“Pathology: what’s the future?”

Pr Eva Compérat

Dpt Pathology

Vienna/Paris

Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	
Receipt of honoraria or consultation fees	Jansen, BMS
Stock shareholder	
Other support (please specify):	

Evolution of PCa reporting

Grading of PCa (prostate cancer)

Gleason grading: 1966-1974 5 patterns

Grading system WHO Mostofi 1975-2002
(I-III)

Gleason grading: 2002-2014

The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Jonathan I. Epstein, MD, William C. Allsbrook, Jr, MD,† Mahul B. Amin, MD,‡ and Lars L. Egevad, MD, PhD,§ and the ISUP Grading Committee‖*

ISUP 2009

International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens: rationale and organization

Lars Egevad[1], John R Srigley[2] and Brett Delahunt[3]

WG3: extraprostatic extension, lymphovascular invasion and locally advanced disease

International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 1: specimen handling

Hemamali Samaratunga[1], Rodolfo Montironi[2], Lawrence True[3], Jonathan I Epstein[4], David F Griffiths[5], Peter A Humphrey[6], Theo van der Kwast[7], Thomas M Wheeler[8], John R Srigley[9], Brett Delahunt[10], Lars Egevad[11] and The ISUP Prostate Cancer Group*

International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 4: seminal vesicles and lymph nodes

Daniel M Berney[1], Thomas M Wheeler[2], David J Grignon[3], Jonathan I Epstein[4], David F Griffiths[5], Peter A Humphrey[6], Theo van der Kwast[7], Rodolfo Montironi[8], Brett Delahunt[9], Lars Egevad[10], John R Srigley[11] and the ISUP Prostate Cancer Group*

International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 2: T2 substaging and prostate cancer volume

Theo H van der Kwast[1], Mahul B Amin[2], Athanase Billis[3], Jonathan I Epstein[4], David Griffiths[5], Peter A Humphrey[6], Rodolfo Montironi[7], Thomas M Wheeler[8], John R Srigley[9], Lars Egevad[10], Brett Delahunt[11] and the ISUP Prostate Cancer Group*

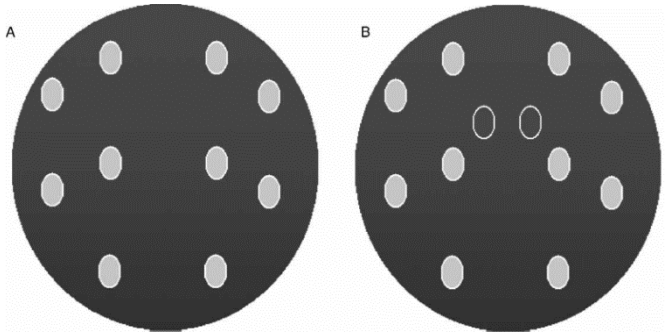
International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 5: surgical margins

Puay Hoon Tan[1], Liang Cheng[2], John R Srigley[3], David Griffiths[4], Peter A Humphrey[5], Theodore H van der Kwast[6], Rodolfo Montironi[7], Thomas M Wheeler[8], Brett Delahunt[9], Lars Egevad[10], Jonathan I Epstein[11] and the ISUP Prostate Cancer Group*

Pathology 2012

- MRI not standardised or in daily practice

Base

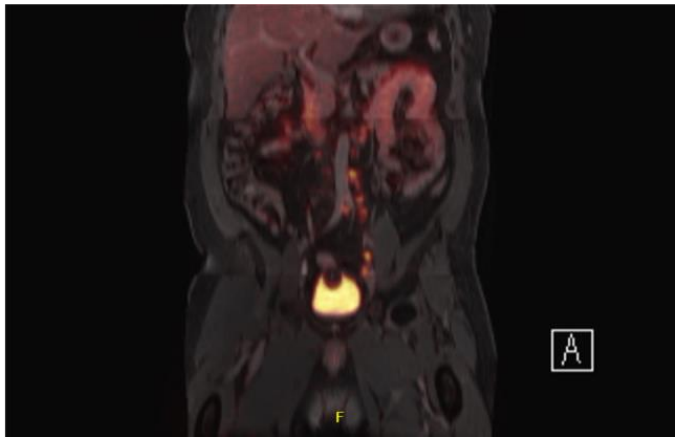


Apex

Table 6: Recommended diagnostic terms to report prostate biopsy findings*

Benign/negative for malignancy. If appropriate, include a description (e.g. atrophy).
Active inflammation, negative for malignancy
Atypical adenomatous hyperplasia/adenosis, no evidence of malignancy
Granulomatous inflammation, negative for malignancy
High-grade PIN, negative for adenocarcinoma
High-grade PIN with atypical glands suspicious for adenocarcinoma
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation suspicious for cancer
Adenocarcinoma

**From Van der Kwast, 2003 (49).*
PIN = prostatic intra-epithelial neoplasia.



Courtesy Dr Hübner

Already recommended terminology EAU

Contemporary Gleason Grading of Prostatic Carcinoma

An Update With Discussion on Practical Issues to Implement the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Jonathan I. Epstein, MD, Mahul B. Amin, MD,† Victor E. Reuter, MD,‡ and Peter A. Humphrey, MD, PhD§*

Table 5 Reporting of Gleason score Prognostic Grade Groups.

The overall Gleason score for this case is based on the core with the highest Gleason score. Gleason scores can be grouped and range from Prognostic Grade Group I (most favorable) to Prognostic Grade Group V (least favorable).

Gleason score ≤ 6:	Prognostic Grade Group I
Gleason score 3 + 4 = 7:	Prognostic Grade Group II
Gleason score 4 + 3 = 7:	Prognostic Grade Group III
Gleason score 8:	Prognostic Grade Group IV
Gleason score 9–10:	Prognostic Grade Group V

TABLE 3. Summary of Recommendations From the 2014 Consensus Meeting

(1) Cribriform glands should be assigned a Gleason pattern 4, regardless of morphology

Pieroazio BJU 2013, AJSP 2014

Contemporary Gleason Grading of Prostatic Carcinoma

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Gleason score 9–10:	Prognostic Grade Group V

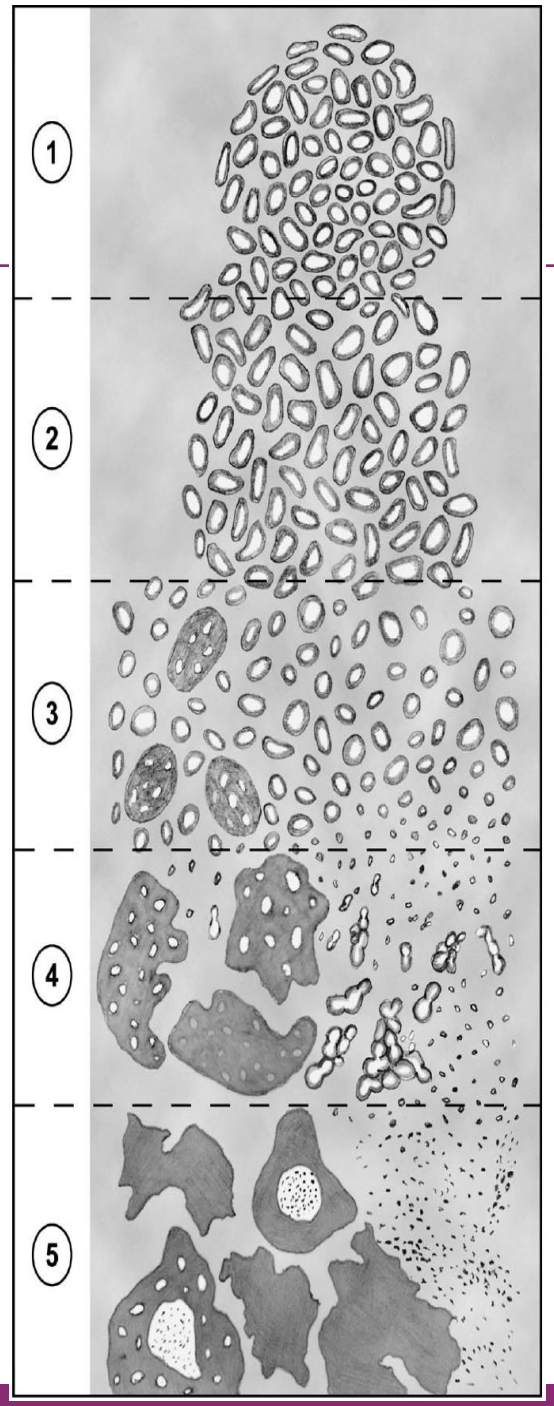
REPORTING PERCENTAGE PATTERN 4

A major new recommendation that came from the 2014 Consensus Conference was to report percent pattern 4 with Gleason score 7 in both needle biopsies and RP specimens. Although this issue was not completely re-

TABLE 3. Summary of Recommendations From the 2014 Consensus Meeting

(1) Cribriform glands should be assigned a Gleason pattern 4, regardless of morphology

Pieroazio BJU 2013, AJSP 2014



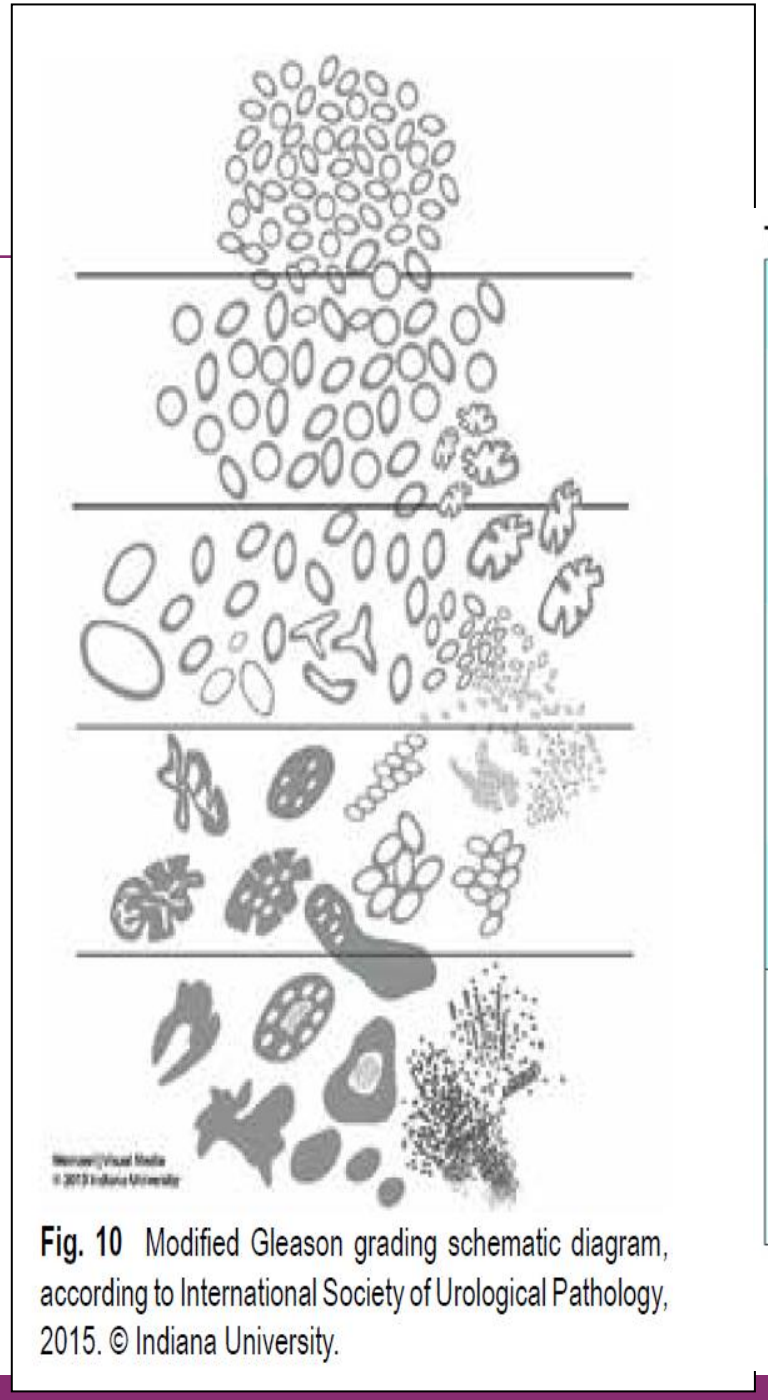
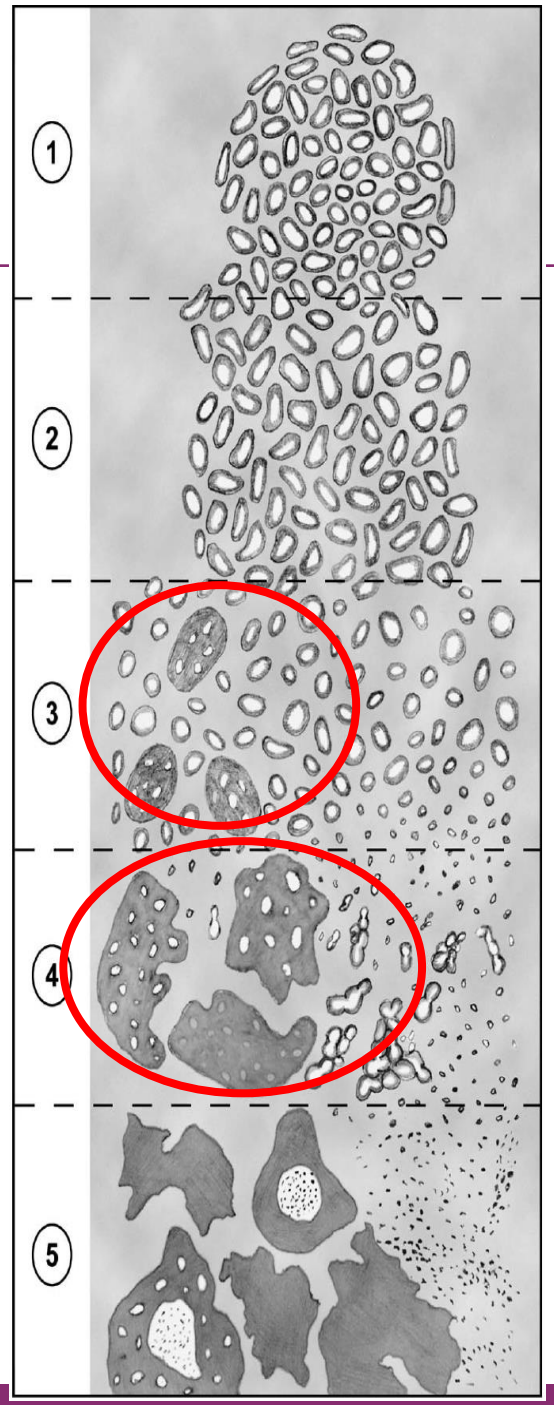


