PD-L1 Digital Quantification

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ESO-ESP Digital Pathology Seminar
11-12 December 2021

Role of the PD-1 Pathway in Cancer
The Broader Picture

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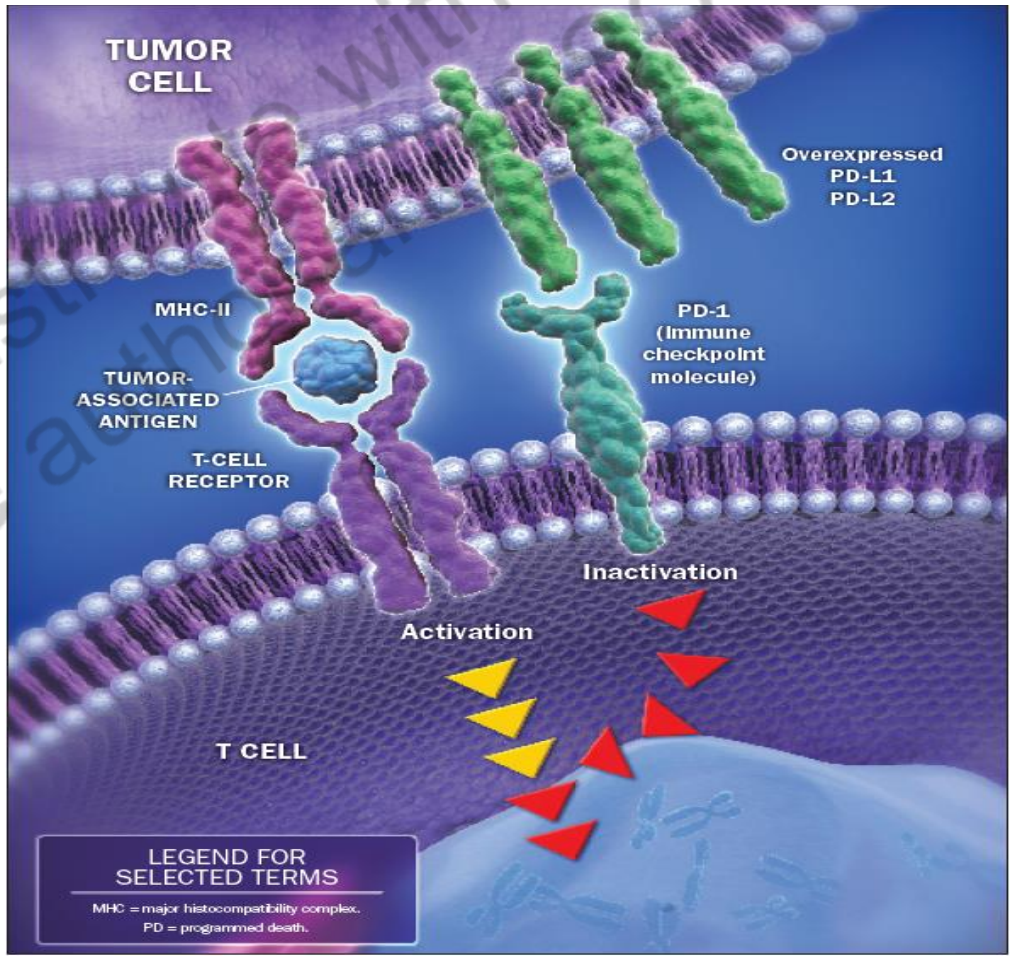
Role of the PD-1 Pathway in Cancer

- Programmed death 1 (PD-1) pathway is an immune checkpoint pathway that is expressed on the surface of activated T cells
- One of its ligands, PD-L1, is highly expressed on the surface of tumor cells
- Binding of PD-1 with PD-L1 inhibits T cell activation, allowing immunosuppression and neoplastic growth



Pardoll DM.
The blockade of immune checkpoints in cancer immunotherapy.
Nat Rev Cancer. 2012;12:252–264.

Anti PD-L1 treatment in Cancer
The Broader Picture

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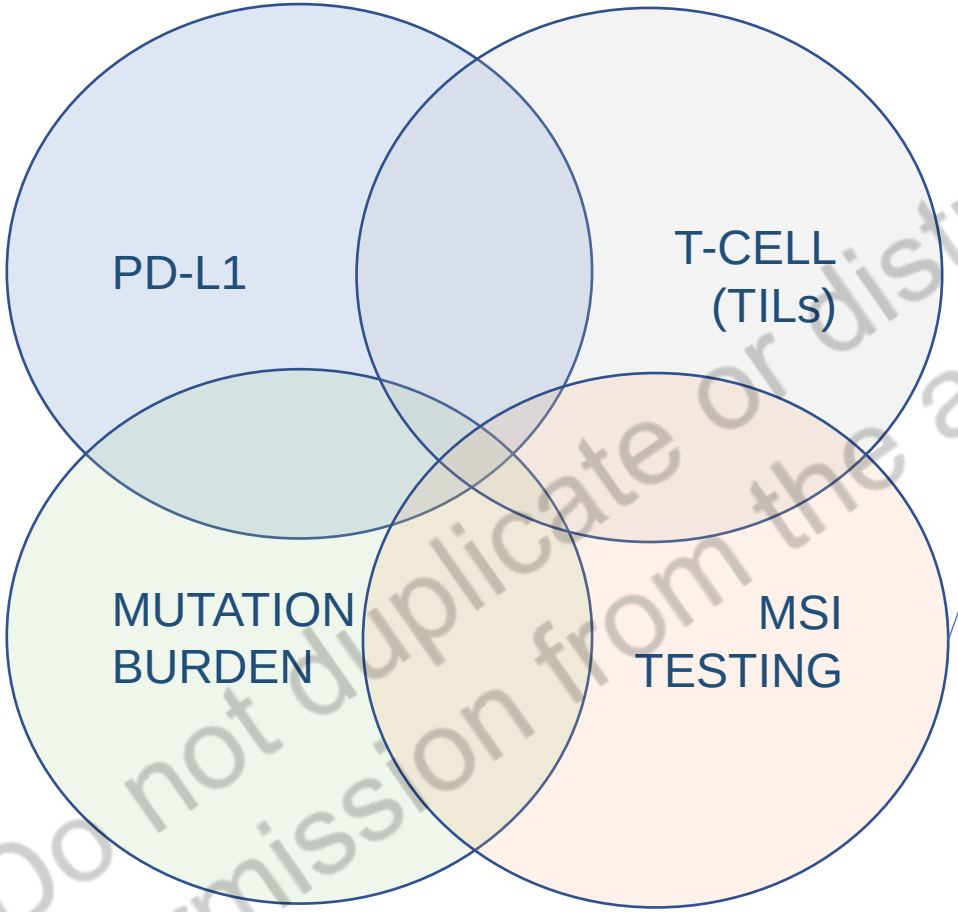
Role of the PD-1 Pathway in Cancer – The Broader Picture



CRC with MSI had significant **upregulation of immune checkpoint proteins, including PD-1 and PD-L1**, enabling them to survive.

Response to PD-1 blockade (perbrolizumab) in stage IV cancer patients

- 11 patients with MSI CRC
- 21 with MSS colorectal cancer
- 9 with MSI noncolorectal cancer (4 ampullary or cholangiocarcinomas, 2 endometrial carcinomas, 2 small bowel carcinomas, and 1 gastric carcinoma).

MSI was a significant predictor of the immune-related objective response rate:

- 40% in dMMR colorectal cancer
- 71% in dMMR non colorectal cancer
- 0% in MMR-proficient colorectal cancer

Llosa NJ, et al. The vigorous immunemicroenvironment of MSI Colon cancer is balanced by multiple counter-inhibitory checkpoints. Cancer Discov 2015;5:43–51.
Le DT, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–20.

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PD-L1 Analysis by IHC
The Wet Lab

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Clone and source and epitope (ECD=extra-cellular domain; ICD=intra-cellular domain)	28-8 Abcam – ECD	22c3 Dako – ECD	SP142 Spring Bio – ICD	SP263 Spring Bio – ECD
IVD class III partner	Dako	Dako	Ventana	Ventana
Scoring method	% cells with membrane staining at any intensity	% cells with membrane staining at any intensity	TC=Tumor cell IC=Immune cell Combine both percentage and subjective intensity	% cells with membrane staining at any intensity
Thresholds	>1% >5% >10%	<1% 1–49% >50%	TC3=TC>50% IC3=IC>10% TC2/IC2=TC or IC>5% TC1/IC1=TC or IC>1%	>25%
Method	Pathologist/ Subjective	Pathologist/ Subjective	Pathologist/ Subjective	Pathologist/ Subjective

Source: David Rimm, MD, PhD

Adapted from:
http://www.captodayonline.com/pd-l1-targeted-therapies-await-standardized-ihc/

Scheel et al., Mod Pathol 2016, 29 1165-72;
Gaule et al., JAMA Oncol 2016, Epub10.1001/jamaoncol.2016.3015;
Neuman et al., J Thorac Oncol 2016, Epub 1010.16/jtho.2016.08.146;
Gatalica et al., ASCO 2016, abstract 11548;
Ratcliffe et al., AACR 2016 abstract LB-094

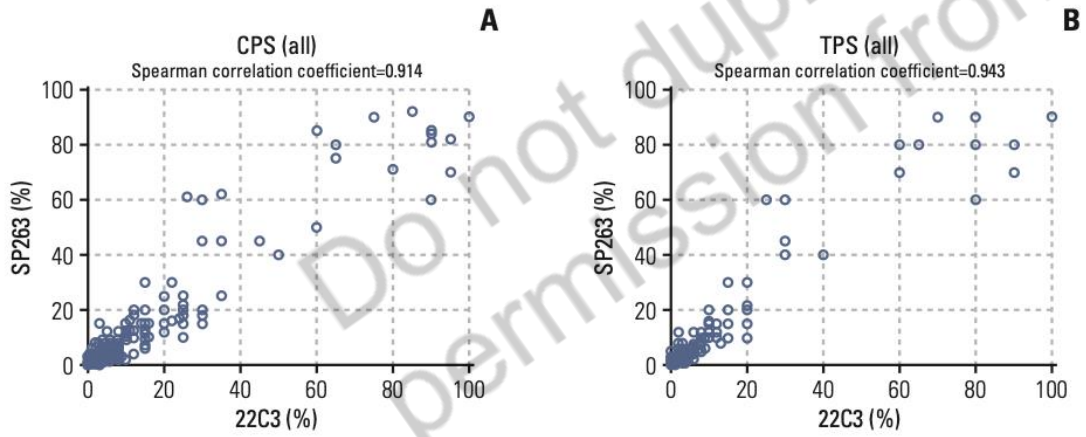


Fig. 2. Correlation between the 22C3 pharmDx and SP263 assay for the combined positive score (CPS) (A) and tumor proportion score (TPS) (B) at the center of the tumor and invasive margin in gastric cancer samples.

