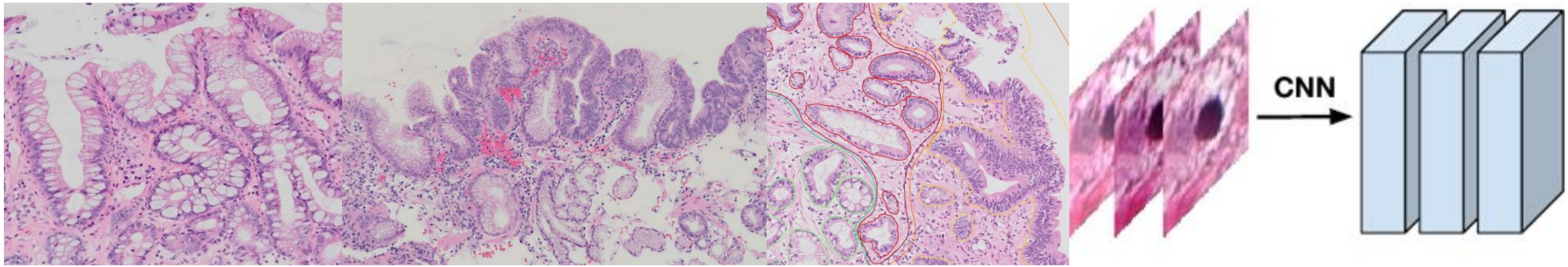
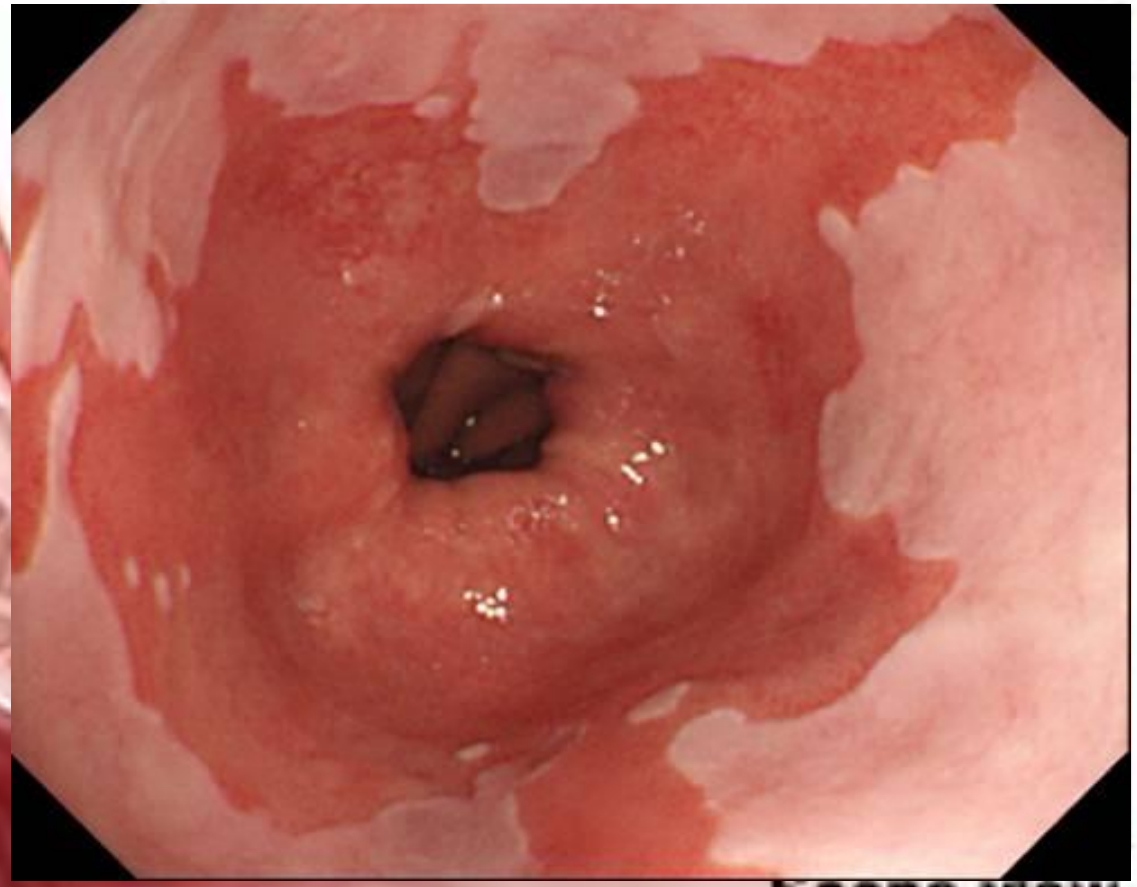
man versus machine: expert histopathology risk stratification in Barrett's esophagus



Sybren L. Meijer

Amsterdam UMC
Universitair Medische Centra

no disclosures



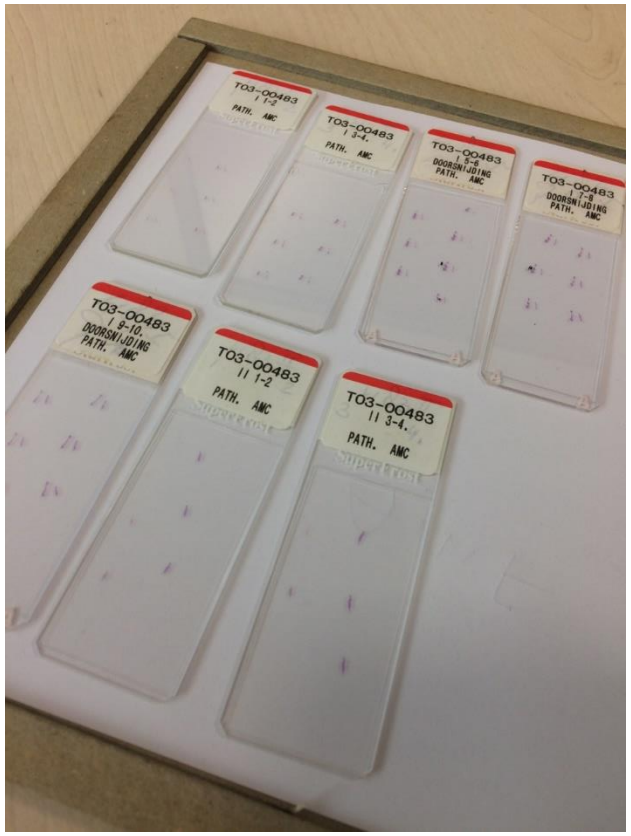
patients with Barrett's Oesophagus

at risk to develop adenocarcinoma

→

Endoscopic surveillance
with biopsies
for risk stratification

Barrett's on biopsy



Normal preexisting squamous epithelium

Squamo columnar junction

Intestinal metaplasia (goblet cells)

Gastric type mucosa

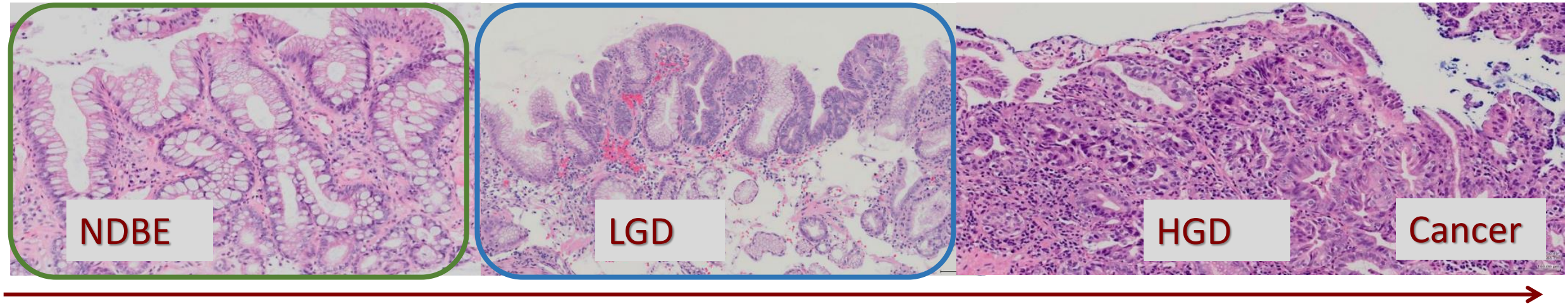
98.54°
x:1.391 cm, y:4.240 mm
100.00 µm

A proportion of patients with Barrett's Oesophagus develop adenocarcinoma

Progression: dysplasia (precursor stage) – carcinoma sequence

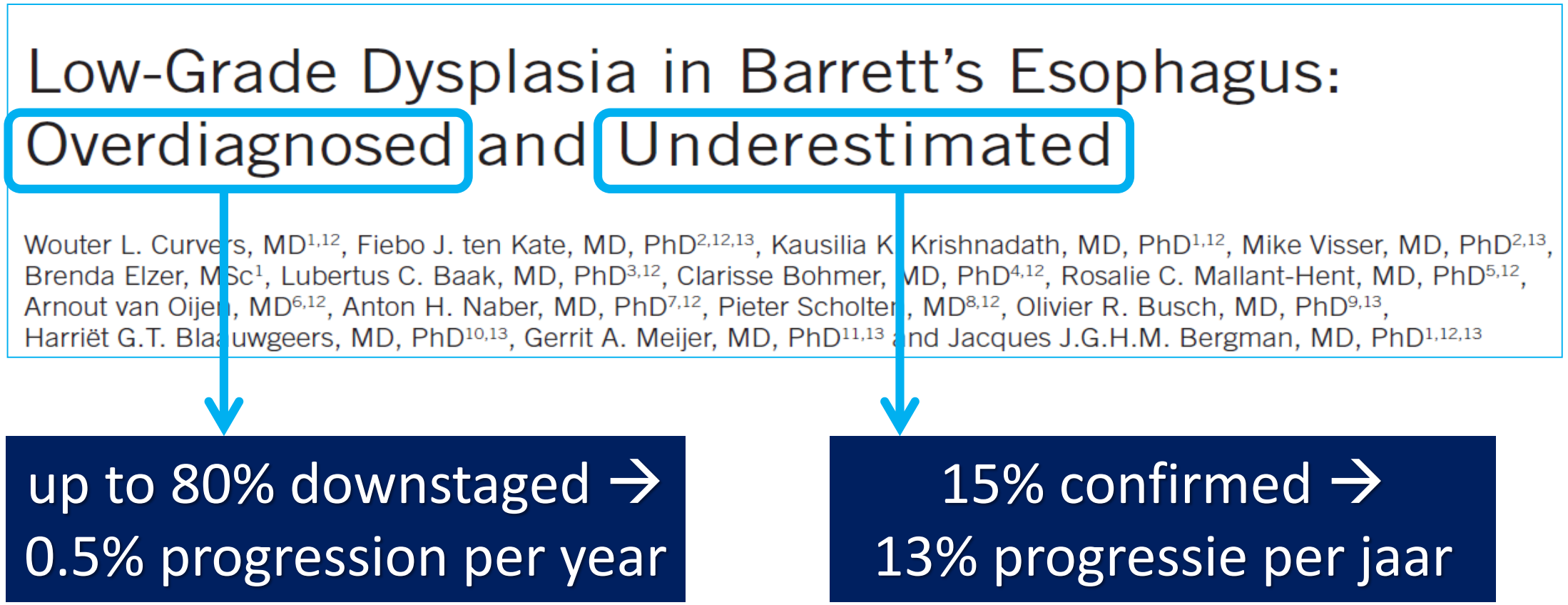
Risk of progression Non Dsyplastic Barrett's epithelium to cancer is low → ~0.3- 0,6 % / year

Path diagnosis of Low Grade Dysplasia on surveilllance: high risk factor for progression



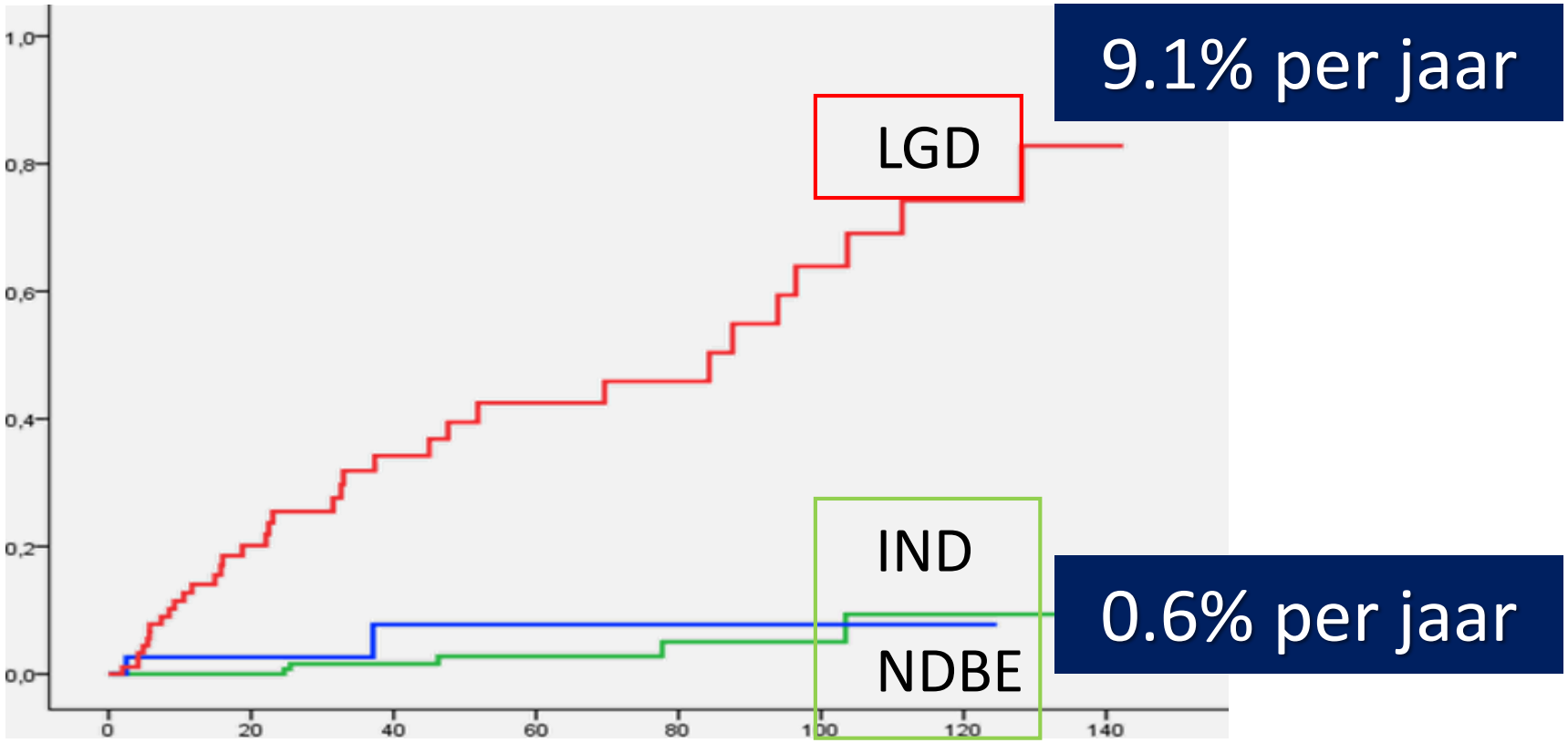
Hvid-Jensen F. NEJM 2011, de Jonge P. Gut 2014; Dutch Barrett guideline

Diagnosis of low grade dysplasia subject to variation



Curvers W. Am J Gastroenterol 2010

Confirmed LGD is a high risk factor for progression

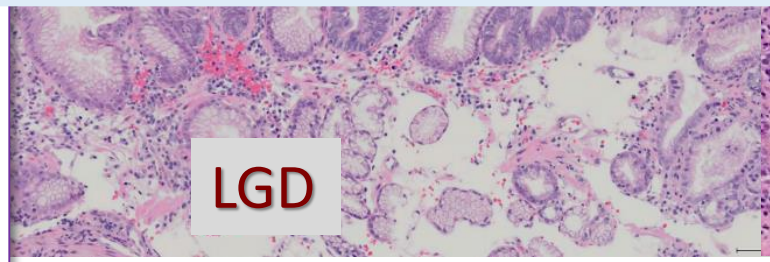


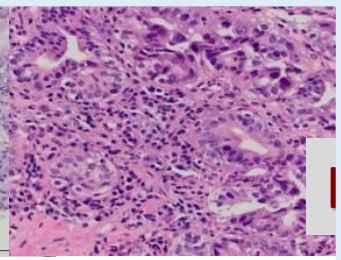
Duits L. Gut 2014

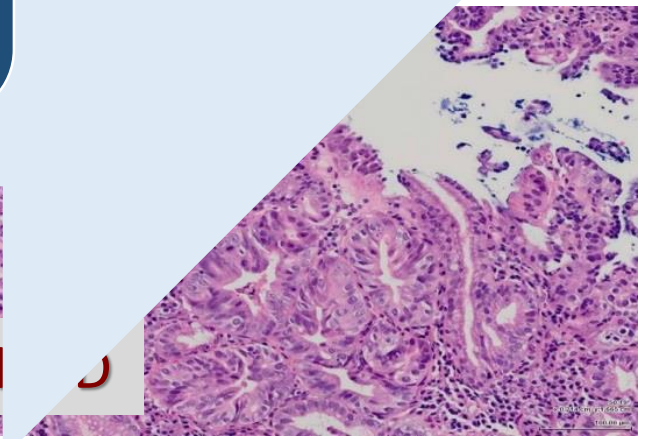
Observer variability has led to need for expert review

