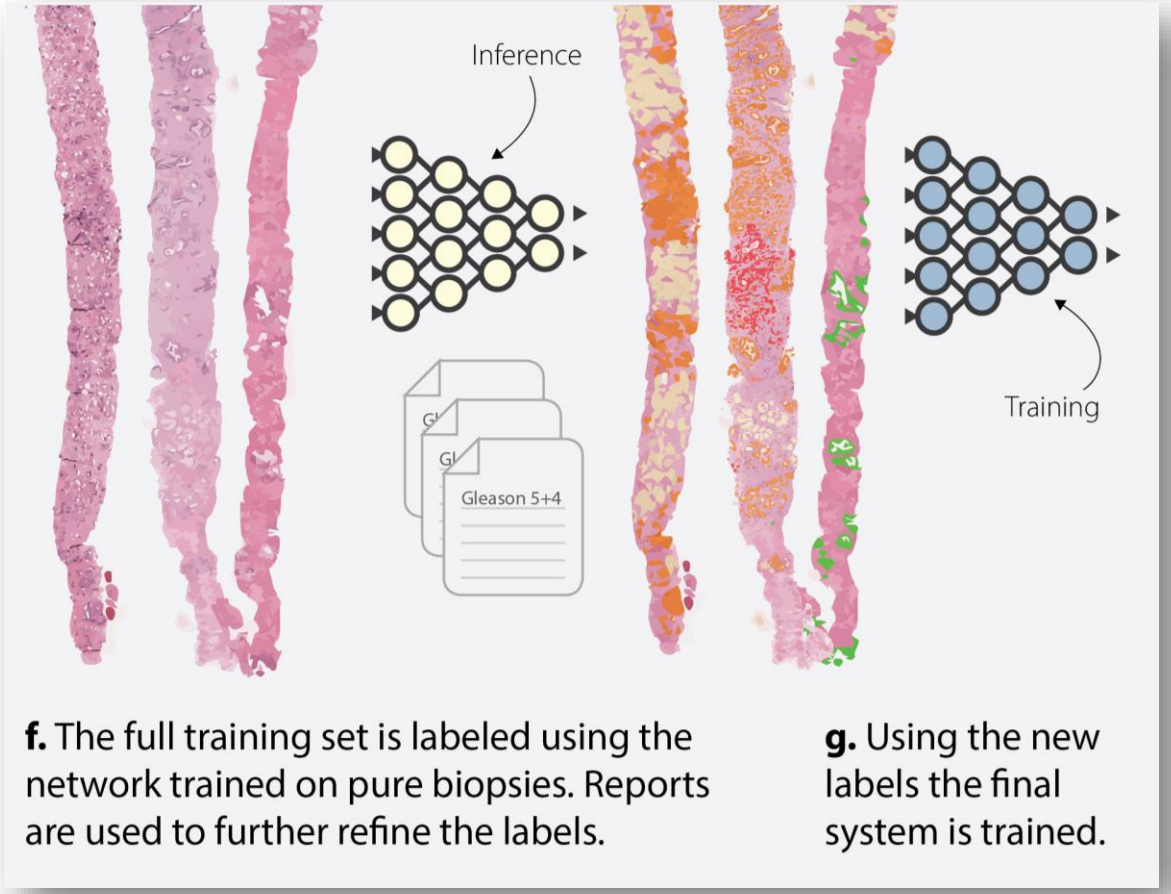
b. First, a rough tumor outline is generated by a tumor detection system.

c. Non-epithelial tissue is then removed by an epithelium segmentation system.

d. The Gleason pattern from the pathologist's report is assigned to the detected tumor area.