Table 4. Interobserver variation between five pathologists by 22C3 pharmDx and SP263 assay

	Intraclass correlation coefficient (lower 95% CI)		Fleiss' Kappa (lower 95% CI)	
	CPS	TPS	CPS ≥ 1	CPS ≥ 10
22C3	0.387 (20.9)	0.596 (40.5)	0.389 (26.4)	0.224 (8.0)
SP263	0.349 (13.5)	0.710 (57.2)	0.256 (15.6)	0.140 (2.4)

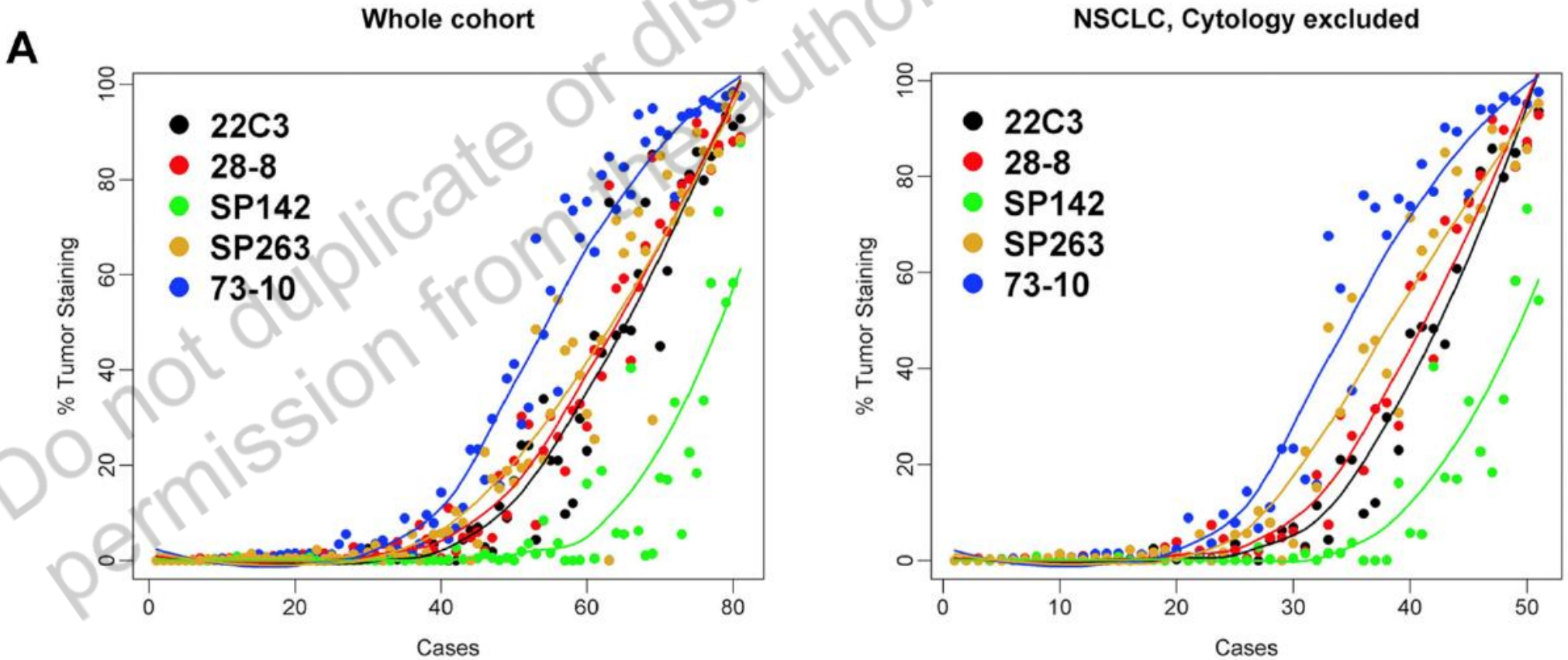
CI, confidence interval; CPS, combined positive score; TPS, tumor proportion score.

Park Y et al Cancer Res Treat. 2020 Jul;52(3):661-670

Published in final edited form as:
J Thorac Oncol. 2018 September ; 13(9): 1302–1311. doi:10.1016/j.jtho.2018.05.013.

PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project

Ming Sound Tsao, MD[a], Keith M. Kerr, MD[b], Mark Kockx, MD, PhD[c], Mary-Beth Beasley, MD[d], Alain C. Borczuk, MD[e], Johan Botling, MD[f], Lukas Bubendorf, MD[g], Lucian Chirieac, MD[h], Gang Chen, MD[i], Teh-Ying Chou, MD, PhD[j], Jin-Haeng Chung, MD, PhD[k], Sanja Dacic, MD, PhD[l], Sylvie Lantuejoul, MD[m], Mari Mino-Kenudson, MD[n], Andre L. Moreira, MD[o], Andrew G. Nicholson, DM[p], Masayuki Noguchi, MD, PhD[q], Giuseppe Pelosi, MD[r], Claudia Poleri, MD[s], Prudence A. Russell, MD[t], Jennifer Sauter, MD[u], Erik Thunnissen, MD, PhD[v], Ignacio Wistuba, MD, PhD[w], Hui Yu, MD, PhD[x], Murry W. Wynes, PhD[y], Melania Pintilie, MSc[z], Yasushi Yatabe, MD, PhD[aa], Fred R. Hirsch, MD, PhD[x,y,*]



PD-L1 Analysis by IHC
The Scoring

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CPS[1-6]	TPS[7]
HNSCC, urothelial carcinoma, gastric or GEJ cancer, esophageal carcinoma, cervical cancer, TNBC Evaluate the number of PD-L1-staining cells (tumour cells, lymphocytes, macrophages) relative to all viable tumour cells	NSCLC Evaluate the percentage of viable tumour cells showing partial or complete membrane staining at any intensity
CPS = $\frac{\text{\# of PD-L1-positive cells}}{\text{Total \# of tumour cells}}$ **x 100**	**TPS =** $\frac{\text{\# of PD-L1-positive tumour cells}}{\text{Total \# of PD-L1–positive + PD-L1–negative tumour cells}}$ **x 100%**
Report CPS as a number. Maximum score is CPS 100	Report TPS as a percentage

CPS, combined positive score; GEJ, gastroesophageal junction; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TNBC, triple negative breast cancer; TPS, tumour proportion score.

1. PD-L1 IHC 22C3 pharmDx for cervical cancer. Interpretation manual. Agilent Technologies, Inc; 2019. 2. PD-L1 IHC 22C3 pharmDx for esophageal squamous cell carcinoma. Interpretation manual. Agilent Technologies, Inc; 2019. 3. PD-L1 IHC 22C3 pharmDx for gastric or gastroesophageal junction adenocarcinoma. Interpretation manual. Agilent Technologies, Inc; 2019. 4. PD-L1 IHC 22C3 pharmDx for head and neck squamous cell carcinoma. Interpretation manual. Agilent Technologies, Inc; June 2019. 5. PD-L1 IHC 22C3 pharmDx for urothelial carcinoma. Interpretation manual. Agilent Technologies, Inc; 2021. 6. PD-L1 IHC 22C3 pharmDx for triple-negative breast cancer. Interpretation manual. Agilent Technologies, Inc; 2020. 7. PD-L1 IHC 22C3 pharmDx for NSCLC. Interpretation manual. Agilent Technologies, Inc; 2019.

PD-L1 Analysis by Digital Quantitation – Why?

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Drug Development

AI-TOOLS AN *BONA FIDE* COMPANION DIAGNOSTICS

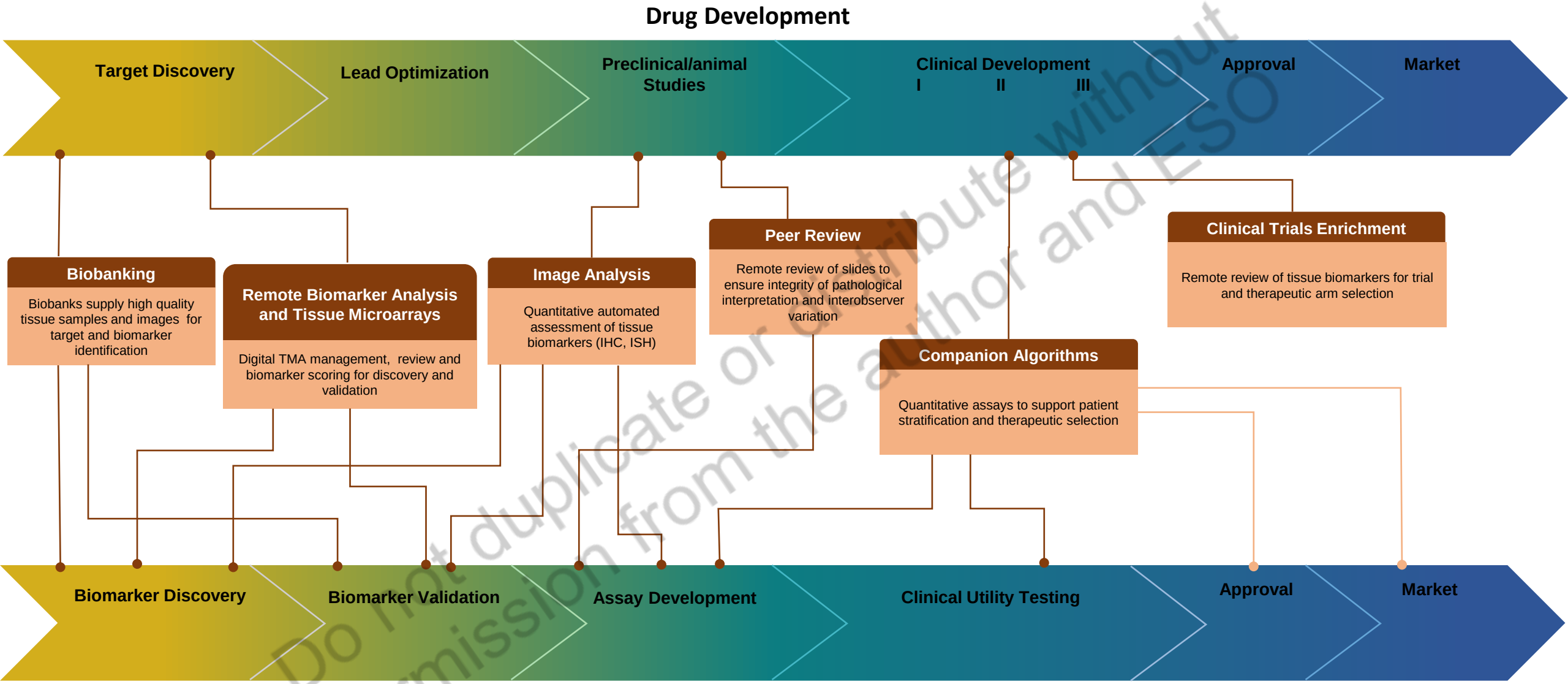
Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices. July 14, 2011

FDA will review targeted drugs for approval only in the context of their corresponding IVDs (biomarkers).

Biomarker Development (Companion Diagnostics)

Hamilton PW, et al, (Salto-Tellez M). Methods. 2014 Nov;70(1):59-73.

Digital Pathology in Drug Development, Biomarker discovery and Stratified Medicine



Hamilton PW, et al, (Salto-Tellez M). Methods. 2014 Nov;70(1):59-73.

PD-L1 Analysis by Digital Quantitation – Why?