- International guidelines recommend that 'all cases of Barrett' ysplasia should be confirmed by a second EXPERT gastro-intestinal pathologist'
- NO definition of EXPERT gastro-intestinal pathologist' exist
- den edict diag

Quantify expertise & homogeneous interpretation







LANS / national network oesophageal neoplasia

National digital pathology panel

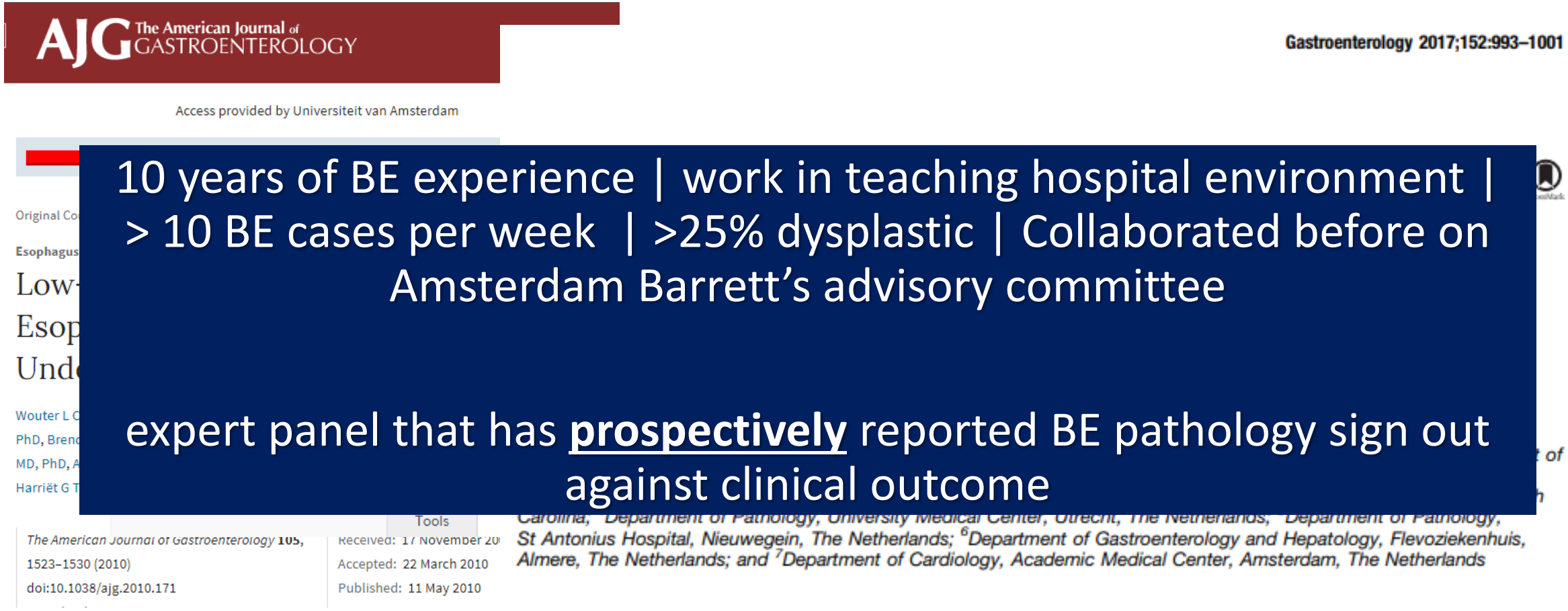
Optimise standard of BE histopathology

Accomodate review for all dysplasia cases in the Netherlands

Homogeneous expert interpretation by large group of pathologists (n = 15) from 9 hospitals

Digital platform

Quantify expertise of 5 ‘core’ pathologists



Digital = conventional microscopy

Diseases of the Esophagus (2017) **30**, 1–7
DOI: 10.1093/dote/dox078

Original Article

Digital microscopy as va
histological evaluation o

M. J. van der Wel,[1,2] L. C. Duits,
O. J. de Boer,[1] J. G. Tijssen,[6] J. J.

Departments of [1] Pathology, and,
nius Hospital, Nieuwegein, and, [4]
of Pathology, Zaans Medical Ce
Amsterdam

Table 2

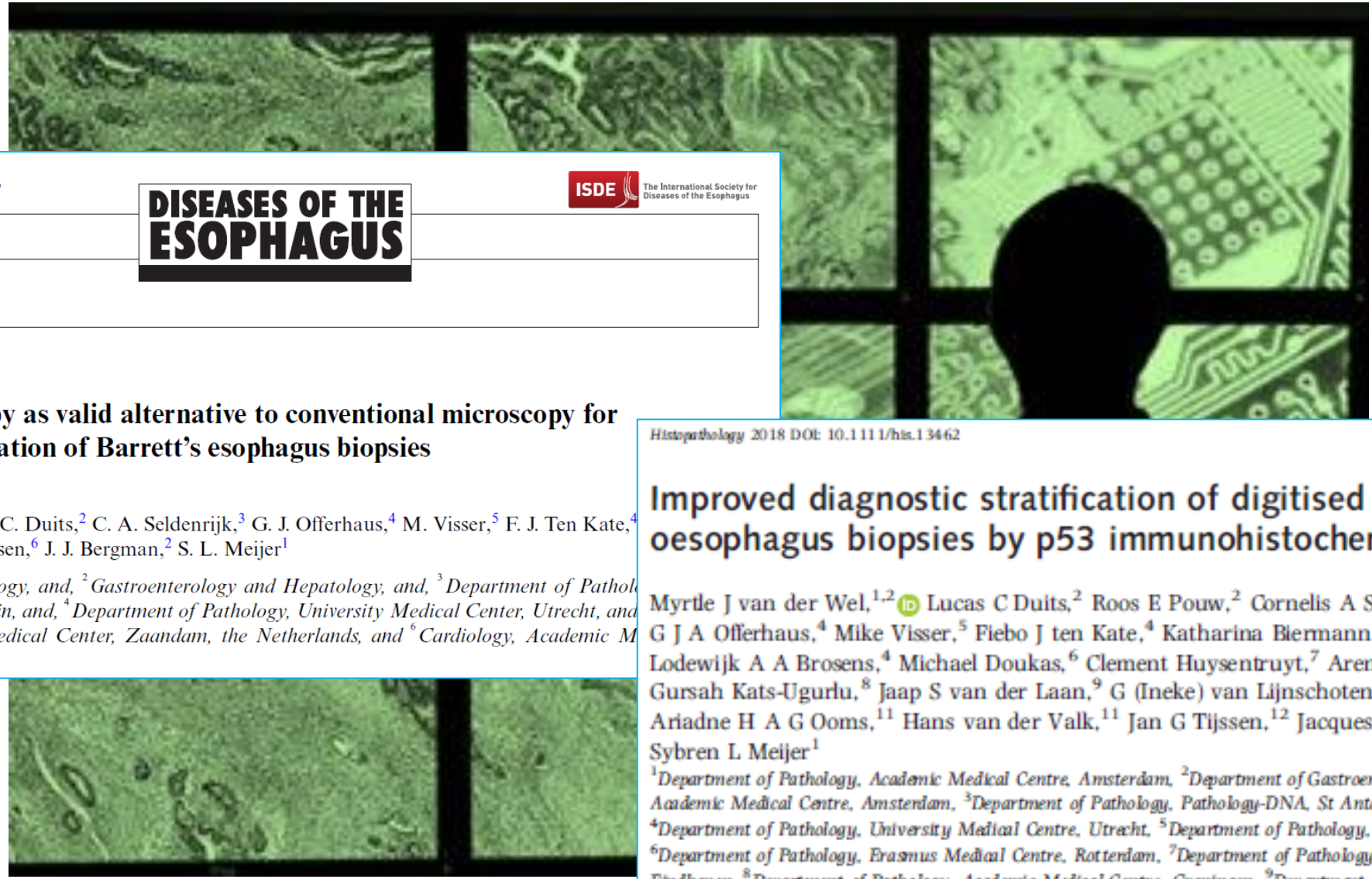
Intraobserver agreement of five expert BE pathologists for digital and conventional microscopy

	Digital microscopy			Conventional microscopy			
Path [†]	Weighted K [‡] (95% CI)	Max K	Weighted/ max K	Weighted K (95% CI)	Max K	Weighted/ max K	*p*-value*
Three categories: NDBE—IND—LGD + HGD [§]							
1	0.85 (0.74–0.95)	0.91	0.92	0.79 (0.68–0.91)	0.90	0.88	
2	0.43 (0.26–0.61)	0.61	0.71	0.78 (0.64–0.91)	0.89	0.87	
3	0.89 (0.81–0.98)	0.97	0.93	0.75 (0.62–0.89)	1.00	0.75	
4	0.54 (0.34–0.74)	0.83	0.65	0.63 (0.44–0.82)	0.71	0.88	
5	0.51 (0.33–0.69)	0.97	0.53	0.77 (0.65–0.90)	0.95	0.82	
Mean	0.64	0.86	0.75	0.74	0.89	0.84	0.35

Table 3

Pairwise interobserver agreement of five expert BE pathologists for digital and conventional microscopy

	Digital microscopy			Conventional microscopy			
Path [†]	Weighted K [‡] (95% CI)	Max K	Weighted/ max K	Weighted K (95% CI)	Max K	Weighted/ max K	*p*-value*
Three categories: NDBE—IND—LGD + HGD [§]							
1–2	0.39 (0.25–0.53)	0.44	0.89	0.53 (0.38–0.69)	0.57	0.95	
1–3	0.78 (0.66–0.90)	0.92	0.85	0.77 (0.65–0.89)	0.93	0.83	
1–4	0.53 (0.35–0.70)	0.65	0.80	0.56 (0.40–0.71)	0.63	0.89	
1–5	0.65 (0.50–0.80)	0.89	0.73	0.60 (0.43–0.76)	0.91	0.66	
2–3	0.35 (0.21–0.49)	0.38	0.91	0.47 (0.31–0.63)	0.53	0.88	
2–4	0.23 (0.11–0.34)	0.23	1.00	0.28 (0.15–0.42)	0.30	0.94	
2–5	0.32 (0.18–0.47)	0.48	0.68	0.49 (0.32–0.66)	0.61	0.81	
3–4	0.57 (0.39–0.75)	0.72	0.79	0.60 (0.43–0.76)	0.65	0.92	
3–5	0.60 (0.44–0.76)	0.84	0.71	0.64 (0.49–0.80)	0.90	0.71	
4–5	0.41 (0.22–0.59)	0.58	0.69	0.52 (0.35–0.68)	0.57	0.92	
Mean	0.48	0.61	0.80	0.55	0.66	0.85	0.17



Diseases of the Esophagus (2017) **30**, 1–7
DOI: 10.1093/dote/dox078

DISEASES OF THE ESOPHAGUS

ISDE The International Society for Diseases of the Esophagus

Original Article

Digital microscopy as valid alternative to conventional microscopy for histological evaluation of Barrett's esophagus biopsies

M. J. van der Wel,[1,2] L. C. Duits,[2] C. A. Seldenrijk,[3] G. J. Offerhaus,[4] M. Visser,[5] F. J. Ten Kate,[4] O. J. de Boer,[1] J. G. Tijssen,[6] J. J. Bergman,[2] S. L. Meijer[1]

Departments of [1]Pathology, and, [2]Gastroenterology and Hepatology, and, [3]Department of Pathol nius Hospital, Nieuwegein, and, [4]Department of Pathology, University Medical Center, Utrecht, and of Pathology, Zaans Medical Center, Zaandam, the Netherlands, and [6]Cardiology, Academic M Amsterdam

Histopathology 2018 DOI: 10.1111/his.13462

Improved diagnostic stratification of digitised Barrett's oesophagus biopsies by p53 immunohistochemical staining

Myrtle J van der Wel,[1,2] Lucas C Duits,[2] Roos E Pouw,[2] Cornelis A Seldenrijk,[3] G J A Offerhaus,[4] Mike Visser,[5] Fiebo J ten Kate,[4] Katharina Biermann,[6] Lodewijk A A Brosens,[4] Michael Doukas,[6] Clement Huysentruyt,[7] Arend Karrenbeld,[8] Gursah Kats-Ugurlu,[8] Jaap S van der Laan,[9] G (Ineke) van Lijnschoten,[7] Freek C P Moll,[10] Ariadne H A G Ooms,[11] Hans van der Valk,[11] Jan G Tijssen,[12] Jacques J Bergman[2] & Sybren L Meijer[1]

[1]Department of Pathology, Academic Medical Centre, Amsterdam, [2]Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, [3]Department of Pathology, Pathology-DNA, St Antonius Hospital, Nieuwegein, [4]Department of Pathology, University Medical Centre, Utrecht, [5]Department of Pathology, Symbiant BV, Alkmaar, [6]Department of Pathology, Erasmus Medical Centre, Rotterdam, [7]Department of Pathology, Stichting PAMM, Eindhoven, [8]Department of Pathology, Academic Medical Centre, Groningen, [9]Department of Pathology, Haga Hospital, The Hague, [10]Department of Pathology, Isala Clinics, Zwolle, [11]Department of Pathology, St Fransiscus Vlietland Gasthuis, Pathan BV, Rotterdam, and [12]Department of Cardiology, Academic Medical Centre, Amsterdam, The Netherlands

Develop quality criteria for assessing BE biopsies

Original Article

Development
criteria for as
Barrett's oeso

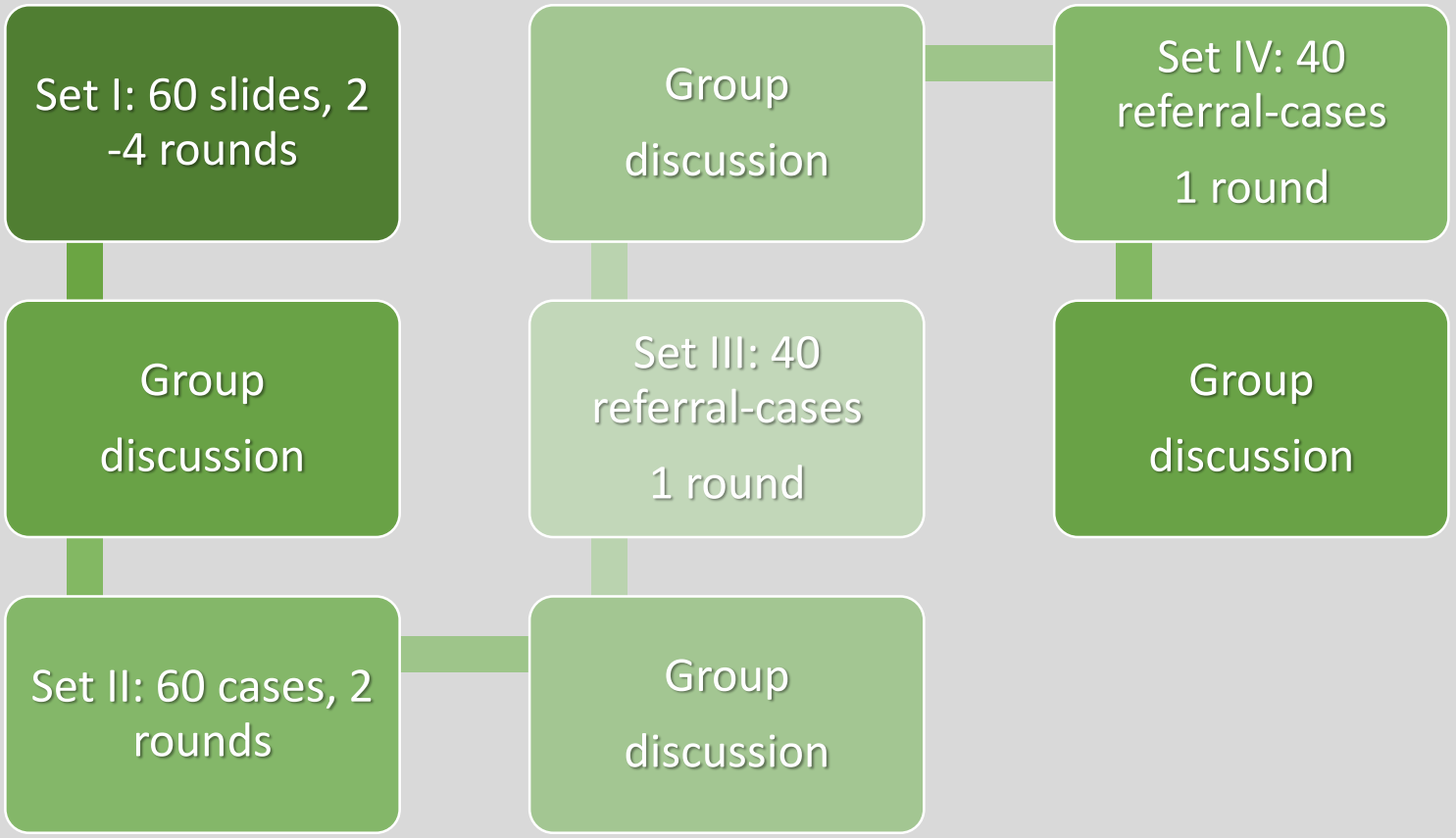
MJ van der Wel[1,2], LC
GJA Offerhaus[4], M Vi
and SL Meijer[1]

Table 7.