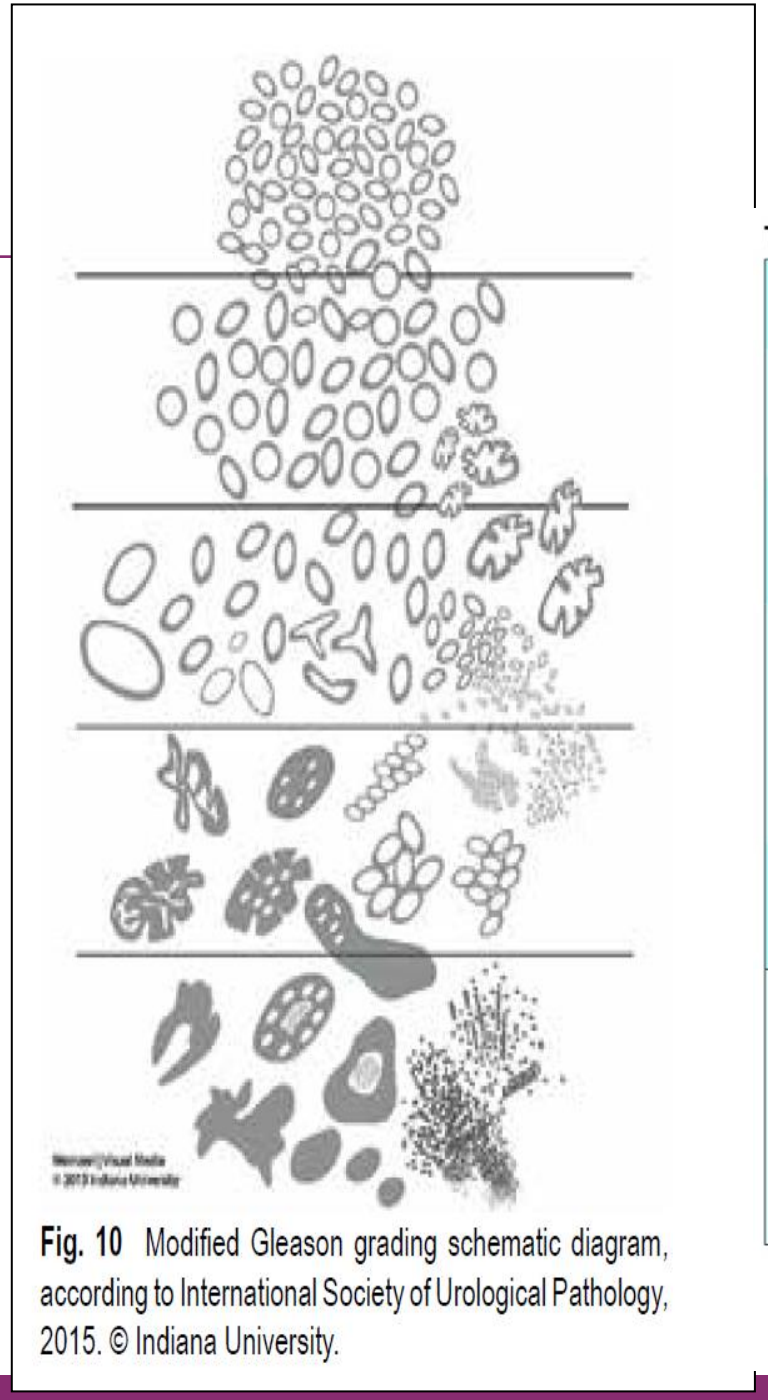
Fig. 10 Modified Gleason grading schematic diagram, according to International Society of Urological Pathology, 2015. © Indiana University.

Table 3.03 Grade groups

Grade group 1 Gleason score ≤6 Only individual discrete well-formed glands
Grade group 2 Gleason score 3+4=7 Predominantly well-formed glands with lesser component of poorly-formed/fused/cribriform glands
Grade group 3 Gleason score 4+3=7 Predominantly poorly-formed/fused/cribriform glands with lesser component of well-formed glands*
Grade group 4 Gleason score 4+4=8; 3+5=8; 5+3=8 - Only poorly-formed/fused/cribriform glands or - Predominantly well-formed glands and lesser component lacking glands** or - Predominantly lacking glands and lesser component of well-formed glands**
Grade group 5 Gleason scores 9–10 Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands*
* For cases with >95% poorly-formed/fused/cribriform glands or lack of glands on a core or at RP, the component of <5% well-formed glands is not factored into the grade. ** Poorly-formed/fused/cribriform glands can be a more minor component From Epstein JI et al. {807B}, with permission.

WHO 2016





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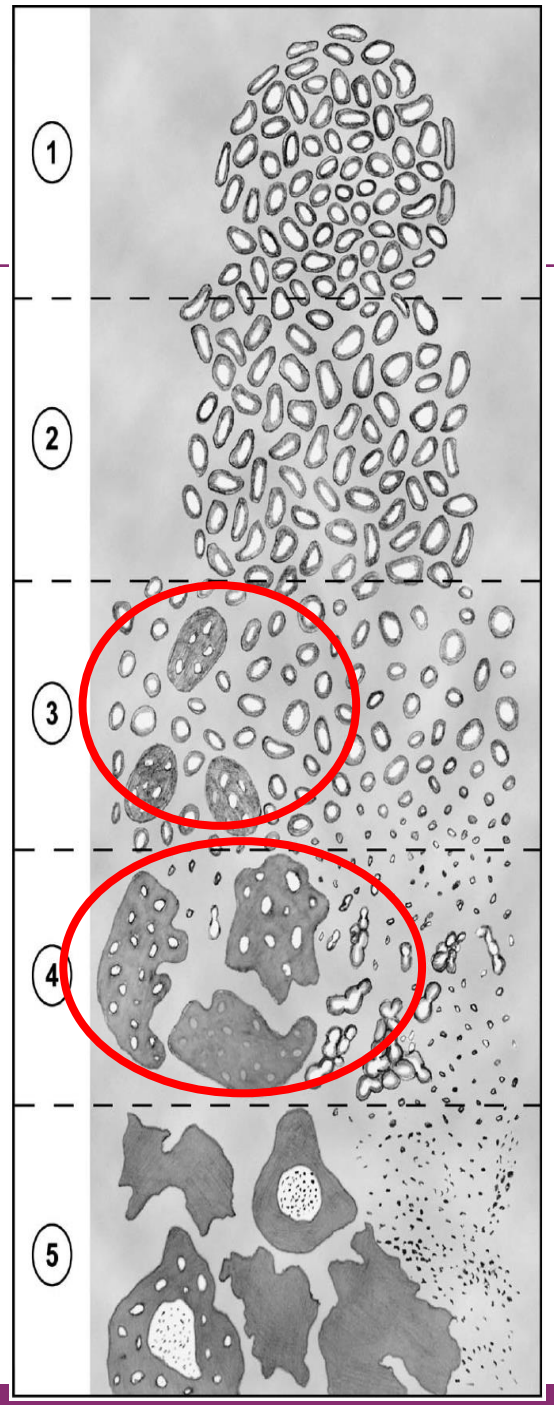

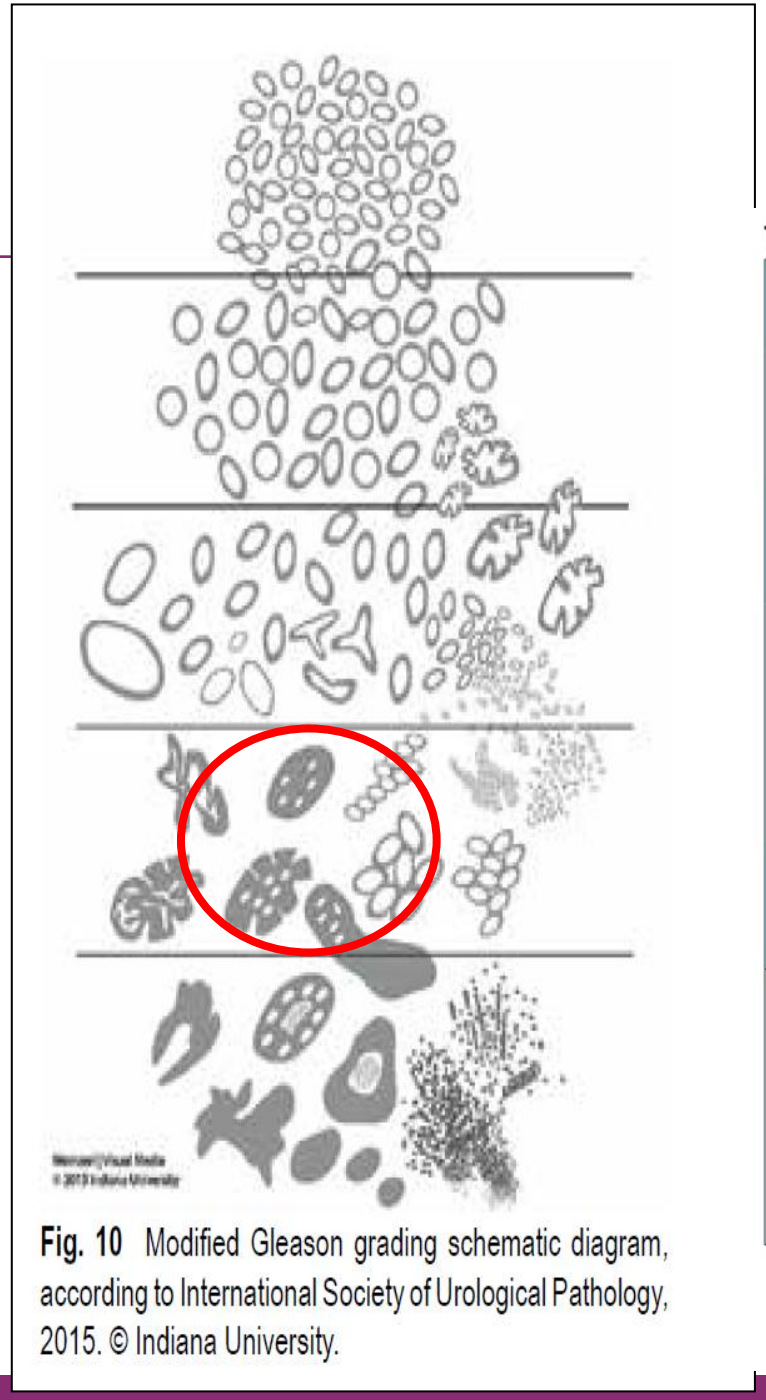

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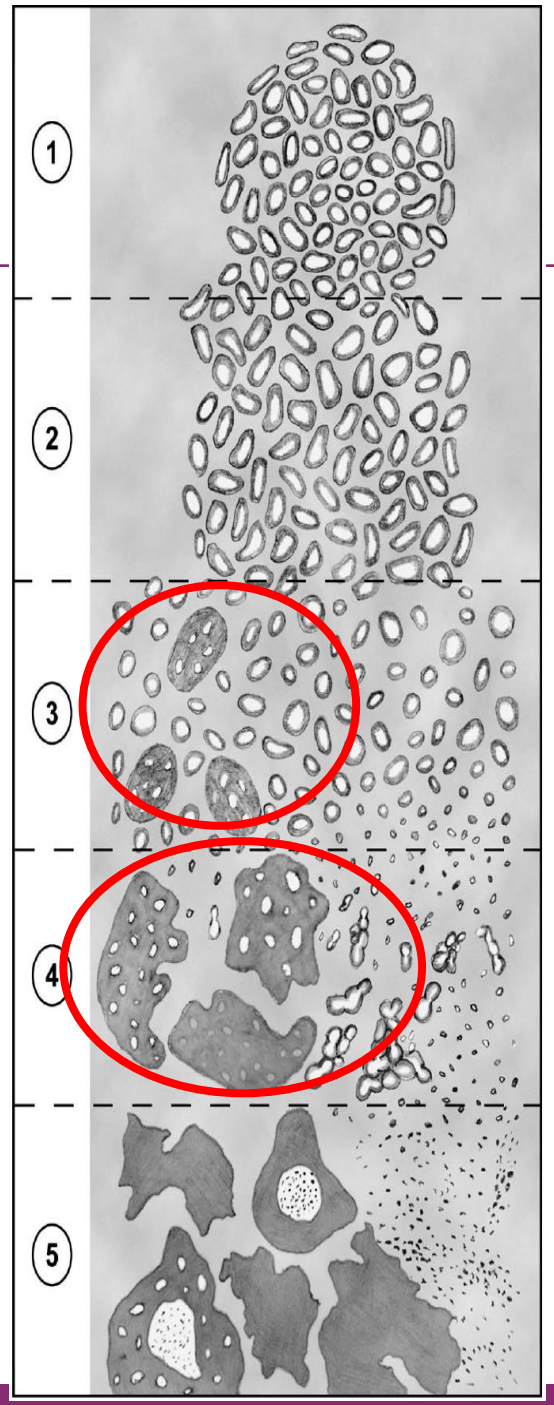