PD-L1 scoring is intrinsically difficult

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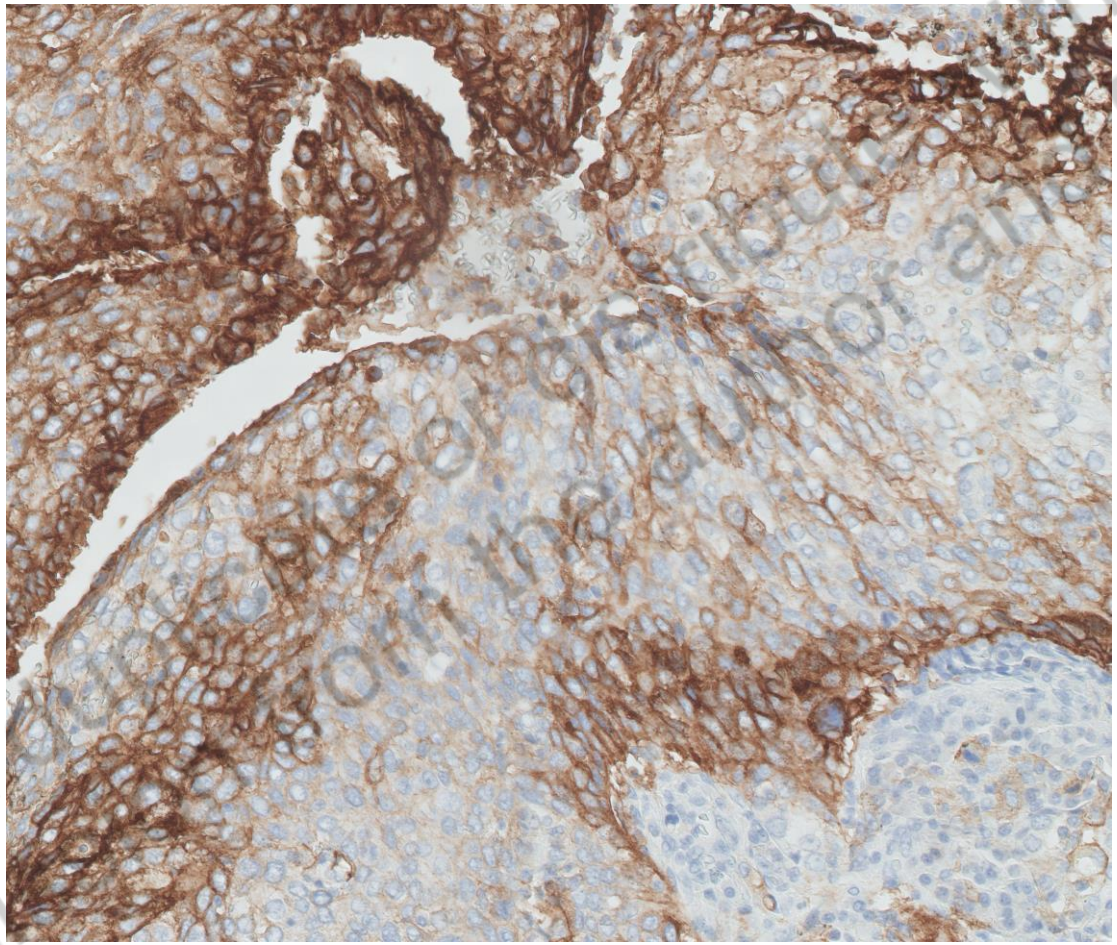
Humphries MP, et al. J Thorac Oncol. 2019 Jan;14(1):45-53.

PD-L1 expression can be very heterogeneous



Examples of PD-L1 positive tumor cells

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Lung Cancer. 2019 Aug; 134: 79–84.
doi: 10.1016/j.lungcan.2019.06.005: 10.1016/j.lungcan.2019.06.005
PMCID: PMC6658831
PMID: 31320000

Heterogeneity of PD-L1 expression in non-small cell lung cancer: Implications for specimen sampling in predicting treatment response

Alexander Haragan,[a,d,*] John K. Field,[a] Michael P.A. Davies,[a] Carles Escriu,[b] Aaron Gruver,[c] and John R. Gosney[d]

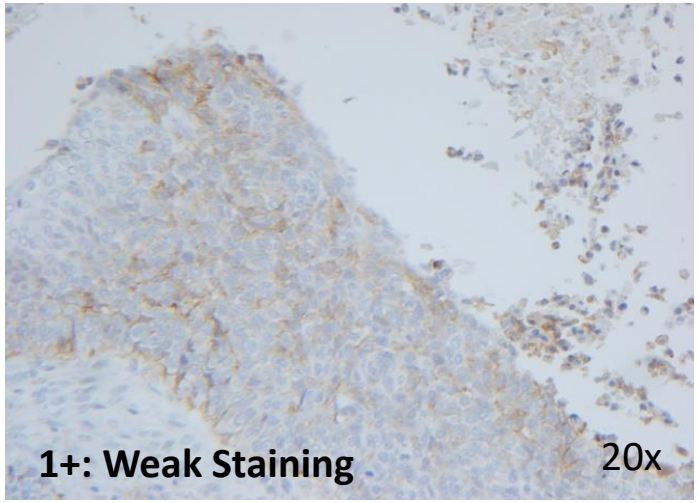
Results

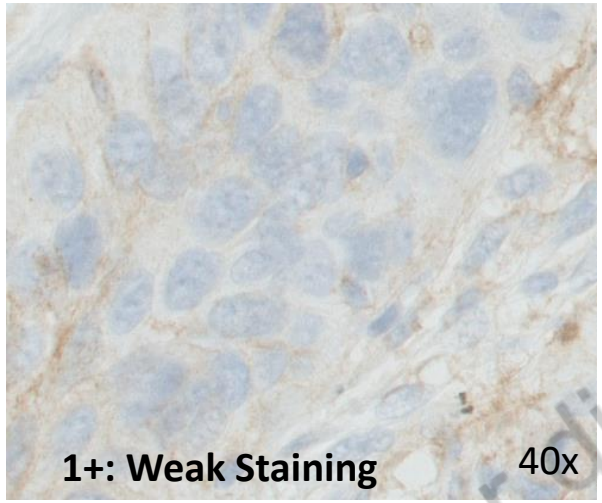
The majority of tumours demonstrated intra-tumoural heterogeneity (small-scale 78%, medium-scale 50%,large-scale 46%).

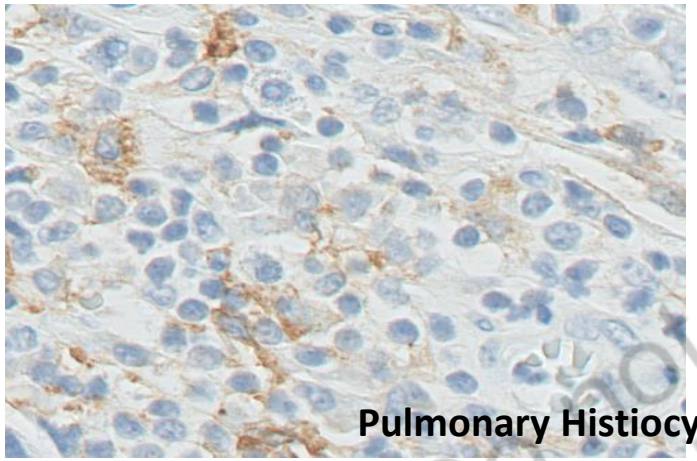
Inter-tumoural heterogeneity between the primary and nodal metastases was present in 53% of cases and, in 17%, between N1 and N2 disease.

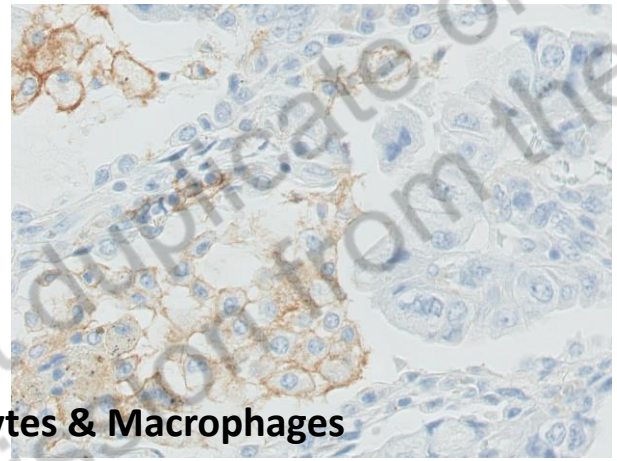
These differences were occasionally sufficient to lead to discrepancy across the ≥1%, ≥25% and ≥50% cut-offs used to guide therapy.

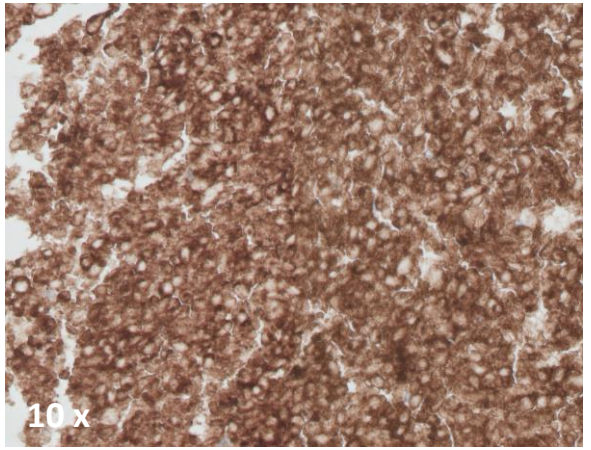
Assessment of PD-L1 by IHC – Potential Pitfalls











Variable expression in necrotic areas

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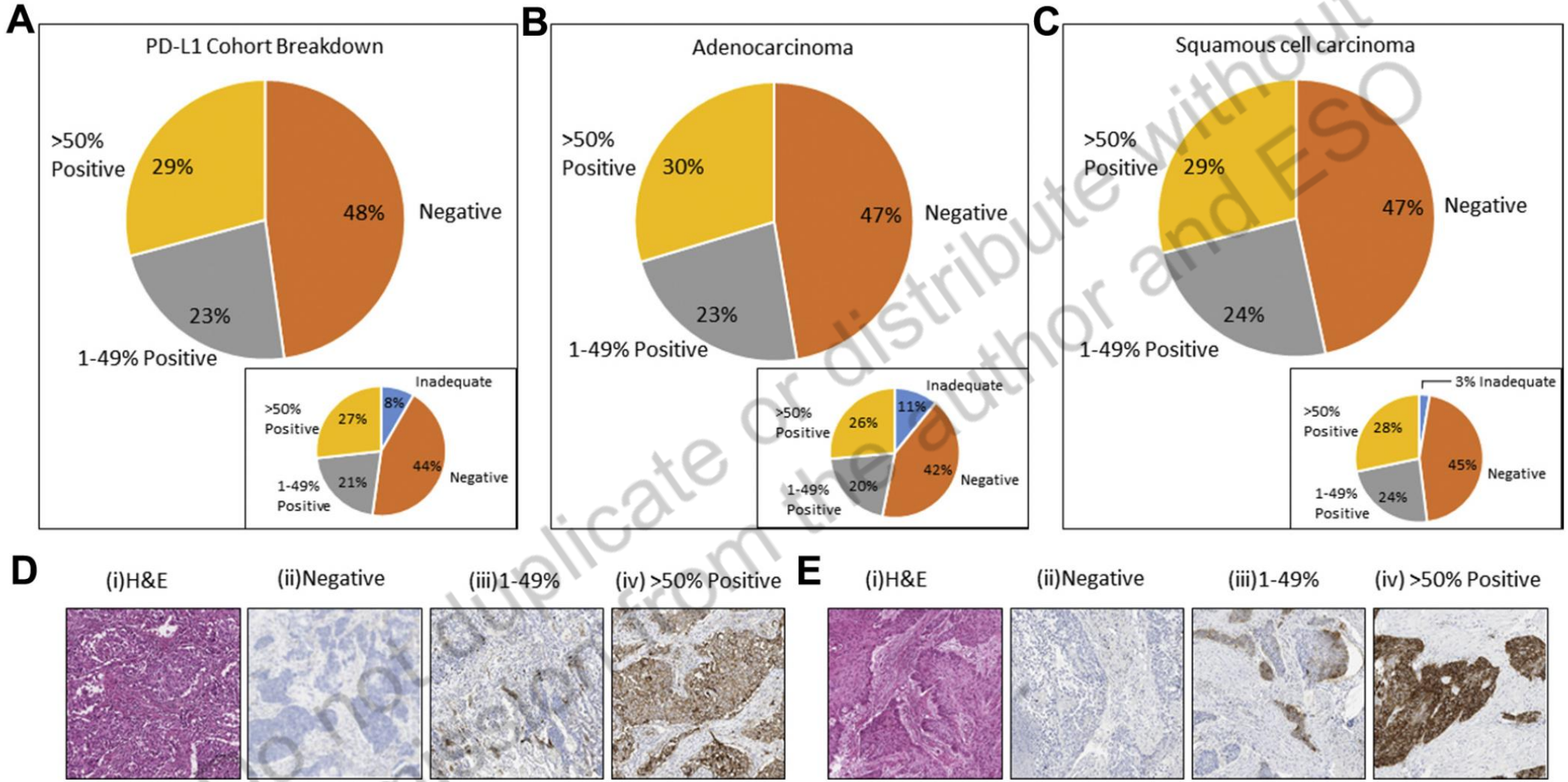
Adapted from: Humphries MP, et al. J Thorac Oncol. 2019 Jan;14(1):45-53.