Values for benchmark quality criteria based on 95% prediction interval of five core pathologists.

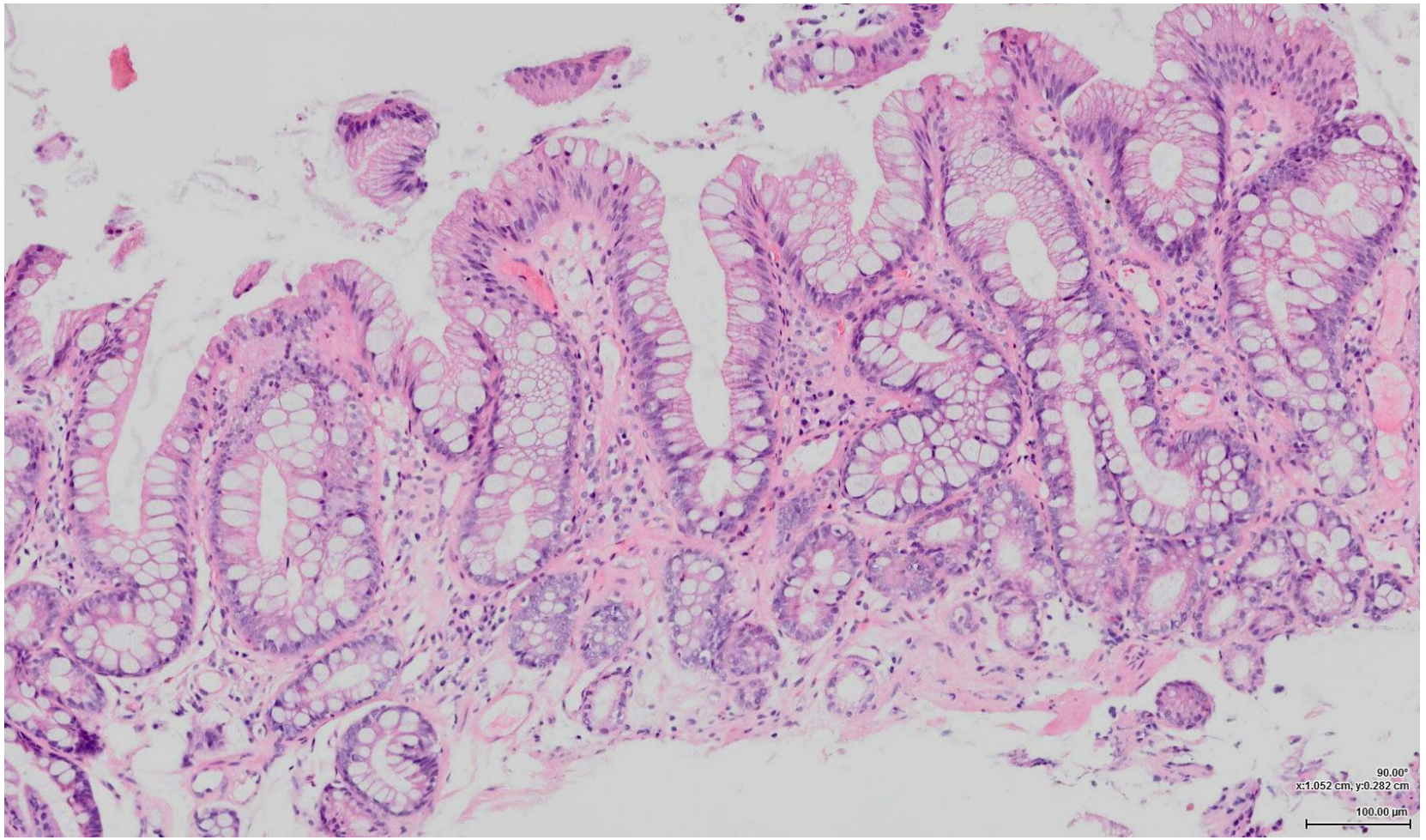
Quality criterium	95% PI core pathologists all cases ($n = 60$)[b]	Benchmark value	95% PI core pathologists' dysplastic cases ($n = 39$)	Benchmark value
Percentage of IND[a] cases (%)	3–14%	≤14%	–2 to 16%	≤16%
Intra-observer agreement in three categories (K)	0.66–1.02	≥0.66	0.39–0.73	≥0.39
Agreement with consensus gold standard diagnosis (%)	82–98%	≥82%	73–104%	≥73%
Consensus HGD cases misdiagnosed as NDBE[d] (%; fraction)	0.8% (1/120)	≤0.8% (1/120)	1.3% (1/78)	≤1.3% (1/78)

Expand panel from 5 -15 pathologists

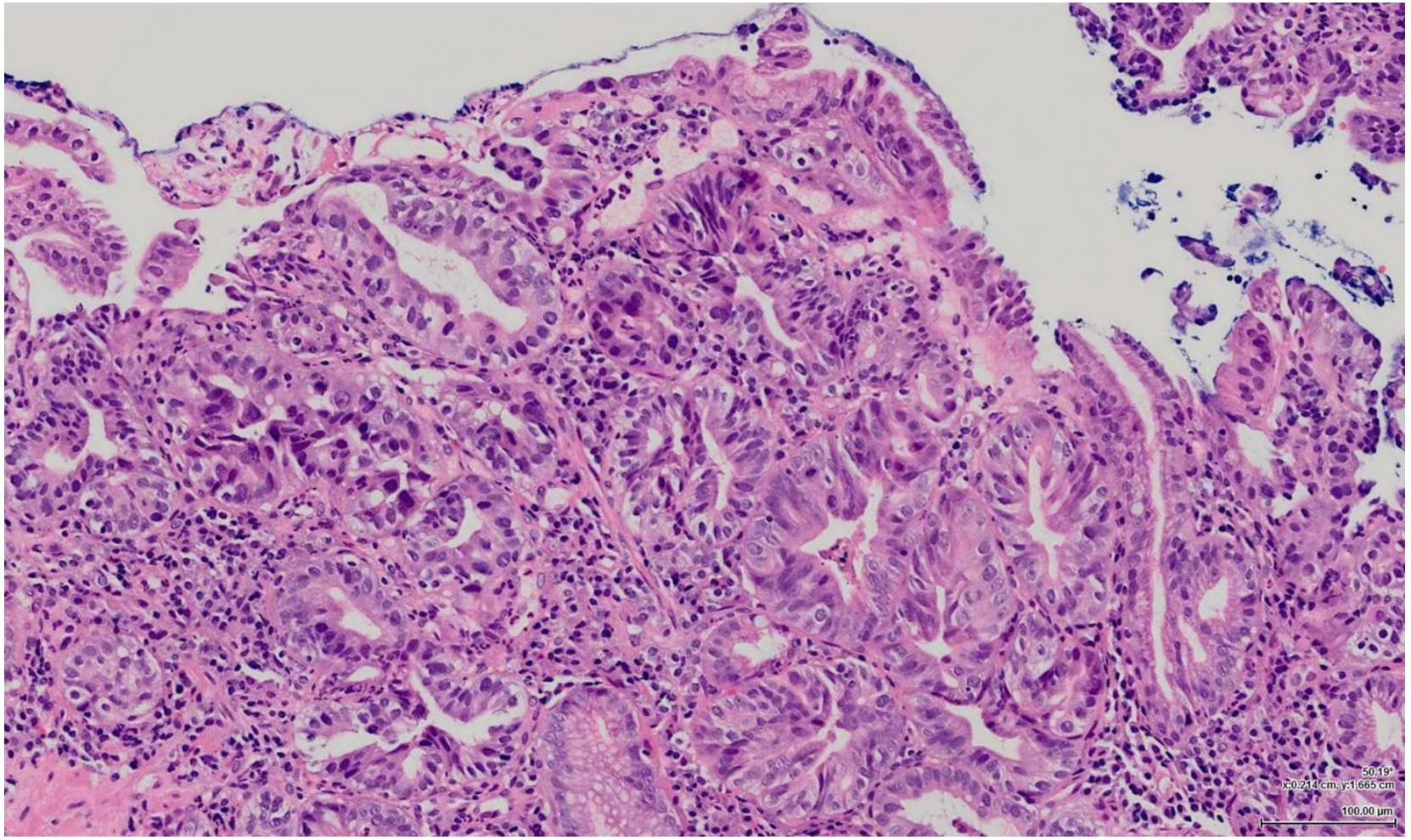


What difficulties are we talking about?

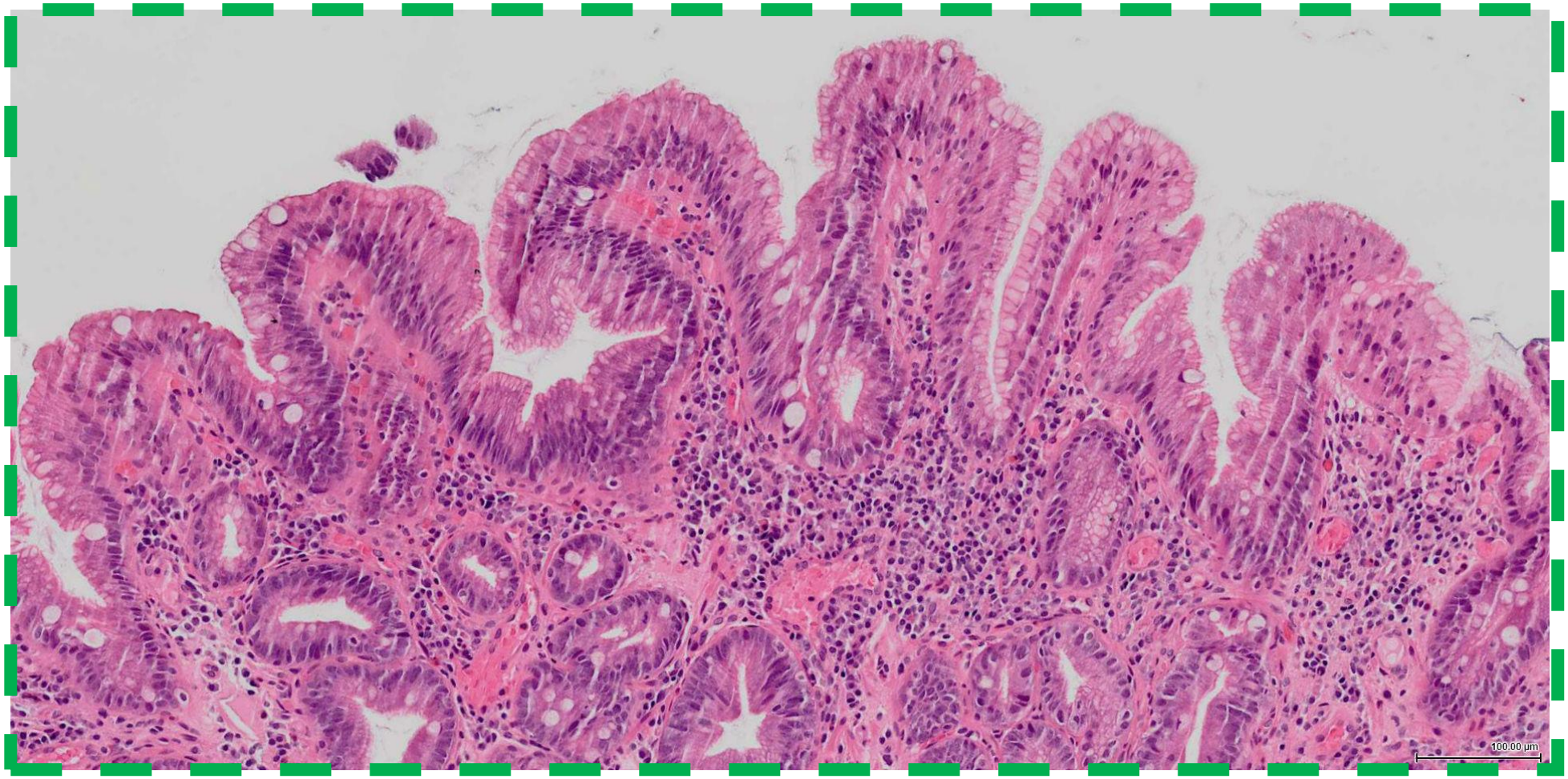
Obvious Non-dysplastic Barrett's:



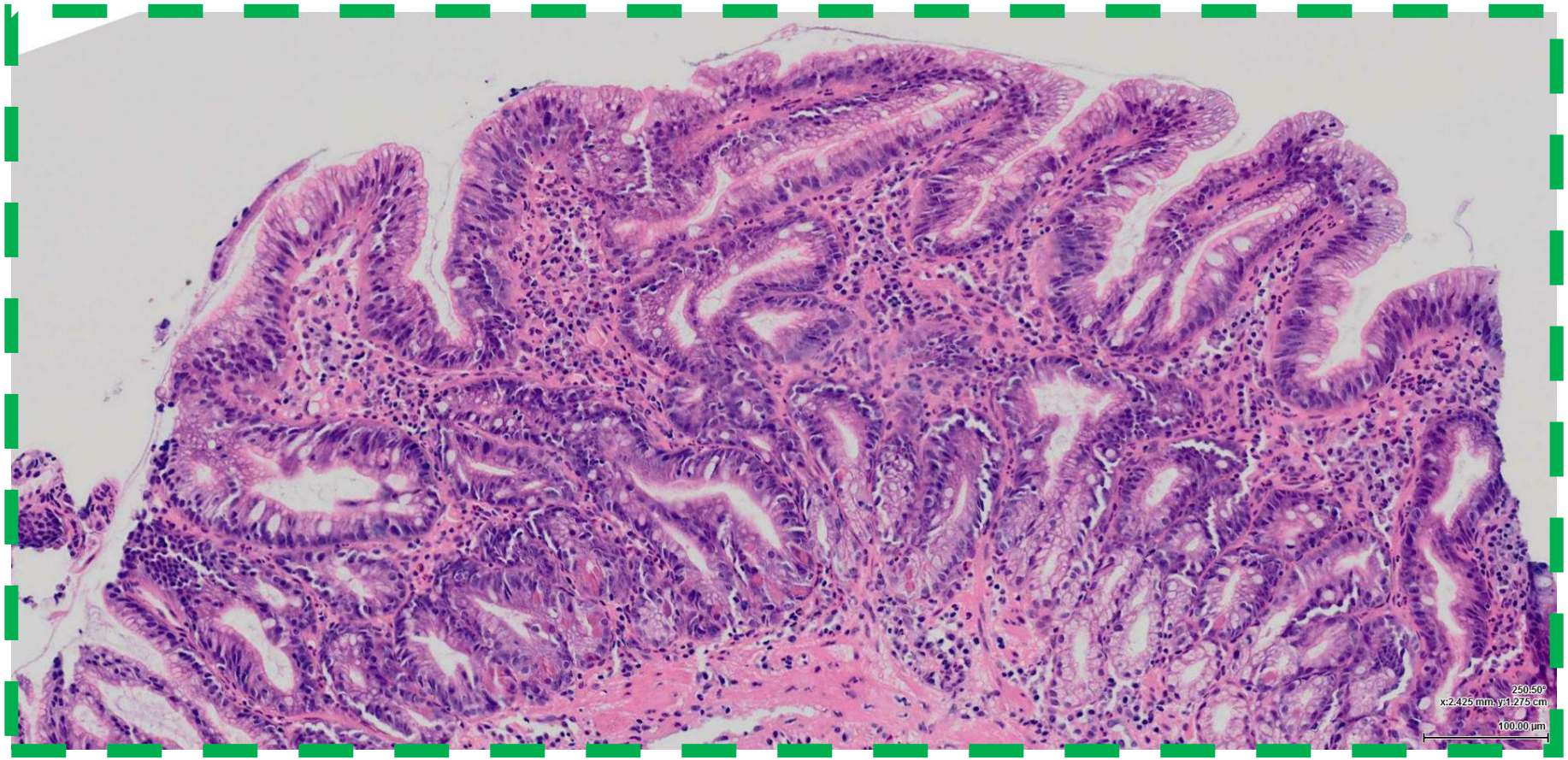
…obvious dysplastic Barrett's

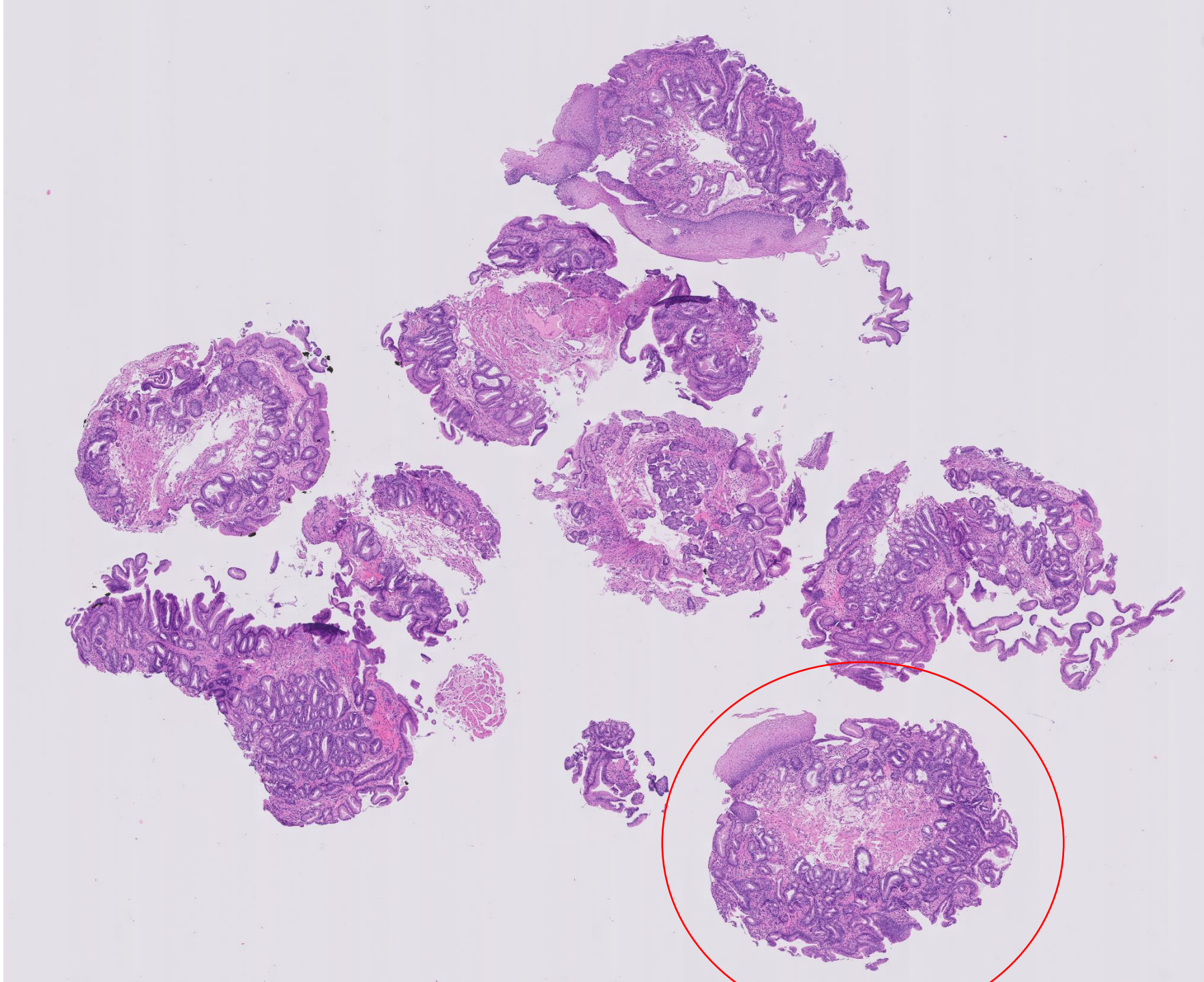


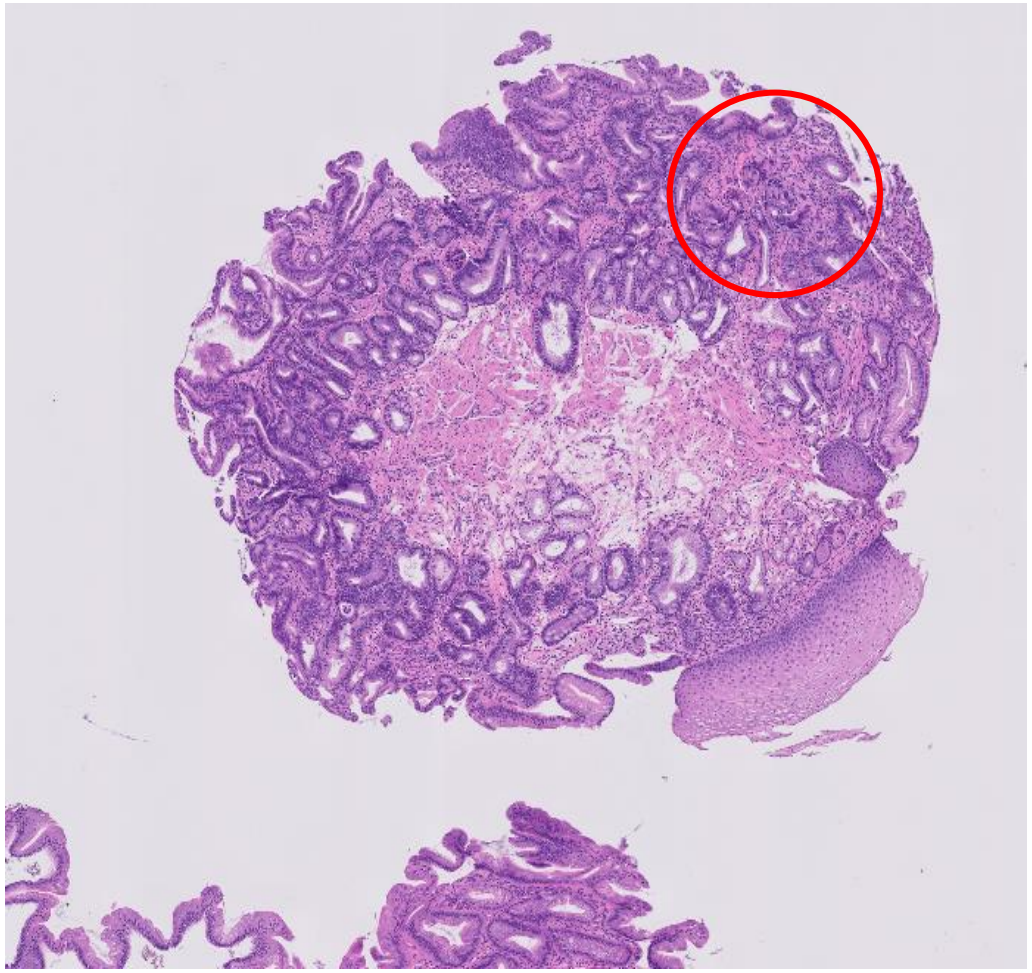
Dysplasia or no dysplasia?

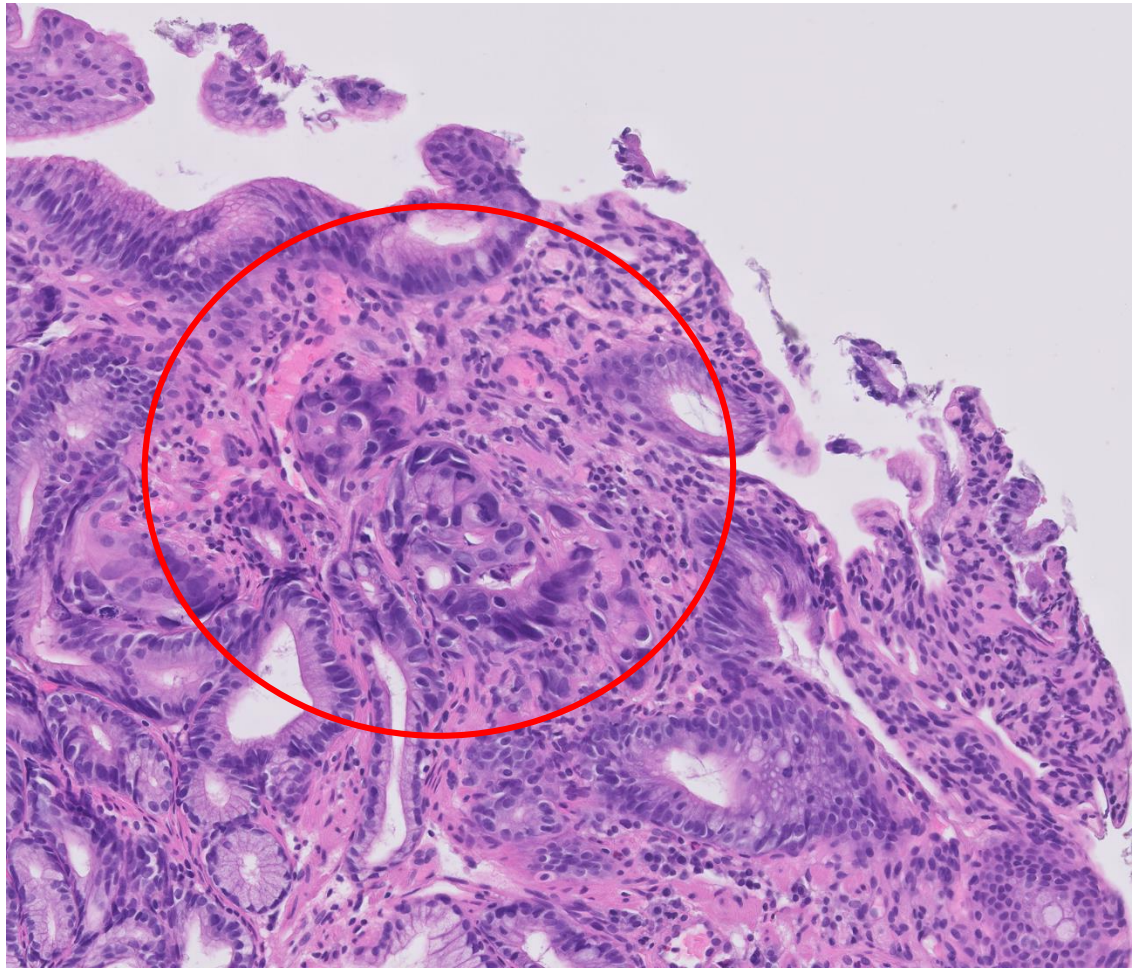


Dysplasia or no dysplasia?









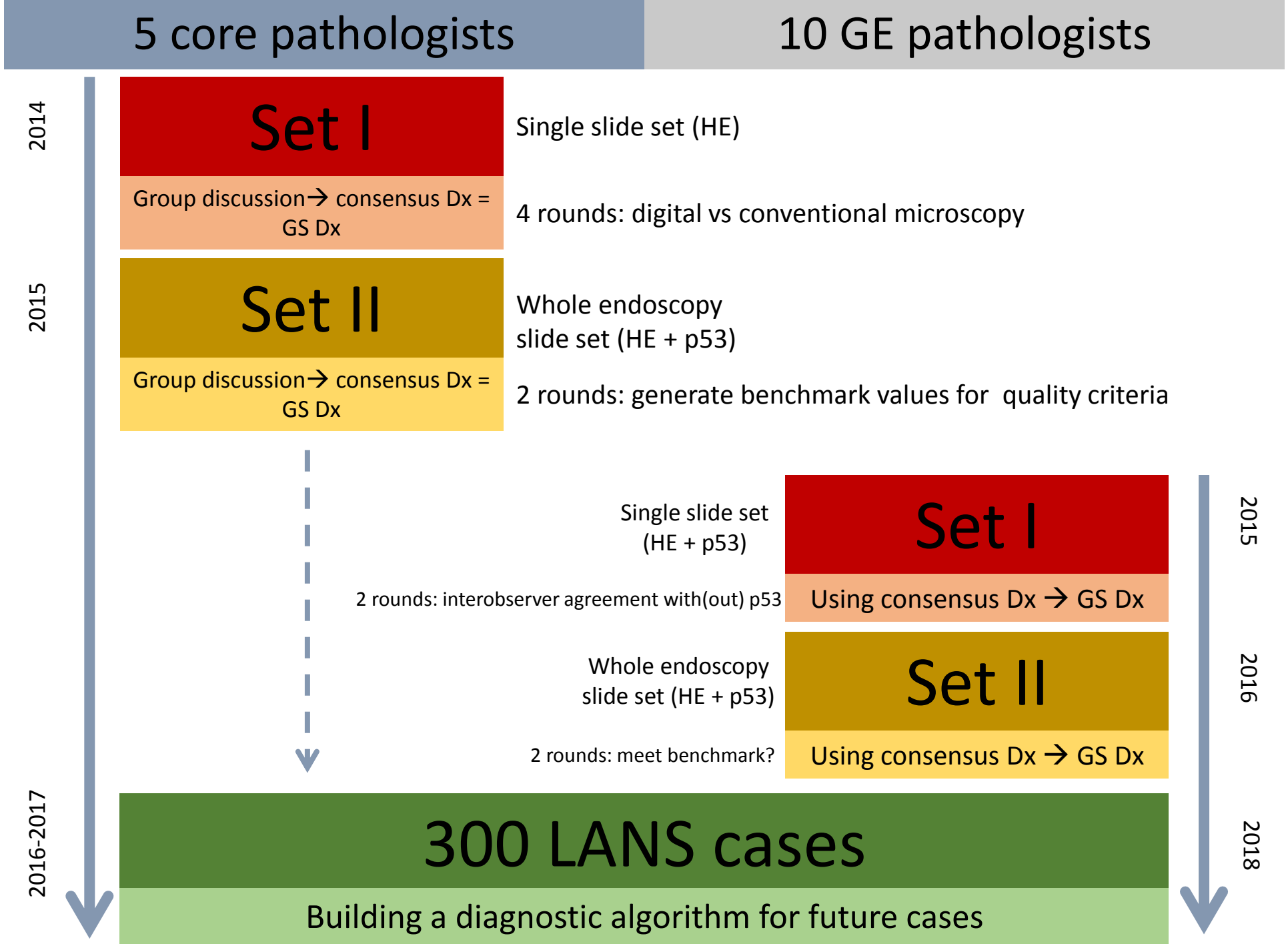

5 core pathologists
10 GE pathologists
2014
2015
2016-2017
Set I
Single slide set (HE)
Group discussion→ consensus Dx = GS Dx
4 rounds: digital vs conventional microscopy
Set II
Whole endoscopy slide set (HE + p53)
Group discussion→ consensus Dx = GS Dx
2 rounds: generate benchmark values for quality criteria
Single slide set (HE + p53)
Set I
2 rounds: interobserver agreement with(out) p53
Using consensus Dx → GS Dx
Whole endoscopy slide set (HE + p53)
Set II
2 rounds: meet benchmark?
Using consensus Dx → GS Dx
2015
2016
2018
300 LANS cases
Building a diagnostic algorithm for future cases

Figure 1: Improvement of Pathologist Expertise on Assessment of Dysplastic BE Biopsies Related to Benchmark Values Over a Timeline of 5 Study Sets

Legend: scale varies from red-orange-yellow to green, with red being least and green being significantly consistent with gold standard diagnosis