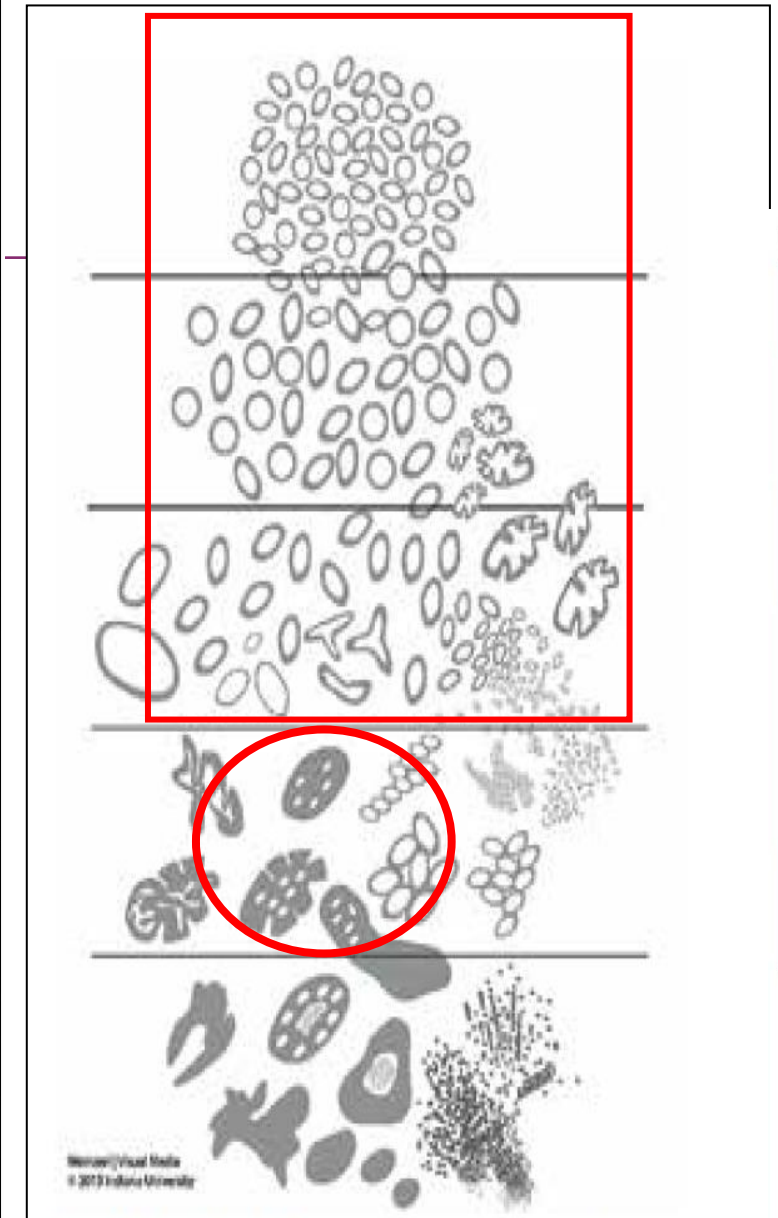

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Similarities and Differences in the 2019 ISUP and GUPS Recommendations on Prostate Cancer Grading: A Guide for Practicing Pathologists

Steven C. Smith, MD, PhD, Jatin S. Gandhi, MD,† Holger Moch, MD,‡ Manju Aron, MD,§ Eva Compérat, MD, PhD,‖ Gladell P. Paner, MD,¶ Jesse K. McKenney, MD,# and Mahul B. Amin, MD***

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s in the 2019 ISUP and
Prostate Cancer Grading:
:ing Pathologists

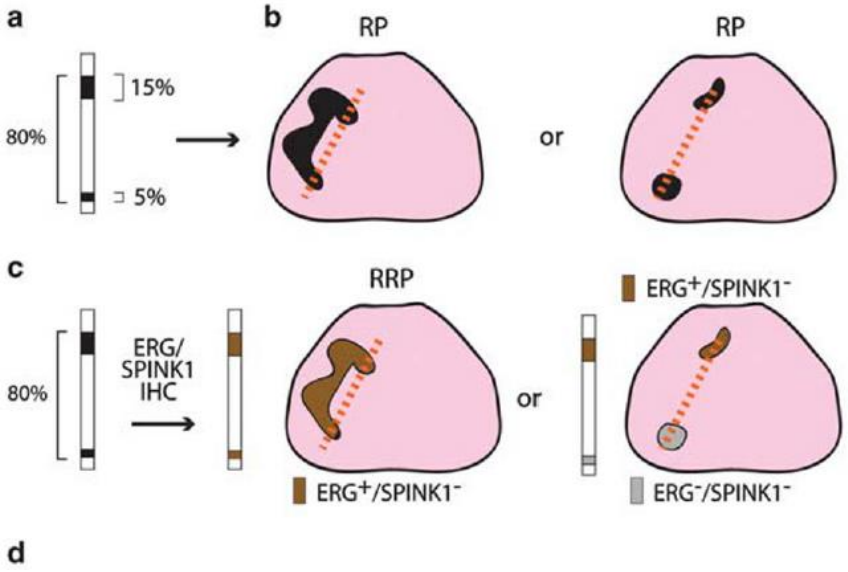
*Gandhi, MD,† Holger Moch, MD,‡ D, PhD,‖ Gladell P. Paner, MD,¶ d Mahul B. Amin, MD***

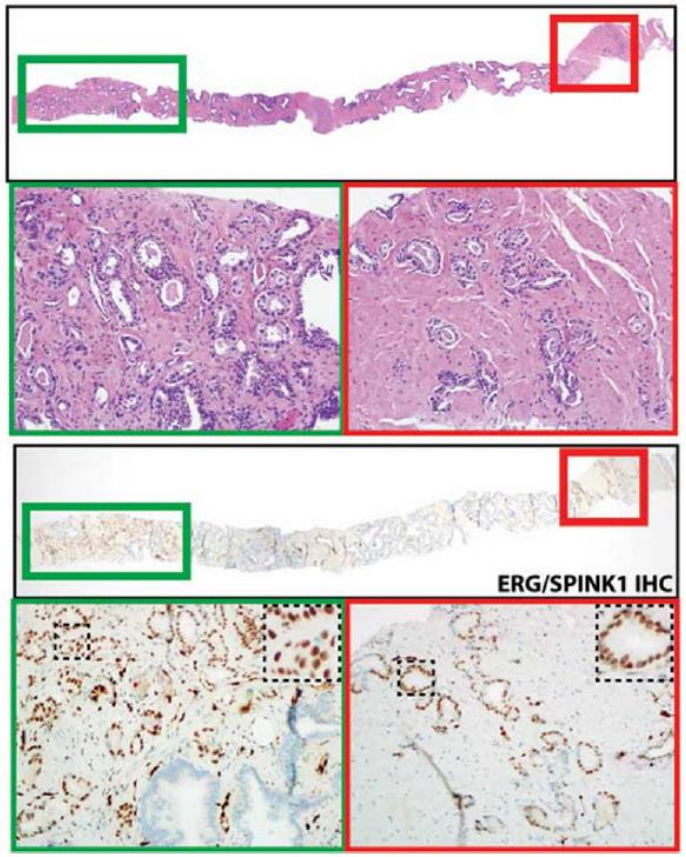
- % of GG 4
- Cribriform /ICD-P report
- GS for each PB
- MRI → global GS
- RPE GG5<5% minor
- Molecular testing on slides (PTEN, Ki-67, ERG, ….)

Tumor heterogeneity

~25% of discontinuously involved PB PCa foci with discordant ERG/SPINK1 status, consistent with multiclonal disease, not enough considered
Impact on AS eligibility?

PCa heterogenous→ Biopsy enough??





Fontugne Mod Path 2016

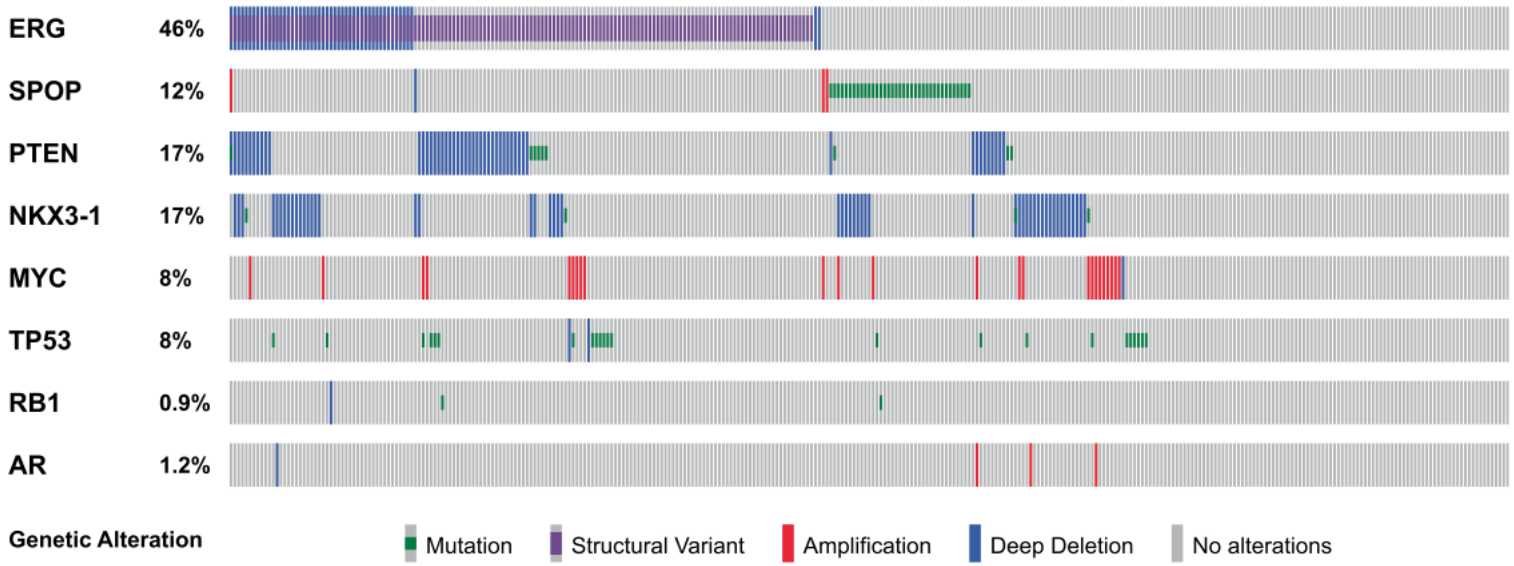


FIGURE 1 A landscape of common somatic alterations in localized prostate cancer from the Cancer Genome Atlas (TCGA) prostate cancer