PDL-1 IHC: Histogenesis-related positivity



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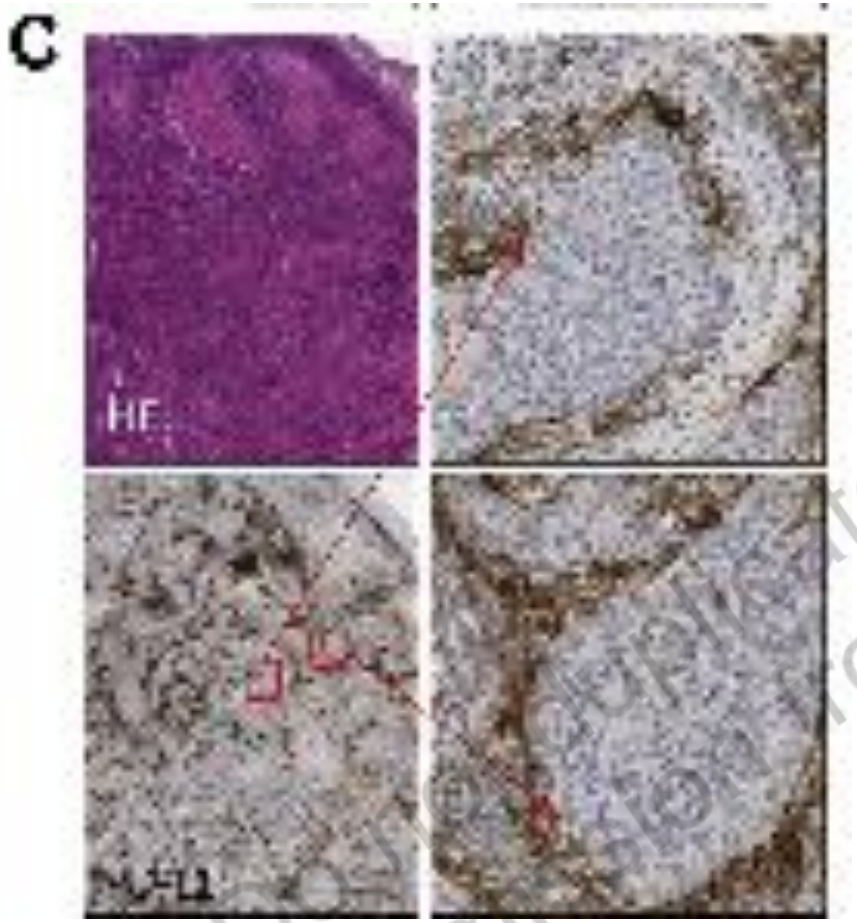
Adapted from: Humphries MP, et al. J Thorac Oncol. 2019 Jan;14(1):45-53.

Assessment of PD-L1 by IHC – More Potential Pitfalls



Sometimes evaluation of a "positive tumour antibody" provides the only reliable means to calculate the "denominator"

"Hugging effect": Only when it is unequivocally clear that malignant epithelial cells are expressing PDL-1 should it be scored as such

On cytology specimens (primarily, but not exclusively) evaluation of a full IHC panel may be relevant to confirm the origin of the PDL-1 expression

Cytoplasmic expression – sometimes due to suboptima fixation:
- If all cytoplasmic: negative
- If a mixture of membranous and cytoplasmic:
the whole group is considered positive

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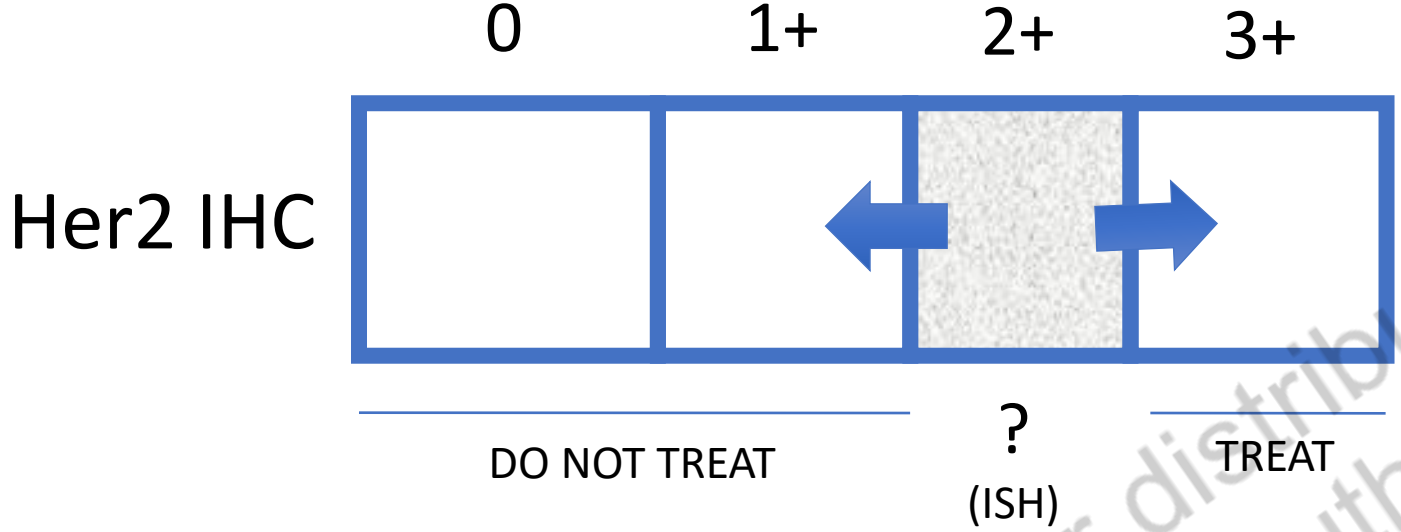
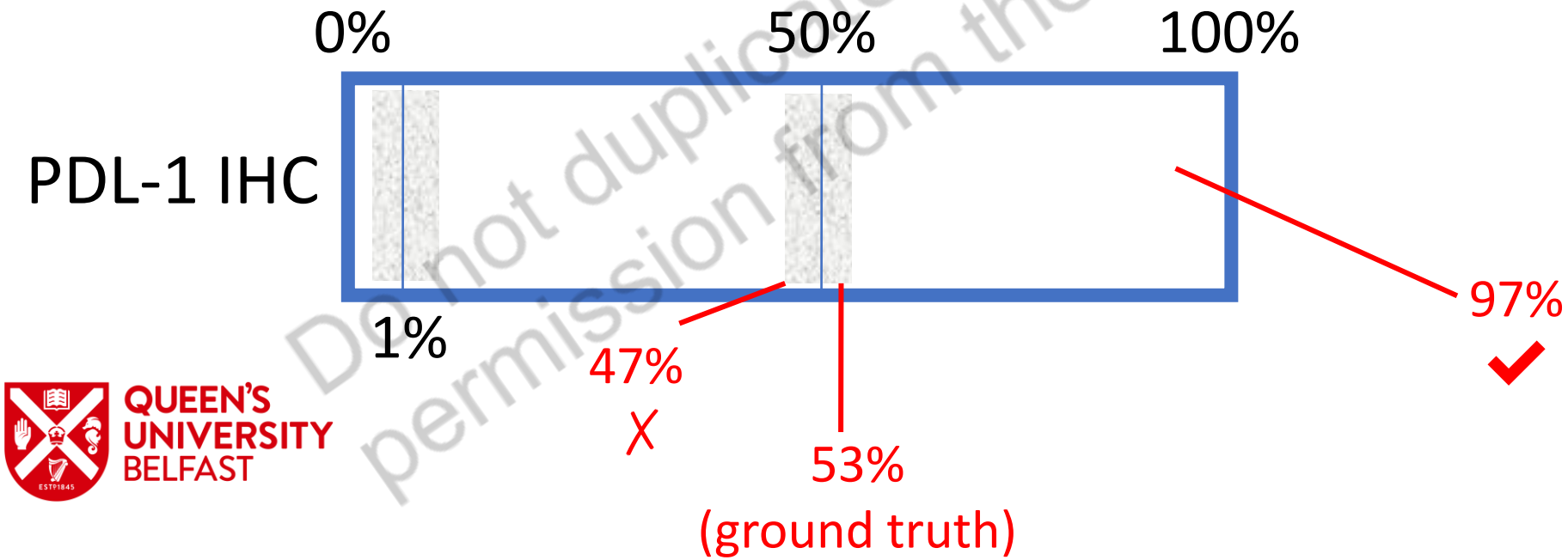
Assessment of PD-L1 by IHC – Test Design



9 – The sharp thresholds add difficulty to this test



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cancers

MDPI

Article

Digital Pathology and PD-L1 Testing in Non Small Cell Lung Cancer: A Workshop Record

Fabio Pagni [1,†], Umberto Malapelle [2,†], Claudio Doglioni [3], Gabriella Fontanini [4], Filippo Fraggetta [5], Paolo Graziano [6], Antonio Marchetti [7], Elena Guerini Rocco [8,9], Pasquale Pisapia [2], Elena V. Vigliar [2], Fiamma Buttitta [7], Marta Jaconi [1], Nicola Fusco [8,9], Massimo Barberis [8,9,*] and Giancarlo Troncone [2]

All cases were shared with 37 general pathologists using e-learning platforms.

71.9% 22C3 pharmDx kit on Dako Autostainer
28.1% SP263 Ventana kit on BenchMark platform.