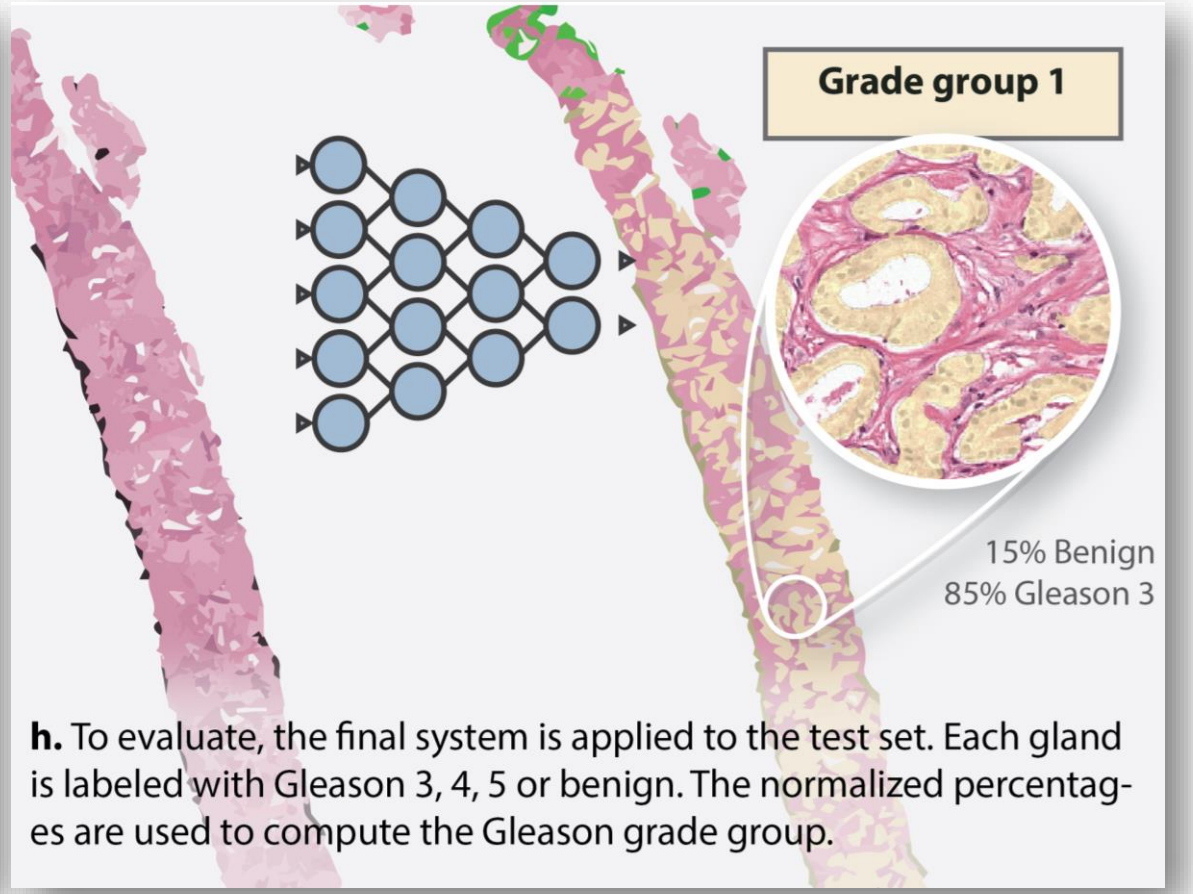
e. A system is trained on pure biopsies only (3+3, 4+4, 5+5). After training, the system can segment patterns individually.

