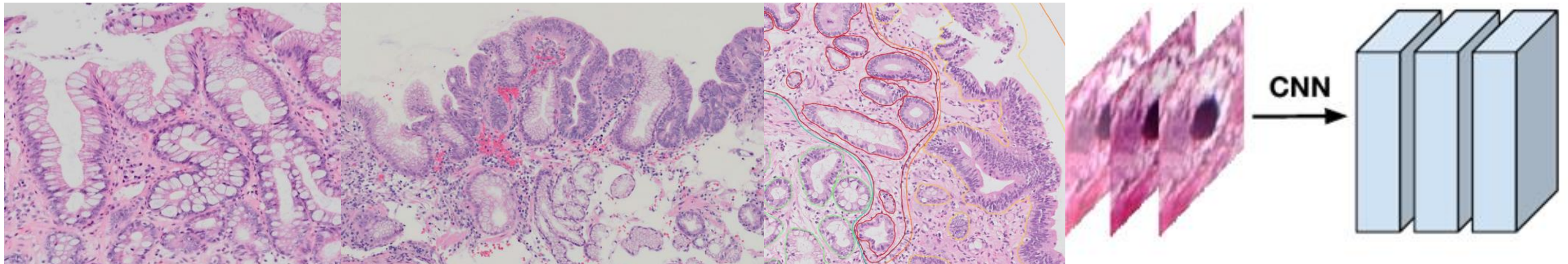
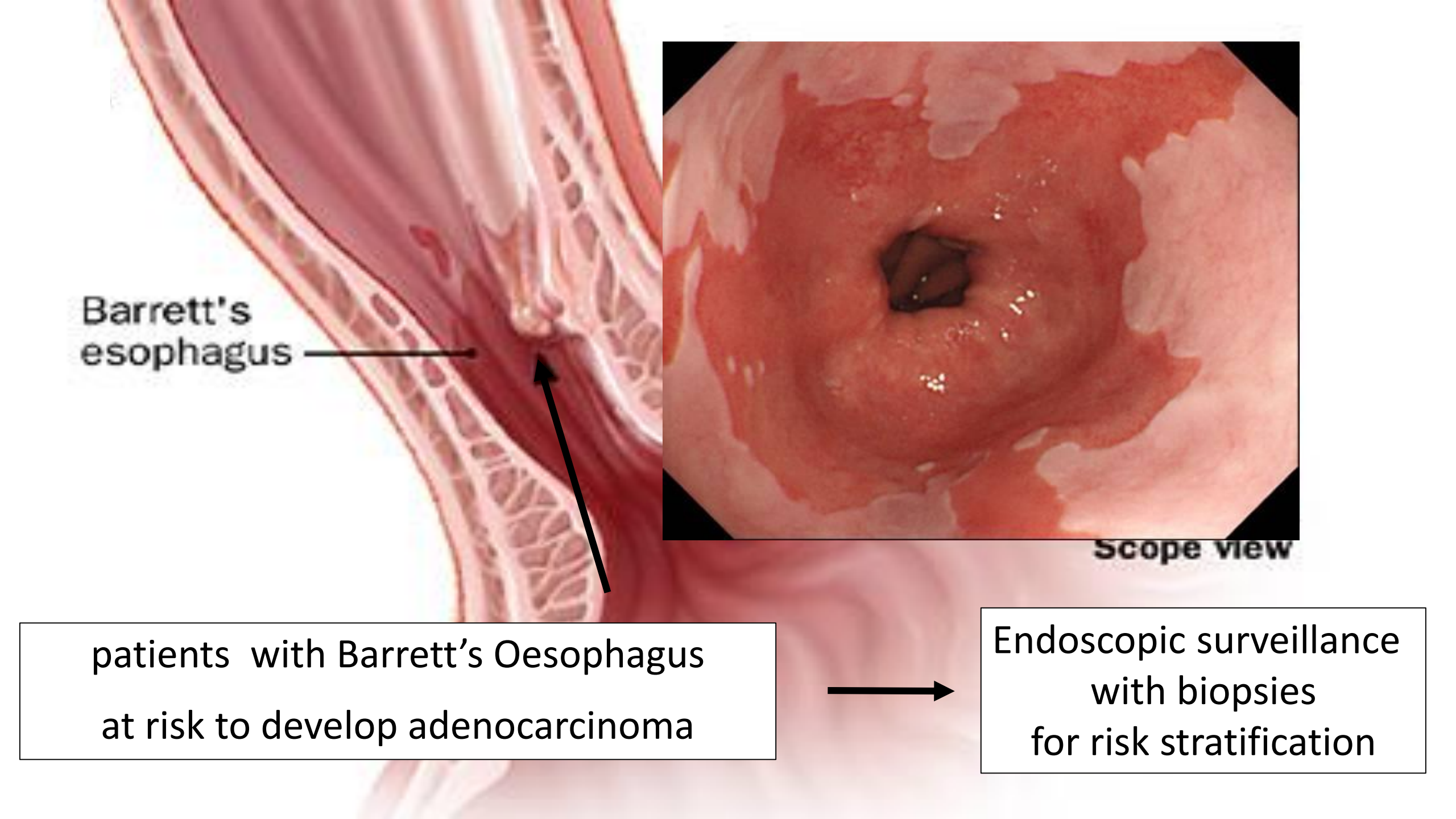


man versus machine: expert histopathology risk stratification in Barrett's esophagus



Sybren L. Meijer

no disclosures



Barrett's
esophagus

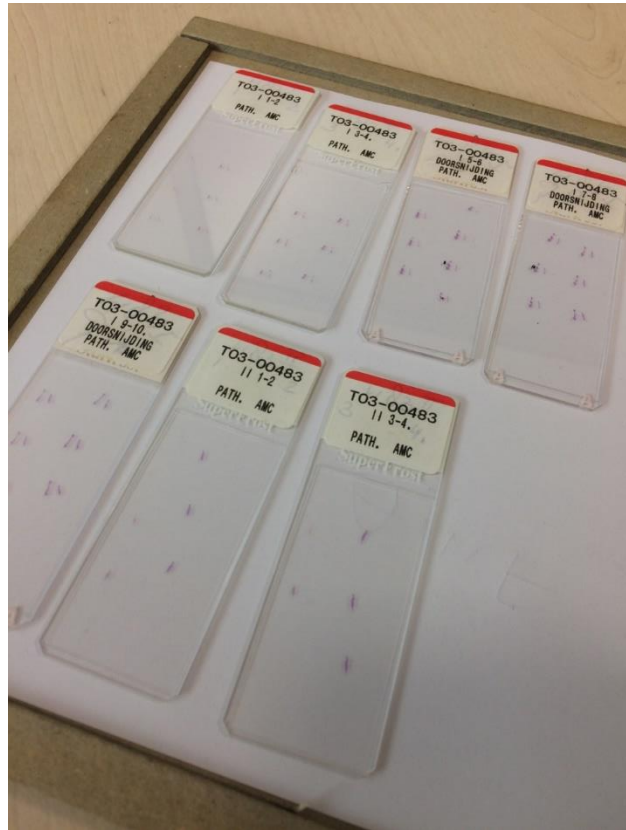
The diagram shows a sagittal cross-section of the esophagus. The upper part is the normal squamous mucosa, and the lower part is the Barrett's esophagus, which is a columnar mucosa. An arrow points from the text 'Barrett's esophagus' to the columnar mucosa. An inset endoscopic view shows the internal surface of the Barrett's esophagus, which is a reddish, velvety mucosa. The text 'Scope view' is written below the inset.

patients with Barrett's Oesophagus
at risk to develop adenocarcinoma



Endoscopic surveillance
with biopsies
for risk stratification

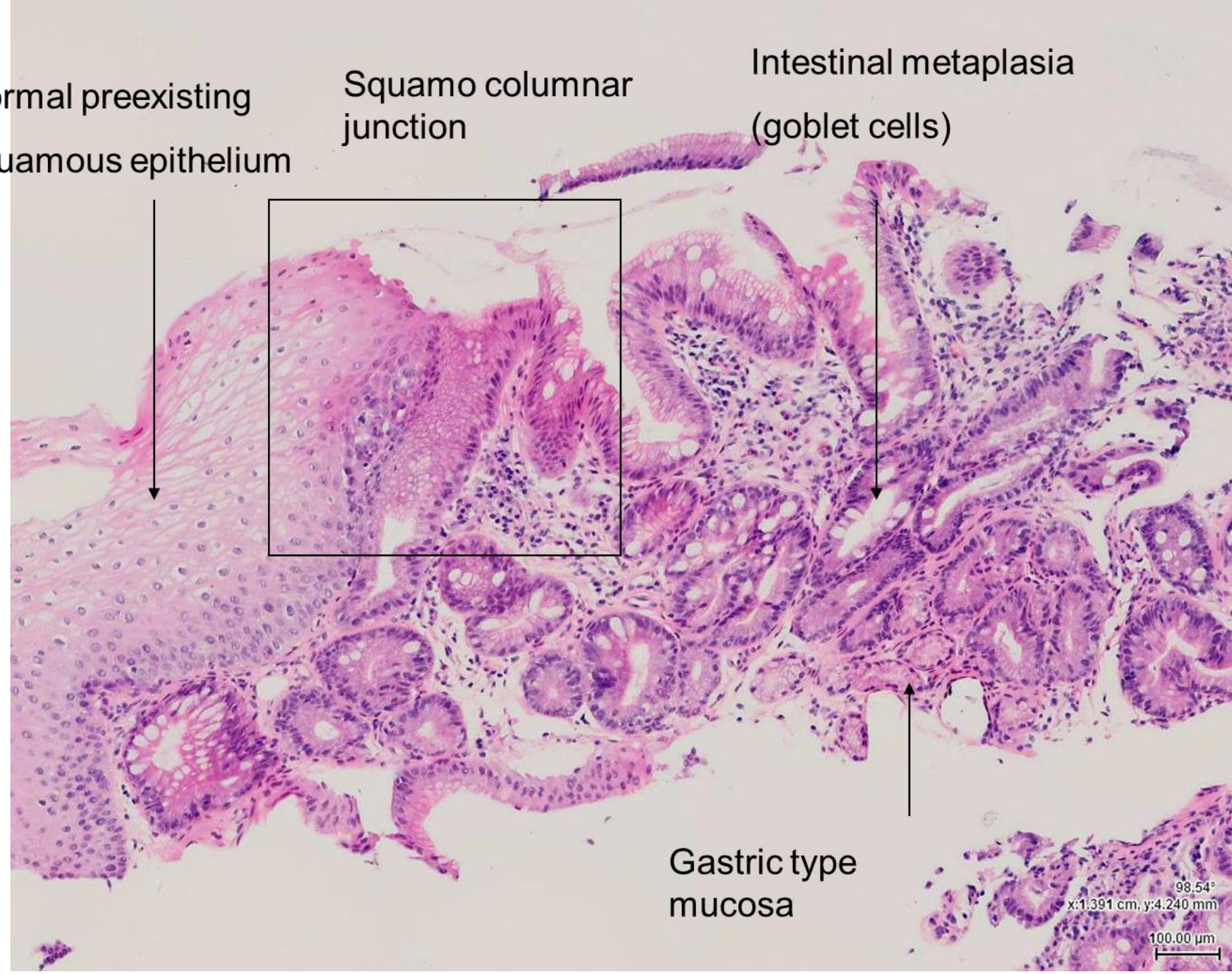
Barrett's on biopsy



Normal preexisting
squamous epithelium

Squamo columnar
junction

Intestinal metaplasia
(goblet cells)