A complete PD-L1 scoring agreement was reached in **57.1% of cases**, whereas a minor disagreement in 16.1% of cases was recorded.
The worst performance was achieved **in the negative cases, with 32.0% disagreement**.
Different clones used: **22.3% (22C3) and 38.1% (SP263)** disagreement

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Jasani *et al. Diagnostic Pathology* (2020) 15:37
https://doi.org/10.1186/s13000-020-00953-9

Diagnostic Pathology

RESEARCH Open Access

Evaluation of an online training tool for scoring programmed cell death ligand-1 (PD-L1) diagnostic tests for lung cancer

Bharat Jasani[1], Gudrun Bänfer[2], Rebecca Fish[3], Wim Waelput[4], Yves Sucaet[5], Craig Barker[3], Jessica L. Whiteley[3], Jill Walker[6], Rudy Hovelinck[7] and Rolf Diezko[2*]

Results: Seven sessions were held and 69 participant pathologists completed the training. Inter-reader concordance indicated high OPA (85–95%) for PD-L1 TC scoring at clinically relevant cut-offs, with Fleiss' Kappa > 0.5.

ORIGINAL ARTICLE

IASLC

The Reproducibility of Histopathologic Assessments of Programmed Cell Death-Ligand 1 Using Companion Diagnostics in NSCLC

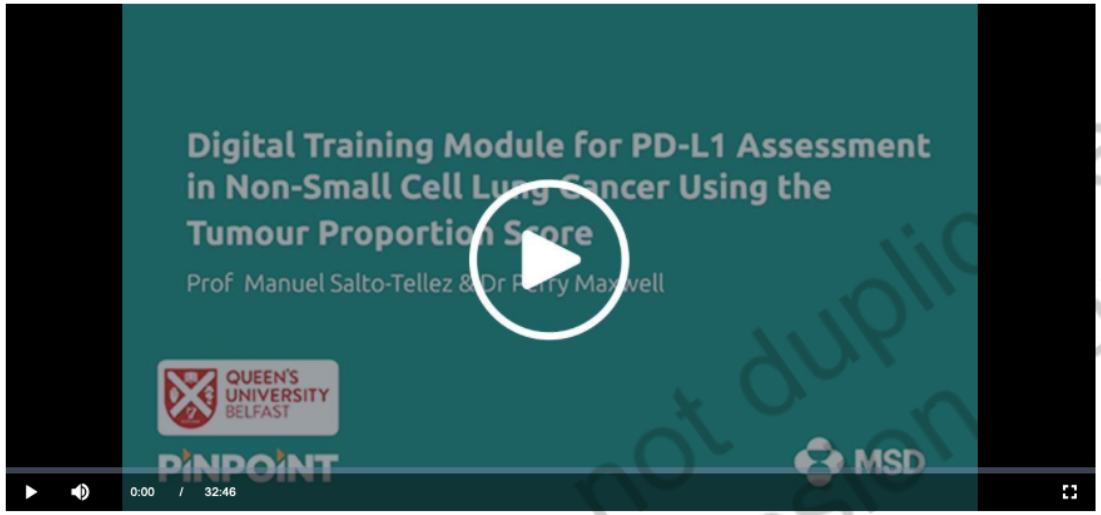
Pei Yuan, MD, Changyuan Guo, MD, PhD, Lin Li, MD, PhD, Lei Guo, BS, Fanshuang Zhang, PhD, Jianming Ying, MD, PhD*

Table 1. Intraobserver and Interobserver Reproducibility of the 22C3 Assay

	Intraobserver (N = 400)[a]		Interobserver (N = 19,000)[b]	
Measurements	1%	50%	1%	50%
CPs	368 (92.0%)	356 (89.0%)	16,468 (86.7%)	16,948 (89.2%)
Negative-negative	35 (8.8%)	281 (70.3%)	3940 (20.7%)	12,179 (64.1%)
Positive-positive	333 (83.2%)	75 (18.7%)	12,528 (66.0%)	4769 (25.1%)
DCPs	32 (8.0%)	44 (11.0%)	2532 (13.3%)	2052 (10.8%)
Measures of agreement (95% CI)				
OPA (%)	92.0 (89.3-94.7)	89.0 (85.9-92.1)	86.7 (86.2-87.1)	89.2 (88.8-89.6)
NPA (%)	68.6 (55.9-81.4)	92.7 (89.8-95.7)	75.7 (74.5-76.8)	92.2 (91.5-93.0)
PPA (%)	95.4 (93.2-97.6)	77.3 (69.0-85.7)	90.8 (90.3-91.3)	82.3 (81.7-82.9)

Digital training module for PD-L1 assessment for non-small cell lung cancer using the tumour proportion score

Prescribing Information (Great Britain) & Prescribing Information (Northern Ireland) [External links]



Prescribing Information (Great Britain) & Prescribing Information (Northern Ireland) [External links]

Length: 32:47

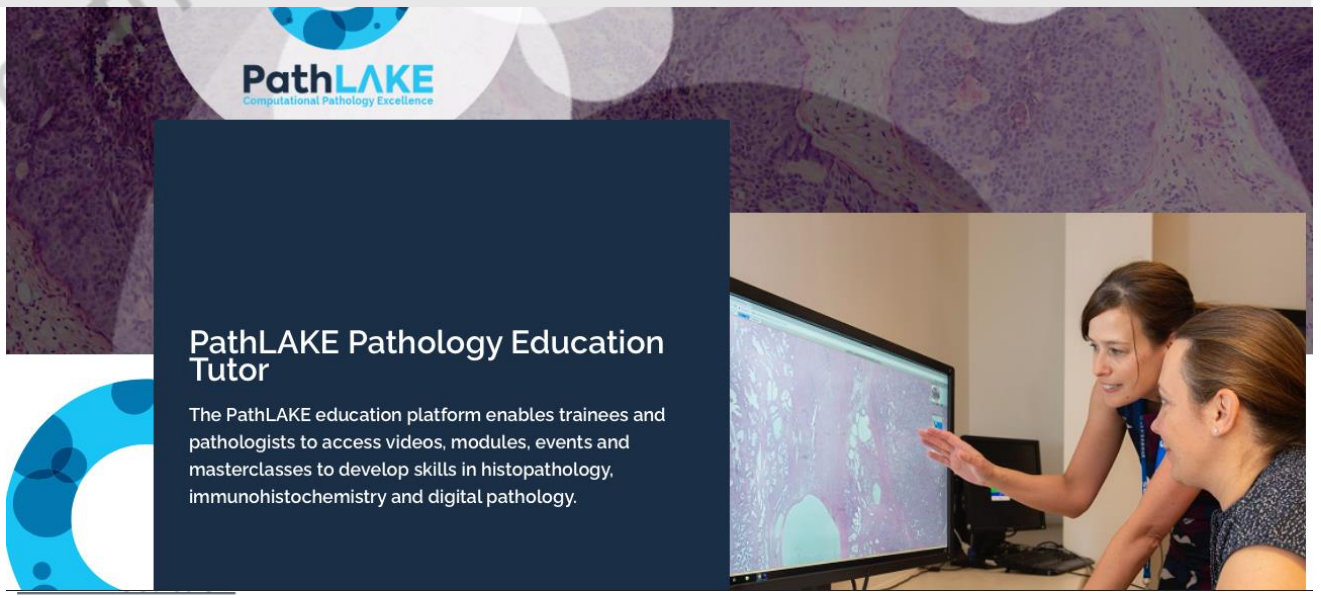
Prof. Manuel Salto-Tellez and Dr Perry Maxwell discuss PD-L1 assessment for NSCLC specimens. This includes the theory behind testing, what they look for and how they assess each specimen. This video was filmed in October 2018.

Join PinPoint **to keep updated with the latest educational materials in PD-L1 testing**

2nd October 2020

PathLAKE PD-L1 Digital Pathology Module Receives CPD Accreditation

PathLAKE is delighted to announce the addition of the PD-L1 module to its Digital Pathology Education Tutor website. It is fully approved by the Royal College of Pathologists and carries two CPD points.



PD-L1 Analysis by Digital Quantitation

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www.nature.com/modpathol

REVIEW ARTICLE OPEN

Digital pathology and artificial intelligence in translational medicine and clinical practice

Vipul Baxi[1] ✉, Robin Edwards[1], Michael Montalto[2] and Saurabh Saha[1]

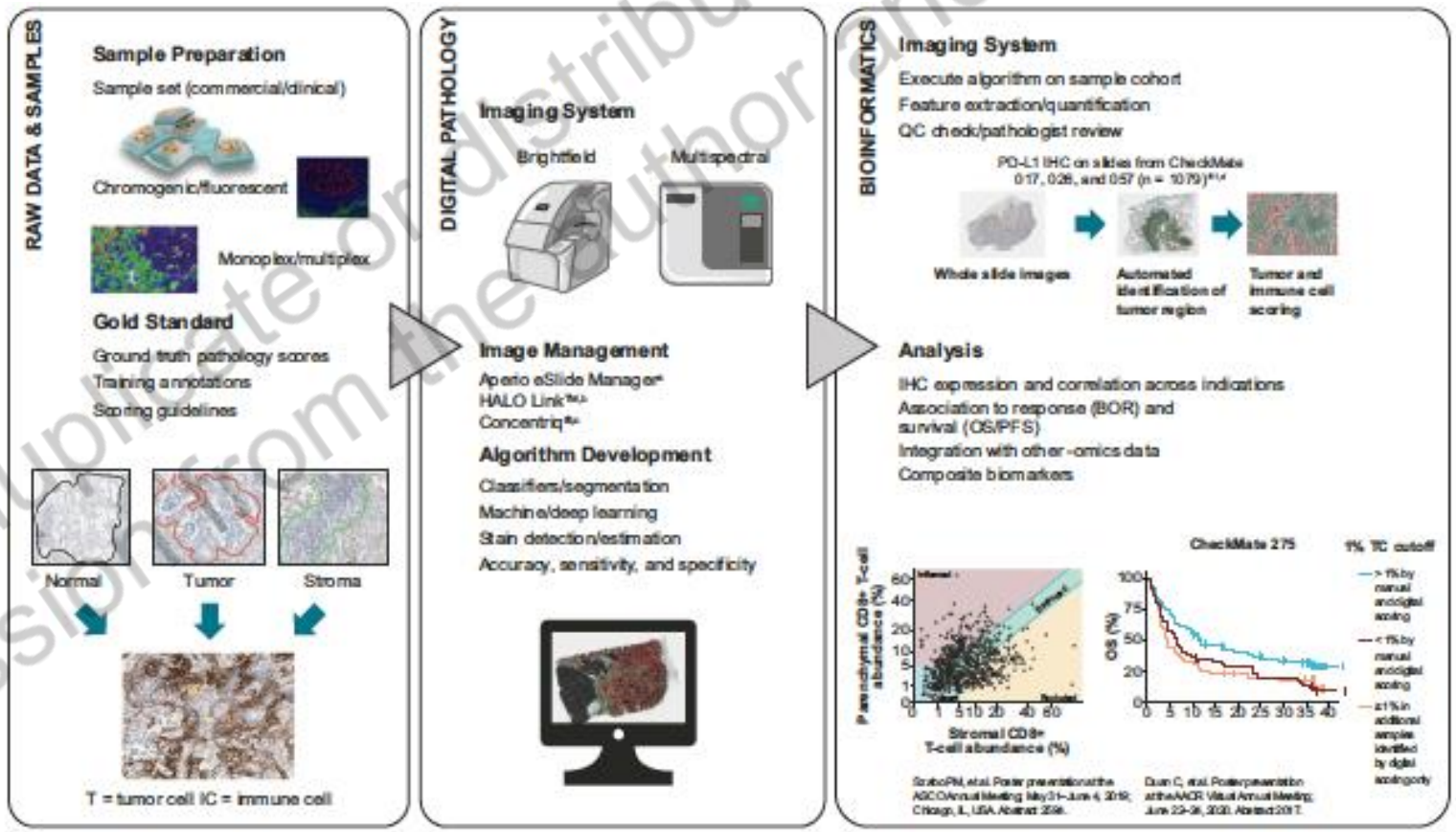


Fig. 2 Digital prognostic pathology workflow. BOR best overall response, IHC immunohistochemistry, OS overall survival, PFS progression-free survival, QC quality control. [a]Leica Biosystems; [b]Indica Labs; [c]Proscia; [d]PD-L1 IHC 28-8 pharmDx. Dako/Agilent Technologies.