<u>2013 – 2018:</u>

15 pathologist

assessed

31500 slides

generating

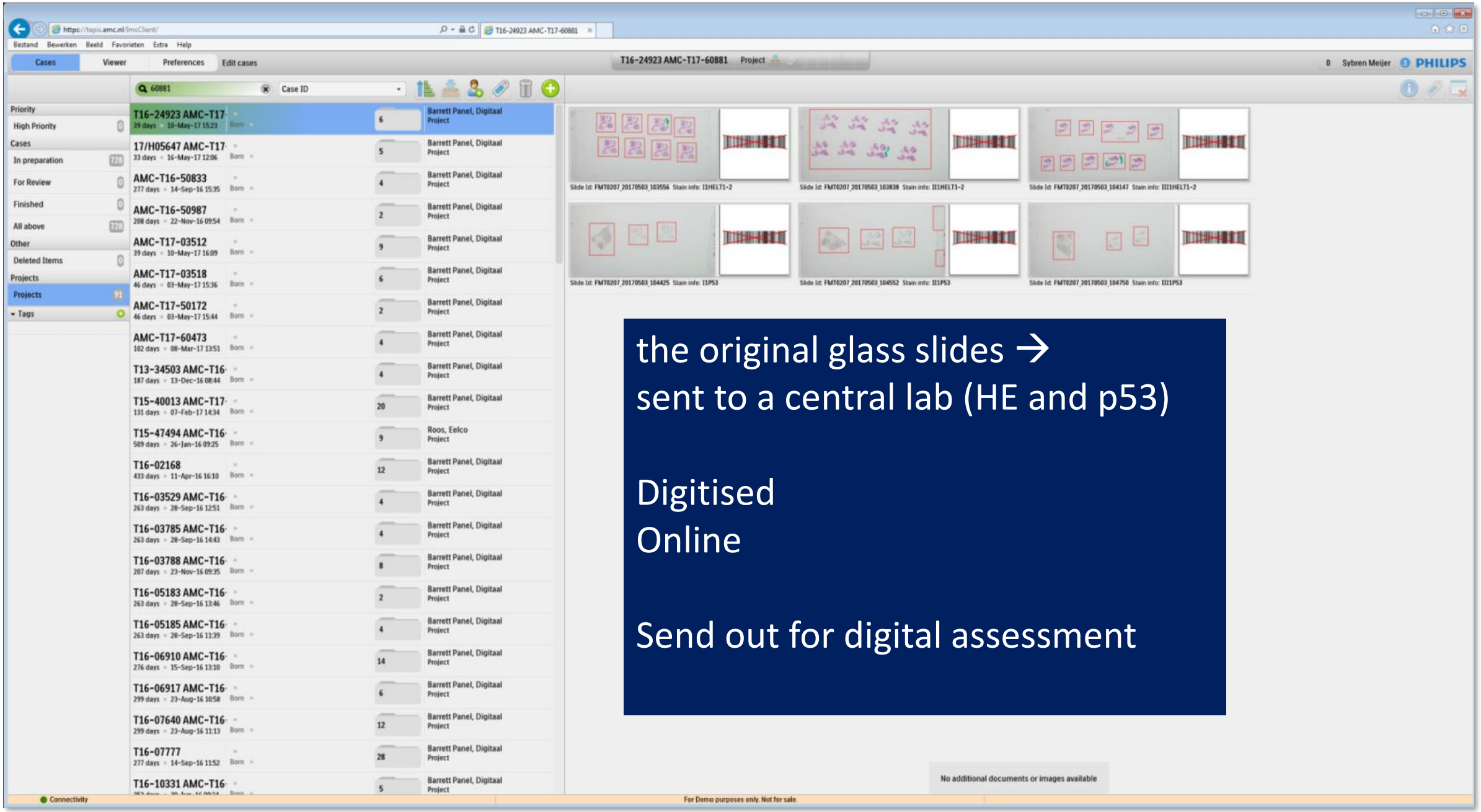
6000 diagnoses

All 15 pathologists adhering to expert benchmark criteria

LGD dysplasia in the Netherlands: Online case review request

Gastroenterologist or pathologist

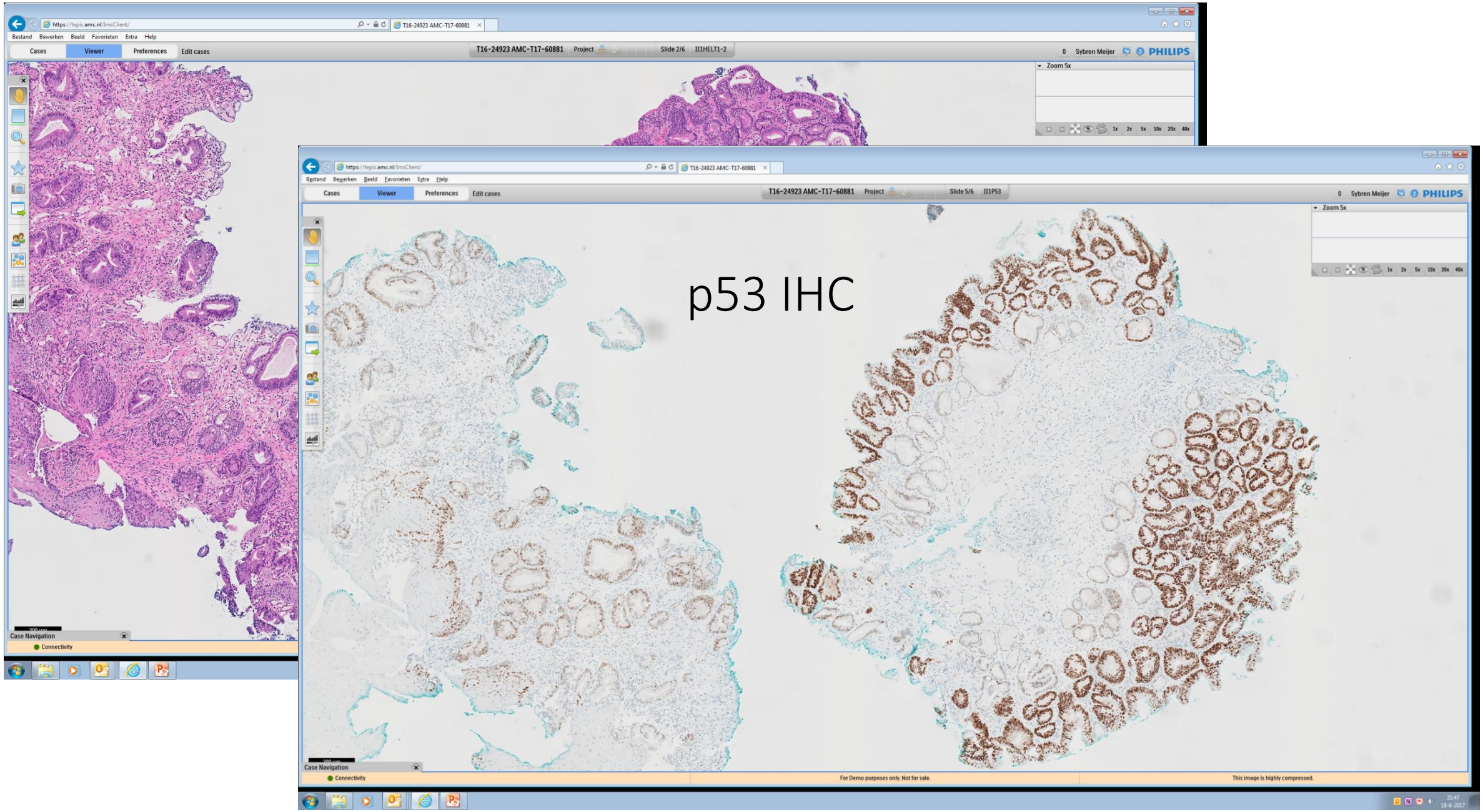
Protected webform on www.barrett.nl

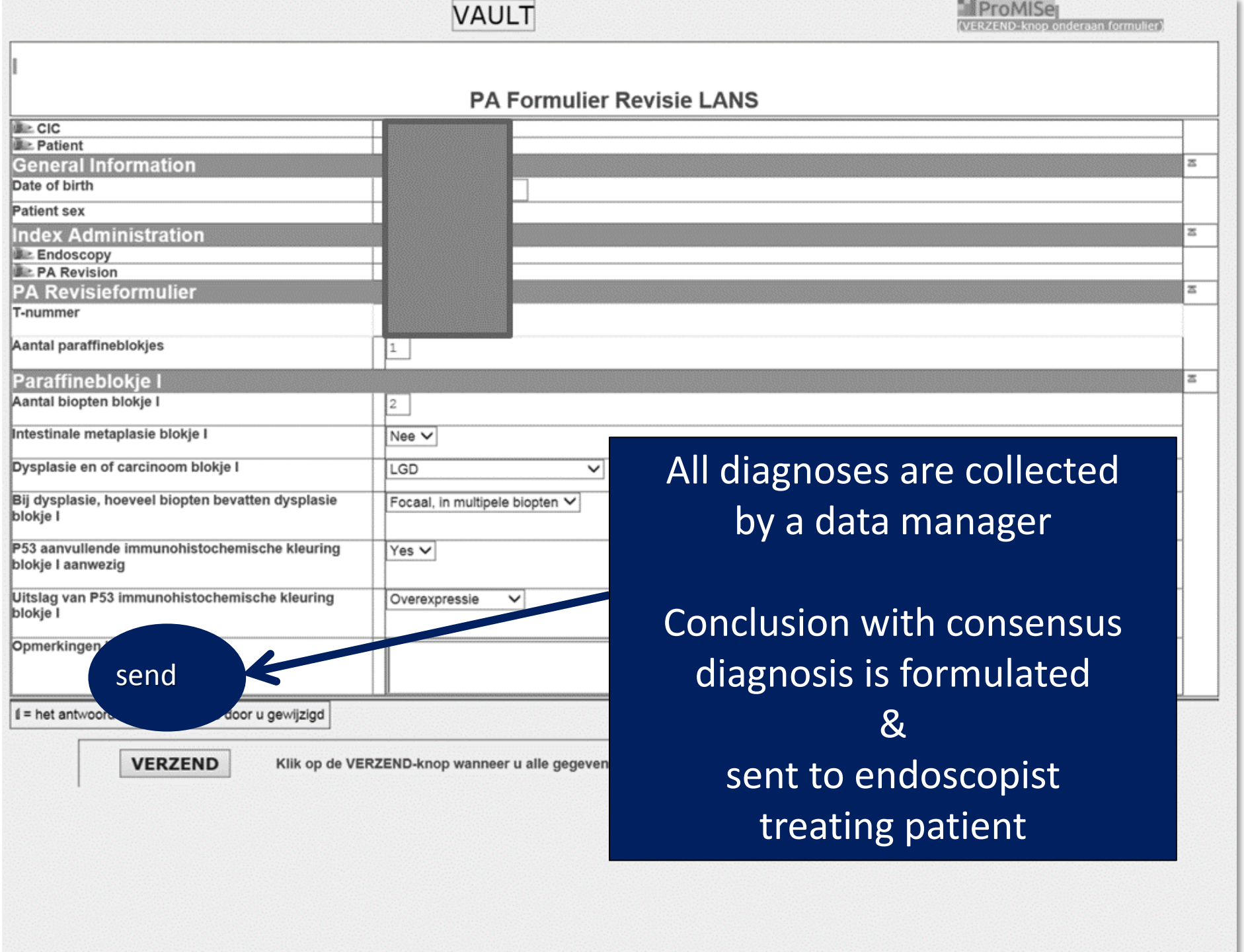


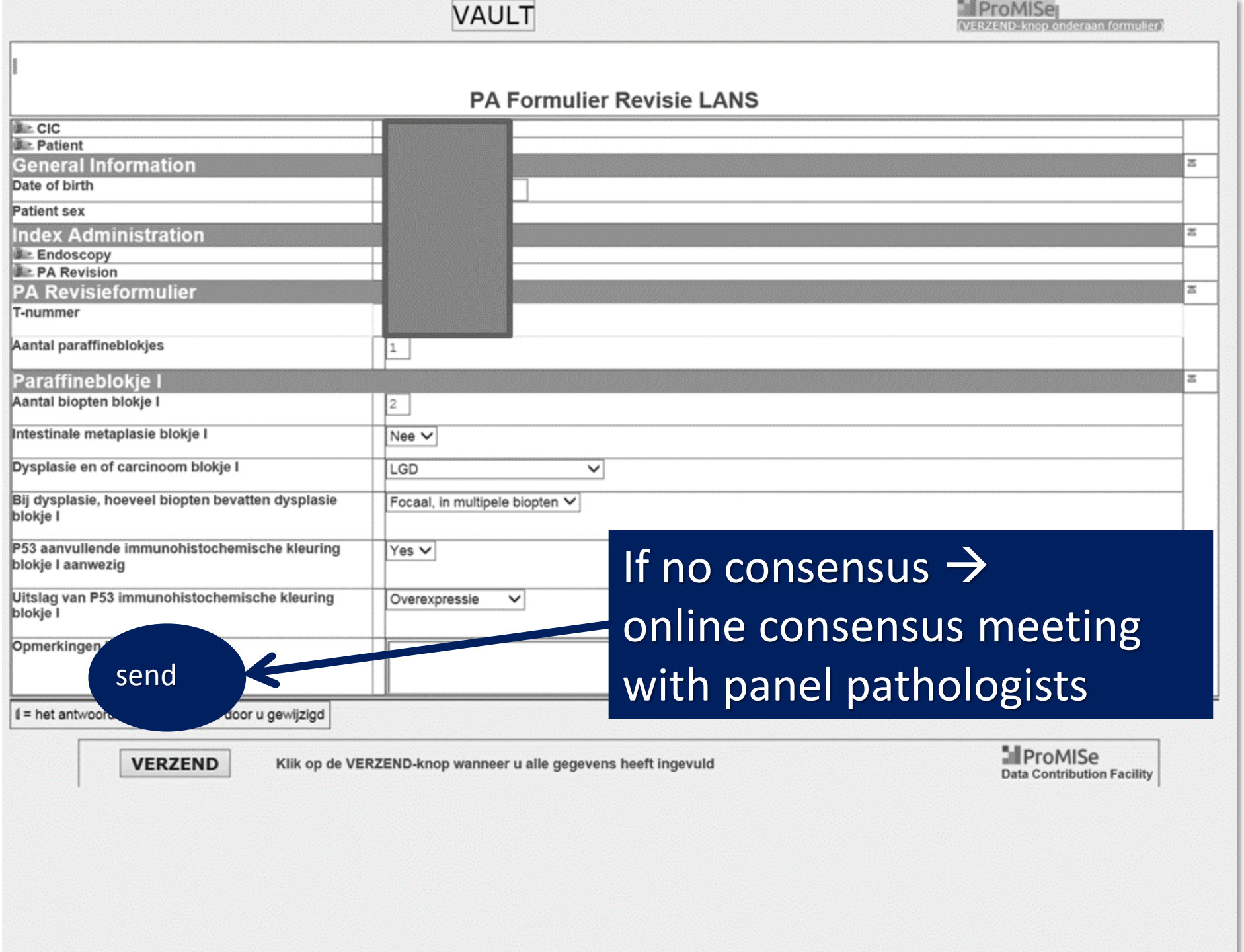
the original glass slides →
sent to a central lab (HE and p53)

Digitised
Online

Send out for digital assessment


p53 IHC


VAULT
ProMISe
(VERZEND-knop onderaan formulier)
PA Formulier Revisie LANS
CIC
Patient
General Information
Date of birth
Patient sex
Index Administration
Endoscopy
PA Revision
PA Revisieformulier
T-nummer
Aantal paraffineblokjes
1
Paraffineblokje I
Aantal biopten blokje I
2
Intestinale metaplasie blokje I
Nee
Dysplasie en of carcinoom blokje I
LGD
Bij dysplasie, hoeveel biopten bevatten dysplasie blokje I
Focaal, in multipele biopten
P53 aanvullende immunohistochemische kleuring blokje I aanwezig
Yes
Uitslag van P53 immunohistochemische kleuring blokje I
Overexpressie
Opmerkingen
send
door u gewijzigd
VERZEND
Klik op de VERZEND-knop wanneer u alle gegeven
All diagnoses are collected by a data manager
Conclusion with consensus diagnosis is formulated
&
sent to endoscopist treating patient