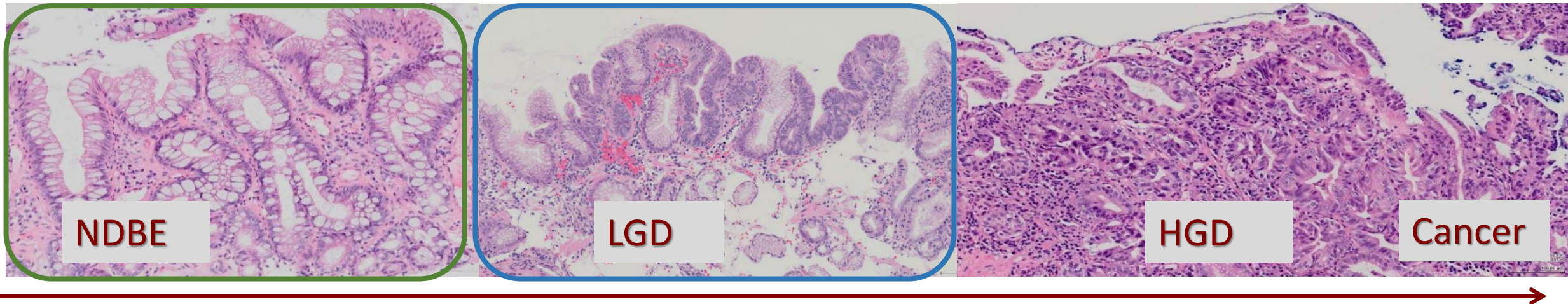


A proportion of patients with Barrett's Oesophagus develop adenocarcinoma

Progression: dysplasia (precursor stage) – carcinoma sequence

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

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



Diagnosis of low grade dysplasia subject to variation

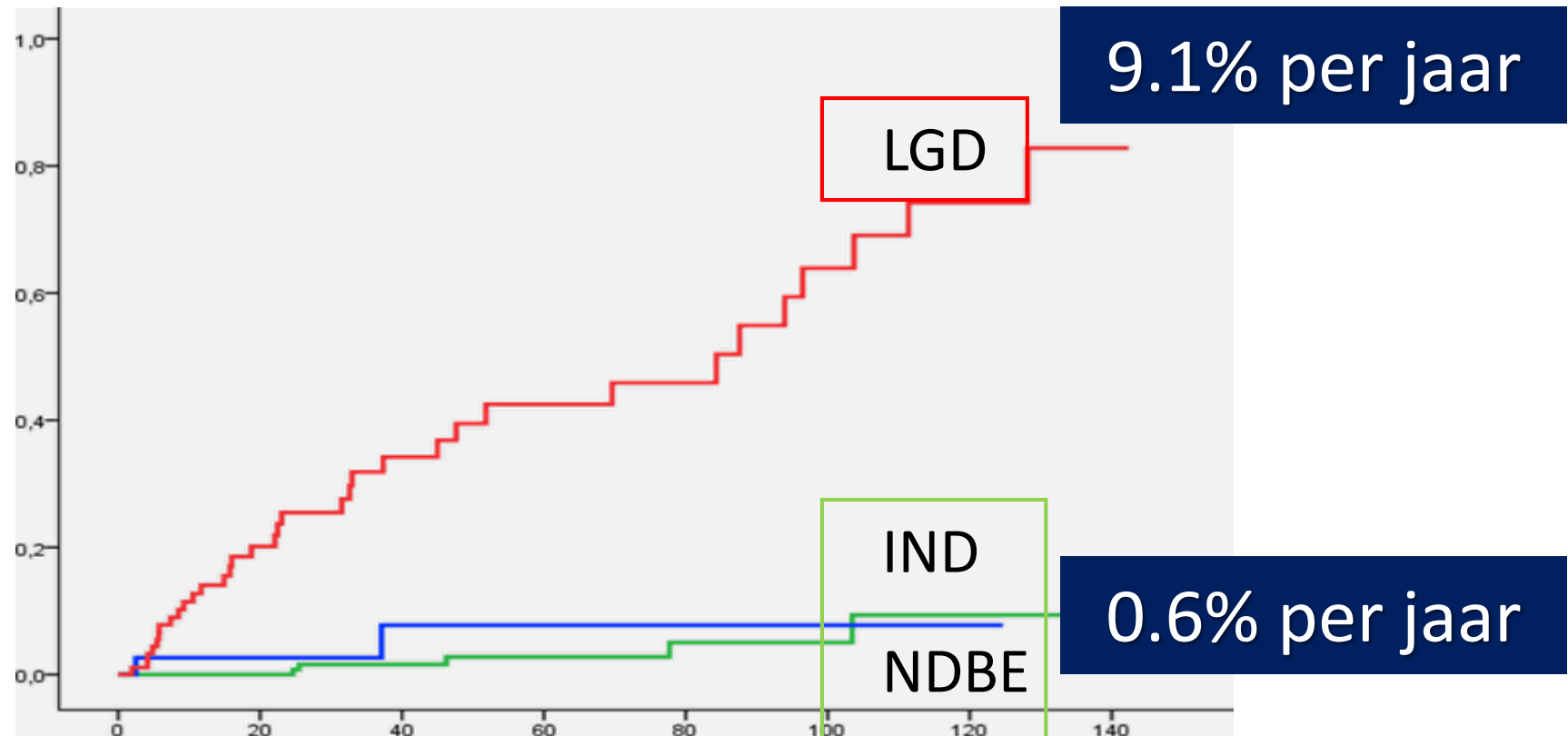
Low-Grade Dysplasia in Barrett's Esophagus: Overdiagnosed and Underestimated

Wouter L. Curvers, MD^{1,12}, Fiebo J. ten Kate, MD, PhD^{2,12,13}, Kausilia K. Krishnadath, MD, PhD^{1,12}, Mike Visser, MD, PhD^{2,13}, Brenda Elzer, MSc¹, Lubertus C. Baak, MD, PhD^{3,12}, Clarisse Bohmer, MD, PhD^{4,12}, Rosalie C. Mallant-Hent, MD, PhD^{5,12}, Arnout van Oijen, MD^{6,12}, Anton H. Naber, MD, PhD^{7,12}, Pieter Scholten, MD^{8,12}, Olivier R. Busch, MD, PhD^{9,13}, Harriët G.T. Blaauwgeers, MD, PhD^{10,13}, Gerrit A. Meijer, MD, PhD^{11,13} and Jacques J.G.H.M. Bergman, MD, PhD^{1,12,13}

up to 80% downstaged →
0.5% progression per year

15% confirmed →
13% progressie per jaar

Confirmed LGD is a high risk factor for progression



Follow-up in months

Duits L. Gut 2014

Observer variability has led to need for expert review

- International guidelines recommend that 'all cases of Barrett's dysplasia should be confirmed by a second EXPERT gastro-intestinal pathologist'
- NO definition of 'EXPERT gastro-intestinal pathologist' exist
- demonstrate the need for expert review to predict
- diagnostic

Quantify expertise &
homogeneous interpretation



LGD

HU

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

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

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

Original Co

Esophagus

Low-

Esop

Unde

Wouter L C

PhD, Brend

MD, PhD, A

Harriët G T

The American Journal of Gastroenterology **105**,
1523–1530 (2010)
doi:10.1038/ajg.2010.171

Received: 17 November 2009
Accepted: 22 March 2010
Published: 11 May 2010

Carolina, ¹Department of Pathology, University Medical Center, Utrecht, The Netherlands; ²Department of Pathology,
St Antonius Hospital, Nieuwegein, The Netherlands; ⁶Department of Gastroenterology and Hepatology, Flevoziekenhuis,
Almere, The Netherlands; and ⁷Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands

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 ¹Pathology, and,
nius Hospital, Nieuwegein, and, ⁴
of Pathology, Zaan Medical Ce
Amsterdam*

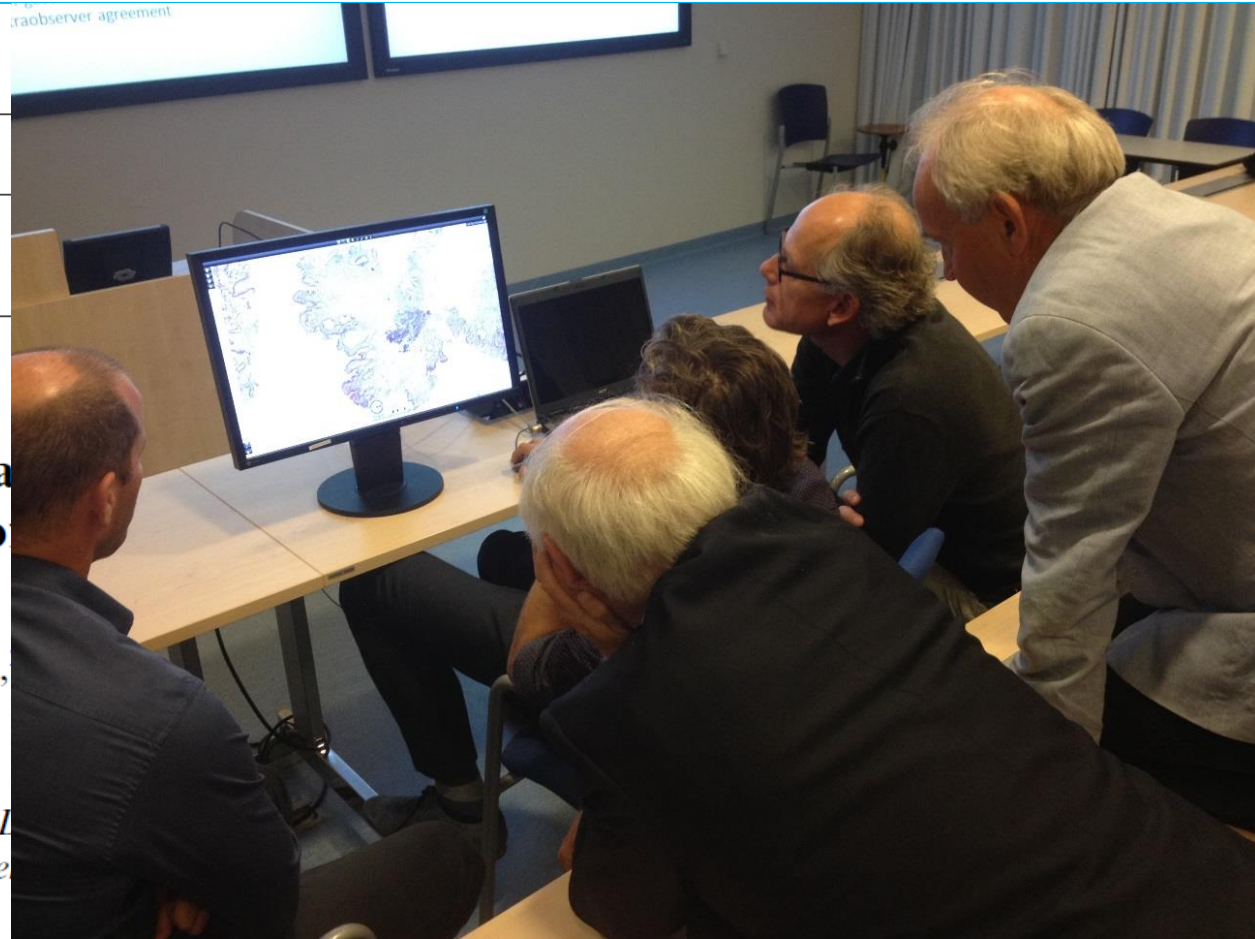


Table 2

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

| | Digital microscopy | | | Conventional microscopy | | | |
|---|-------------------------|-------|-----------|-------------------------|-------|-----------|----------|
| | Weighted K [‡] | | Weighted/ | Weighted K | | Weighted/ | |
| Path [†] | (95% CI) | Max K | max K | (95% CI) | Max K | 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 | | | |
|---|------------------------------|--------------|--------------|-------------------------|--------------|--------------|------------------|
| | Weighted κ^{\ddagger} | | Weighted/ | Weighted κ | | Weighted/ | |
| Path [†] | (95% CI) | Max κ | max κ | (95% CI) | Max κ | max κ | <i>p</i> -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 |

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. Meijer¹

Departments of ¹Pathology, and, ²Gastroenterology and Hepatology, and, ³Department of Pathology, Nieuwegein, and, ⁴Department of Pathology, University Medical Center, Utrecht, and, ⁵Department of Pathology, Zaanse Medical Center, Zaanse, the Netherlands, and ⁶Cardiology, Academic Medical Center, Amsterdam

Histopathology 2018 DOI: 10.1111/his.13462

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

Myrte 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 Flebo 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 Bergman² & Sybren L Meijer¹

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

Develop quality criteria for assessing BE biopsies

Original Article

Development of quality criteria for assessing Barrett's oesophagus biopsies

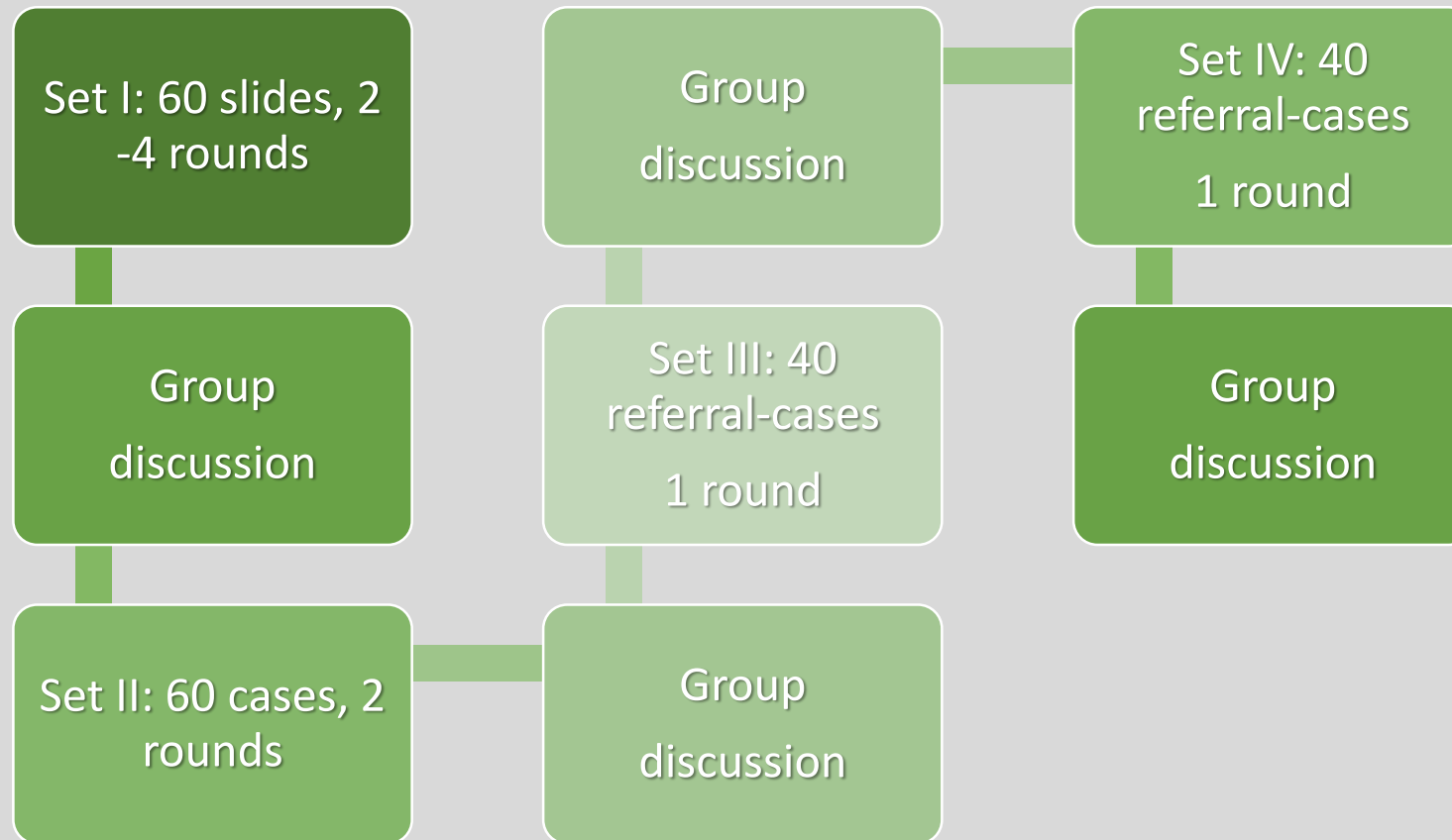
MJ van der Werf^{1,2}, LC GJA Offerhaus⁴, M Vi³ and SL Meijer¹

Table 7.