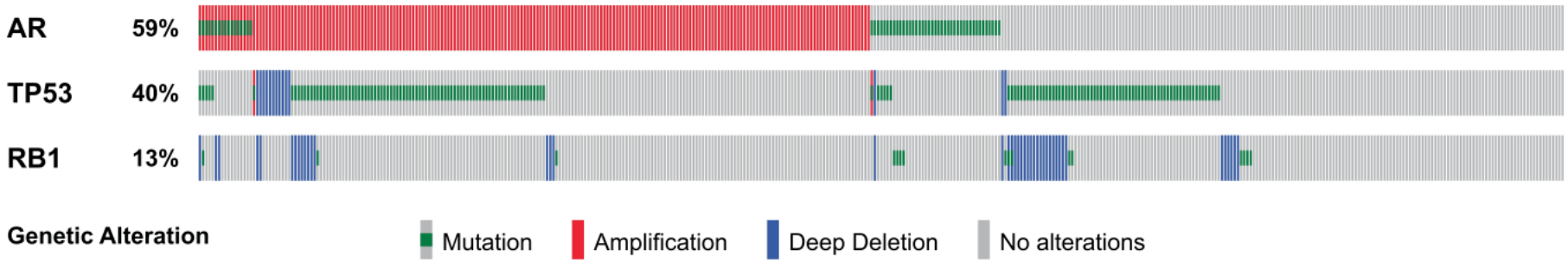


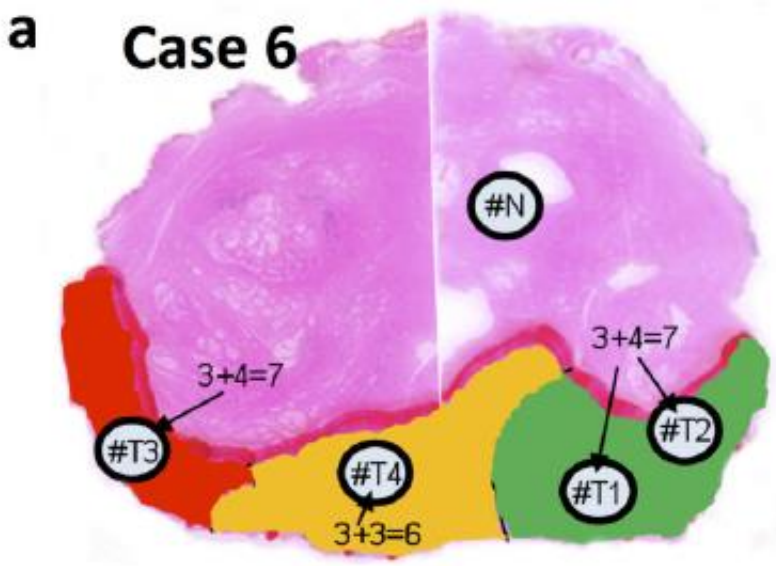
FIGURE 2 The landscape of advanced castration-resistant prostate cancer (CRPC) from the CRPC500 SU2C PCF study.[36] After AR signaling

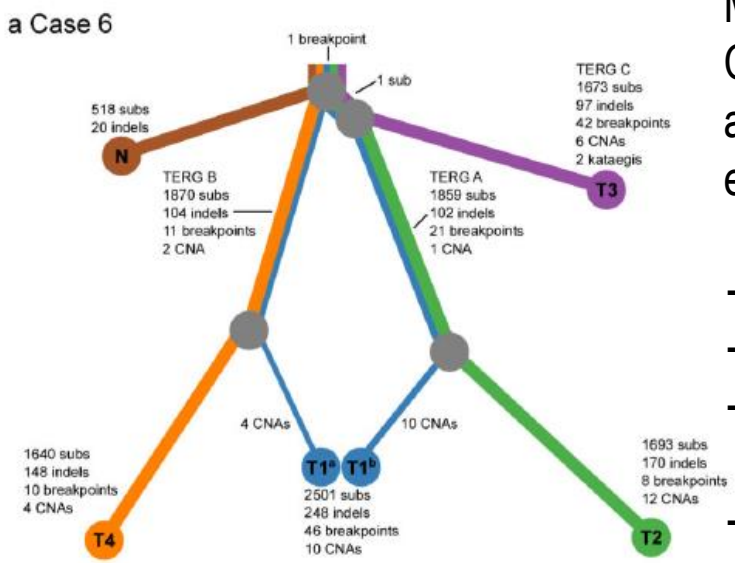
Nat Genet. 2015 April ; 47(4): 367–372. doi:10.1038/ng.3221.

Analysis of the Genetic Phylogeny of Multifocal Prostate Cancer Identifies Multiple Independent Clonal Expansions in Neoplastic and Morphologically Normal Prostate Tissue

A full list of authors and affiliations appears at the end of the article.

Up to 80% heterogenous!!! High genomic diversity!





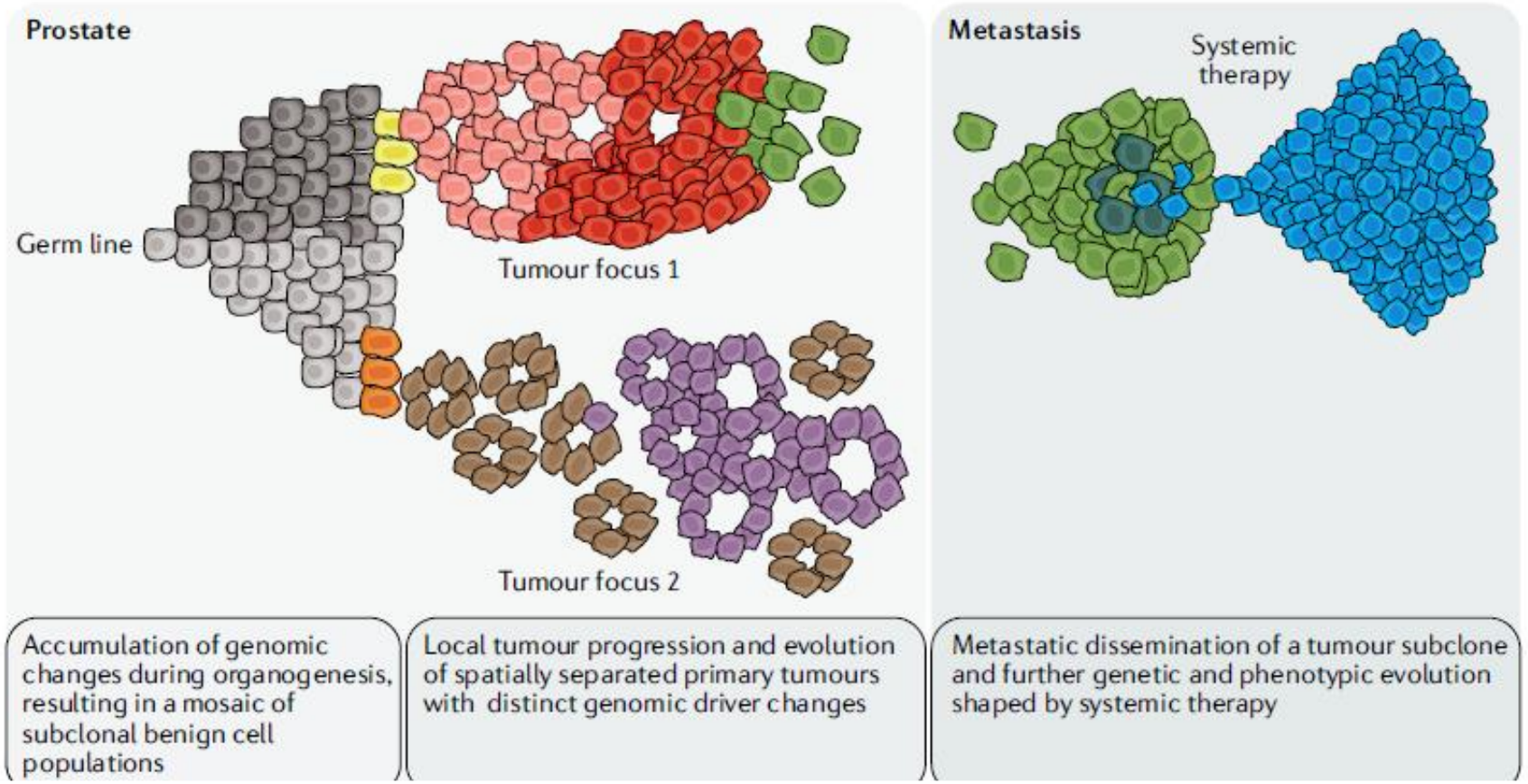
Multiple independent disease clones
Common set of somatic aberrations
and „private“ abberations in
each subclone

→ Multimodal therapy?
→ Focal therapy?
→ Field changes!!!

→ Seeding from same place in distant waves
→ Also from one M+ to another
→ Surgical removal to eliminate seeding

Genomic and phenotypic heterogeneity in prostate cancer

Michael C. Haffner[1,2,3]✉, Wilbert Zwart[4], Martine P. Roudier[5], Lawrence D. True[2], William G. Nelson[3,6,7], Jonathan I. Epstein[3,6,7], Angelo M. De Marzo[3,6,7], Peter S. Nelson[1] and Srinivasan Yegnasubramanian[6]



Average: 19% of mutations in RP were seen in matched PB

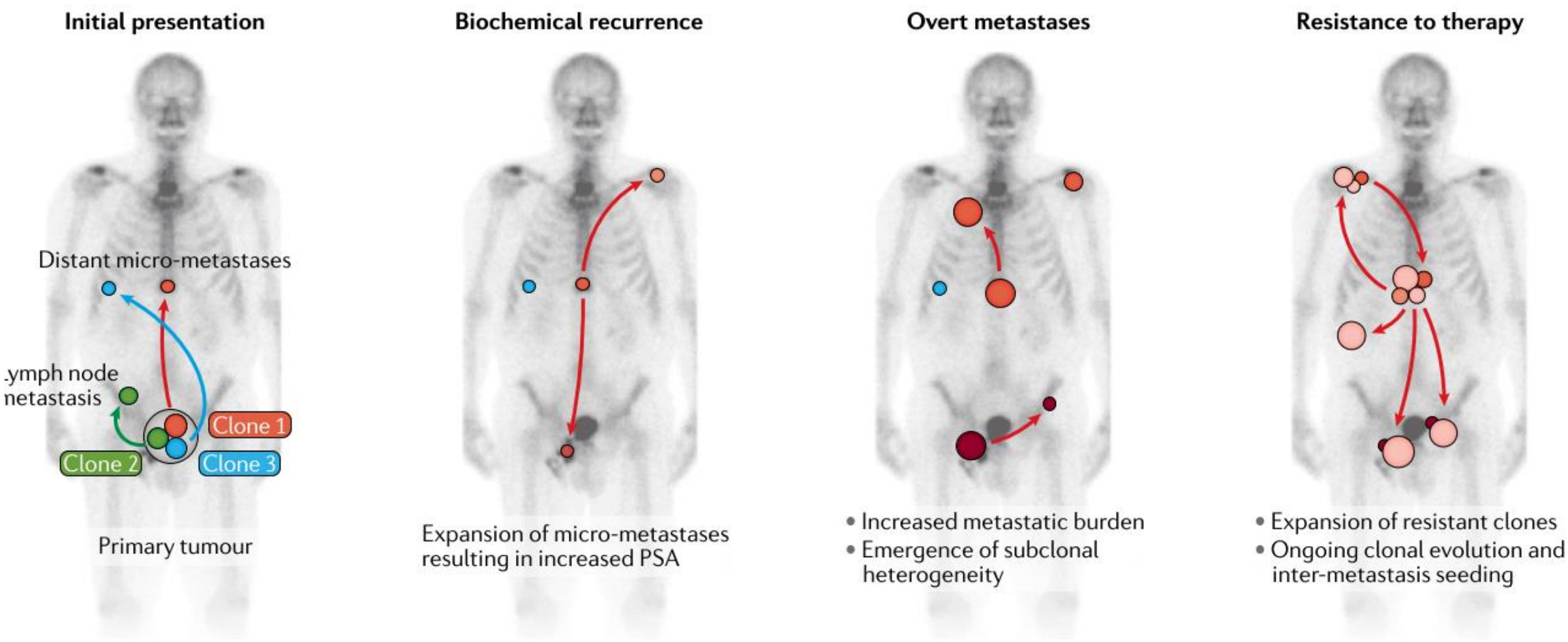
PB adequat to detect all spatially and molecularly distinct PCa areas? Diff risk scores in diff foci

Primary PCa → decisions on treatment of distant M+!!

Multifocality a barrier for biomarker development and implementation

Molecular imaging??