VAULT
ProMISe
(VERZEND-knop onderaan formulier)
PA Formulier Revisie LANS
CIC
Patient
General Information
Date of birth
Patient sex
Index Administration
Endoscopy
PA Revision
PA Revisieformulier
T-nummer
Aantal paraffineblokjes
1
Paraffineblokje I
Aantal biopten blokje I
2
Intestinale metaplasie blokje I
Nee
Dysplasie en of carcinoom blokje I
LGD
Bij dysplasie, hoeveel biopten bevatten dysplasie blokje I
Focaal, in multipele biopten
P53 aanvullende immunohistochemische kleuring blokje I aanwezig
Yes
Uitslag van P53 immunohistochemische kleuring blokje I
Overexpressie
Opmerkingen
send
If no consensus →
online consensus meeting
with panel pathologists
door u gewijzigd
VERZEND
Klik op de VERZEND-knop wanneer u alle gegevens heeft ingevuld
ProMISe
Data Contribution Facility

national network oesophageal neoplasia CASE REVIEW

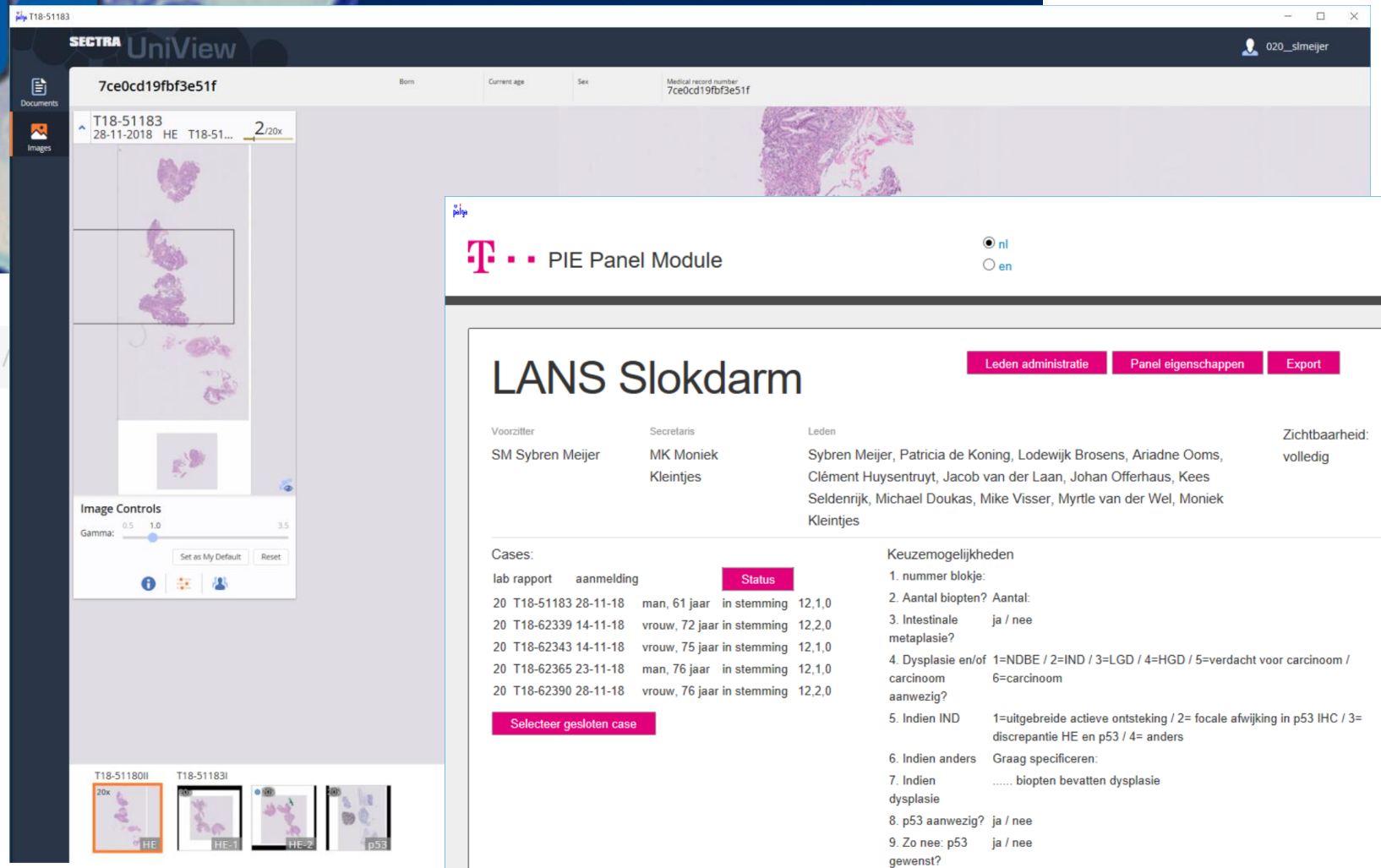
		Cases
	Referral diagnosis)	NDBE 15 (6%) IND 65 (25%) LGD 158 (62%) HGD 17 (7%)
		255
Confirmed Dx		155 (61%)
Altered Dx		100 (39%)
	Downstaged	61 (61%)
	Upstaged	39 (39%)

Intranet

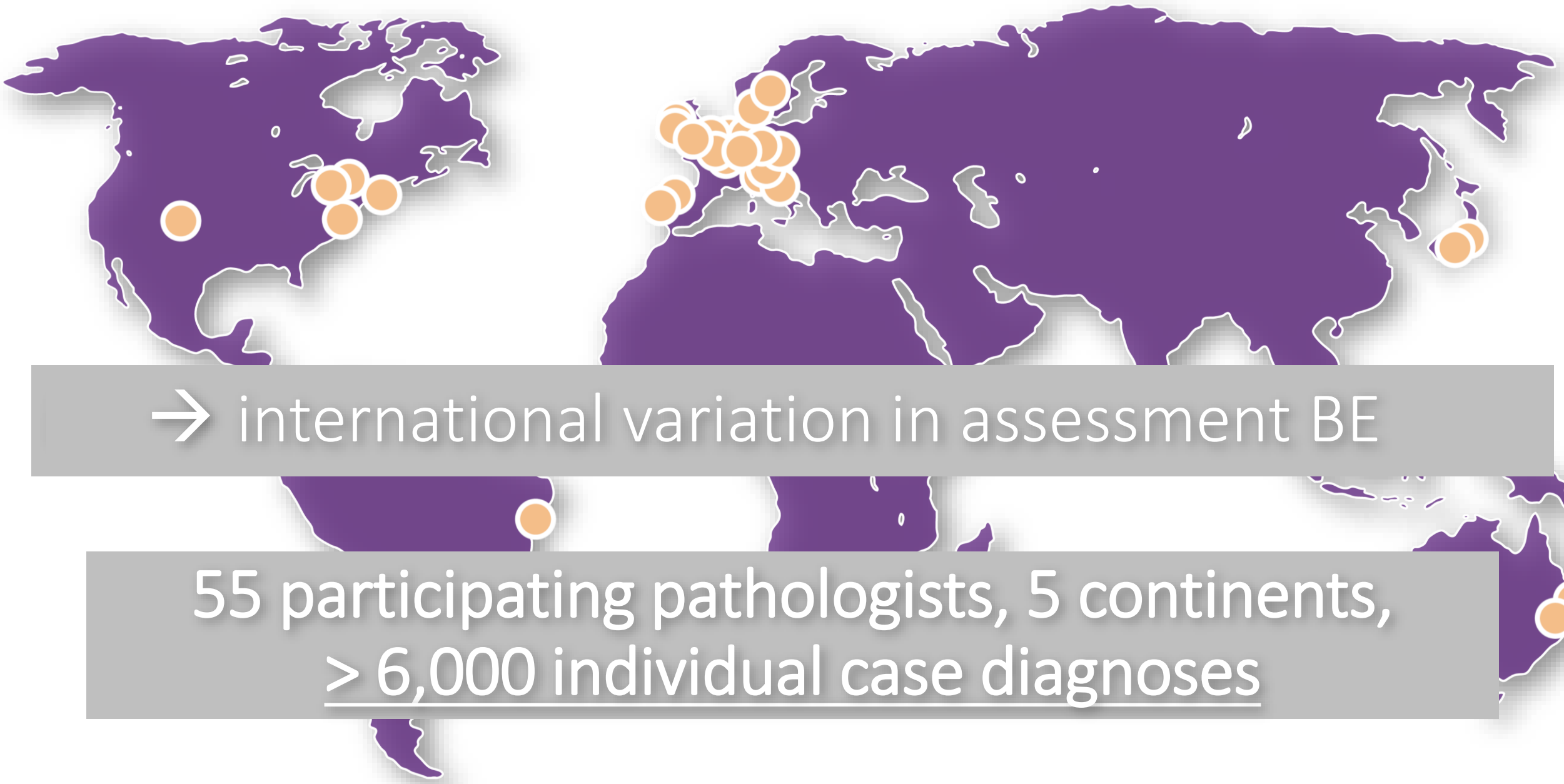
Over ons ▾ Agenda Nieuws Voorlichting ▾ Openbare datab

Home / / Professionals /

- Professionals
- Protocollen
- Moleculaire diagnostiek

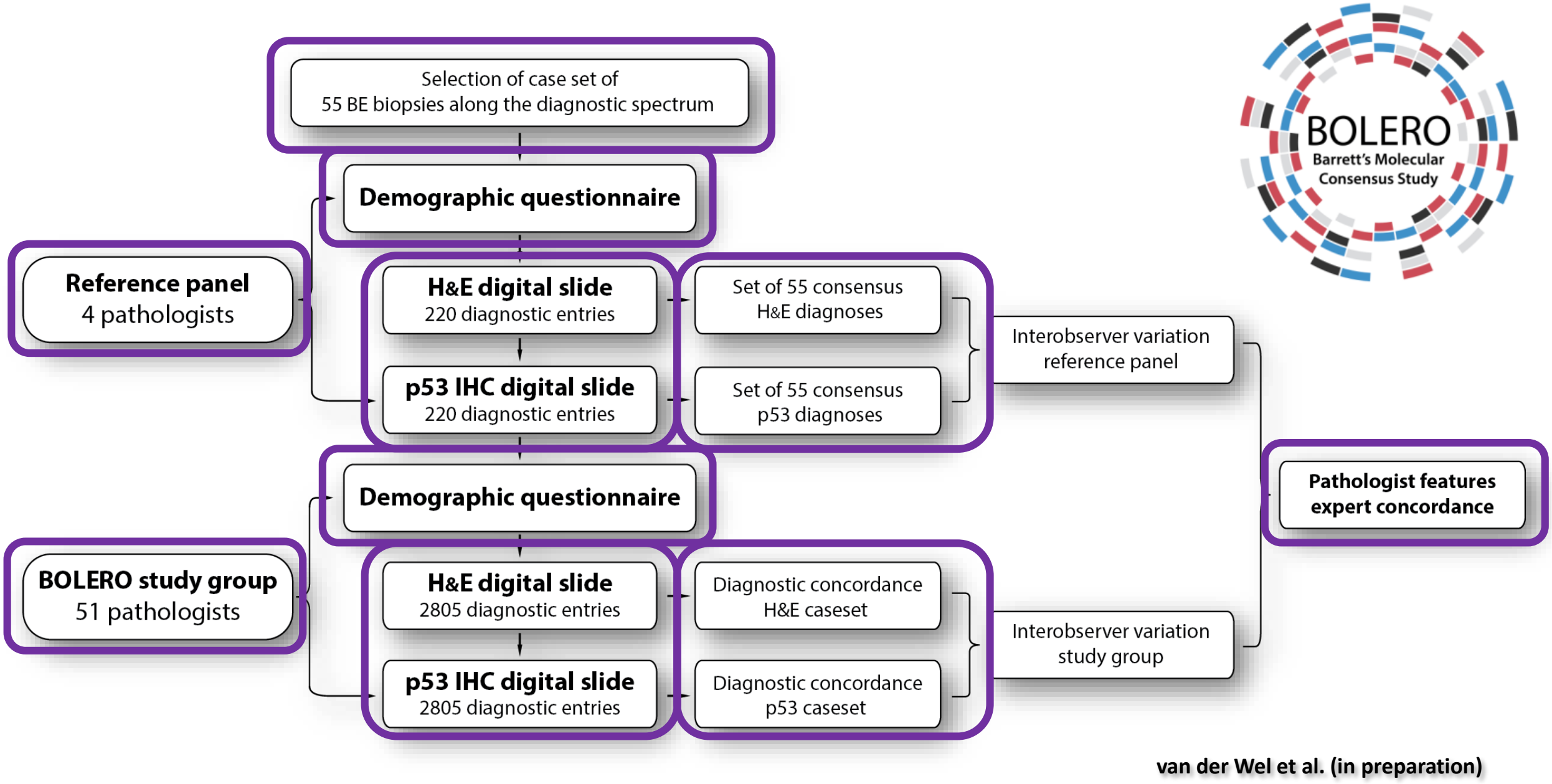


set up homogeneous expert digital pathology platform



→ international variation in assessment BE

55 participating pathologists, 5 continents,
> 6,000 individual case diagnoses



BOLERO
Barrett's Molecular Consensus Study

van der Wel et al. (in preparation)

Reference panel ‘core’ pathologists

AJG The American Journal of GASTROENTEROLOGY

Gastroenterology 2017;152:993–1001

expert panel that has **prospectively** reported BE pathology sign out against clinical outcome

> 10 years of BE experience | work in teaching hospital environment | > 10 BE cases per week | >25% dysplastic | Collaborated before on Amsterdam Barrett’s advisory committee

Original Co

Esophagus

Low-
Esop
Und

Wouter L C
PhD, Brenda Etz
MD, PhD, Arnou
Harriët G T Blaa

Citation Tools

[1]Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands; [2]Department of Pathology, Academic Medical Center, Amsterdam, The Netherlands; [3]Center for Esophageal Diseases and Swallowing, Department of Medicine, Division of Gastroenterology, University of North Carolina School of Medicine, Chapel Hill, North Carolina; [4]Department of Pathology, University Medical Center, Utrecht, The Netherlands; [5]Department of Pathology, St Antonius Hospital, Nieuwegein, The Netherlands; [6]Department of Gastroenterology and Hepatology, Flevoziekenhuis, Almere, The Netherlands; and [7]Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands

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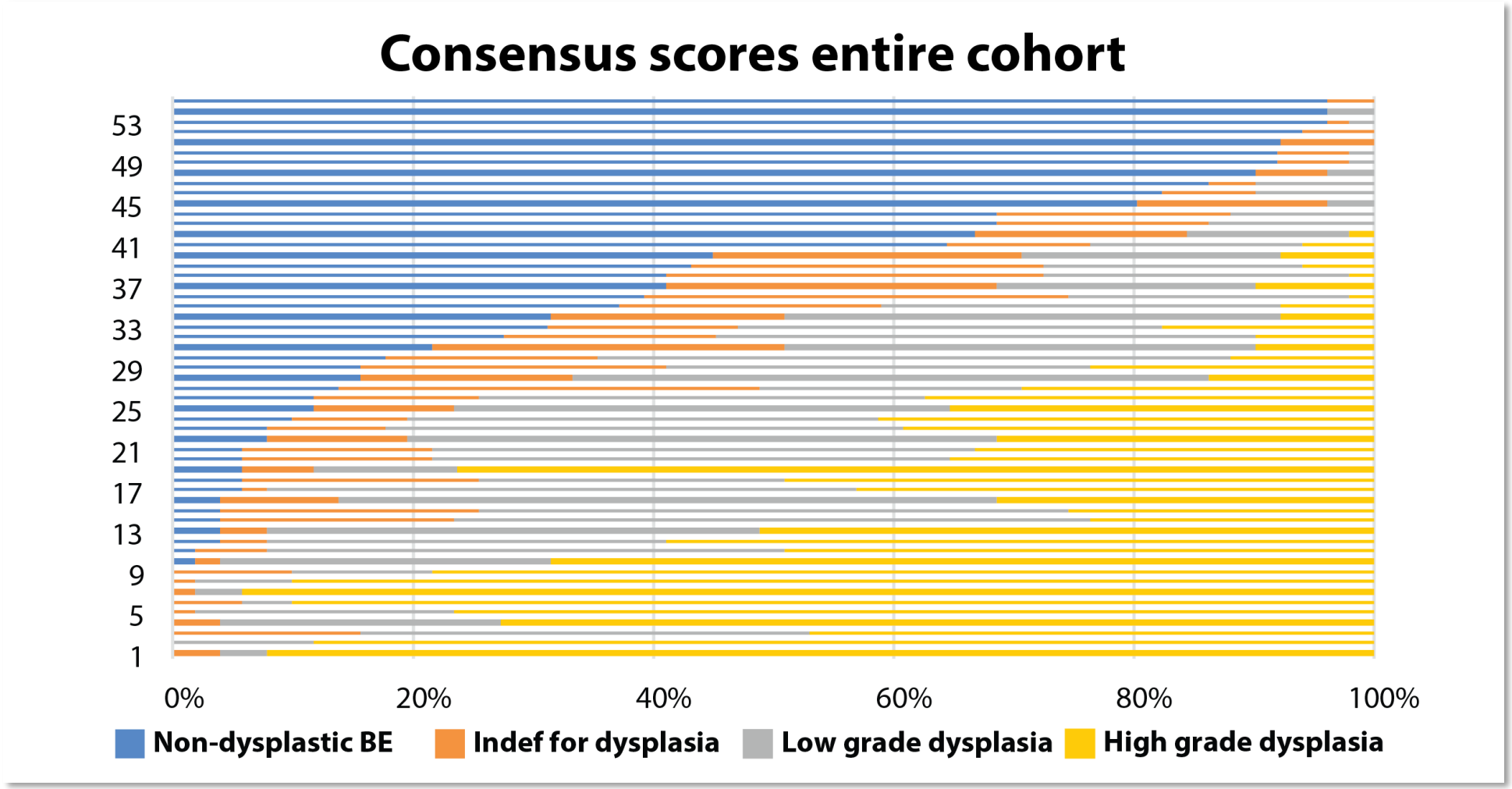
Accepted: 22 March 2010
Published: 11 May 2010

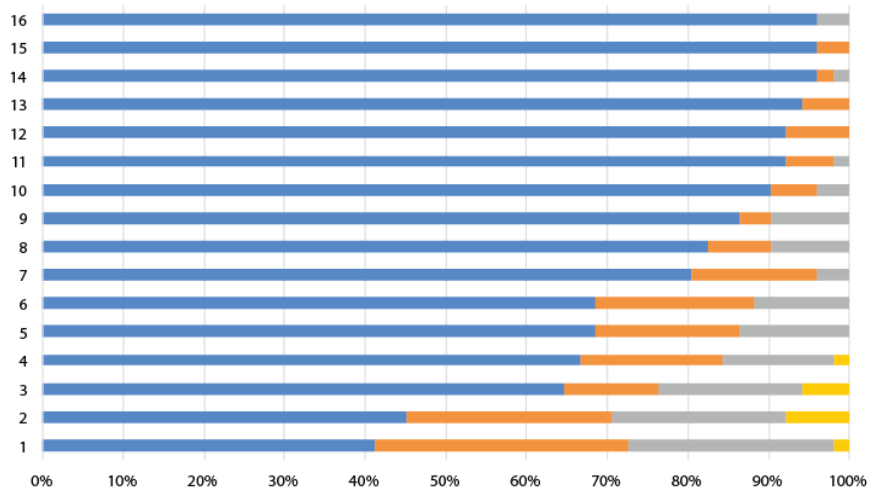
DEMOGRAPHIC FEATURES REFERENCE PANEL (N=4) AND STUDY PATHOLOGISTS (N=51)