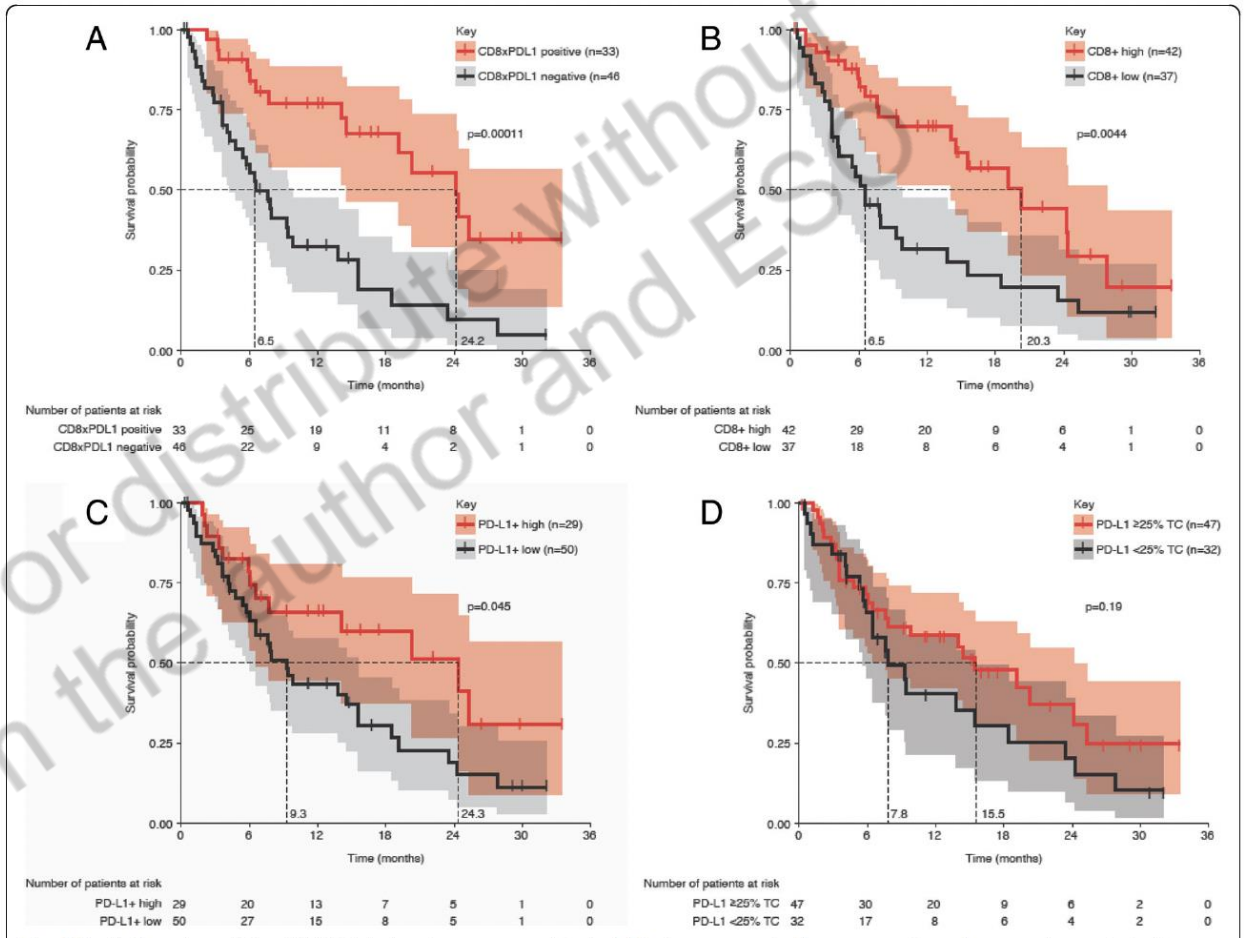
Althammer *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:121
https://doi.org/10.1186/s40425-019-0589-x

Journal for ImmunoTherapy of Cancer

RESEARCH ARTICLE Open Access

Automated image analysis of NSCLC biopsies to predict response to anti-PD-L1 therapy

Sonja Althammer[1], Tze Heng Tan[2], Andreas Spitzmüller[2], Lorenz Rognoni[2], Tobias Wiestler[2], Thomas Herz[2], Moritz Widmaier[2], Marlon C. Rebelatto[3], Helene Kaplon[4,5,6], Diane Damotte[4,5,6], Marco Alifano[5,7], Scott A. Hammond[3], Marie-Caroline Dieu-Nosjean[4,5,6,8], Koustubh Ranade[9], Guenter Schmidt[2], Brandon W. Higgs[3] and Keith E. Steele[3*]



- 163 patients in Study 1108/NCT01693562, a Phase 1/2 trial to evaluate durvalumab across multiple tumor types, including NSCLC,
- A separate cohort of 199 non-ICT- patients.
- Developer XD™ 2.7 software.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

IOTECH IMMUNO-ONCOLOGY TECHNOLOGY

REVIEW

Development and applications of computer image analysis algorithms for scoring of PD-L1 immunohistochemistry

L. J. Inge* & E. Dennis

Roche Tissue Diagnostics, Tucson, USA

Table 2. Overview of selected programmed cell death ligand 1 (PD-L1) image analysis (IA) algorithms.

Author	ML method	Tumor type	Scoring type	Sample dataset	Relevant data	Reference
Koelzer et al.	Random forest/ supervised learning	Melanoma	%TC	69 samples of melanoma	Pearson correlation coefficient ($r = 0.97$, $P < 0.0001$) between pathologist and IA	42
Kim et al.	Supervised learning	Gastric cancer	CPS	39 patients with clinical response to pembrolizumab	Correlation of PD-L1 positivity with patient (RFS) outcome [HR 0.536 (95% CI 0.316 −0.94), $P = 0.0294$]	43
Humphries et al.	Supervised learning	TNBC	% positive PD-L1	90 samples with clinical outcome	Correlation of PD-L1 positivity with patient (RFS) outcome [HR 0.536 (95% CI 0.316 −0.94), $P = 0.0294$]	44
Kapil et al	GAN/semi-supervised learning	NSCLC (biopsies)	TPS[a]	270 needle core biopsies; 60 slides used for concordance of manual to IA scores	IA scoring concordance with visual scores (OPA = 0.88, NPA = 0.88, PPA = 0.85; Lin's CCC = 0.94; Pearson CCC = 0.95)	45
Taylor et al.	Supervised learning with feedback loop	NSCLC	%TC, %IC	230 cases	Concordance (Lin's CCC) of IA with three pathologists (%TC = 0.81, 0.78, 0.68; %IC = 0.62, 0.53, 0.88)	46

%IC, percentage of PD-L1-positive immune cells; %TC, percentage of PD-L1-positive tumour cells; CCC, concordance correlation coefficient; CI, confidence interval; CPS, combined positive score; GAN, generative adversarial network; HR, hazard ratio; ML, machine learning; NPA, negative percent agreement; NSCLC, non-small cell lung cancer; OPA, overall percent agreement; PPA, positive percent agreement; RFS, relapse-free survival; TNBC, triple-negative breast cancer; TPS, tumor proportion score.

[a] TPS calculated from positive and negative pixels.

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Research Article

Automated Tumour Recognition and Digital Pathology Scoring Unravels New Role for PD-L1 in Predicting Good Outcome in ER-/HER2+ Breast Cancer

Matthew P. Humphries,[1] Sean Hynes,[1] Victoria Bingham,[1] Delphine Cougot,[2] Jacqueline James,[1] Farah Patel-Socha,[2] Eileen E. Parkes,[1] Jaine K. Blayney,[1] Michael A. O'Rorke,[3] Gareth W. Irwin,[1] Darragh G. McArt,[1] Richard D. Kennedy,[1] Paul B. Mullan,[1] Stephen McQuaid,[1] Manuel Salto-Tellez,[1] and Niamh E. Buckley[1,4]

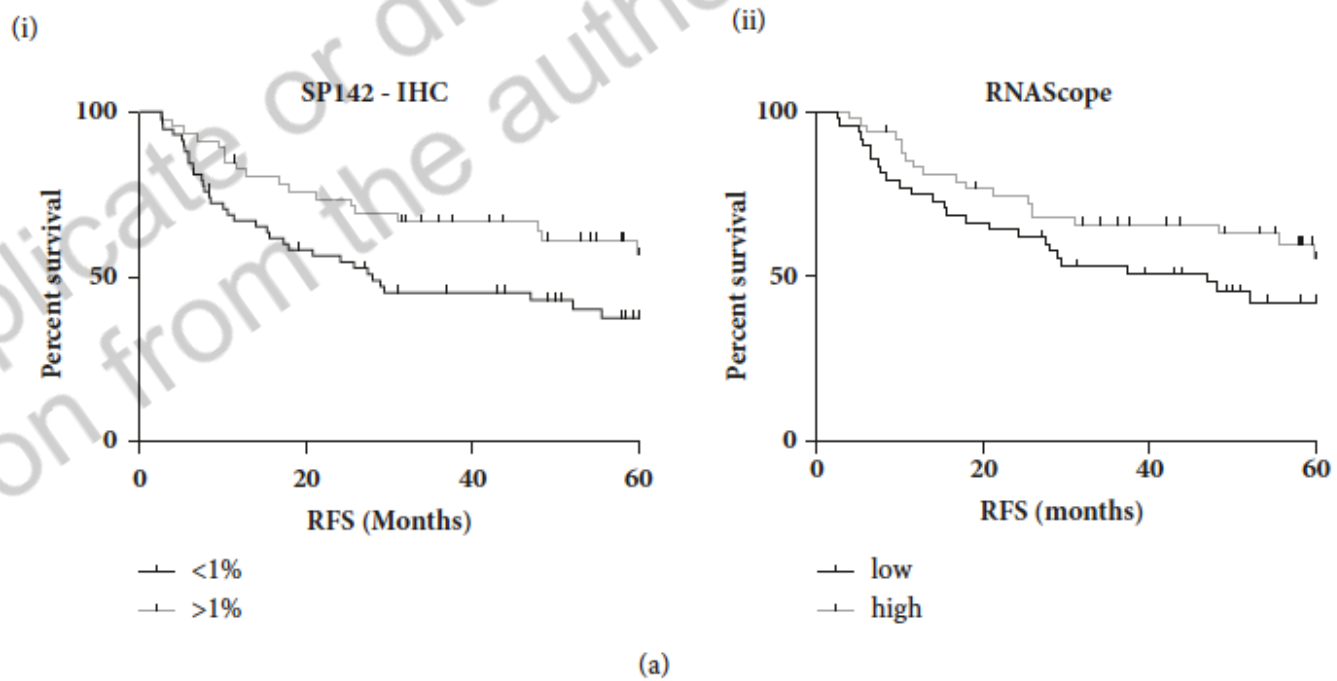

FIGURE 3: Kaplan Meier Plots of relapse free survival stratified based on PD-L1 expression above or below 1% as determined by the (i) SP142 or (ii) by RNAScope.