Bulten W, et al. https://arxiv.org/abs/1907.07980



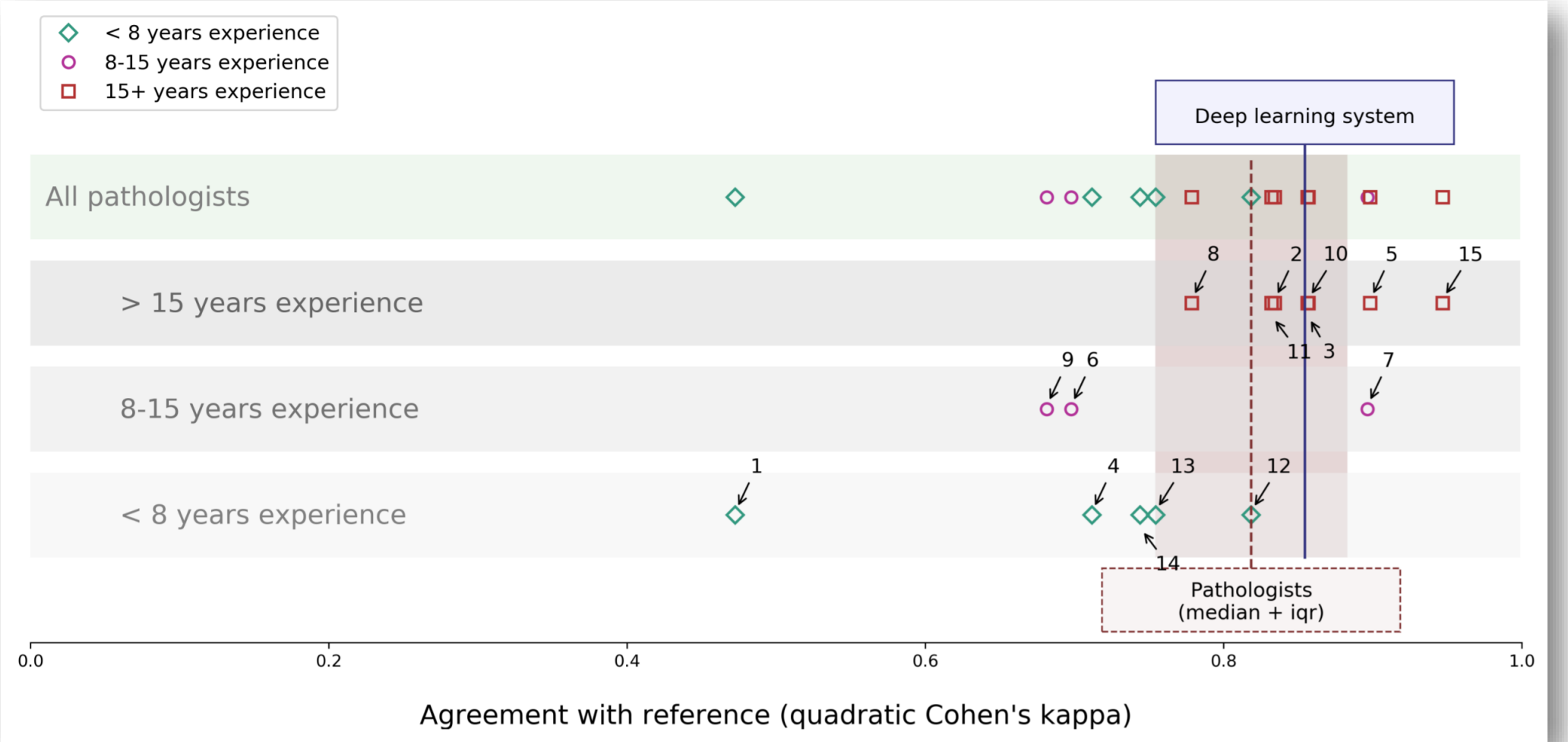
f. The full training set is labeled using the network trained on pure biopsies. Reports are used to further refine the labels.

g. Using the new labels the final system is trained.



h. To evaluate, the final system is applied to the test set. Each gland is labeled with Gleason 3, 4, 5 or benign. The normalized percentages are used to compute the Gleason grade group.

Bulten W, et al. https://arxiv.org/abs/1907.07980


< 8 years experience
8-15 years experience
15+ years experience
Deep learning system
All pathologists
> 15 years experience
8-15 years experience
< 8 years experience
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Agreement with reference (quadratic Cohen's kappa)

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Health

Pathologists shortage 'delaying cancer diagnosis'