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

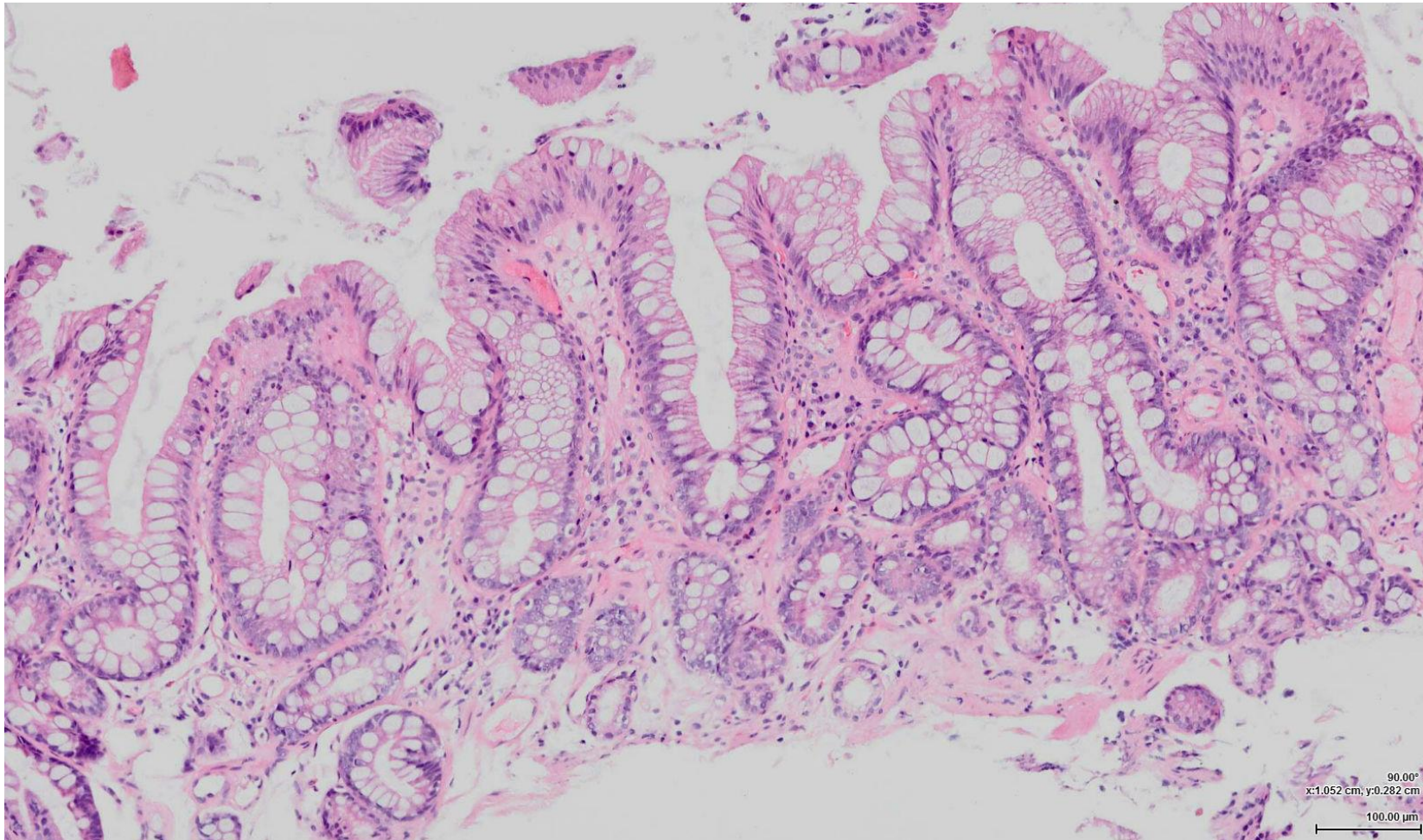
| Quality criterium | ^b | | ^b | |
|--|---|------------------|---|-----------------|
| | 95% PI core pathologists all cases (<i>n</i> = 60) | Benchmark value | 95% PI core pathologists' dysplastic cases (<i>n</i> = 39) | Benchmark value |
| Percentage of IND ^a cases (%) | 3–14% | ≤14% | –2 to 16% | ≤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 ^d misdiagnosed as NDBE (%) fraction) | 0.8% (1/120) | ≤0.8% (1/120) | 1.3% (1/78) | ≤1.3% (1/78) |

Expand panel from 5 -15 pathologists

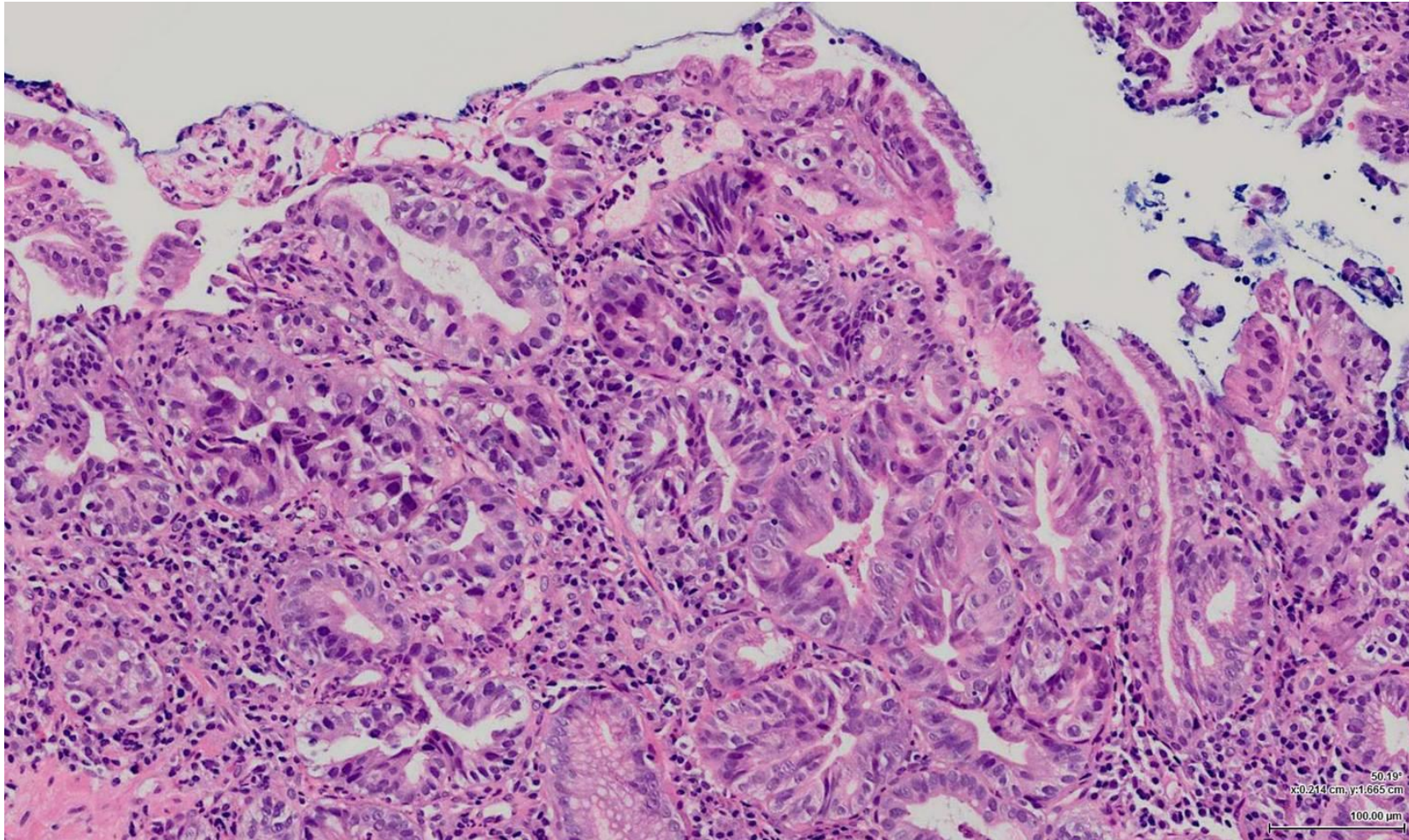


What difficulties are we talking about?

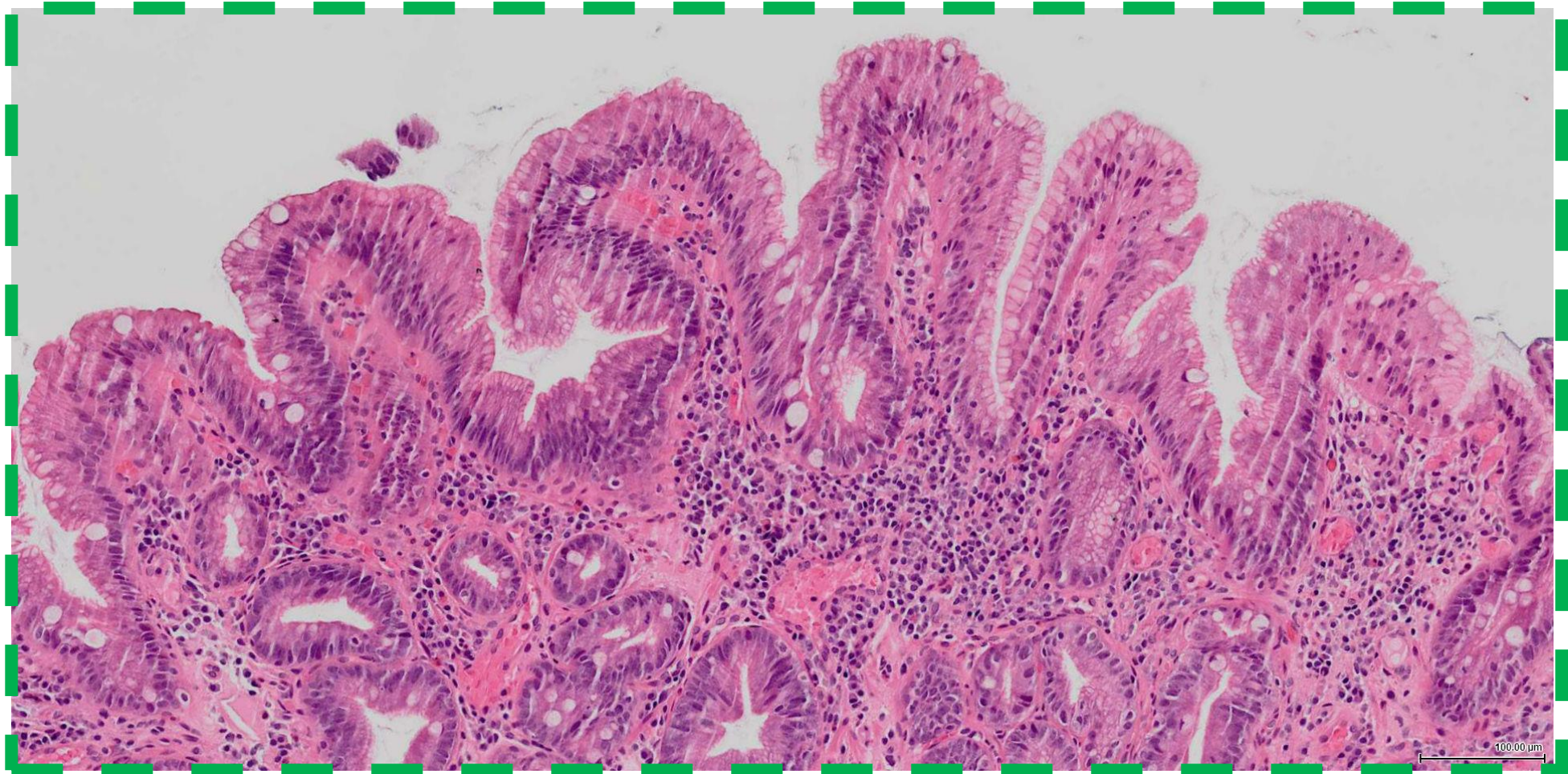
Obvious Non-dysplastic Barrett's:



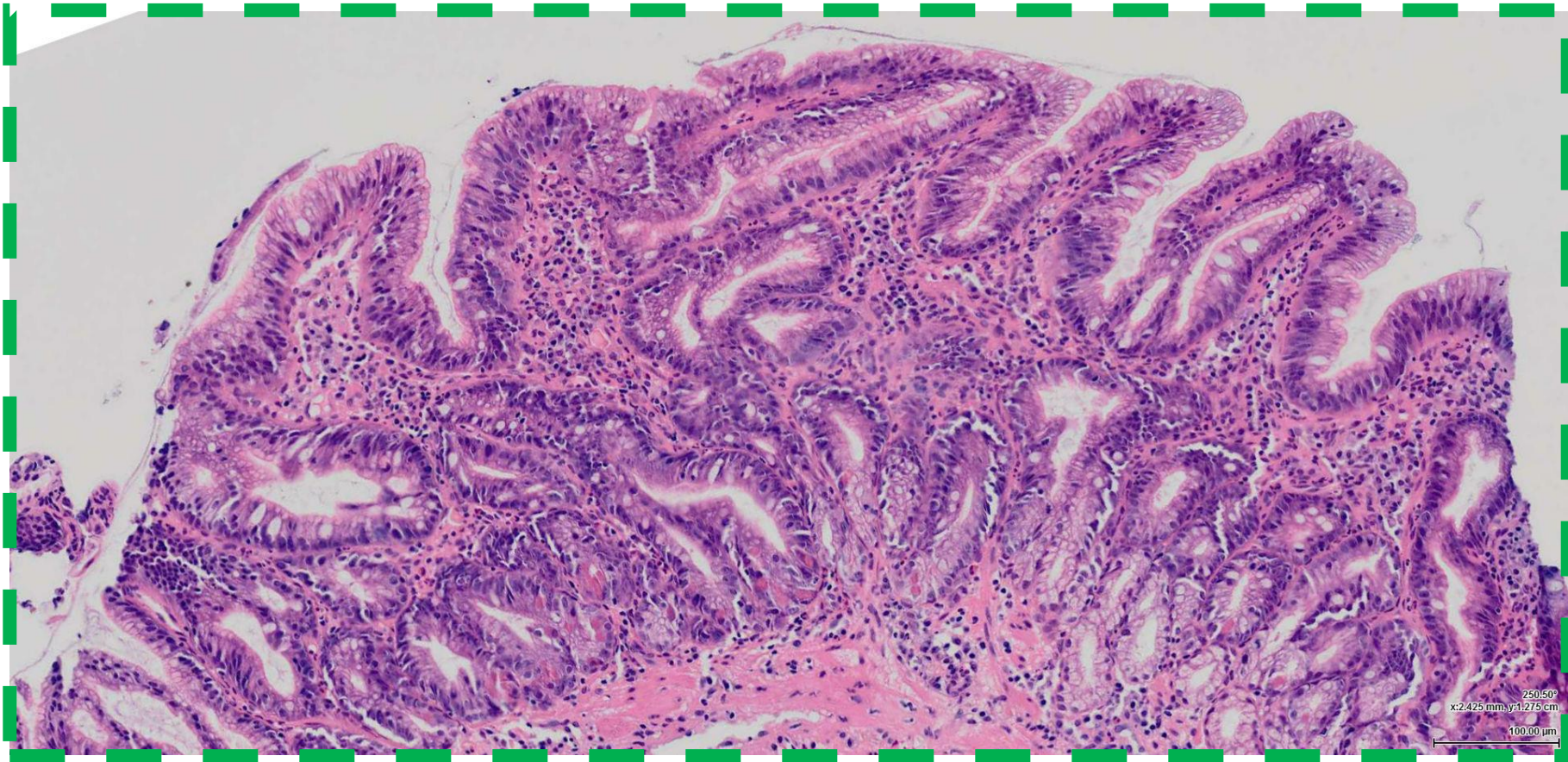
...obvious dysplastic Barrett's

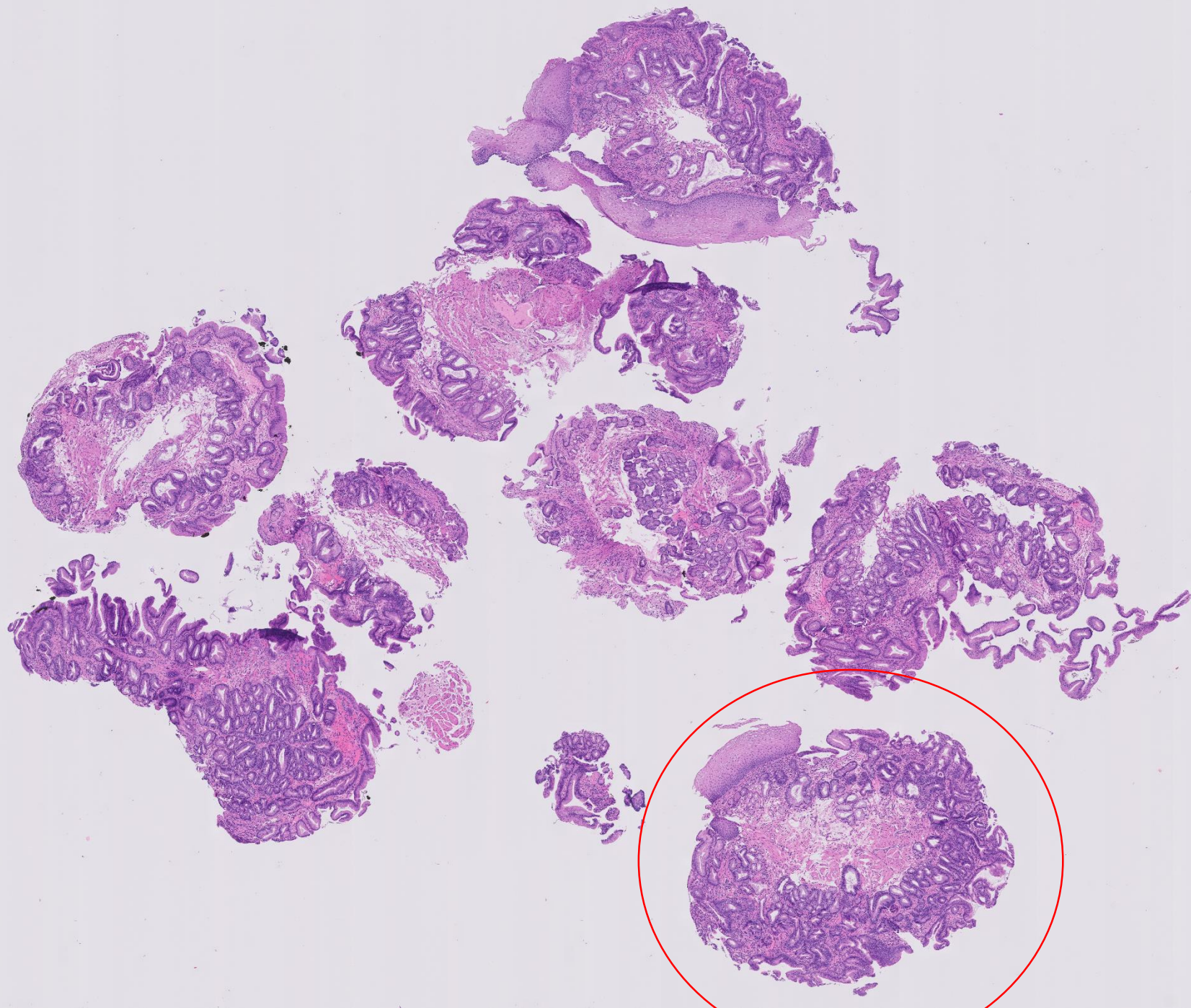


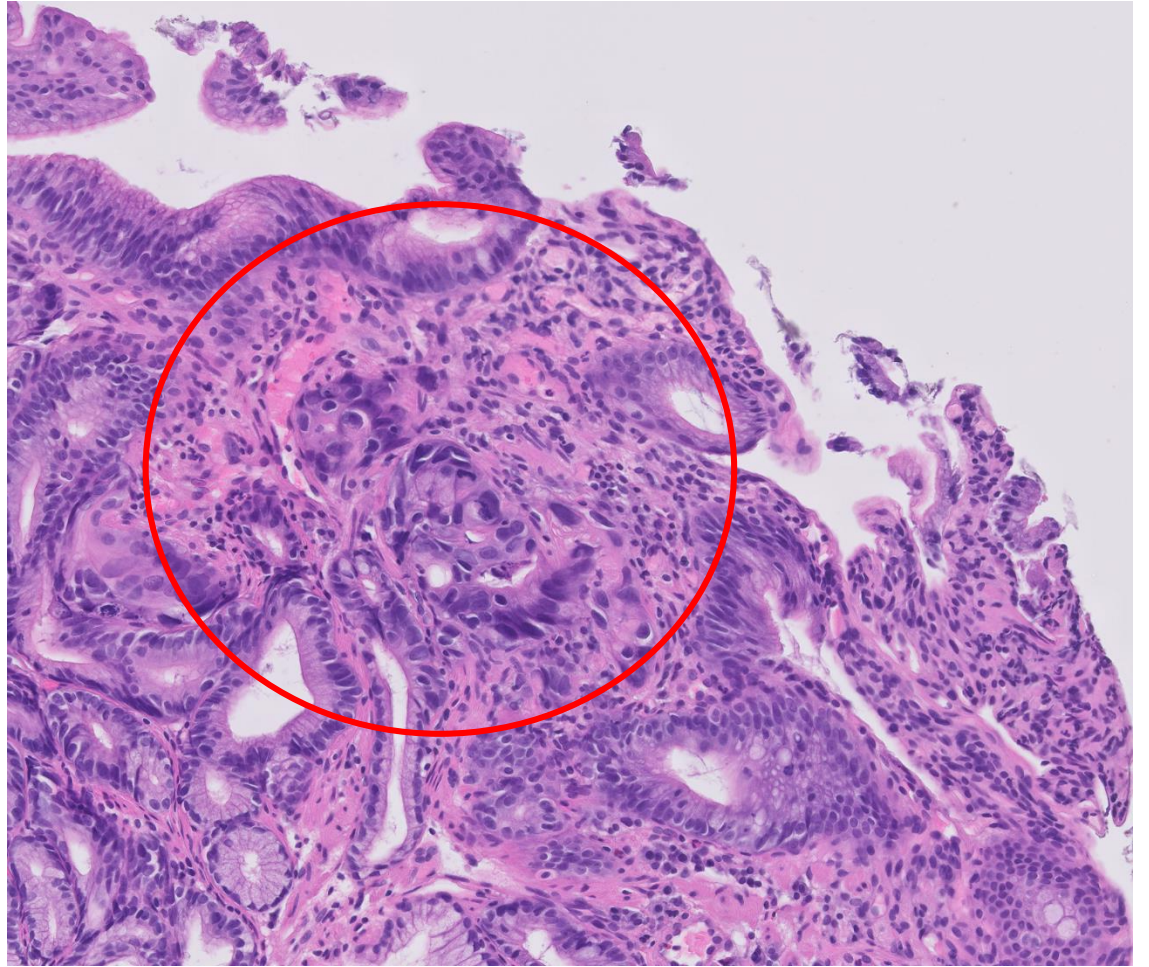
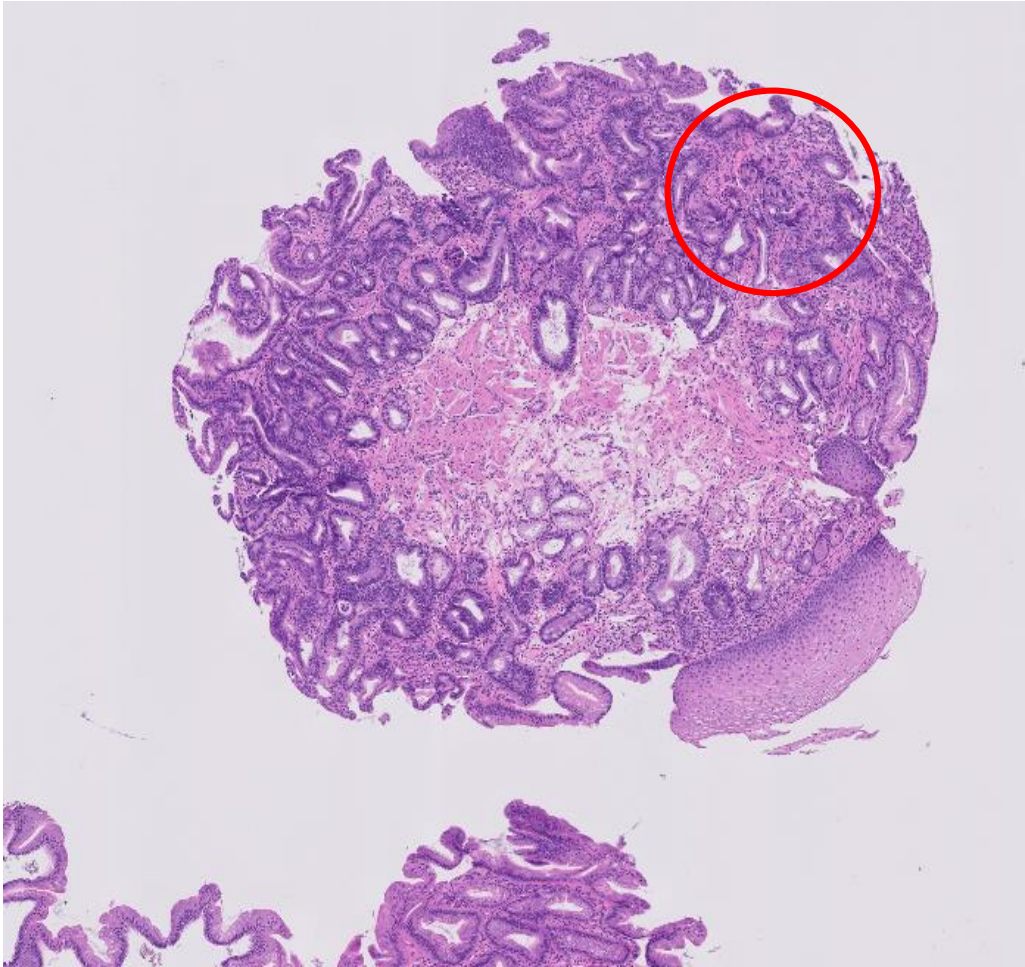
Dysplasia or no dysplasia?



Dysplasia or no dysplasia?







5 core pathologists

10 GE pathologists

2014

Set I

Single slide set (HE)

Group discussion → consensus Dx =
GS Dx

4 rounds: digital vs conventional microscopy

2015

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

2016-2017

300 LANS cases

Building a diagnostic algorithm for future cases

2015

2016

2018

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



2013 – 2018:
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

Barrett.nl > Informatie over de Barrett slokdarm & behandelmethoden

HOME BARRETT SLOKDARM BEHANDELING ONDERZOEK REVISIE AANVRAGEN Zoek

Revisie aanvragen

Via [deze link](#) kan een revisie worden aangevraagd (alleen door artsen).
Wij streven ernaar aangevraagde revisies binnen 6 weken te verwerken, wij zijn hierbij echter ook afhankelijk van hoe snel wij de opgevraagde coupes ontvangen.

De cases die ter revisie worden aangeboden worden verwerkt door het Landelijk Adviesorgaan Neoplasie Slokdarm (LANS). Dit revisiepanel is opgericht om mede-beoordeling van dysplastische cases bij patiënten met een Barrett slokdarm te vergemakkelijken. Het panel bestaat uit expert pathologen met veel ervaring op het gebied van Barrett slokdarm.

REVISIE AANVRAGEN

WIE ZIJN WIJ?

VEELGESTELDE VRAGEN

VERKLARENDE WOORDENLIJST

LINKS

Informatiefolders downloaden

Voor patiënten

Barrett slokdarm
Algemene informatie over de Barrett slokdarm.