npj | Breast Cancer

www.nature.com/npjbcancer

ARTICLE OPEN

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How can artificial intelligence models assist PD-L1 expression scoring in breast cancer: results of multi-institutional ring studies

Xinran Wang[1,7], Liang Wang[2,7], Hong Bu[3], Ningning Zhang[1], Meng Yue[1], Zhanli Jia[1], Lijing Cai[1], Jiankun He[1], Yanan Wang[4], Xin Xu[5], Shengshui Li[6], Kaiwen Xiao[2], Kezhou Yan[2], Kuan Tian[2], Xiao Han[2], Junzhou Huang[2], Jianhua Yao[2]✉ and Yueping Liu[1]✉

*The proposed AI-assisted method **can help** pathologists at all levels to improve the PD-L1 assay (SP-142) IC assessment in breast cancer in terms of both accuracy and concordance.*

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FDA NEWS RELEASE

FDA Authorizes Software that Can Help Identify Prostate Cancer

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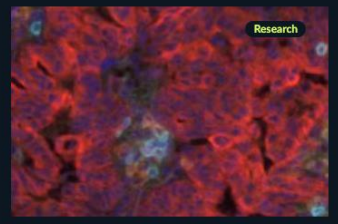
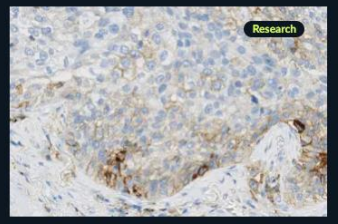
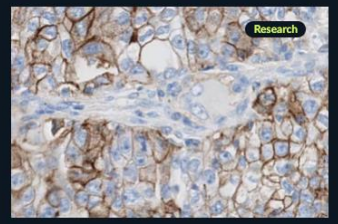


Multiplex, Lung Cancer, TME (Akoya Biosciences, Inc.) #10166

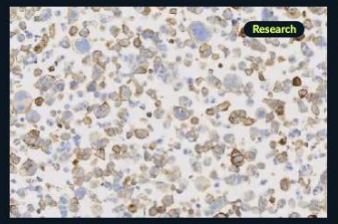


PD-L1, Melanoma, TME #10123

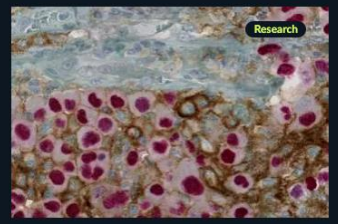
PD-L1, Germinal Center Detection, AI #10163



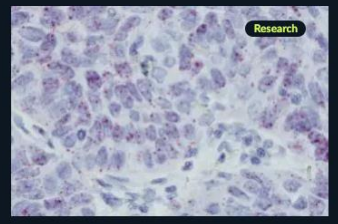
PD-L1, Lung Cancer, TME #10124



PD-L1, Cell Lines, Cancer #10092



PD-L1+SOX10, Melanoma, TME #10125



PD-L1 RISH, Lung cancer, TME #10151

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Mindpeak PD-L1 Quantifier

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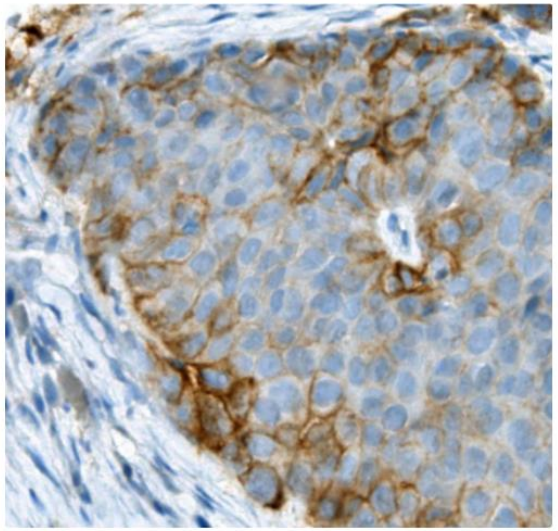
Lung | Detection of NSCLC | PD-L1

The first AI solution for PD-L1 to detect and quantify diagnostically relevant cells in non-small-cell lung carcinoma (NSCLC)

The first AI solution for PD-L1 supports cancer experts in the challenging assessment of PD-L1 stained lung tissue. It identifies tumorous and inflammatory cells and quantifies them to support scoring. Mindpeak PD-L1 Quantifier for NSCLC helps to achieve accurate results without the need of manual fine-tuning. It is optimized to account for the typical lab-specific variations and supports tissue slides stained with the most common PD-L1 clones.

Mindpeak PD-L1 Quantifier is Research Use Only, not for use in diagnostic procedures.



Analyse image

uPath PD-L1 (SP263) image analysis, NSCLC (CE-IVD)

Ready-to-use, fast, consistent and automated algorithm for clinical decision support

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Histopathology

Histopathology 2018, 73, 397–406. DOI: 10.1111/his.13528

Digital image analysis improves precision of PD-L1 scoring in cutaneous melanoma

Viktor H Koelzer,[1,2,*] Aline Gisler,[1,*] Jonathan C Hanhart,[1,*] Johannes Griss,[3] Stephan N Wagner,[3] Niels Willi,[1] Gieri Cathomas,[1] Melanie Sachs,[1] Werner Kempf,[4] Daniela S Thommen[5,6] & Kirsten D Mertz[1]

ARTICLES

https://doi.org/10.1038/s41591-018-0057-z

nature medicine

A transcriptionally and functionally distinct PD-1^{+} CD8^{+} T cell pool with predictive potential in non-small-cell lung cancer treated with PD-1 blockade

Daniela S. Thommen[1,2*], Viktor H. Koelzer[3,4,13], Petra Herzig[1,13], Andreas Roller[5,13], Marcel Trefny[1], Sarah Dimeloe[6], Anna Kiialainen[5], Jonathan Hanhart[3], Catherine Schill[7], Christoph Hess[6], Spasenija Savic Prince[8], Mark Wiese[9], Didier Lardinois[9], Ping-Chih Ho[10], Christian Klein[11], Vaios Karanikas[11], Kirsten D. Mertz[3], Ton N. Schumacher[2,14] and Alfred Zippelius[1,12,14*]

PD-L1 Analysis by Digital Quantitation… …beyond IHC?

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Published in final edited form as:
Lab Invest. 2020 October ; 100(10): 1311–1317. doi:10.1038/s41374-020-0424-5.

Digital quantitative assessment of PD-L1 using digital spatial profiling

Swati Gupta[1], **Jon Zugazagoitia**[1], **Sandra Martinez-Morilla**[1], **Kit Fuhrman**[2], **David L. Rimm**[1,3]

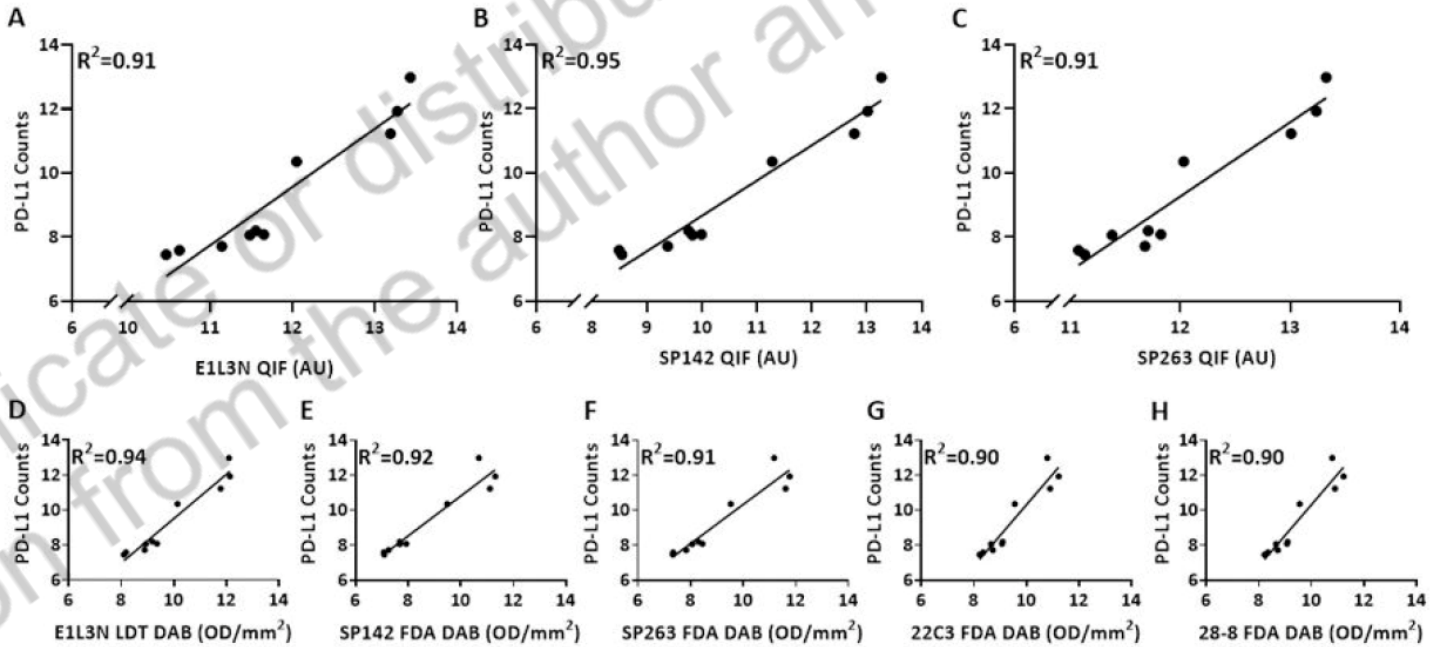


Figure 3: Correlation of Log_2 transformed PD-L1 data from GeoMx DSP, QIF and IHC DAB.
Regression of PD-L1 protein expression by DSP with (A-C) QIF assay performed using 3 antibodies (E1L3N, SP142, and SP263) and (D-H) IHC DAB assay performed using 5 antibodies (E1L3N, SP142, SP263, 22C3 and 28–8). Each dot represents average of 2 TMAs (GeoMx DSP), 3 TMAs (QIF) and 20 TMAs (IHC DAB) with 3 pellet per cell clone in one TMA.