By
5 li

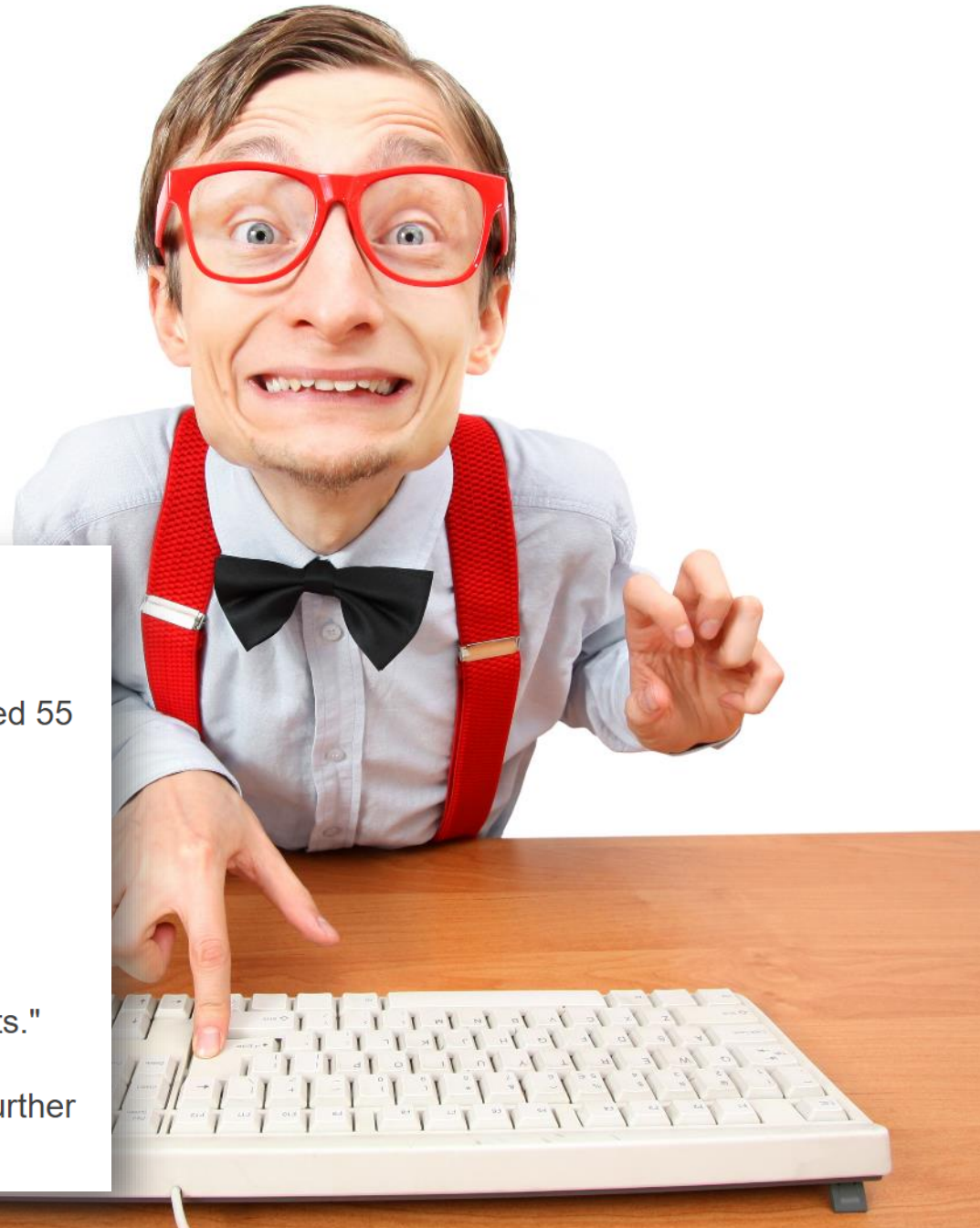
The report says histopathologists are facing intense pressure from increasing workloads due to new NHS screening programmes.

It also warns of an approaching retirement crisis - with a quarter of all staff aged 55 or over.