Endoscopische resectie

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

No additional documents or images available

For Demo purposes only. Not for sale.

Connectivity

Bestand Bewerken Beeld Favorieten Extra Help

Cases Viewer Preferences Edit cases

T16-24923 AMC-T17-60881 Project

0 Sybren Meijer PHILIPS

60881 Case ID

Priority

High Priority 0

Cases

In preparation 728

For Review 0

Finished 0

All above 728

Other

Deleted Items 0

Projects

Projects 91

Tags

T16-24923 AMC-T17-60881 29 days 10-May-17 15:23 Born 6 Barrett Panel, Digitaal Project

17/H05647 AMC-T17-60881 33 days 16-May-17 12:06 Born 5 Barrett Panel, Digitaal Project

AMC-T16-50833 277 days 14-Sep-16 15:35 Born 4 Barrett Panel, Digitaal Project

AMC-T16-50987 208 days 22-Nov-16 09:54 Born 2 Barrett Panel, Digitaal Project

AMC-T17-03512 39 days 10-May-17 16:09 Born 9 Barrett Panel, Digitaal Project

AMC-T17-03518 46 days 03-May-17 15:36 Born 6 Barrett Panel, Digitaal Project

AMC-T17-50172 46 days 03-May-17 15:44 Born 2 Barrett Panel, Digitaal Project

AMC-T17-60473 102 days 08-Mar-17 13:51 Born 4 Barrett Panel, Digitaal Project

T13-34503 AMC-T16-60881 187 days 13-Dec-16 08:44 Born 4 Barrett Panel, Digitaal Project

T15-40013 AMC-T17-60881 131 days 07-Feb-17 14:34 Born 20 Barrett Panel, Digitaal Project

T15-47494 AMC-T16-60881 509 days 26-Jan-16 09:25 Born 9 Roos, Eelco Project

T16-02168 433 days 11-Apr-16 16:10 Born 12 Barrett Panel, Digitaal Project

T16-03529 AMC-T16-60881 263 days 28-Sep-16 12:51 Born 4 Barrett Panel, Digitaal Project

T16-03785 AMC-T16-60881 263 days 28-Sep-16 14:43 Born 4 Barrett Panel, Digitaal Project

T16-03788 AMC-T16-60881 207 days 23-Nov-16 09:35 Born 8 Barrett Panel, Digitaal Project

T16-05183 AMC-T16-60881 263 days 28-Sep-16 13:46 Born 2 Barrett Panel, Digitaal Project

T16-05185 AMC-T16-60881 263 days 28-Sep-16 11:39 Born 4 Barrett Panel, Digitaal Project

T16-06910 AMC-T16-60881 276 days 15-Sep-16 13:10 Born 14 Barrett Panel, Digitaal Project

T16-06917 AMC-T16-60881 299 days 23-Aug-16 10:58 Born 6 Barrett Panel, Digitaal Project

T16-07640 AMC-T16-60881 299 days 23-Aug-16 11:13 Born 12 Barrett Panel, Digitaal Project

T16-07777 277 days 14-Sep-16 11:52 Born 28 Barrett Panel, Digitaal Project

T16-10331 AMC-T16-60881 277 days 14-Sep-16 11:52 Born 5 Barrett Panel, Digitaal Project

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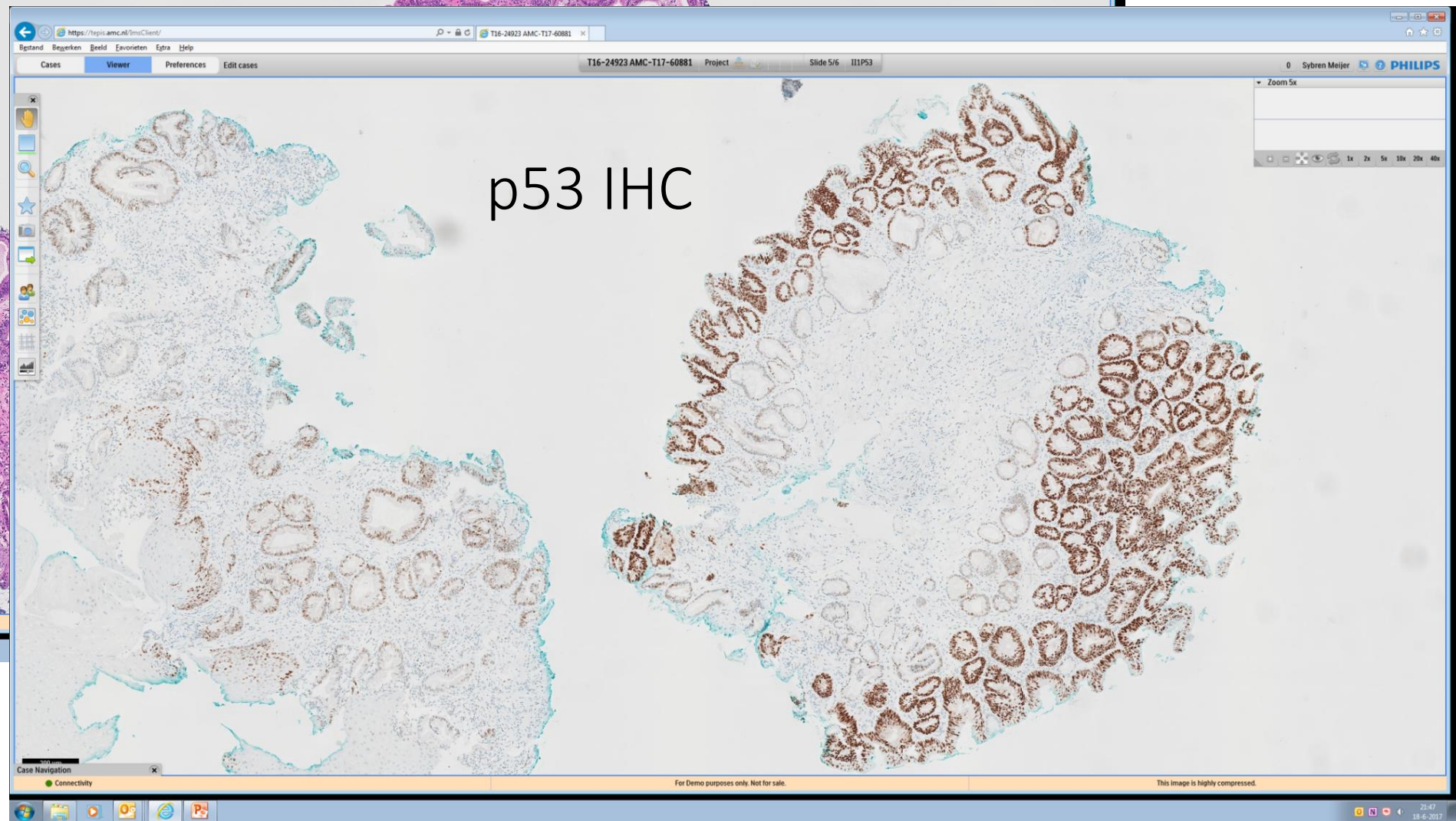
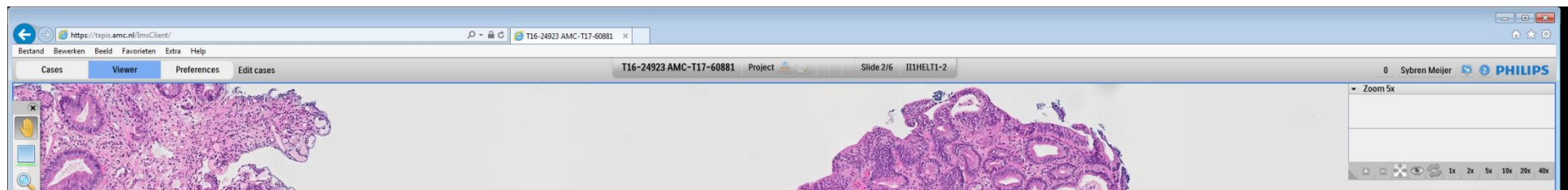
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Slide Id: FMT0207_20170503_104425 Stain info: IIIIP53

Slide Id: FMT0207_20170503_104552 Stain info: IIIIP53

Slide Id: FMT0207_20170503_104750 Stain info: IIIIP53



PA Formulier Revisie LANS

| | | |
|---|----------------------------|----|
| CIC | | |
| Patient | | |
| General Information | | 25 |
| Date of birth | | |
| Patient sex | | |
| Index Administration | | 25 |
| Endoscopy | | |
| PA Revision | | |
| PA Revisieformulier | | 25 |
| T-nummer | | |
| Aantal paraffineblokjes | 1 | |
| Paraffineblokje I | | 25 |
| Aantal bipten blokje I | 2 | |
| Intestinale metaplasie blokje I | Nee | |
| Dysplasie en of carcinoom blokje I | LGD | |
| Bij dysplasie, hoeveel bipten bevatten dysplasie blokje I | Focaal, in multiple bipten | |
| P53 aanvullende immunohistochemische kleuring blokje I aanwezig | Yes | |
| Uitslag van P53 immunohistochemische kleuring blokje I | Overexpressie | |
| Opmerkingen | | |
| (! = het antwoord is gewijzigd door u) | | |
| VERZEND Klik op de VERZEND-knop wanneer u alle gegevens hebt ingevuld | | |

send

All diagnoses are collected
by a data manager

Conclusion with consensus
diagnosis is formulated
&
sent to endoscopist
treating patient

PA Formulier Revisie LANS

| | | |
|---|----------------------------|----|
| CIC | | |
| Patient | | |
| General Information | | 25 |
| Date of birth | | |
| Patient sex | | |
| Index Administration | | 25 |
| Endoscopy | | |
| PA Revision | | |
| PA Revisieformulier | | 25 |
| T-nummer | | |
| Aantal paraffineblokjes | 1 | |
| Paraffineblokje I | | 25 |
| Aantal bipten blokje I | 2 | |
| Intestinale metaplasie blokje I | Nee | |
| Dysplasie en of carcinoom blokje I | LGD | |
| Bij dysplasie, hoeveel bipten bevatten dysplasie blokje I | Focaal, in multiële bipten | |
| P53 aanvullende immunohistochemische kleuring blokje I aanwezig | Yes | |
| Uitslag van P53 immunohistochemische kleuring blokje I | Overexpressie | |
| Opmerkingen | | |

send

! = het antwoord is niet door u gewijzigd

If no consensus →
online consensus meeting
with panel pathologists

VERZEND

Klik op de VERZEND-knop wanneer u alle gegevens heeft ingevuld

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%)

T18-51183

Documents

Images

7ce0cd19fbf3e51f

Born

Current age

Sex

Medical record number: 7ce0cd19fbf3e51f

T18-51183

28-11-2018

HE

T18-51...

2x/20x

Image Controls

Gamma: 0.5 1.0 3.5

Set as My Default

Reset

T18-51180II

T18-51183I

20x

HE

HE-1

HE-2

p53

nl

en

LANS Slokdarm

Leden administratie

Panel eigenschappen

Export

Voorzitter

Secretaris

Leden

Zichtbaarheid:

SM Sybren Meijer

MK Moniek Kleintjes

Sybren Meijer, Patricia de Koning, Lodewijk Brosens, Ariadne Ooms, Clément Huysentruyt, Jacob van der Laan, Johan Offerhaus, Kees Seldenrijk, Michael Doukas, Mike Visser, Myrtle van der Wel, Moniek Kleintjes

volledig

Cases:

lab rapport

aanmelding

Status

| | | | | | |
|----|-----------|----------|----------------|-------------|--------|
| 20 | T18-51183 | 28-11-18 | man, 61 jaar | in stemming | 12,1,0 |
| 20 | T18-62339 | 14-11-18 | vrouw, 72 jaar | in stemming | 12,2,0 |
| 20 | T18-62343 | 14-11-18 | vrouw, 75 jaar | in stemming | 12,1,0 |
| 20 | T18-62365 | 23-11-18 | man, 76 jaar | in stemming | 12,1,0 |
| 20 | T18-62390 | 28-11-18 | vrouw, 76 jaar | in stemming | 12,2,0 |

Selecteer gesloten case

Keuzemogelijkheden

1. nummer blokje:

2. Aantal bipten? Aantal:

3. Intestinale metaplasie? ja / nee

4. Dysplasie en/of carcinoom 1=NDBE / 2=IND / 3=LGD / 4=HGD / 5=verdacht voor carcinoom / 6=carcinoom

5. Indien IND 1=uitgebreide actieve ontsteking / 2= focale afwijking in p53 IHC / 3= discrepantie HE en p53 / 4= anders

6. Indien anders Graag specificeren:

7. Indien dysplasie bipten bevatten dysplasie

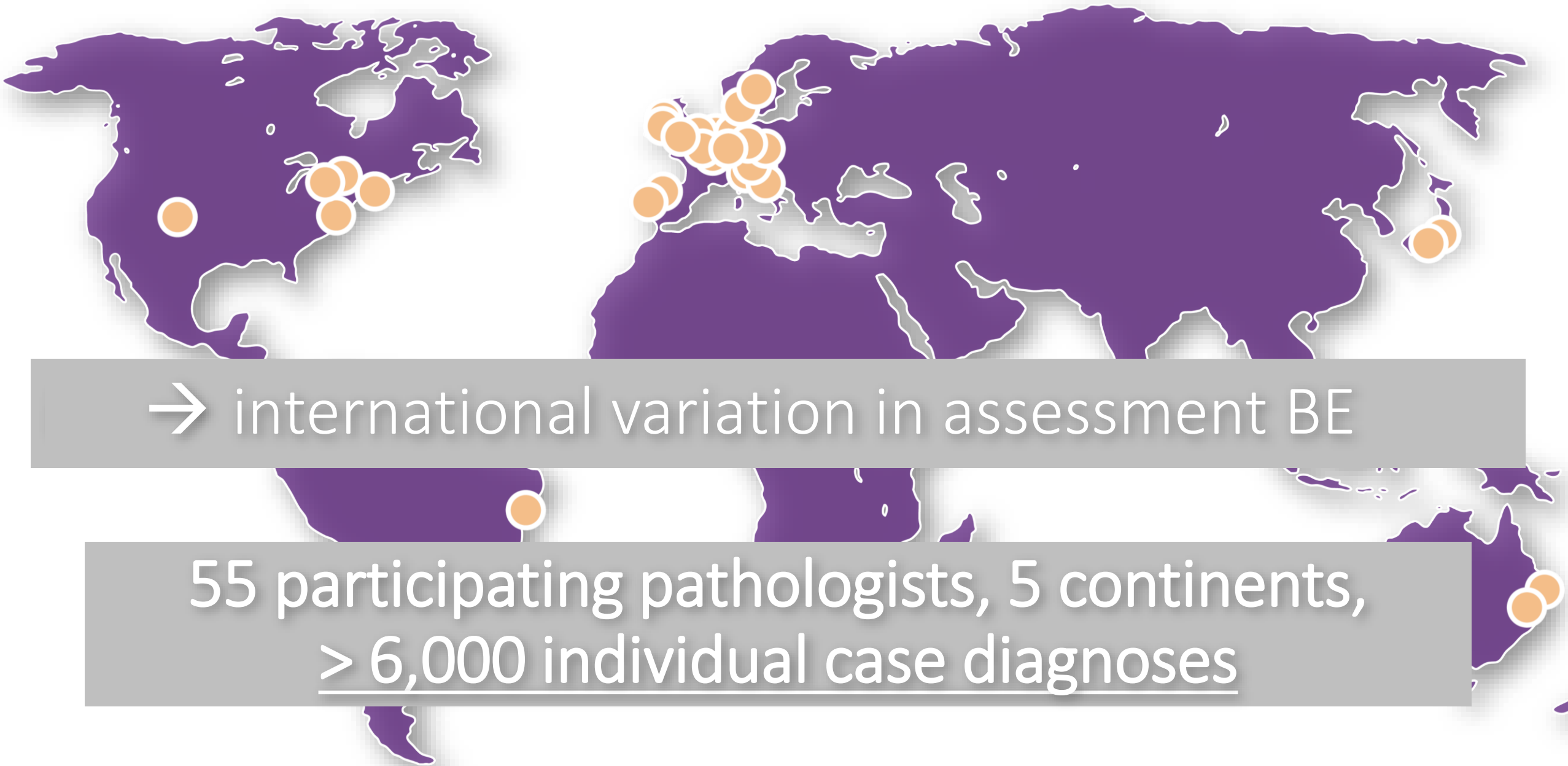
8. p53 aanwezig? ja / nee

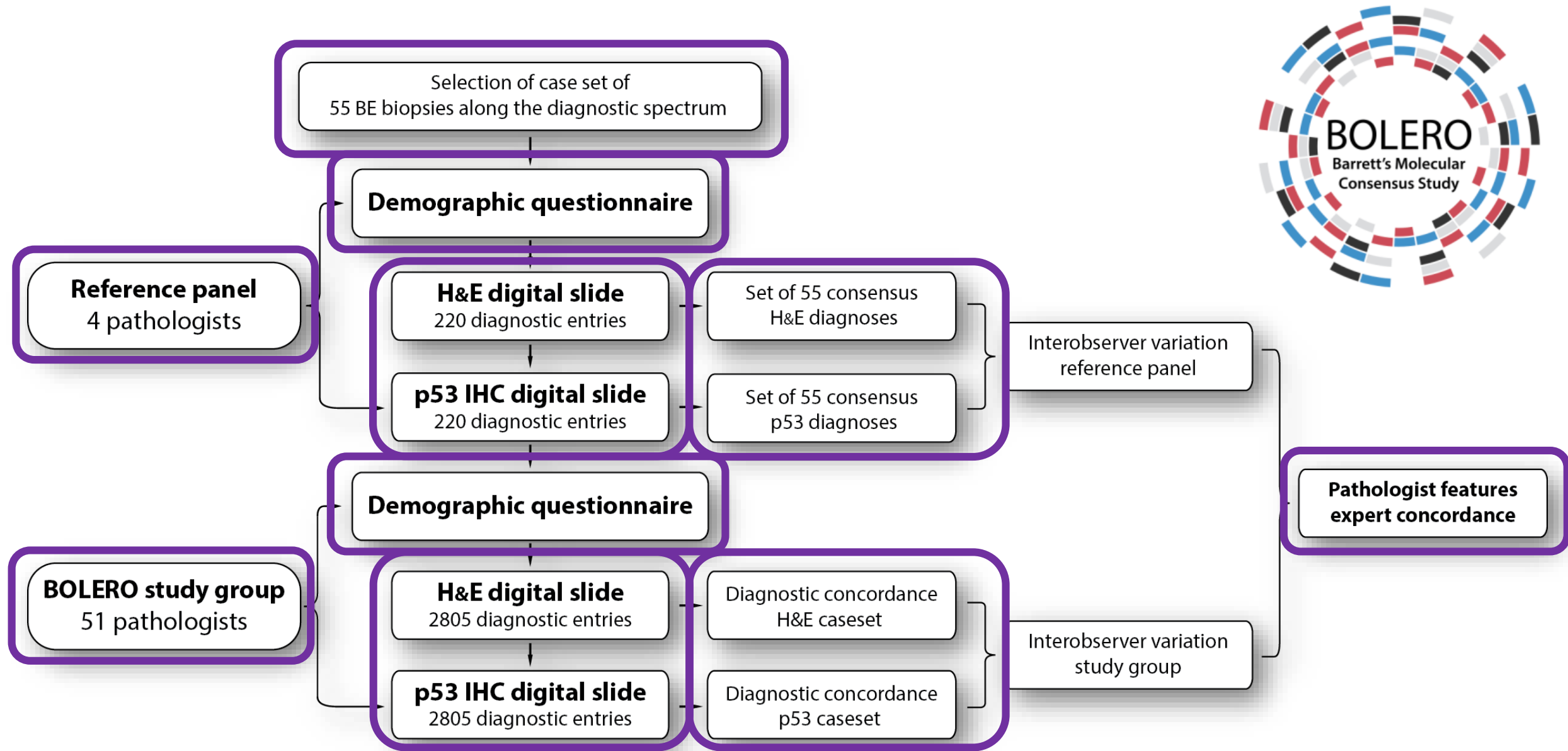
9. Zo nee: p53 gewenst? ja / nee

10. Uitslag p53 1= Wild-type / 2= overexpression / 3= null-mutation / 4=double clone / 5= heterogeen



set up homogeneous expert digital pathology platform





Reference panel 'core' pathologists

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

Unde

Wouter L C

PhD, Brenda Etz

MD, PhD, Arnou

Harriët G T Blaas



Citation
Tools

The American Journal of Gastroenterology **105**,
1523–1530 (2010)
doi:10.1038/ajg.2010.171

Received: 17 November 2009
Accepted: 22 March 2010
Published: 11 May 2010

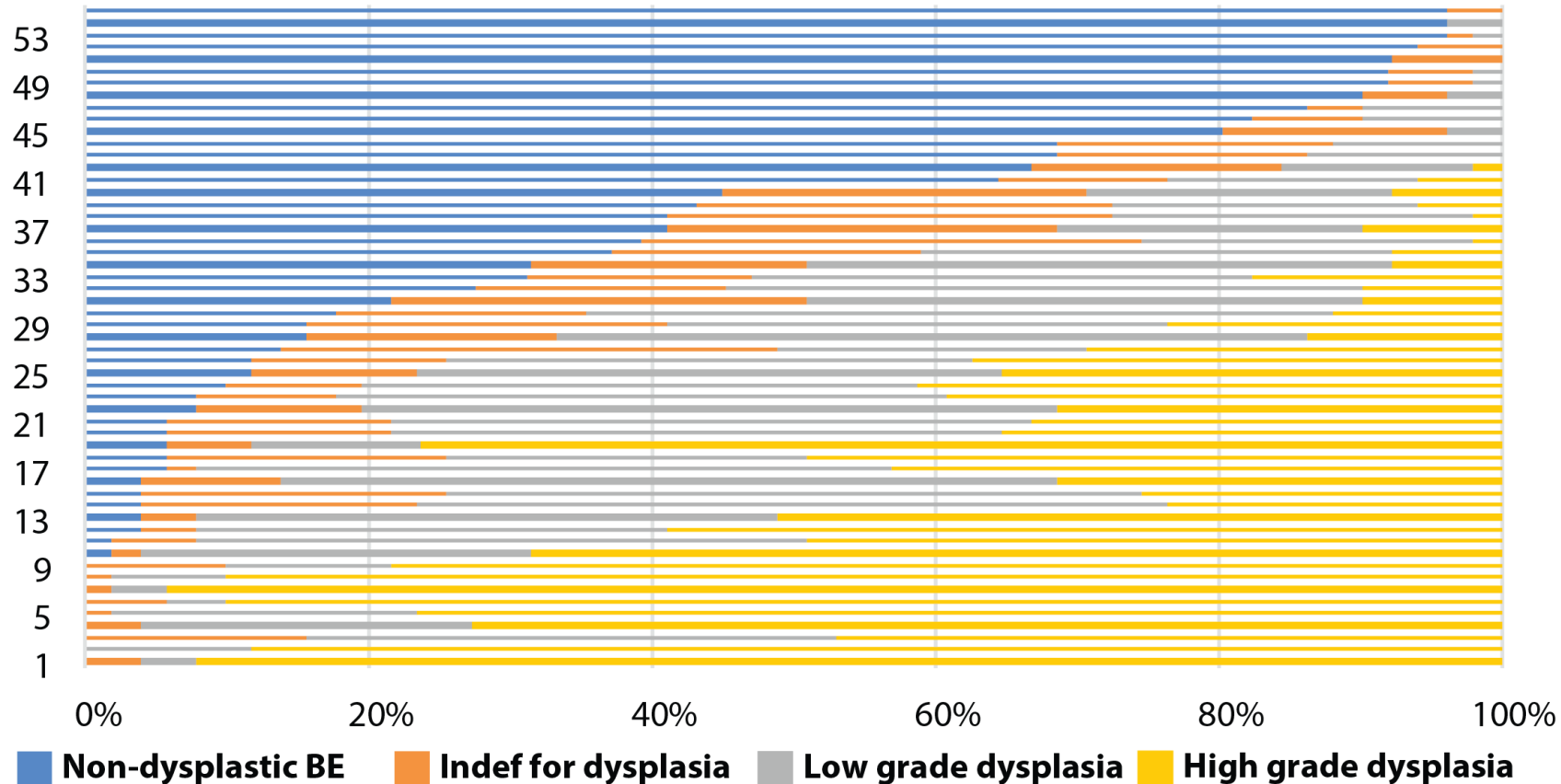
¹Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands; ²Department of Pathology, Academic Medical Center, Amsterdam, The Netherlands; ³Center for Esophageal Diseases and Swallowing, Department of Medicine, Division of Gastroenterology, University of North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

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

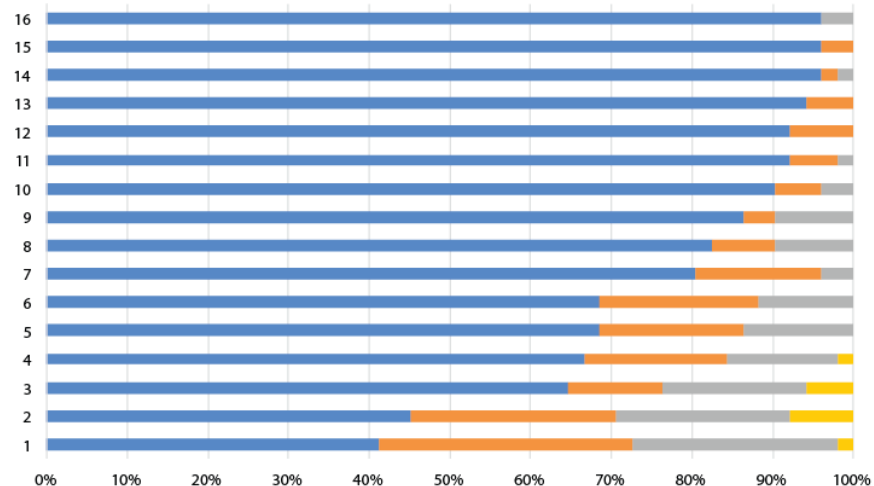
| Clinical practice and experience (more than 1 option possible) | Ref panel | % | Total group | % | p-value* |
|--|-----------|-----|-------------|----|----------|
| Academic teaching hospital | 3 | 75 | 41 | 80 | 0.904 |
| District general hospital | 1 | 25 | 16 | 31 | 0.921 |
| Private practice | 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)