Nat Review 2021



Haffner 2021 Nat rev

Virchows Arch (2011) 459:175–182
DOI 10.1007/s00428-011-1106-x

ORIGINAL ARTICLE

Interactive digital slides with heat maps: a novel method to improve the reproducibility of Gleason grading

Lars Egevad · Ferran Algaba · Daniel M. Berney · Liliane Boccon-Gibod · Eva Compérat · Andrew J. Evans · Rainer Grobholz · Glen Kristiansen · Cord Langner · Gina Lockwood · Antonio Lopez-Beltran · Rodolfo Montironi · Pedro Oliveira · Matthias Schwenkglenks · Ben Vainer · Murali Varma · Vincent Verger · Philippe Camparo

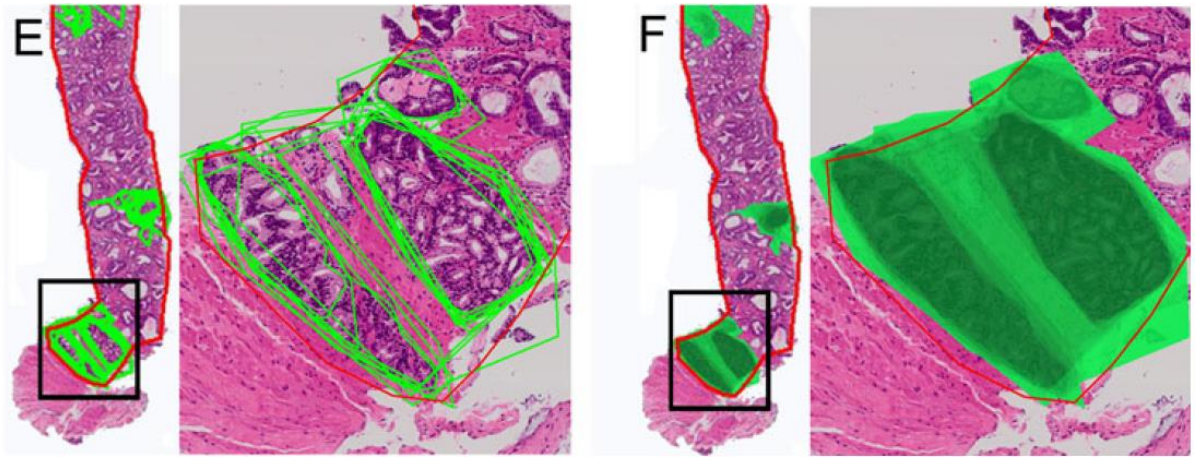


Table 1 Fifteen consensus cases with at least 67% agreement for Gleason score categories

	Gleason score categories					
Case	5–6	7 (3+4)	7 (4+3)	8	9	Agreement (%)
1	**12**	3	0	0	0	80
2	0	**10**	2	3	0	67
4	2	**10**	3	0	0	67
6	2	**11**	1	0	1	73
10	**13**	2	0	0	0	87
12	1	**11**	1	2	0	73
14	0	1	**13**	0	1	87
15	1	**10**	3	1	0	67
16	0	**13**	1	1	0	87
17	**11**	3	1	0	0	73
18	**10**	4	1	0	0	67
19	**11**	4	0	0	0	73
21	1	0	**11**	3	0	73
22	1	**14**	0	0	0	93
23	**12**	3	0	0	0	80

Number of votes for most commonly assigned grade shown in bold

Virchows Arch (2011) 459:175–182
DOI 10.1007/s00428-011-1106-x

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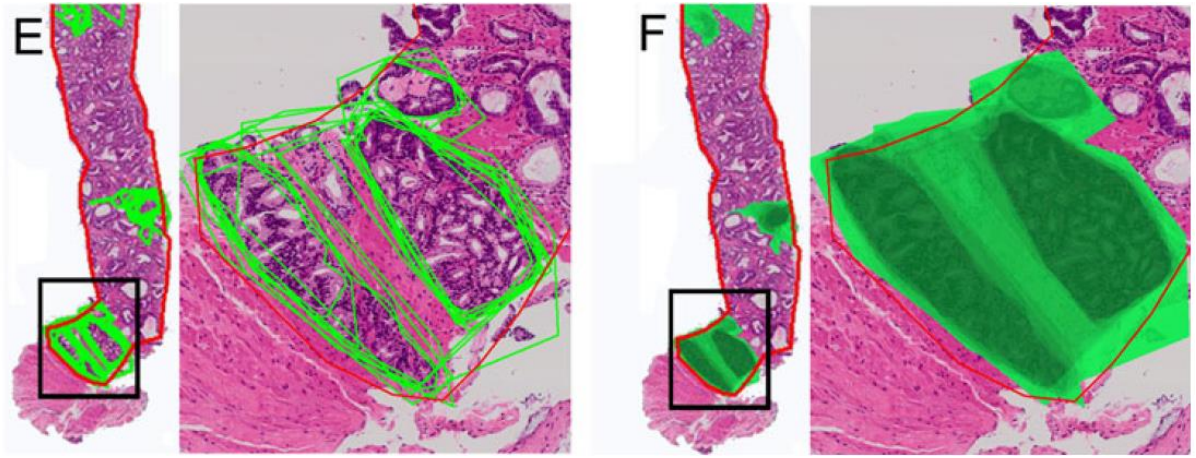

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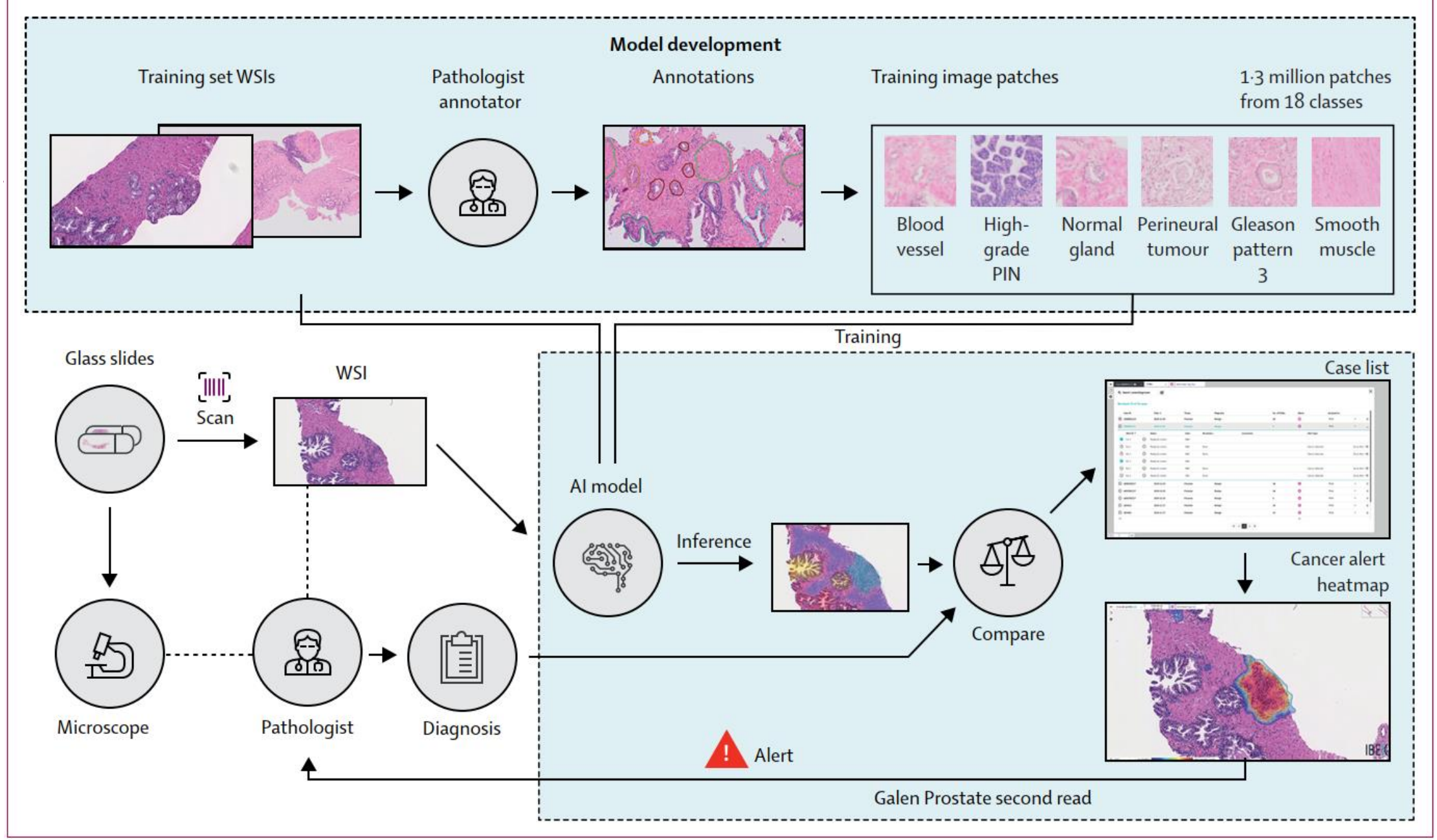
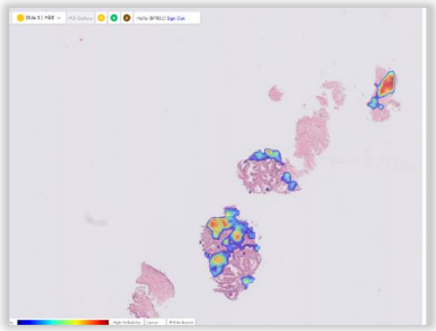
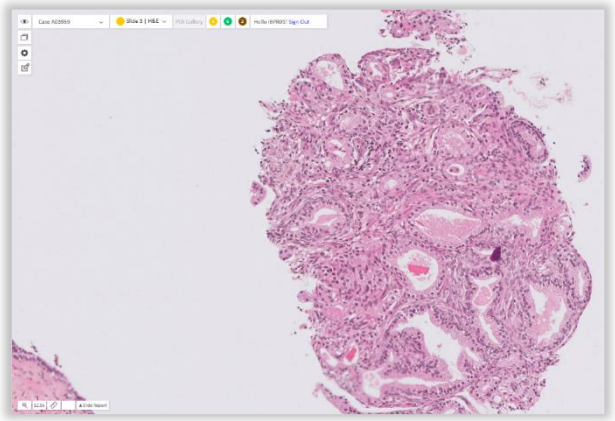


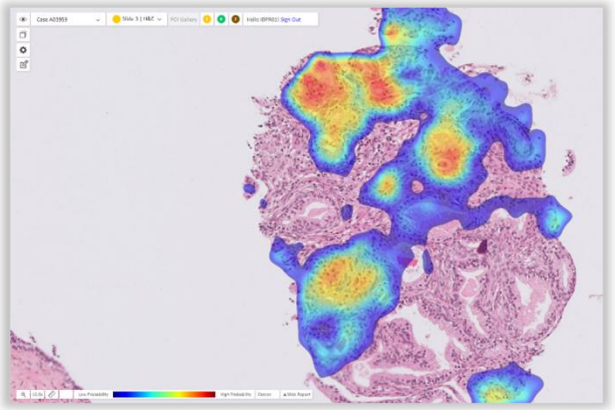
Figure 1: **Overview of the algorithm and clinical deployment of the Galen Prostate second read system**
AI=artificial intelligence. WSI=whole image slide. PIN=prostatic intraepithelial neoplasia.