Clinical practice and experience (more than 1 option possible)	**Ref panel**	**%**	**Total group**	**%**	**p-value***
Academic teaching hospital	3	75	41	80	0.904
District general hospital	1	25	16	31	0.921
Private practice	1	25	11	22	0.951
GI-pathology fellowship participation	2	50	27	53	0.949
Main practice size					0.445
9 pathologists or less	0	0	14	27	
10 pathologists or more	4	100	36	71	
Years' experience					0.680
0-4	1	25	8	16	
5-9	1	25	9	18	
10-19	0		18	35	
20 or more	2	50	15	29	

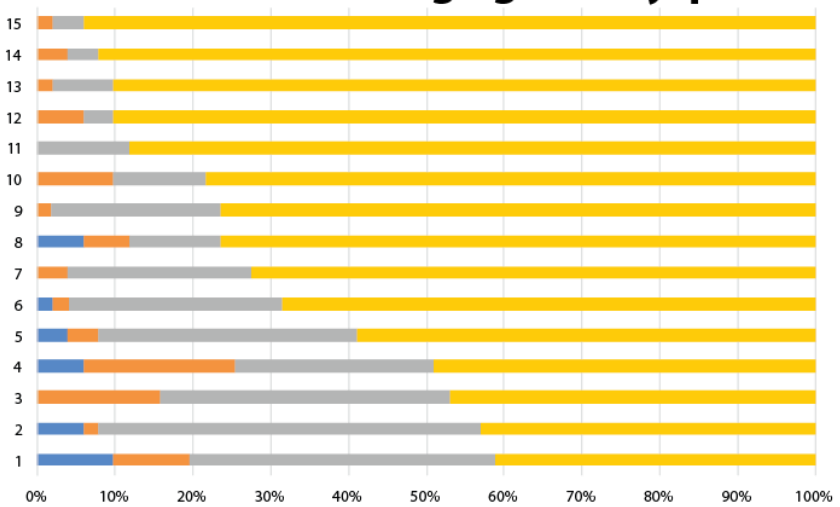
ALL DIAGNOSTIC ASSESSMENTS (H&E STAGE) (55 PATHOLOGISTS; >3,000 CASE DIAGNOSES)



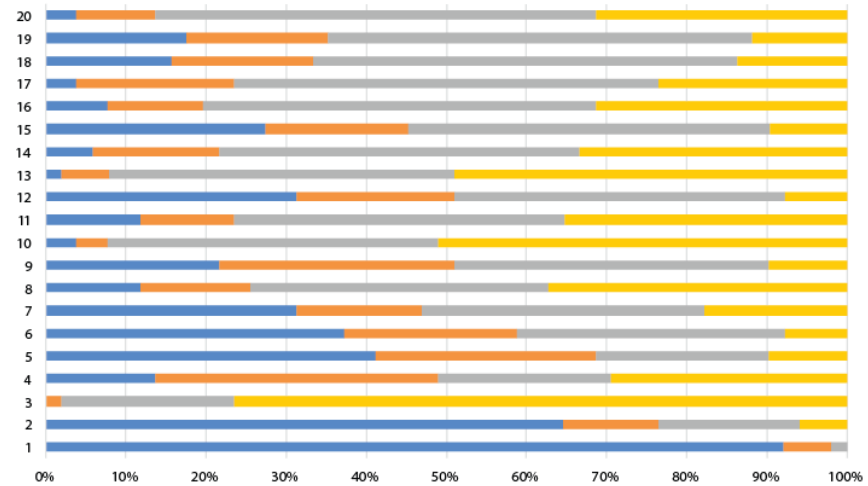
Consensus scores non-dysplastic BE



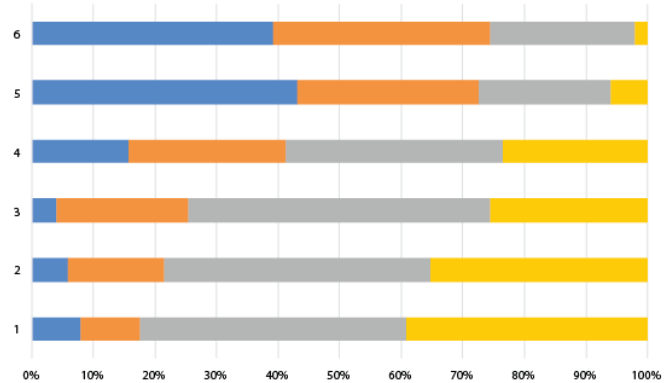
Consensus scores high grade dysplasia



Consensus scores low grade dysplasia



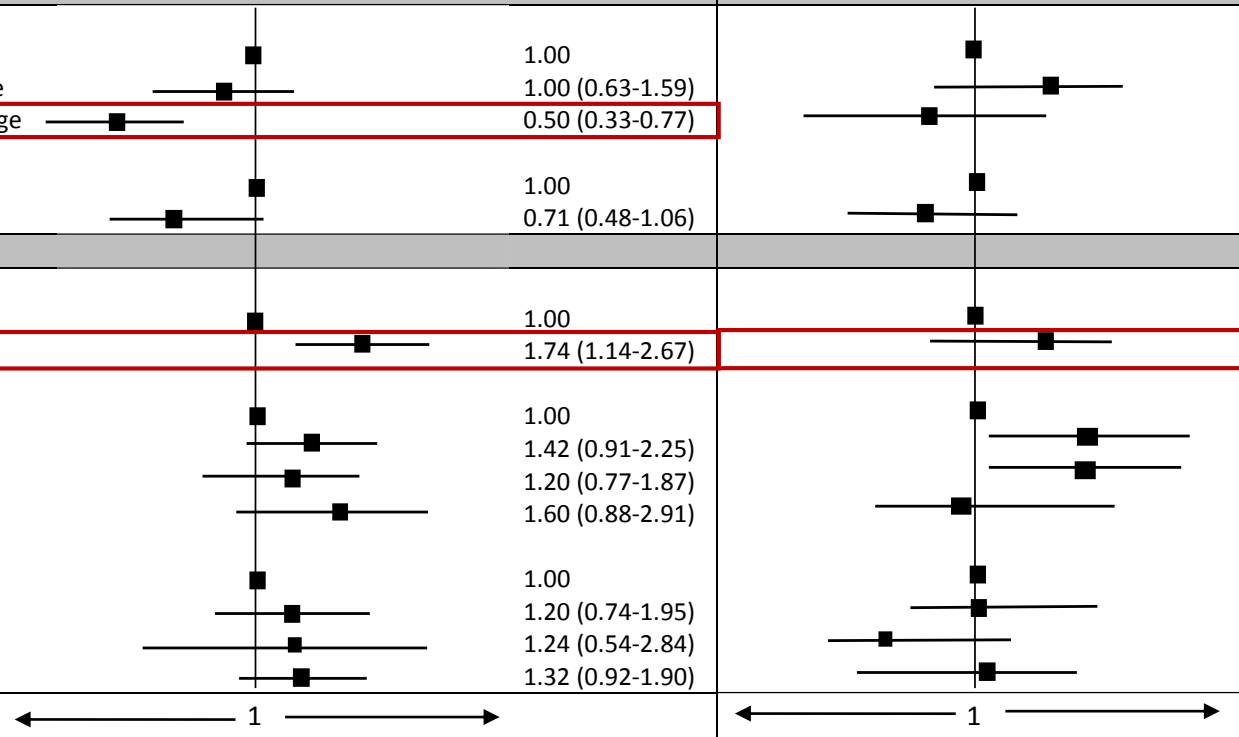
Consensus scores indefinite for dysplasia



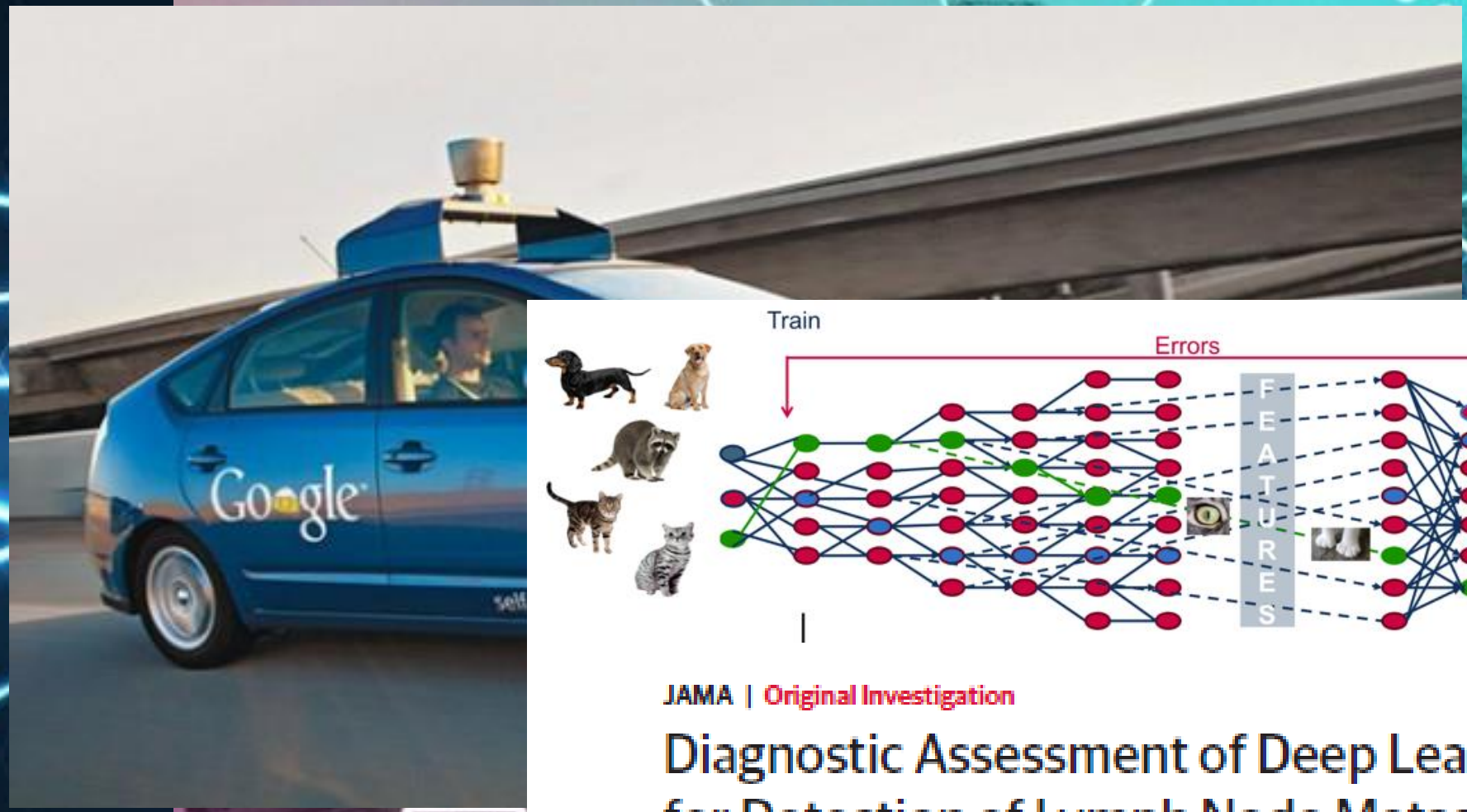
Non-dysplastic BE Indef for dysplasia Low grade dysplasia High grade dysplasia

MULTIVARIATE ANALYSIS OF DEMOGRAPHIC PREDICTORS ON DIAGNOSTIC PERFORMANCE

Characteristic	H&E digital slide review Odds ratio (95%CI)	p53 stained slide review Odds ratio (95% CI) *
'Protective' factors		
Age/experience		
Any age/0-4 years experience	1.00	1.00
Disproportionately more experience to age	1.00 (0.63-1.59)	1.46 (0.88-2.44)
5+ years experience commensurate with age	0.50 (0.33-0.77)	0.89 (0.55-1.43)
Interest in Whole slide imaging		
No	1.00	1.00
Yes	0.71 (0.48-1.06)	0.84 (0.56-1.27)
'Risk' factors		
District general hospital work setting		
No	1.00	1.00
Yes	1.74 (1.14-2.67)	1.46 (0.92-2.30)
Number Barrett's cases viewed per week		
0-4	1.00	1.00
5-9	1.42 (0.91-2.25)	1.75 (1.07-2.85)
10-19	1.20 (0.77-1.87)	1.75 (1.08-2.82)
20+	1.60 (0.88-2.91)	0.92 (0.44-1.92)
Guidelines used		
North American	1.00	1.00
British	1.20 (0.74-1.95)	1.06 (0.62-1.82)
Japanese	1.24 (0.54-2.84)	0.43 (0.18-1.21)
Other	1.32 (0.92-1.90)	1.15 (0.79-1.68)



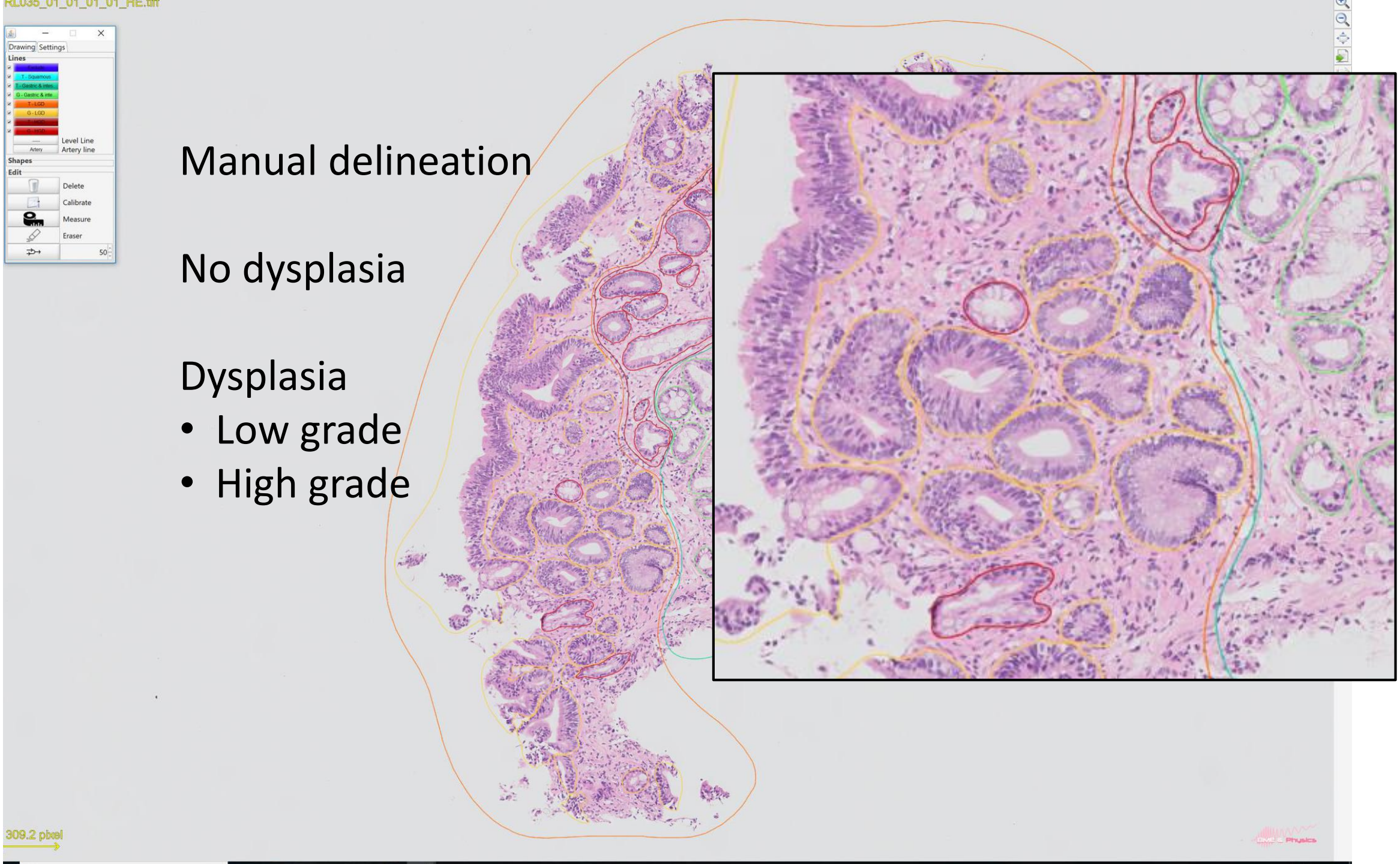
Subjective interpretation → Variation in diagnostic accuracy
55 pathologist compared to gold standard diagnosis