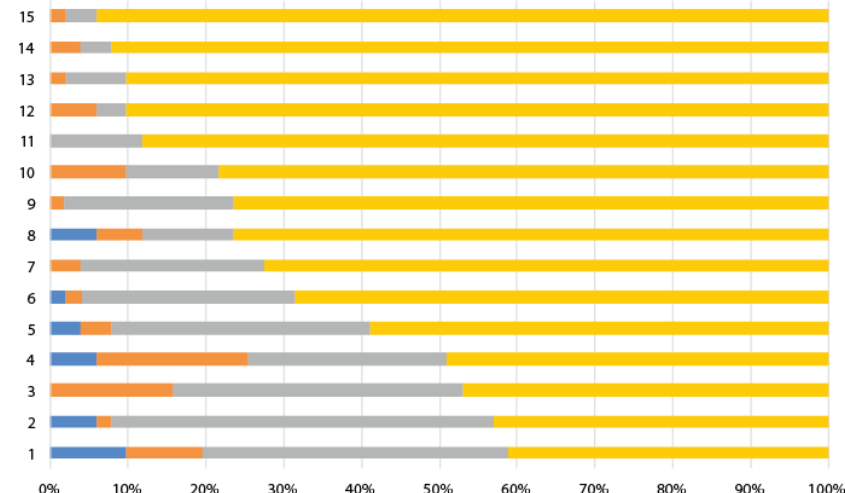
Consensus scores entire cohort



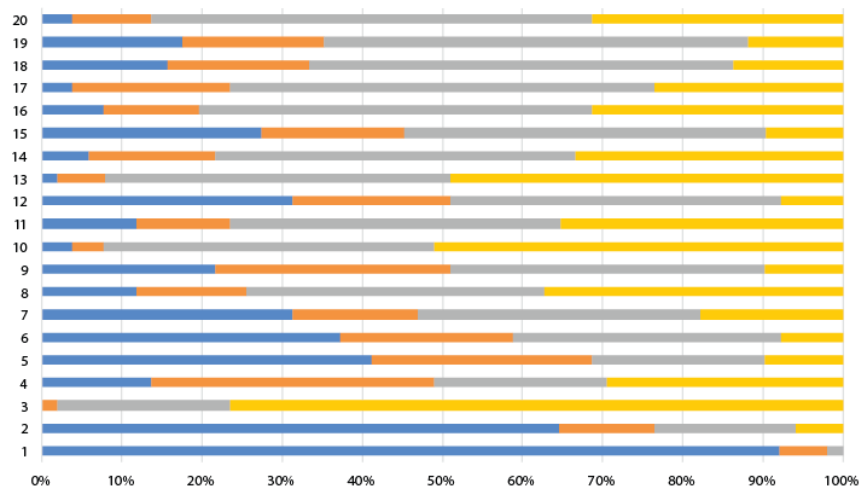
Consensus scores non-dysplastic BE



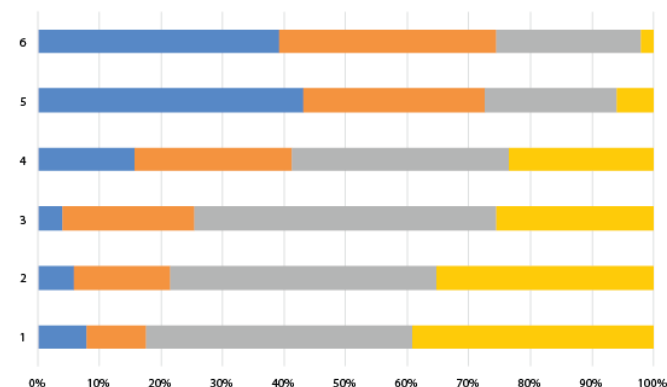
Consensus scores high grade dysplasia



Consensus scores low grade dysplasia



Consensus scores indefinite for dysplasia

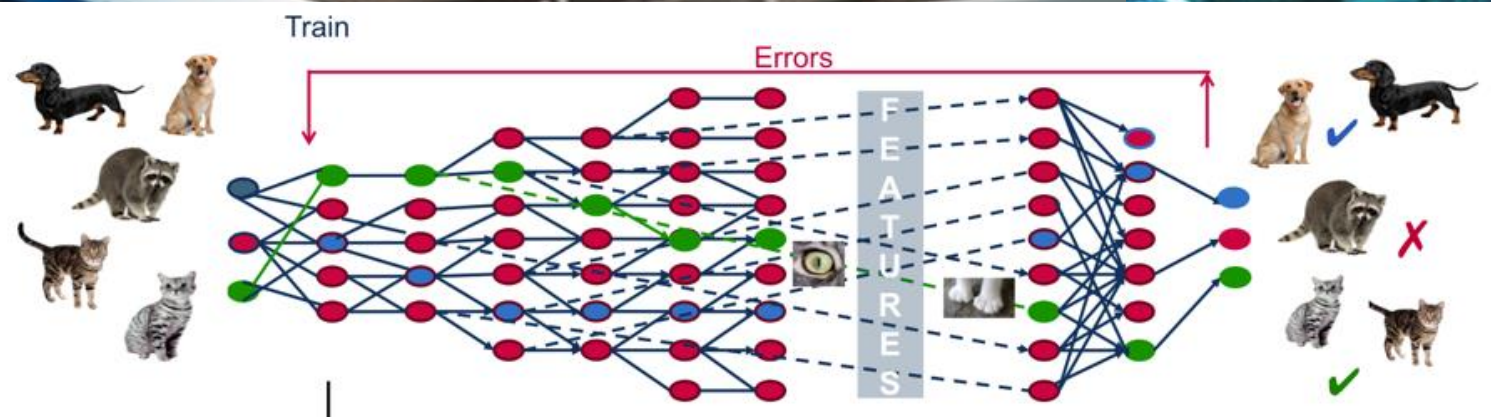
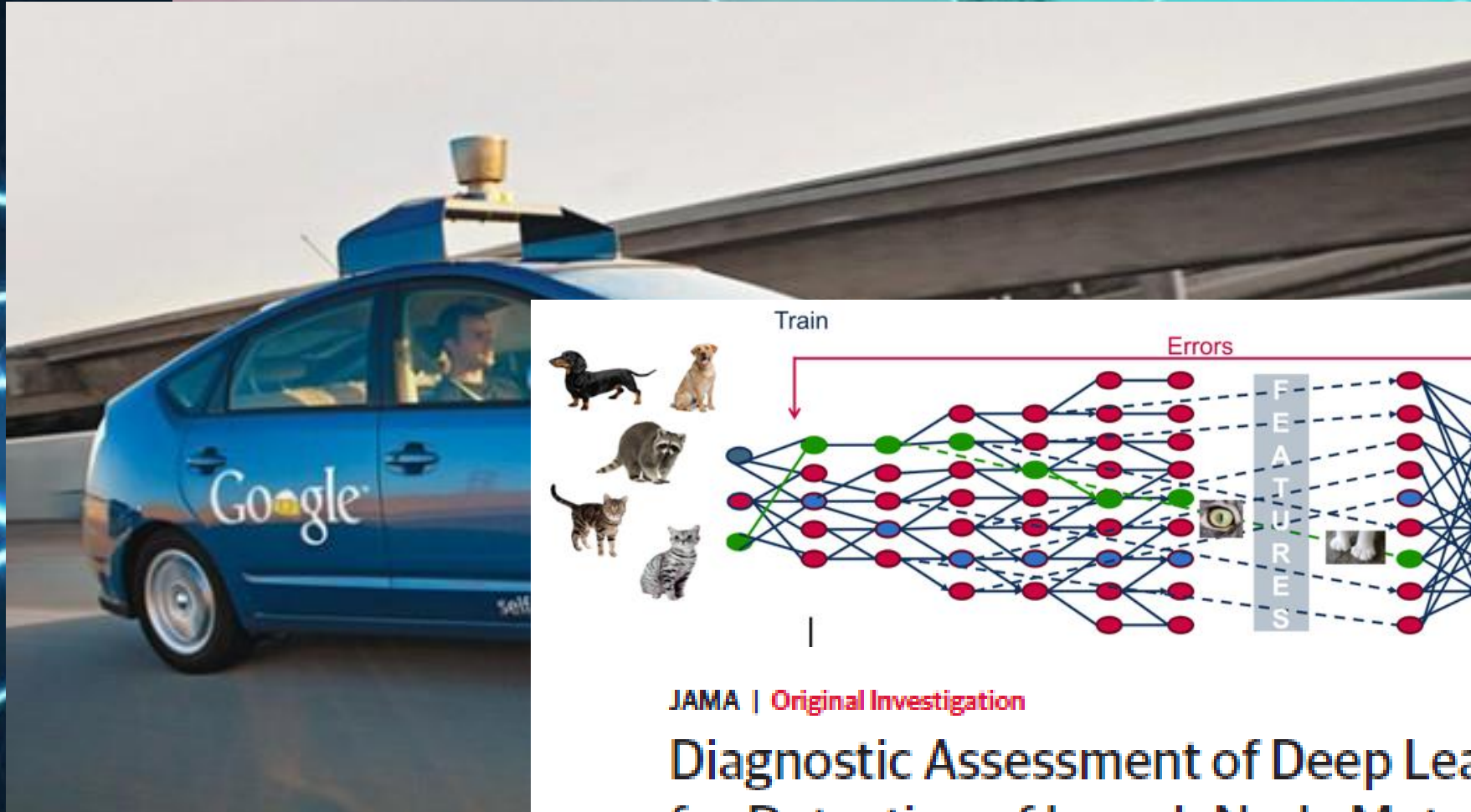


■ Non-dysplastic BE
 ■ Indef for dysplasia
 ■ Low grade dysplasia
 ■ High grade dysplasia

MULTIVARIATE ANALYSIS OF DEMOGRAPHIC PREDICTORS ON DIAGNOSTIC PERFORMANCE

| | H&E digital slide review | | p53 stained slide review | |
|---|--------------------------|-----------------------|--------------------------|--------------------------|
| Characteristic | | Odds ratio (95%CI) | | Odds ratio (95% CI) * |
| <i>'Protective' factors</i> | | | | |
| 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) |
| <i>'Risk' factors</i> | | | | |
| 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

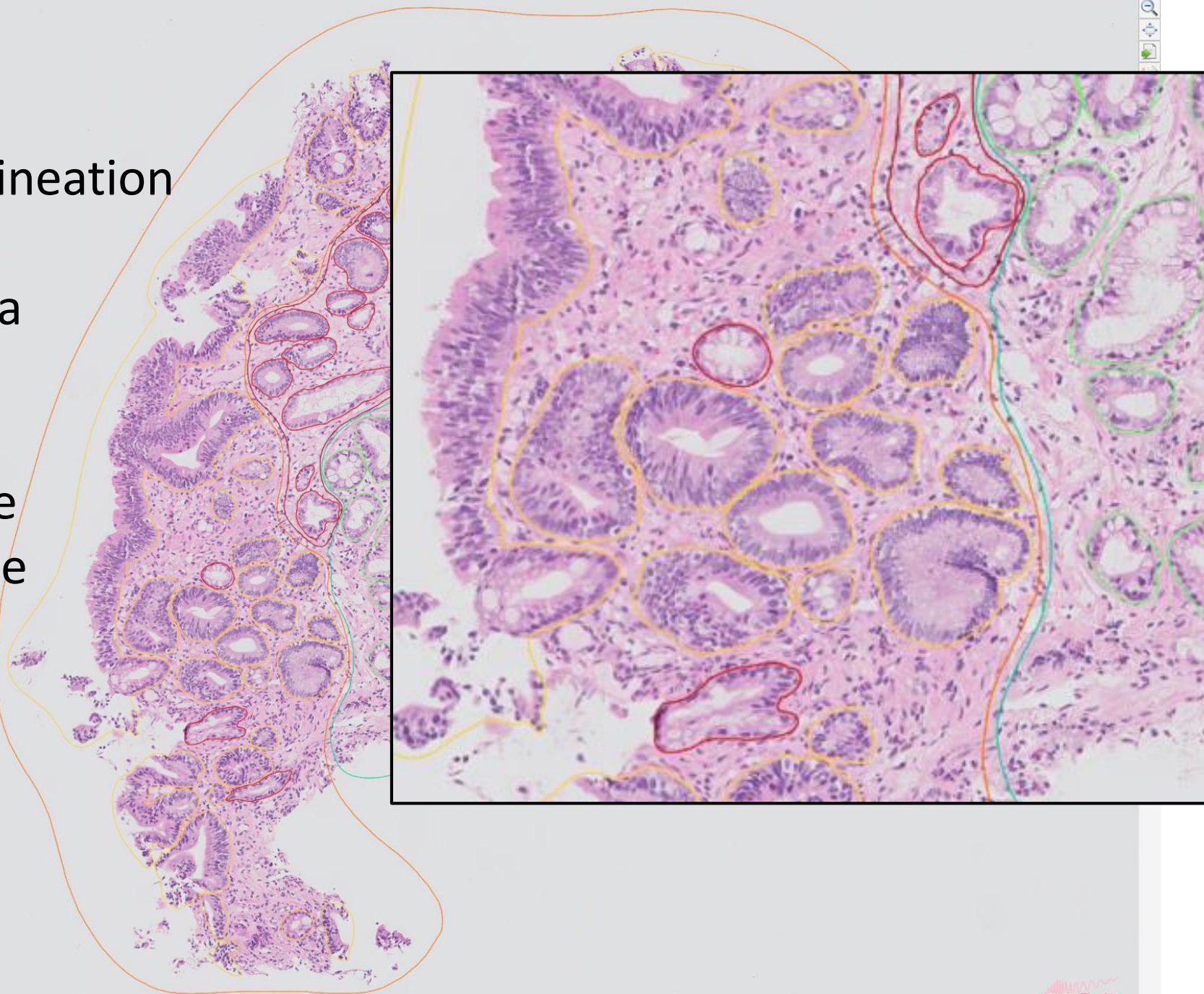


Manual delineation

No dysplasia

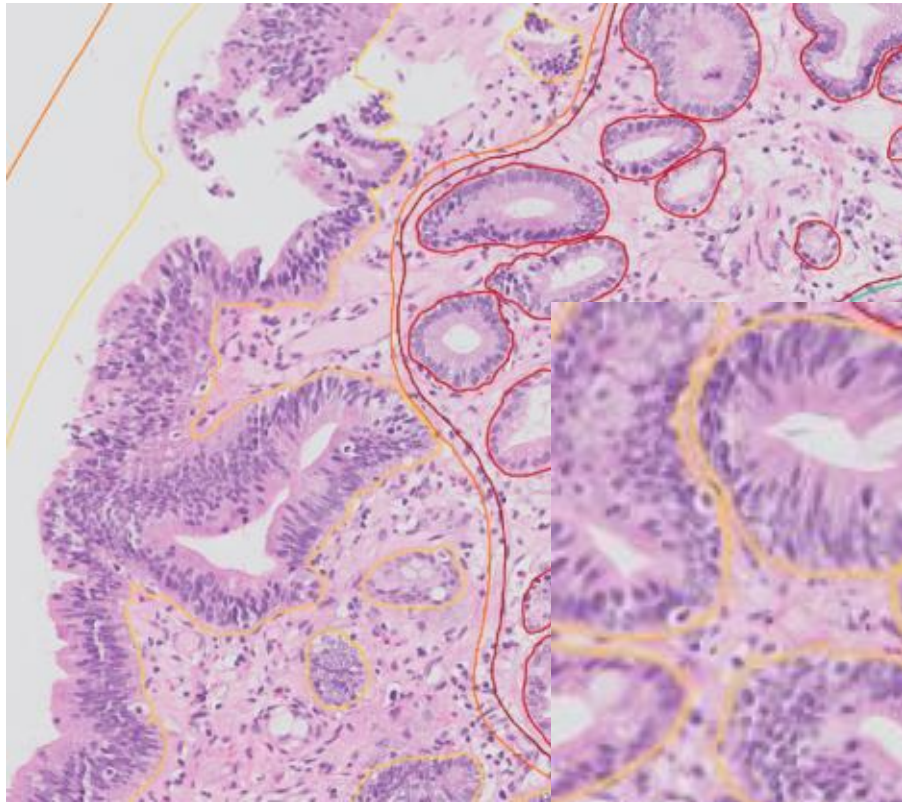
Dysplasia

- Low grade
- High grade



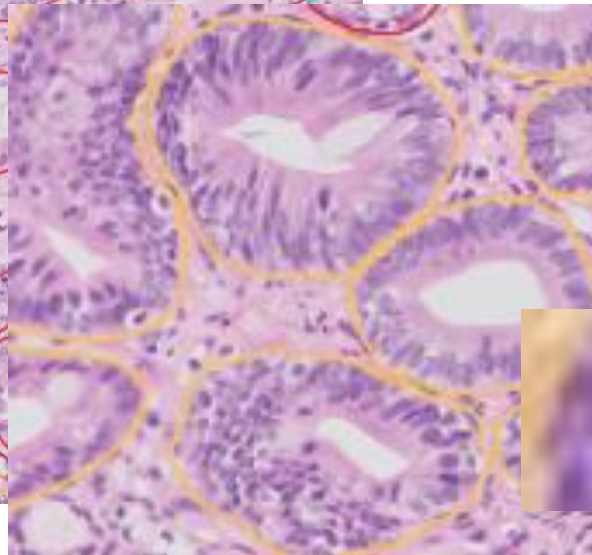
First experiment concentrate on nuclear features