Cancers Missed by Pathologists

Case with a single cancer slide





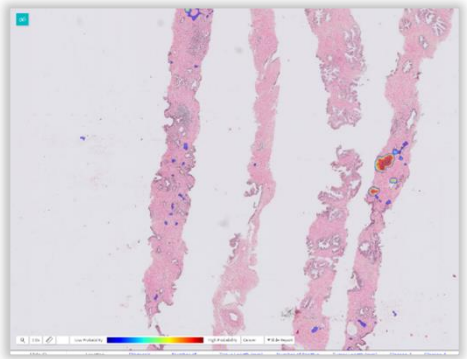


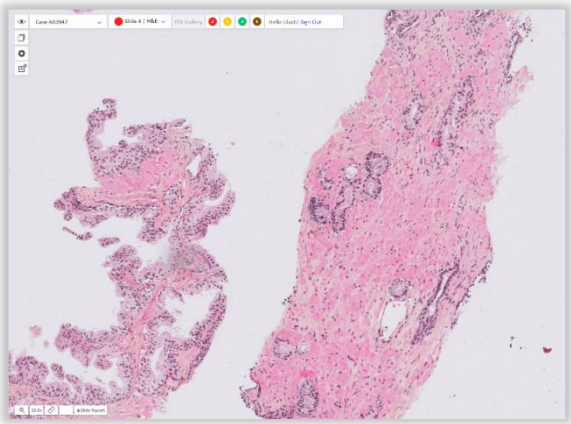
MIC pathologist: Benign

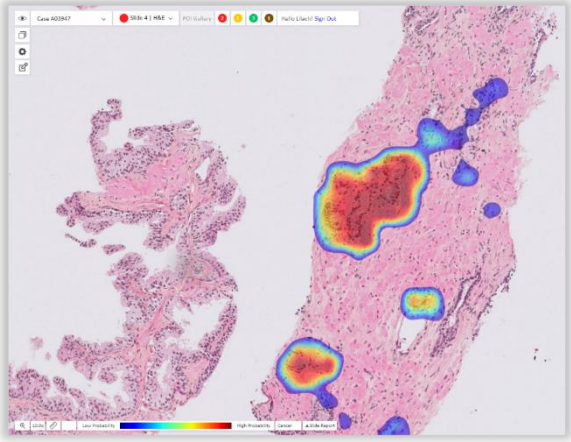
GP pathologist: AdC G4+3

Ground Truth ► AdC G3+4, 3 mm

Small focus of G6







MIC pathologist: Benign

GP pathologist: AdC G3+3, 0.5mm

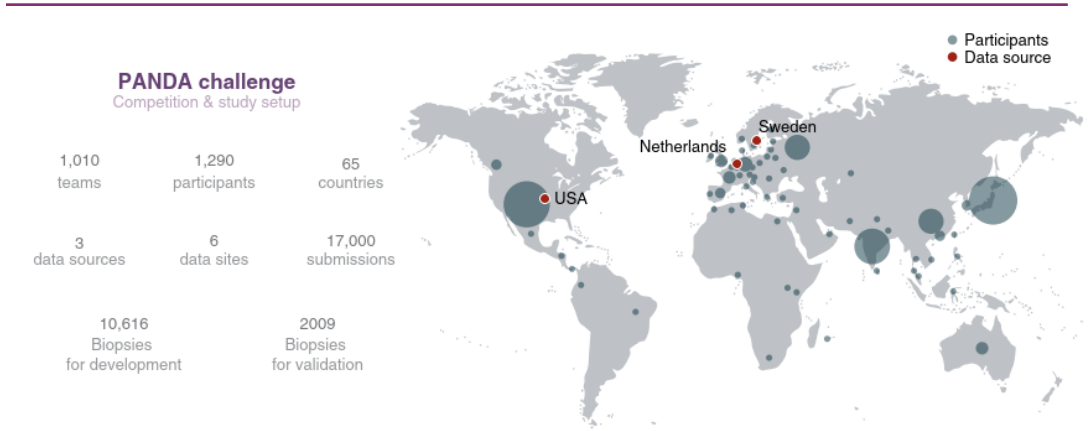
Ground Truth ► AdC G3+3, 0.5mm

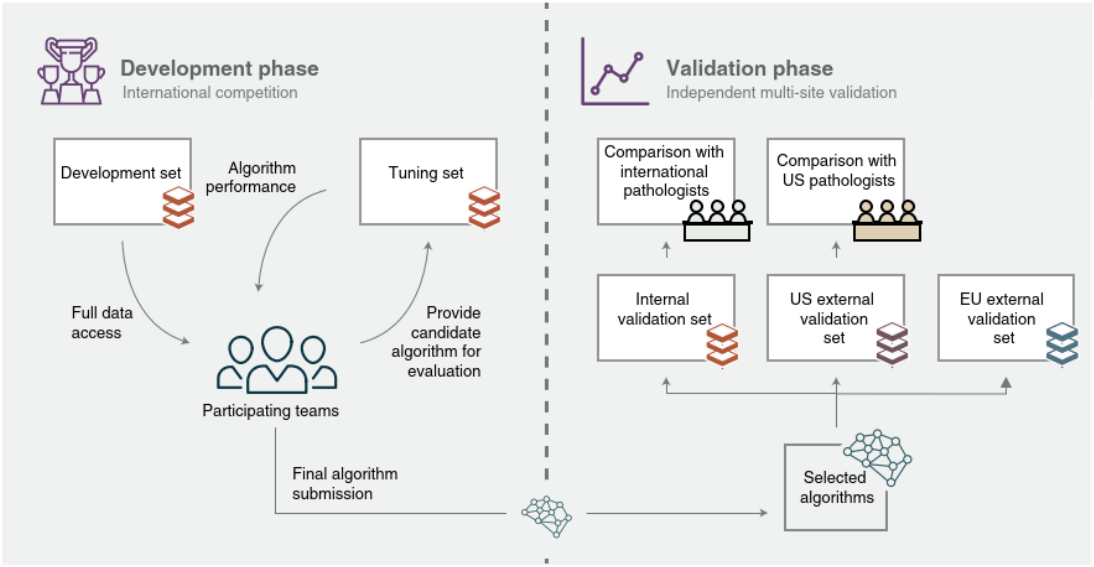
Artificial intelligence for diagnosis and Gleason grading of prostate cancer: the PANDA challenge

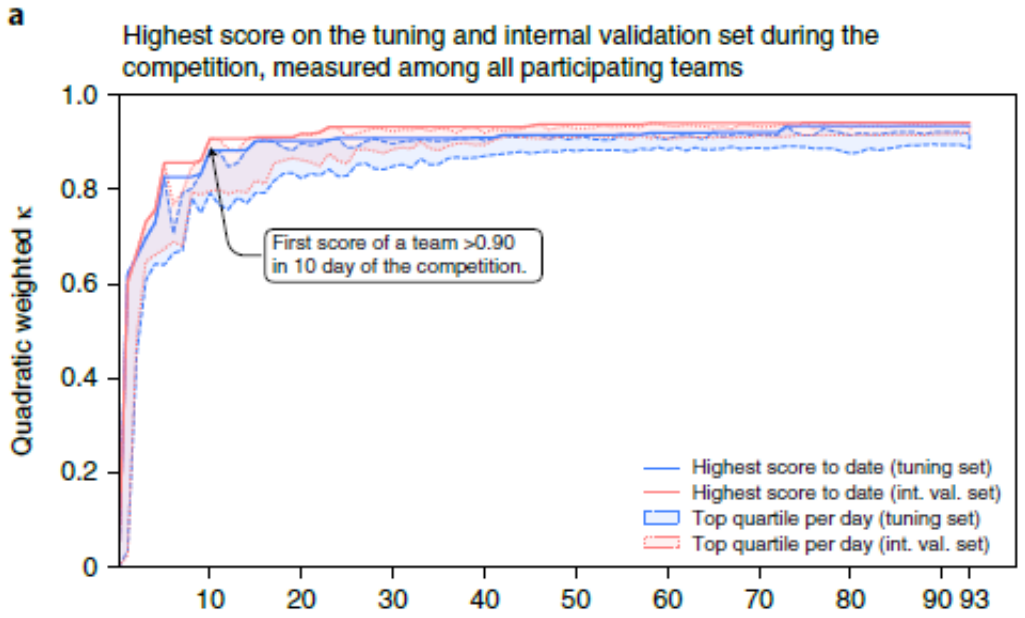
Wouter Bulten[1,60] ✉, Kimmo Kartasalo[2,3,60] ✉, Po-Hsuan Cameron Chen[4,60] ✉, Peter Ström[2], Hans Pinckaers[1], Kunal Nagpal[4], Yuannan Cai[4], David F. Steiner[4], Hester van Boven[5], Robert Vink[6], Christina Hulsbergen-van de Kaa[6], Jeroen van der Laak[1,7], Mahul B. Amin[8], Andrew J. Evans[9], Theodorus van der Kwast[10], Robert Allan[11], Peter A. Humphrey[12], Henrik Grönberg[2,13], Hemamali Samaratunga[14], Brett Delahunt[15], Toyonori Tsuzuki[16], Tomi Häkkinen[3], Lars Egevad[17], Maggie Demkin[18], Sohier Dane[18], Fraser Tan[4], Masi Valkonen[19], Greg S. Corrado[4], Lily Peng[4], Craig H. Mermel[4], Pekka Ruusuvuori[3,19,61], Geert Litjens[1,61], Martin Eklund[2,61] and the PANDA challenge consortium*

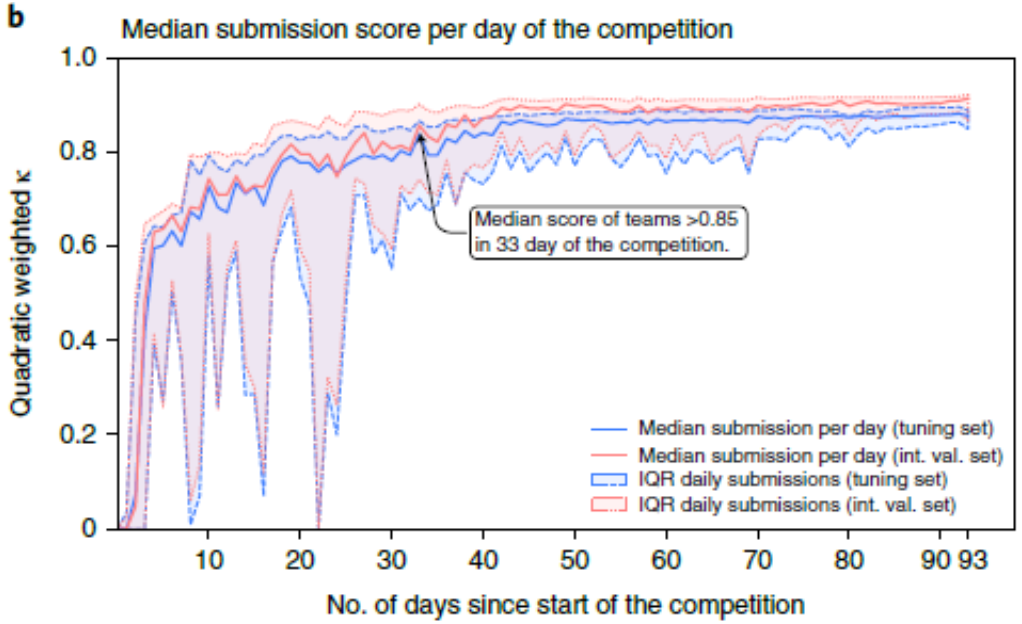
- Develop reproducible AI algorithms for Grading
- 10616 digitized PB
- Compare EU and US
- Competition and Validation phase
- 1010 teams submitted at least 1 algorithm
- Algorithm blinded and internal validation
  - Than 32 Mill predictions made by all algorithms
  - 33 rd day of competition all teams κ 0.86

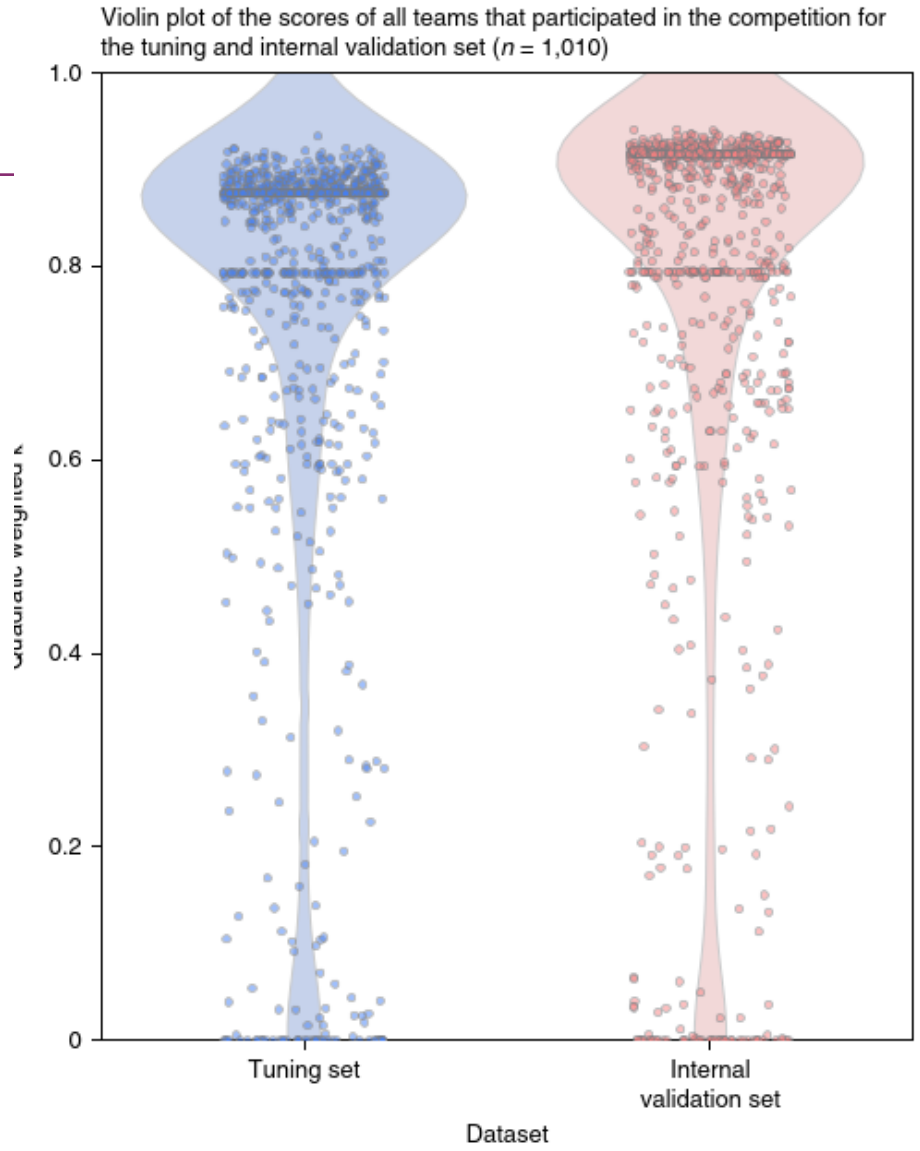
Prostate cANcer graDe Assessment



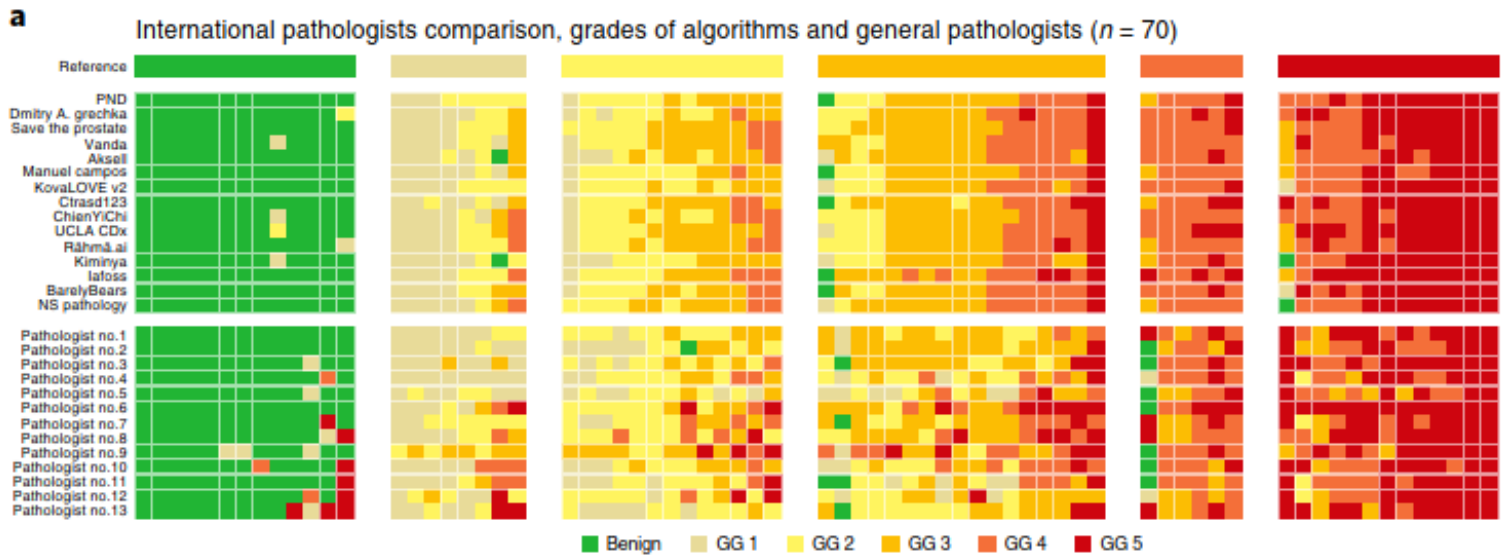



a
Highest score on the tuning and internal validation set during the competition, measured among all participating teams
Quadratic weighted κ
1.0
0.8
0.6
0.4
0.2
0
First score of a team >0.90 in 10 day of the competition.
Highest score to date (tuning set)
Highest score to date (int. val. set)
Top quartile per day (tuning set)
Top quartile per day (int. val. set)
10 20 30 40 50 60 70 80 90 93