JAMA | Original Investigation

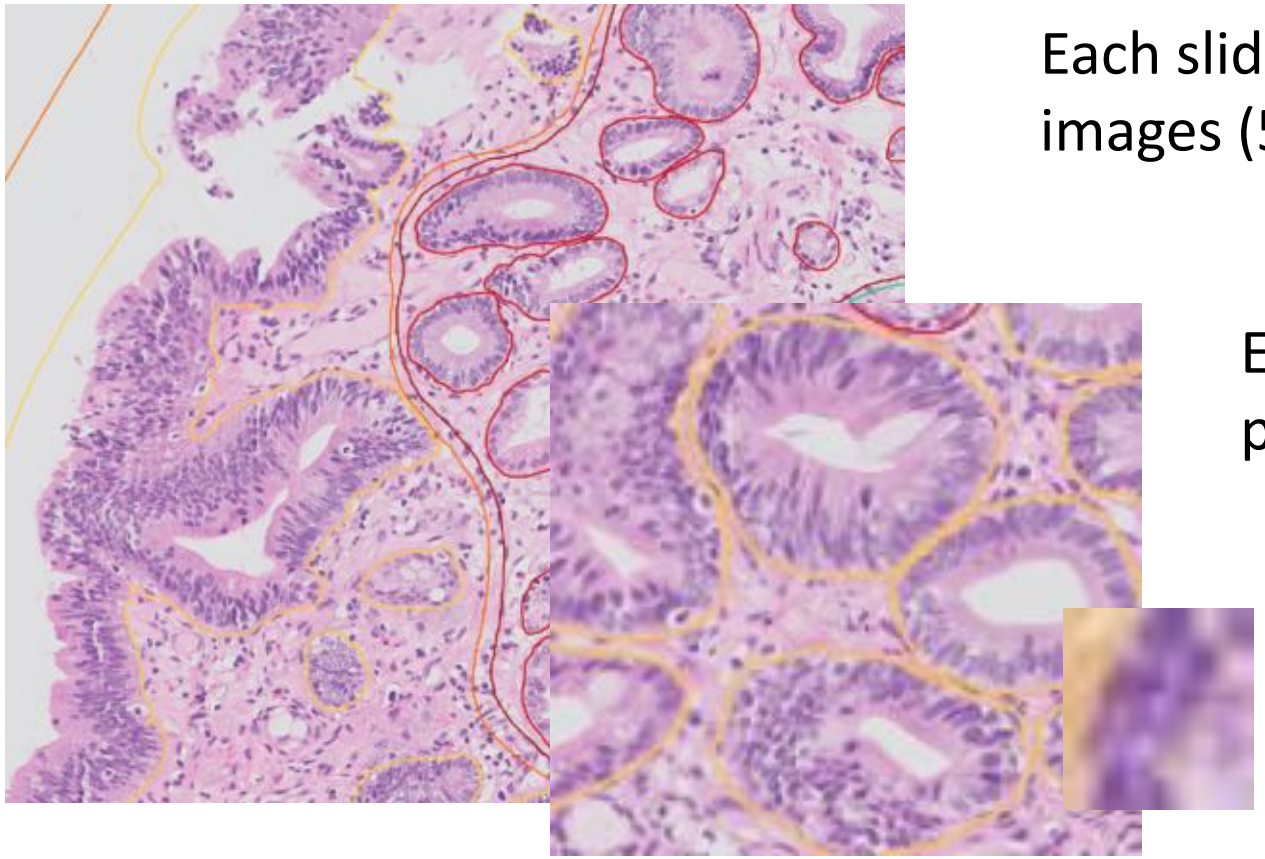
Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women With Breast Cancer

Babak Ehteshami Bejnordi, MS; Mitko Veta, PhD; Paul Johannes van Diest, MD, PhD; Bram van Ginneken, PhD; Nico Karssemeijer, PhD; Geert Litjens, PhD; Jeroen A. W. M. van der Laak, PhD; and the CAMELYON16 Consortium


Drawing
Settings
Lines
Level Line
Artery line
Shapes
Edit
Delete
Calibrate
Measure
Eraser
50
Manual delineation
No dysplasia
Dysplasia
• Low grade
• High grade
309.2 pixel

First experiment concentrate on nuclear features

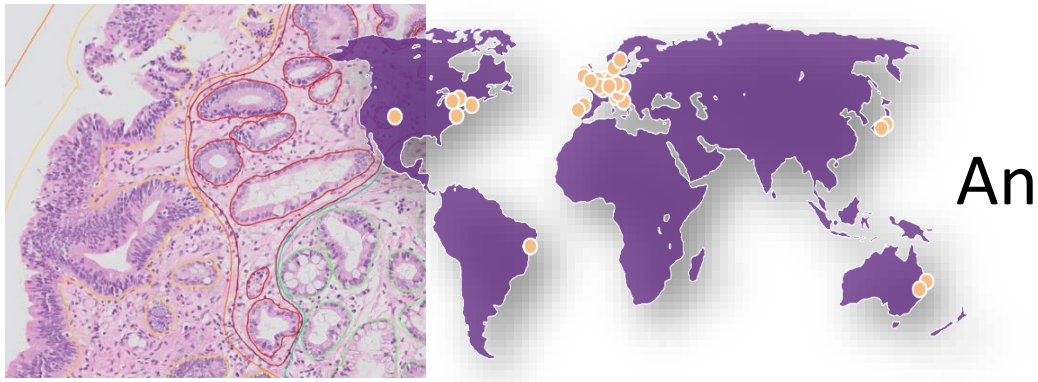
process collections of image patches containing nuclei



Each slide divided into smaller images (500 × 500 pix)

Each small image = a collection of patches (27 × 27 pix)

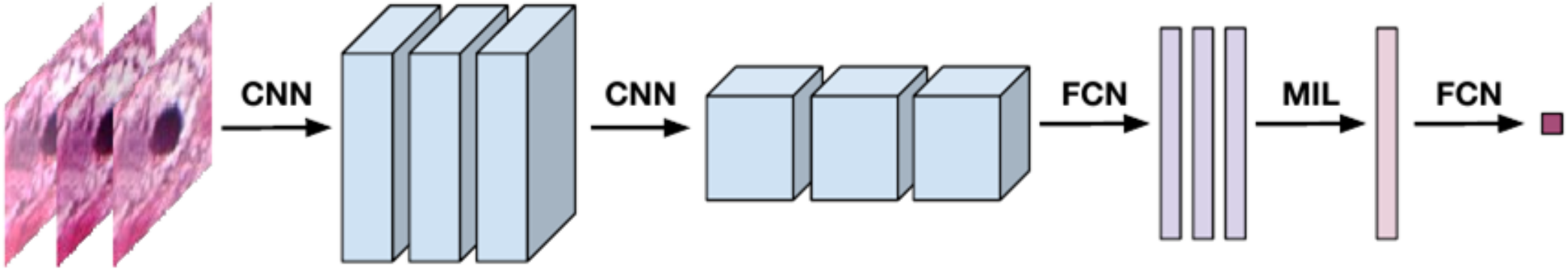
A patch contains a nucleus in the center



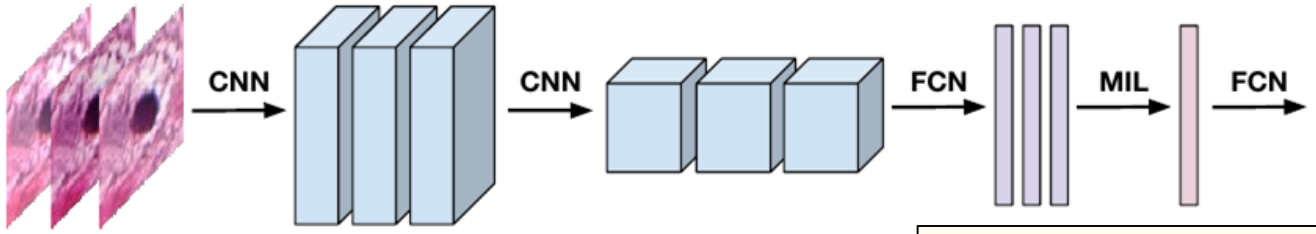
Annotated 21 cases

- 9 training set
- 6 validation set
- 6 test set

Use **multiple instance learning** with **deep learning** for feature extraction and classification



computer performance vs gold standard diagnosis



MIL pooling	Accuracy
MAJORITY CLASS	52.1%
MAX	58.7% ± 1.8%
	67.2% ± 2.5%
	65.9% ± 3.5%
	70.1% ± 1.7%

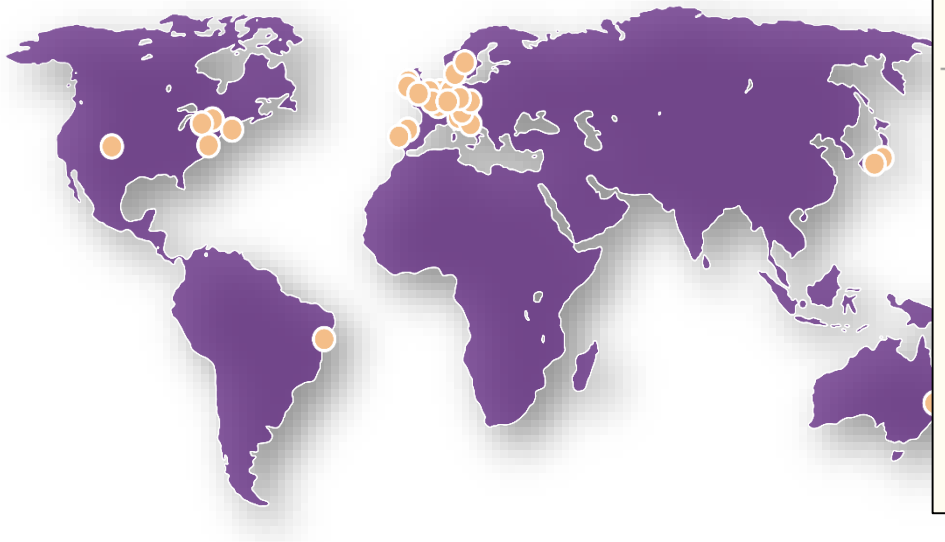


Table 7.

Values for benchmark quality criteria based on 95% prediction

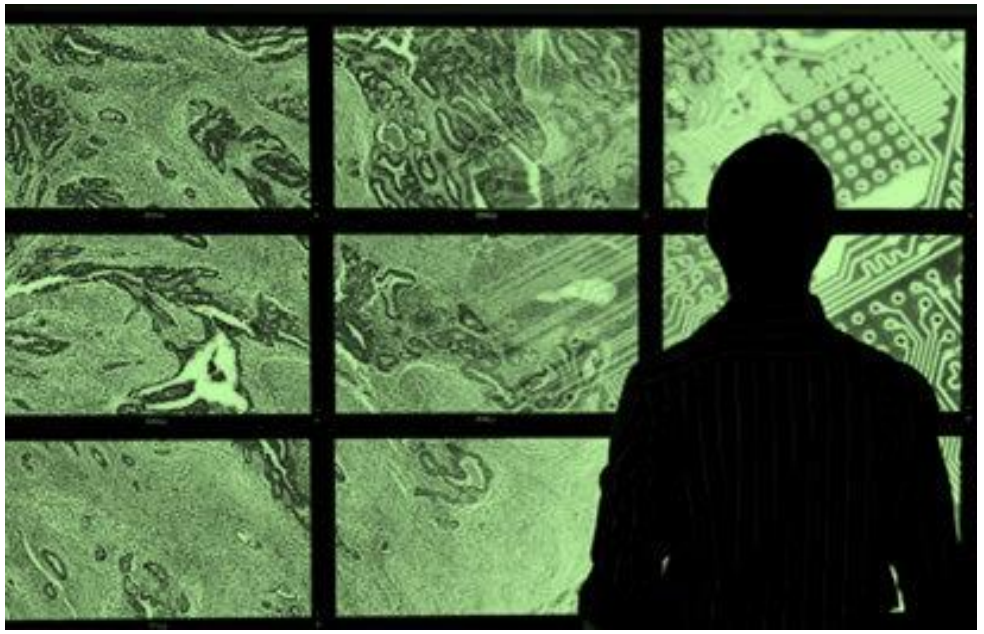
Quality criterium	95% PI[b] core pathologists all cases ($n = 60$)	Benchmark value
Percentage of IND[a] cases (%)	3–14%	≤14%
Intra-observer agreement in three categories (K)	0.66–1.02	≥0.66
Agreement with consensus gold standard diagnosis (%)	82–98%	≥82%
Consensus HGD[c] cases misdiagnosed as NDBE[d] (%; fraction)	0.8% (1/120)	≤0.8% (1/120)

Not an expert yet

Conclusions

Optimal risk stratification in Barrett's Esophagus related dysplasia

- second opinion ; panel
- training pays off
- at least 5 years of experience
- use p53 IHC



Digital pathology

- comparable to glass slide diagnostics
- Excellent platform for panel diagnostics and international collaboration

Computational pathology


COMPUTER
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YOU'RE
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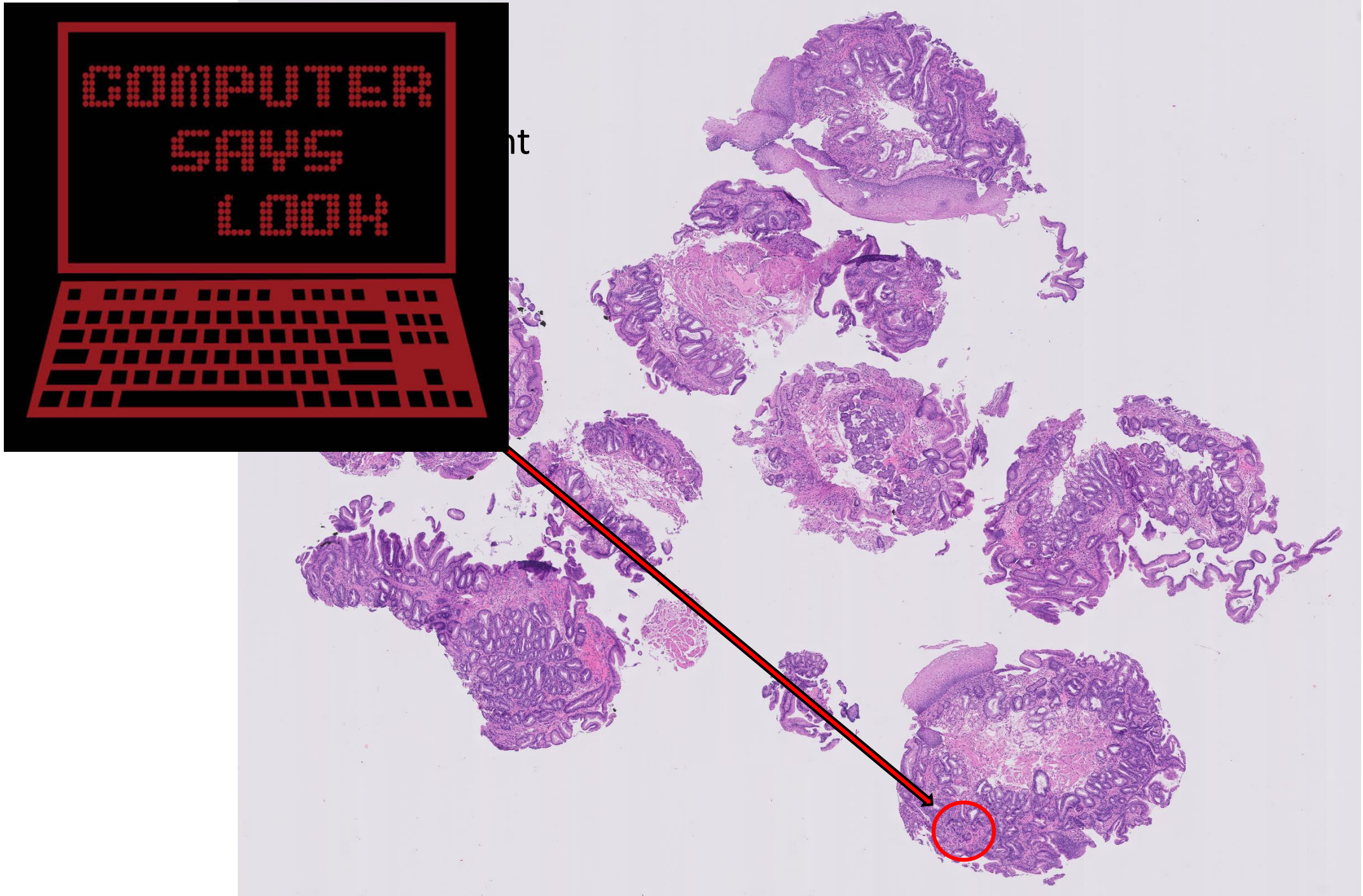
COMPUTER
SAYS
LOOK

Thank you

LANS Pathology

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Kees Seldenrijk
Johan Offerhaus
Mike Visser
Fiebo ten Kate sr.
Katharina Biermann
Lodewijk Brosens
Michael Doukas
Clément Huysentruyt
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