process collections of image patches containing nuclei

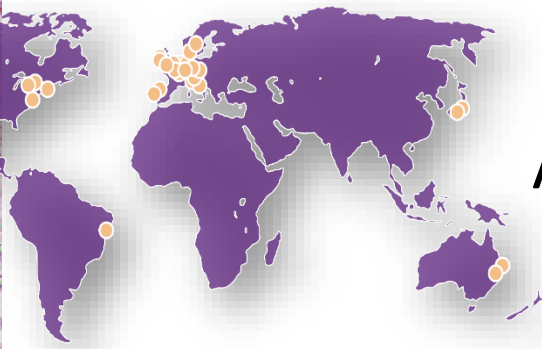
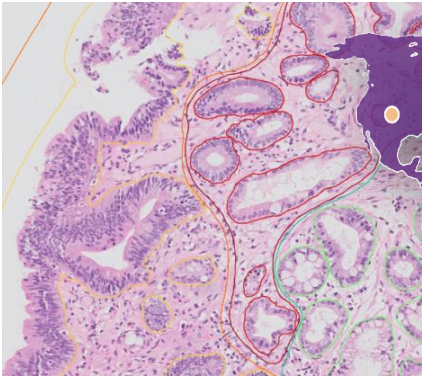


Each slide divided into smaller images (500×500 pix)

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



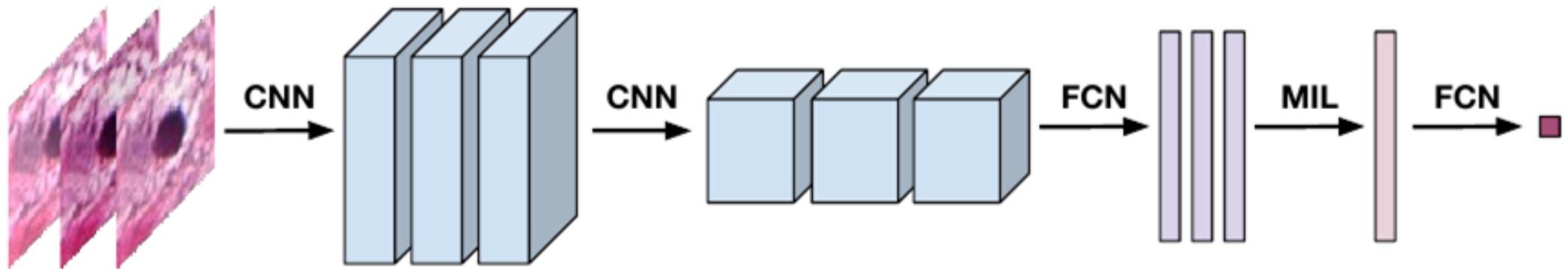
A patch contains a nucleus in the center



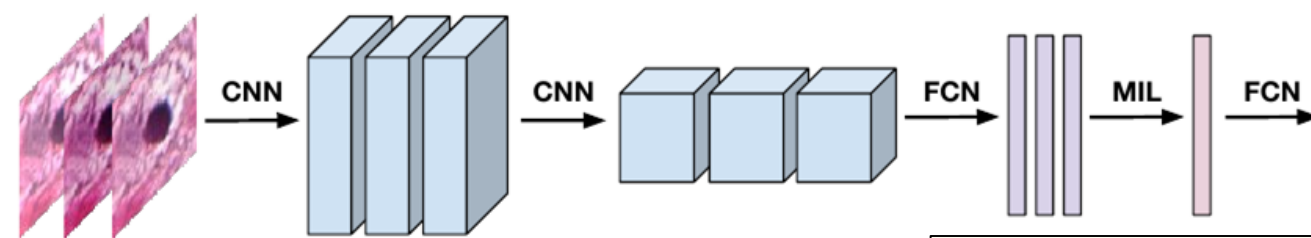
Annotated 21 cases

- 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

MAJORITY CLASS

MAX

MEAN

Accuracy

52.1%

58.7% \pm 1.8%

67.2% \pm 2.5%

65.9% \pm 3.5%

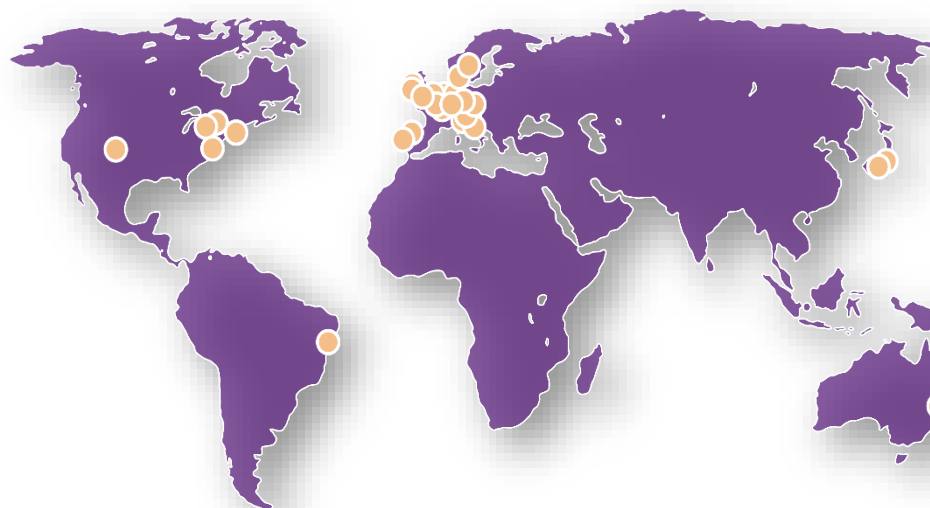
70.1% \pm 1.7%

Table 7.

Values for benchmark quality criteria based on 95% prediction

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

Not an expert yet



Conclusions

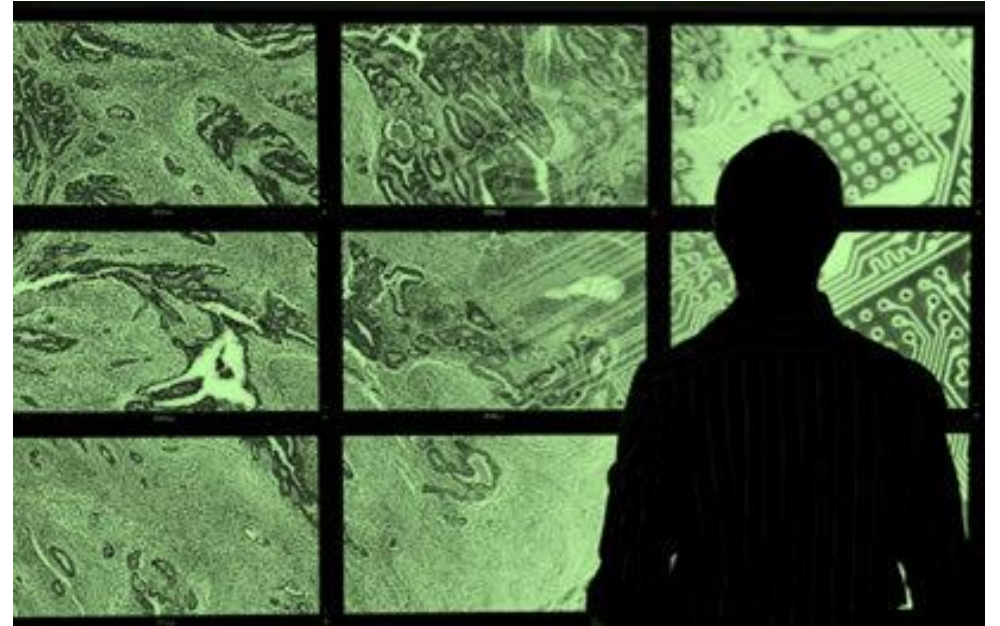
Optimal risk stratification in Barrett's Esophagus related dysplasia

- 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



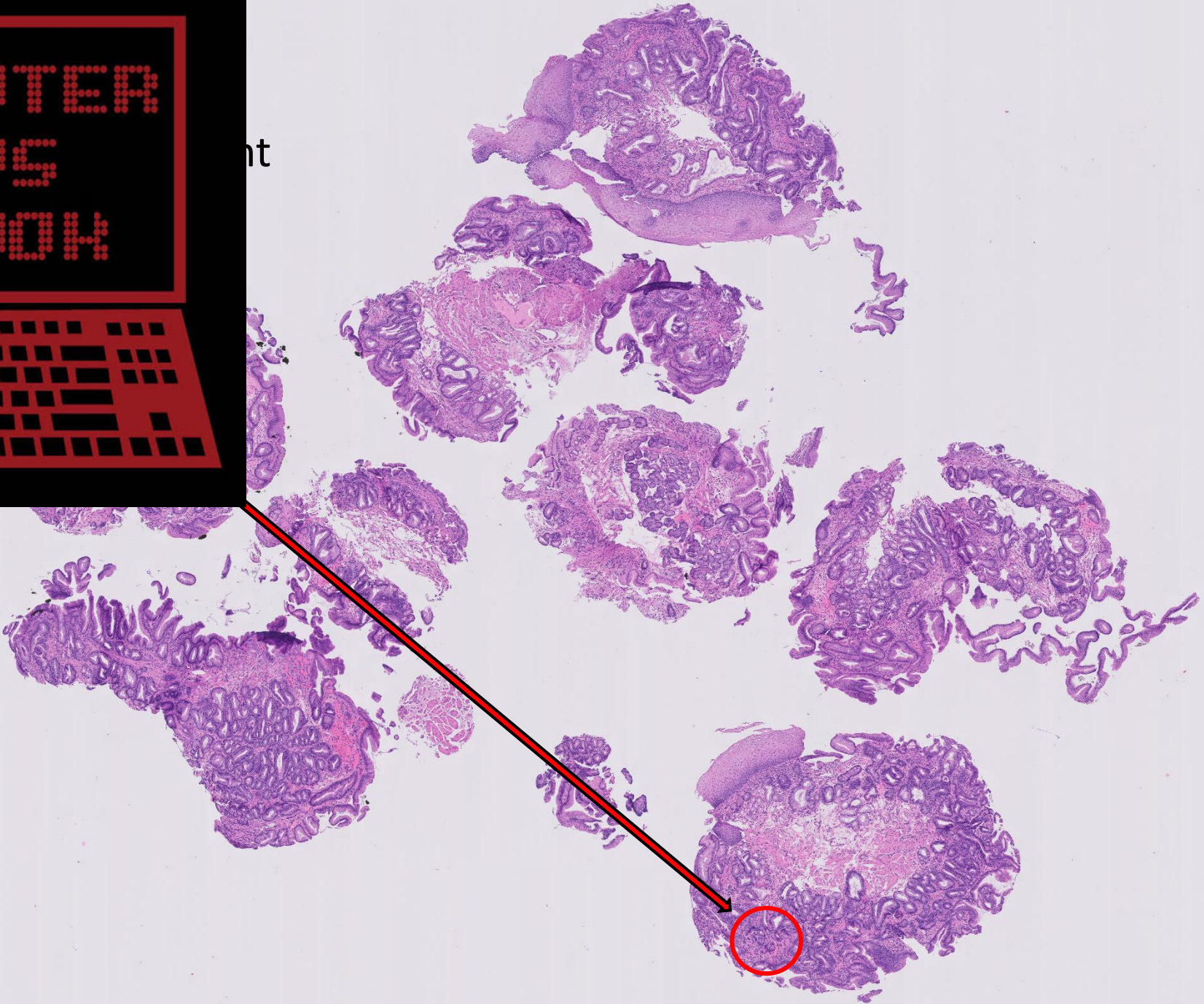
COMPUTER
SALES

YOU'RE
D





nt



Thank you

LANS Pathology

Myrtle van der Wel

Kees Seldenrijk

Johan Offerhaus

Mike Visser

Fiebo ten Kate sr.

Katharina Biermann

Lodewijk Brosens

Michael Doukas

Clément Huysentruyt

Arend Karrenbeld

Ineke van Lijnschoten

Freek Moll

Ariadne Ooms

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200 µm