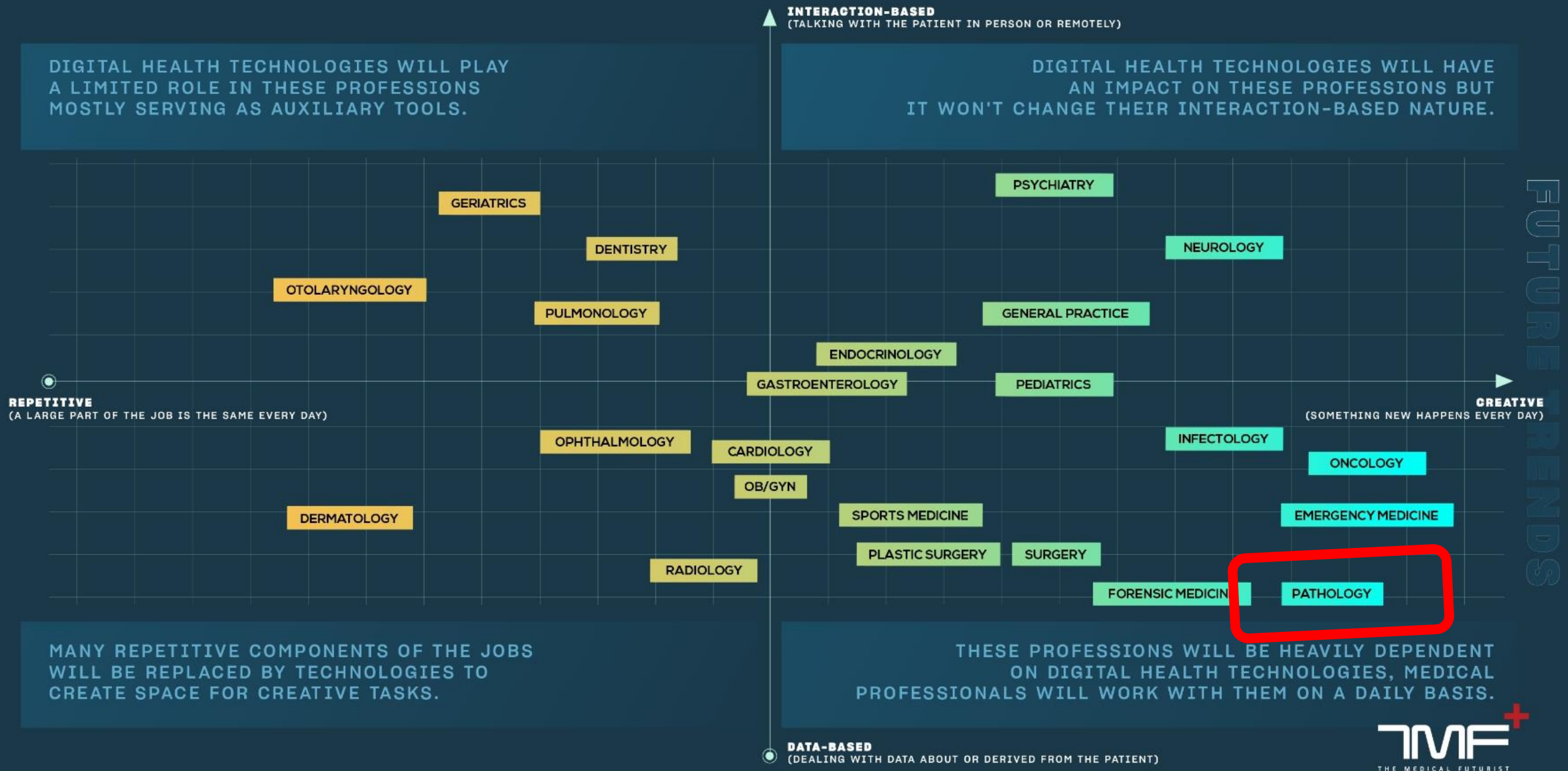
"If this trend continues unchecked, clinical services could be in jeopardy," Prof Martin said.

"Making sure pathology services can cope with current and future demand is essential if we are to ensure early diagnosis and improve outcomes for patients."