b
Median submission score per day of the competition
Quadratic weighted κ
1.0
0.8
0.6
0.4
0.2
0
Median score of teams >0.85 in 33 day of the competition.
Median submission per day (tuning set)
Median submission per day (int. val. set)
IQR daily submissions (tuning set)
IQR daily submissions (int. val. set)
10 20 30 40 50 60 70 80 90 93
No. of days since start of the competition


Violin plot of the scores of all teams that participated in the competition for the tuning and internal validation set (n = 1,010)
1.0
0.8
0.6
0.4
0.2
0
Tuning set
Internal validation set
Dataset

In the US external validation set, tumor identification was confirmed by immunohistochemistry, supporting the finding that the algorithms missed fewer cancers than the pathologists.



We found that a group of AI Gleason grading algorithms developed during a global competition generalized well to intercontinental and multinational cohorts with pathologist-level performance. On all external validation sets, the algorithms achieved high agreement with uropathologists and high sensitivity for malignant biop-

In the external validation sets, the main algorithm error mode was overdiagnosing benign cases as ISUP GG 1.

Limitations

15 teams out of 1010
Only 1 biopsy
Acinar Adk
Retrospective
Non clinical setting
Mainly „White countries“
Problem of non malignant PB

Artificial intelligence in prostate histopathology: where are we in 2021?

André Oszwald[a], *Gabriel Wasinger*[a], *Benjamin Pradere*[b]
Shahrokh F. Shariat[b] *and Eva M. Compérat*[a]

KEY POINTS

- Many artificial intelligence-based tools perform on par with expert pathologists in performing specific tasks, such as detection of prostate cancer and Gleason grading
- Artificial intelligence may soon be introduced into common practice by for initial screening, second review, and automated quantitative tasks, such as measuring cancer length in positive biopsy cores.
- Artificial intelligence can assist researchers in achieving insight into biology, and its use is increasingly expanding beyond simple classification tools ('benign vs. tumor', 'GS 6 vs. 7–10').

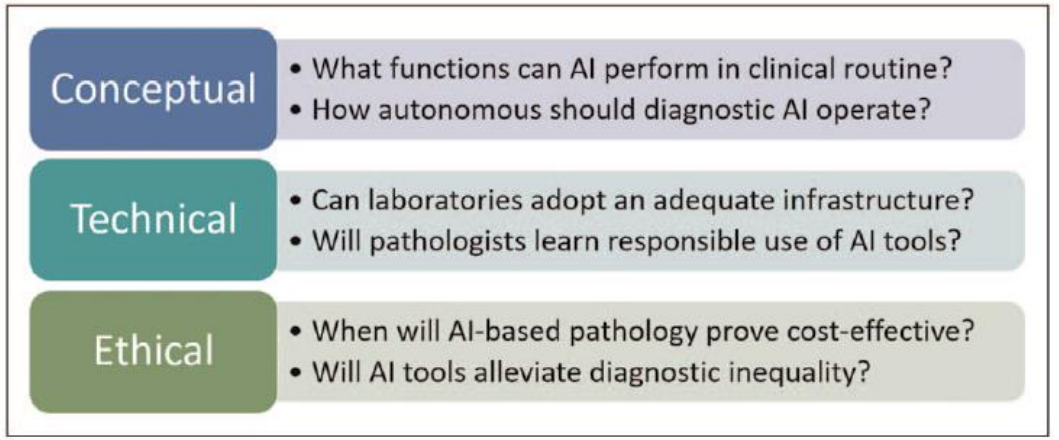
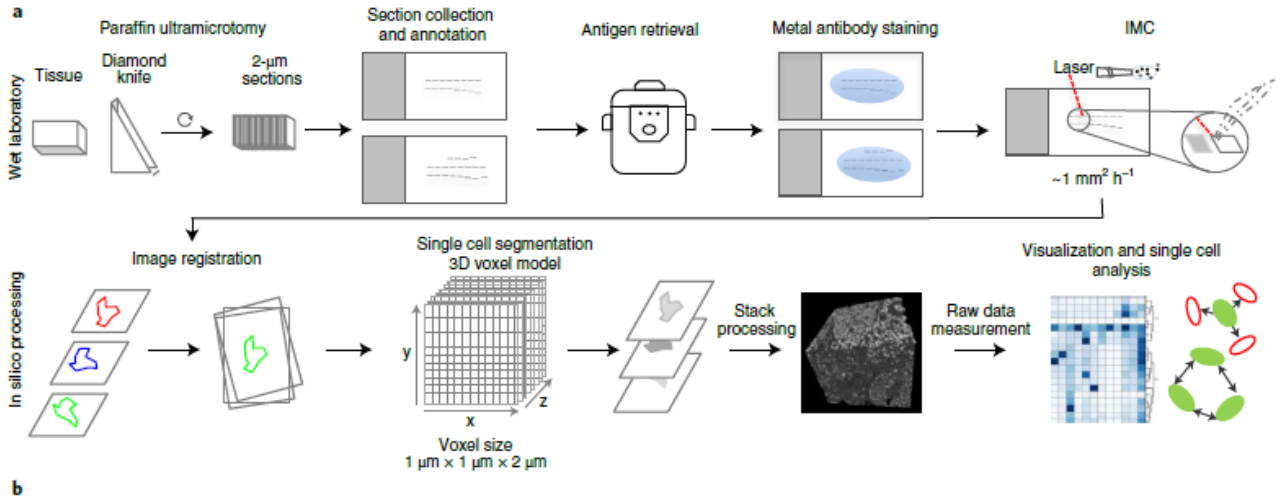


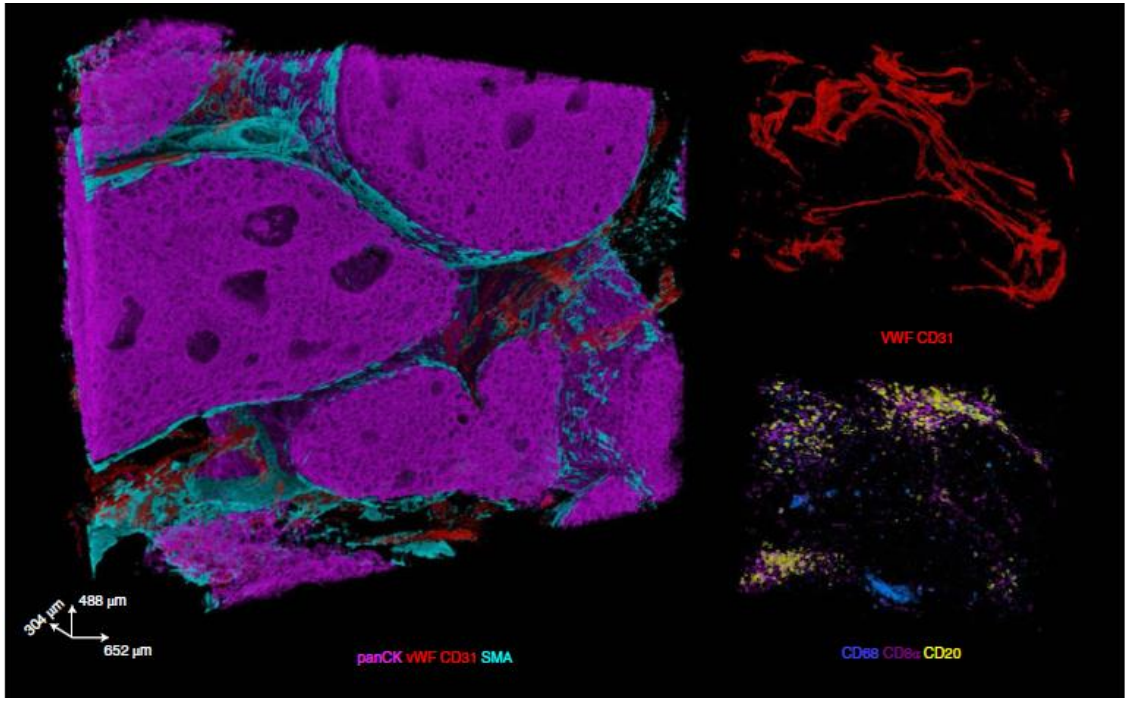
FIGURE 1. Challenges and issues in artificial intelligence-based prostate histopathology.

cautious deployment. In parallel, artificial intelligence may aid in enhancing and redefining pathological standards in research applications. Redefining the role of the pathologists in this rapidly evolving field will be as important as tackling the respective technical challenges in order to prepare for the advent of artificial intelligence in pathology.

Three-dimensional imaging mass cytometry for highly multiplexed molecular and cellular mapping of tissues and the tumor microenvironment

Laura Kuett[1,2,22], Raúl Catena[1,3,22], Alaz Özcan[1,20], Alex Plüss[1,21], Cancer Grand Challenges IMAXT Consortium*, Peter Schraml[4], Holger Moch[4], Natalie de Souza[1,5] and Bernd Bodenmiller[1,2]





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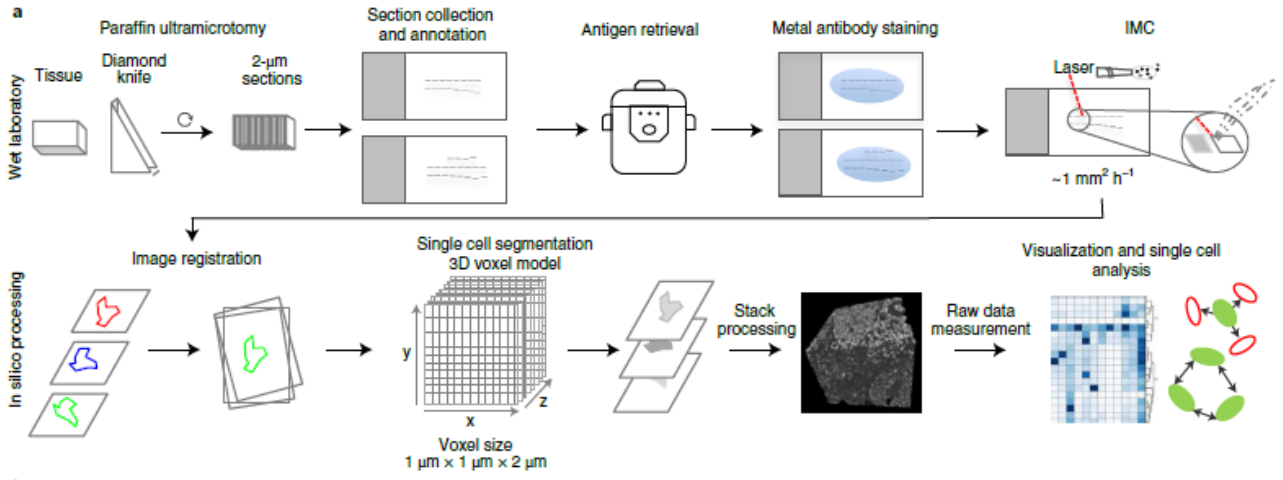