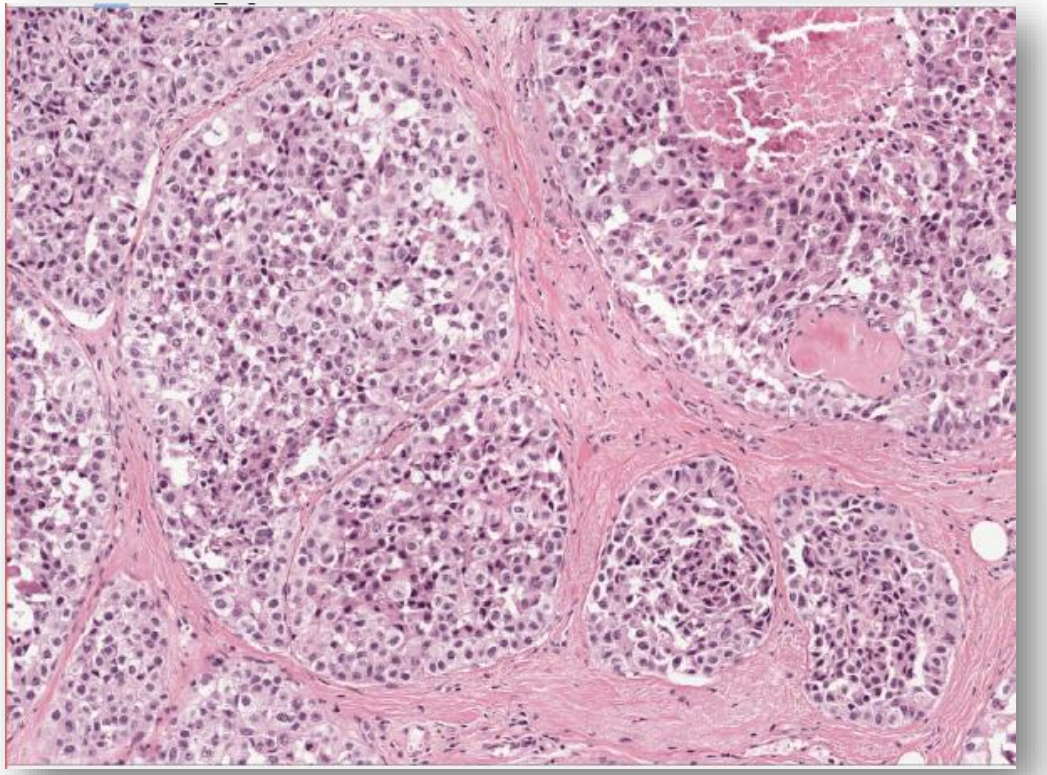
The college is calling for more funded training places, better IT systems and further investment in pathology services.

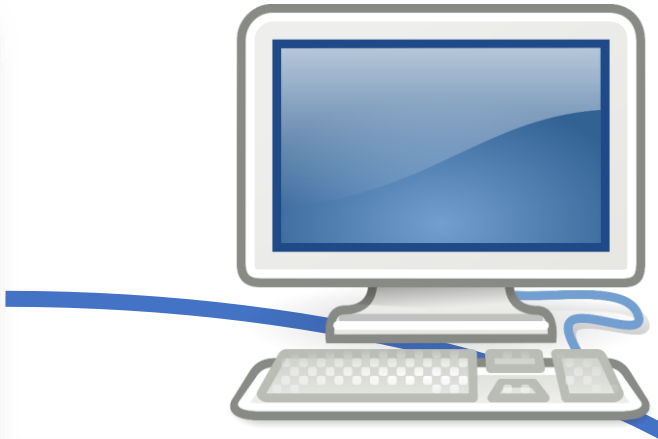


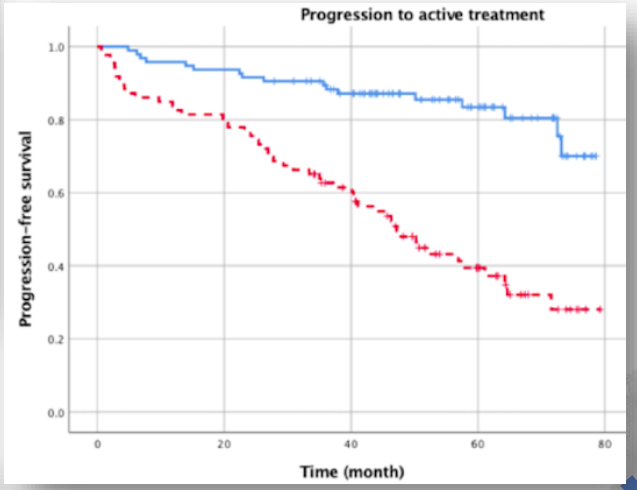
WILL DIGITAL HEALTH TECHNOLOGY REPLACE PHYSICIANS?



THE MEDICAL FUTURIST






Progression to active treatment
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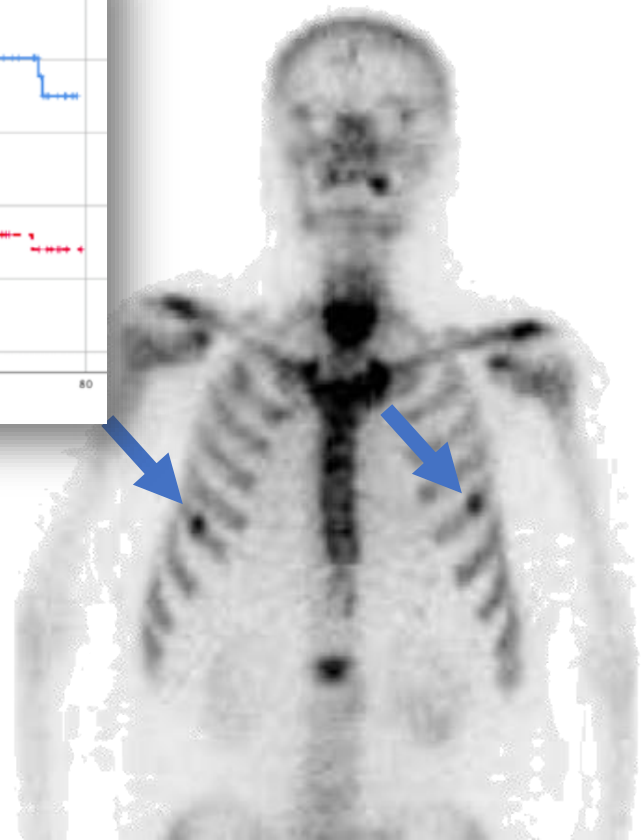
Time (month)



What is Usability?

- **Usability** is *"the extent to which the product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use."*[1]
- Usability is defined by five quality components:
  1. Learnability
  2. Efficiency
  3. Memorability
  4. Errors
  5. Satisfaction

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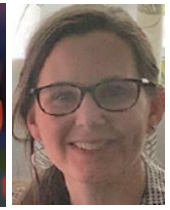
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Scientific staff

Caner Mercan

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David Tellez

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Thomas de Bel

PhD student

Hans Pinckaers

PhD student

Jasper Linmans

PhD student

Mart van Rijthoven

PhD student

Maschenka Balkenhol

Pathology resident and PhD student

Meyke Hermsen

PhD student

Oscar Geessink

PhD student

Péter Bándi

PhD student

Witali Aswolinskiy

Postdoctoral researcher

Wouter Bulten

PhD student

Yiping Jiao

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Zaneta Swiderska-Chadaj

Postdoctoral researcher

John-Melle Bokhorst

PhD student

https://www.computationalpathologygroup.eu

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NEWS

Breast Cancer Testing Scandal Shines Spotlight on Black Box of Clinical Laboratory Testing

by Karyn Hede

A Canadian p… into botched est… has shaken p… cer care and rais… er-sight of la… al tests tha… e wi… nt breast … receiv… c inq… way in N… is … investigating … … wn of estrogen …

…tween 1997 and 2005 … t 1,000 breast cancer pati… correct test results of the … their breast tumors. Of these pa… than 100 have since died, leav… families wondering if inaccurat… cost their loved ones' lives.

Nearly every newly diagn… breast cancer tumor is tested to de… its ER … whose tumors … R posi… therapies such … against …

report the conclusions of the inquiry and will make recommendations for systemic change at the laboratory in July. Separately, more than 200 patients affected by the ER test are participating in a class-action lawsuit against Eastern Health.

An investigative article on the retesting published in the *St. John's Independent*, a weekly newspaper, sparked public outrage … and eventually led to the inquiry, which has revealed overworked pathologists and a … of standards at the Newfoundland …

"Right now what happens is people cover their heads and say, 'Oh yes, that's a problem in Newfoundland or New Brunswick, and they are far, far away. It couldn't happen here. Our understanding is that it could happen many …

Many positions are being filled by foreign-trained pathologists who often work for years without certification by the Royal College of Physicians and Surgeons, Denic said.

Although Canada has a national health care system, health care delivery is handled regionally, with each province operating by its own standards. For example, Newfoundland has no regulatory body that accredits or sets standards for conduct of clinical laboratory tests, whereas Ontario has strict laboratory accreditation requirements. Similarly, in the United States clinical laboratories are regulated on a state-by-state basis, with only 12 states requiring certification of laboratory personnel. The only federal U.S. standard is the Clinical Laboratory Improvement Amendments of 1988, which set a minimum standard of compliance but does not require professional certification for laboratories or their personnel.

"There is really no way of knowing who is working and what their credentials are," said Elissa Passiment, executive director of the American Society for Clinical …

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