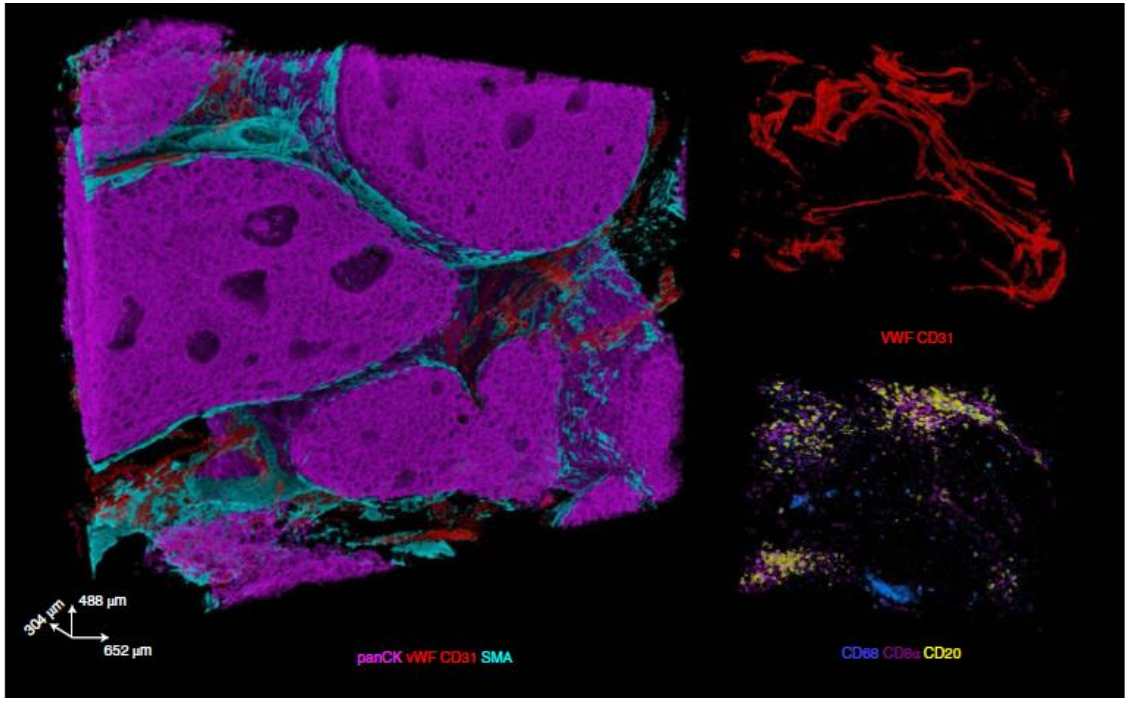

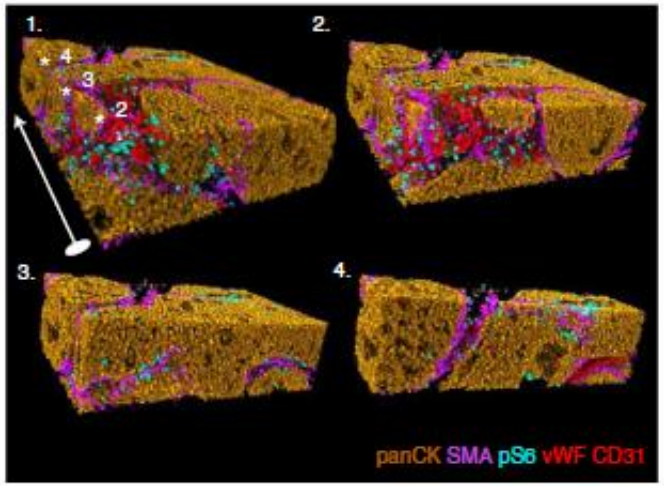

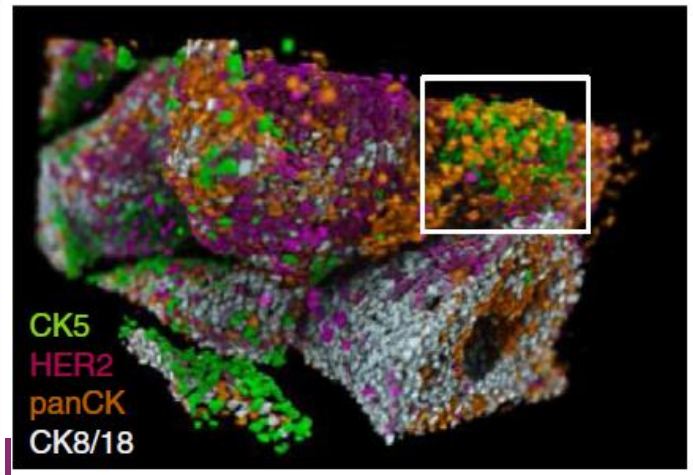

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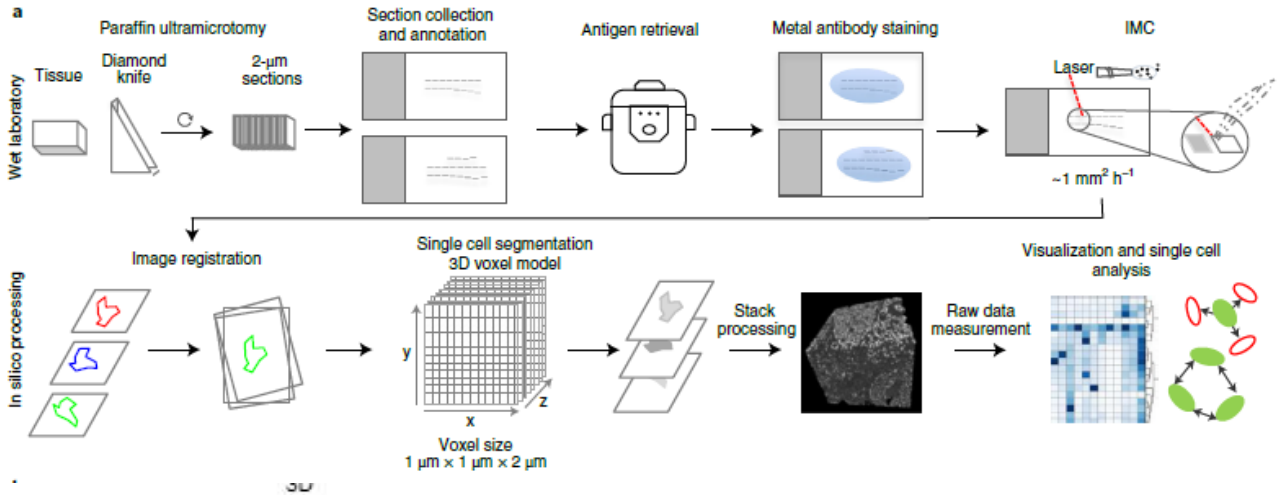
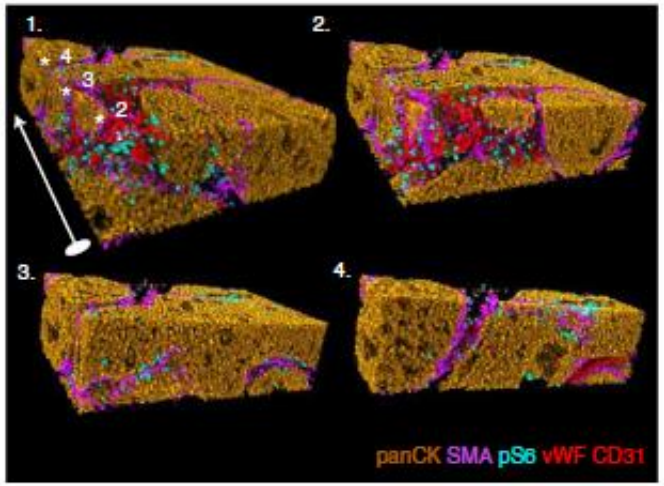
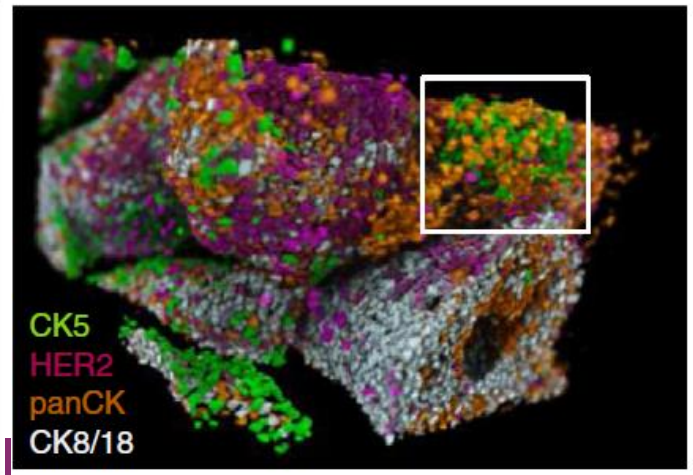
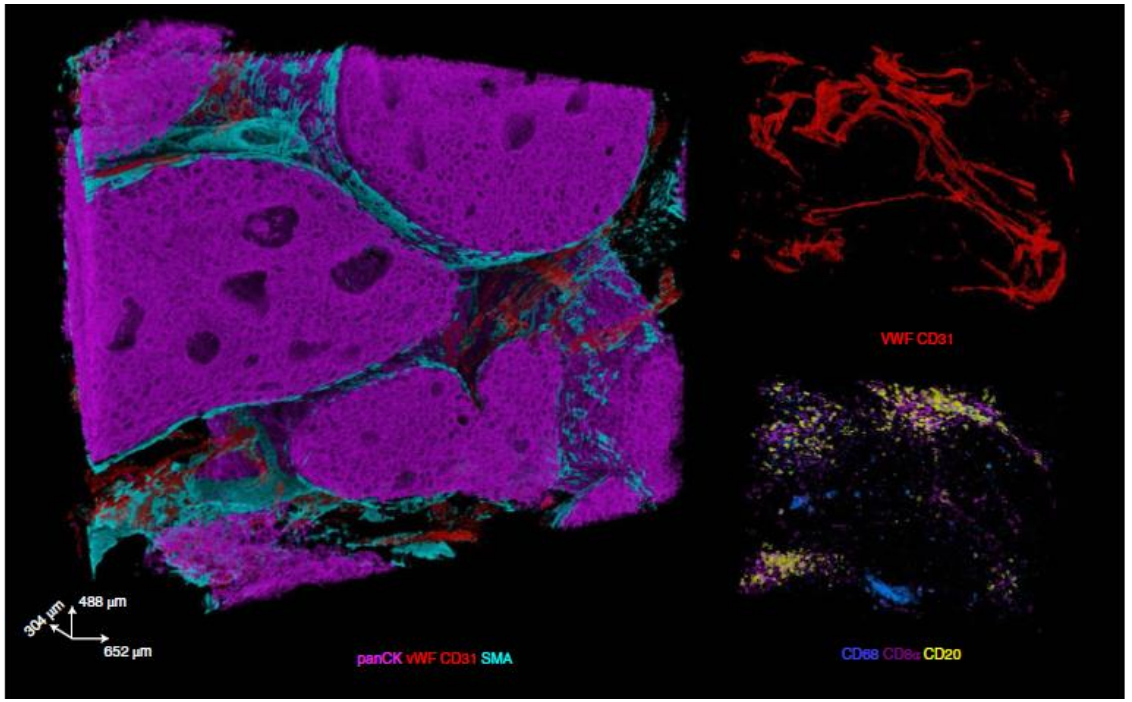








3D models

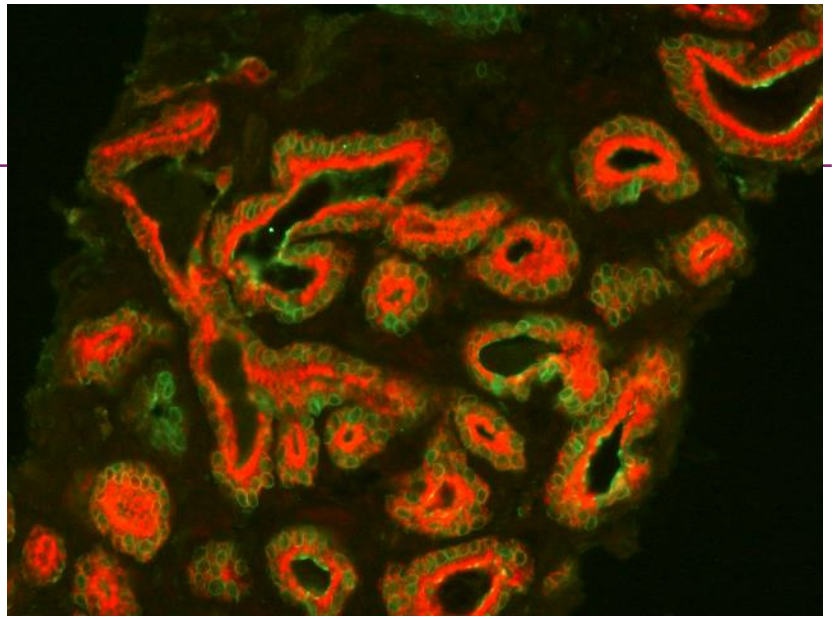
Cellular and microenvironmental heterogeneity

Cell-tissue level organisation

See tumor cell invasion, insights into cellular microenvironment

Tissue architecture

Take home



- **We understand the different diseases better**
  - Different disease OMPCa and PMPCa?
  - Still more work to do with better cohorts and international collaborative trials

- **Pathology** getting preciser and still strong player
- Many grey zones although frequent disease
- 3D models to give detailed insight → future!!

- **Genetic** testing
- Good testing→ good material (number of T cells, which tissue..)
- Ablation of M+

- **AI** problems of
  - Cost and laboratory infrastructure (digital workflow)
    - Technique, storage,…