Original Investigation

FREE

July 18, 2019

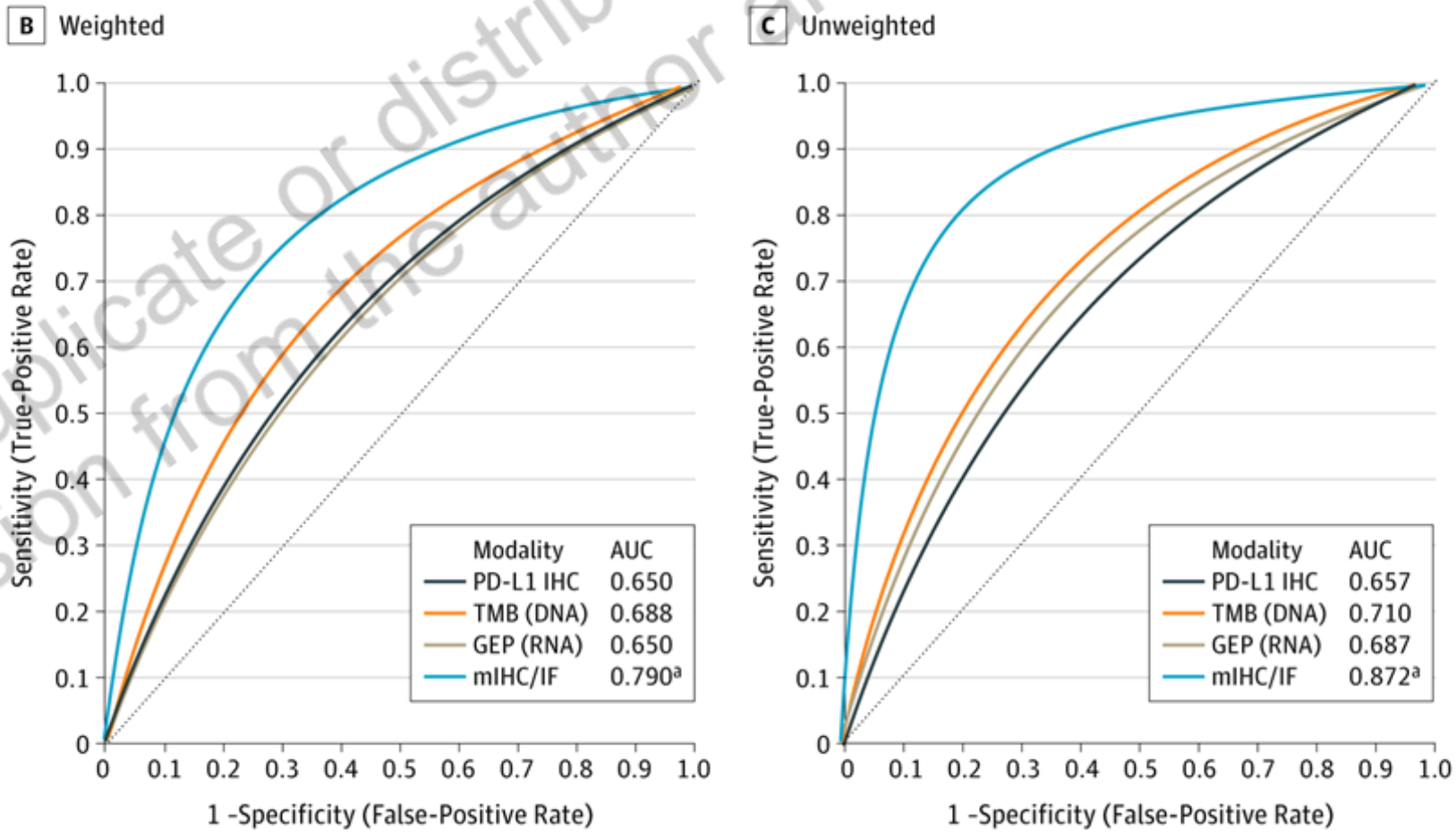
Comparison of Biomarker Modalities for Predicting Response to PD-1/PD-L1 Checkpoint Blockade

A Systematic Review and Meta-analysis

Steve Lu[1]; Julie E. Stein, MD[1]; David L. Rimm, MD, PhD[2]; et al

» Author Affiliations | Article Information

JAMA Oncol. 2019;5(8):1195-1204. doi:10.1001/jamaoncol.2019.1549



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A

Manual Assessment \ Digital Assessment	<1%	1-49%	>50%
<1%	4	2	0
1-49%	0	16	1
>50%	0	3	5

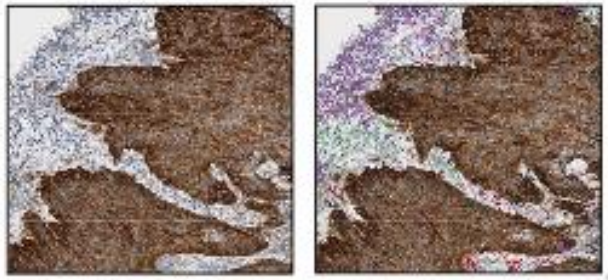
B

Manual Assessment \ Digital Assessment	<1%	1-49%	>50%
<1%	10	5	0
1-49%	1	6	0
>50%	0	0	9

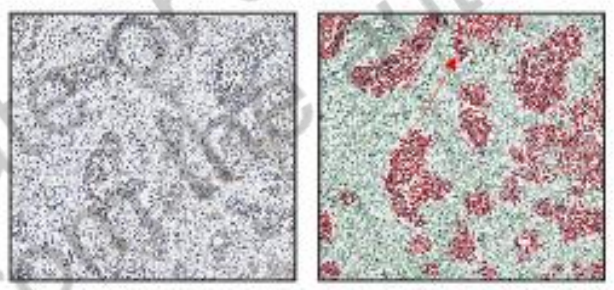
27% discrepancies

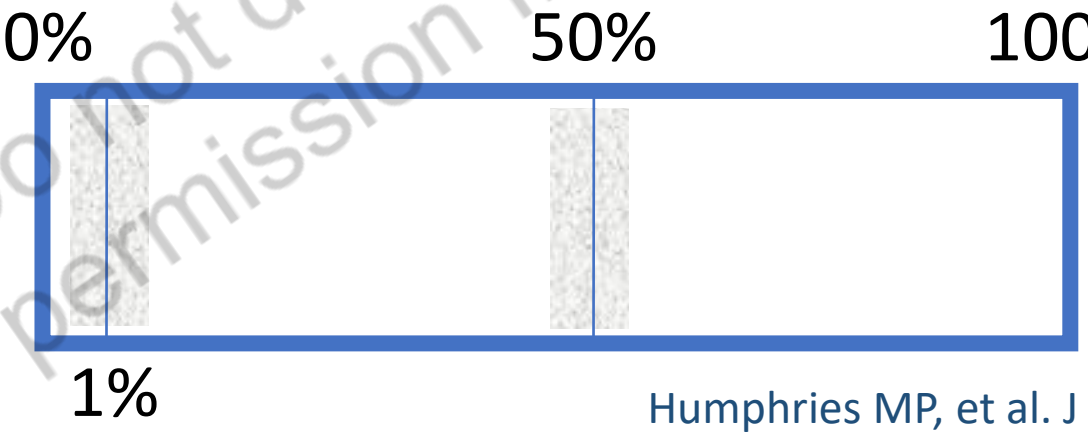
Most of these discrepancies were around the <1% - 3% threshold, Some around the 45%-55% threshold.

C



D





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Humphries MP, et al. J Thorac Oncol. 2019 Jan;14(1):45-53.

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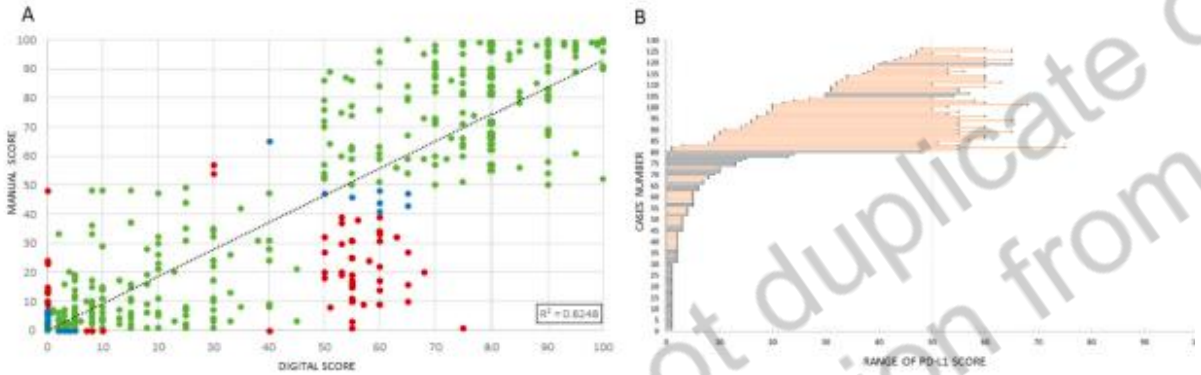
Article

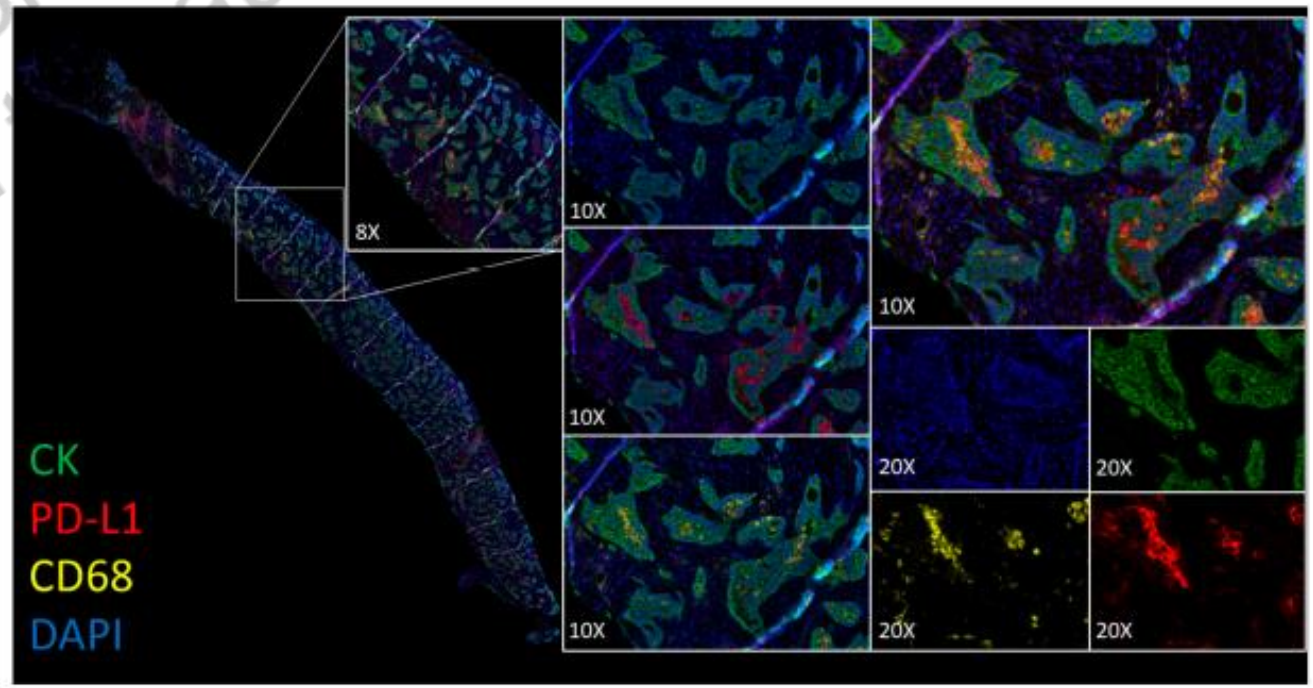
Improving the Diagnostic Accuracy of the PD-L1 Test with Image Analysis and Multiplex Hybridization

Matthew P. Humphries [1], Victoria Bingham [1], Fatima Abdullahi Sidi [1], Stephanie G. Craig [1], Stephen McQuaid [1,2,3], Jacqueline James [1,2,3] and Manuel Salto-Tellez [1,2,*]

Table 2. Sensitivity and specificity data.

		PD-L1 DAB IHC		
		Positive	**Negative**	**Total**
PD-L1 Multiplex	**Positive**	141	15	156
	Negative	4	170	174
	Total	145	185	330





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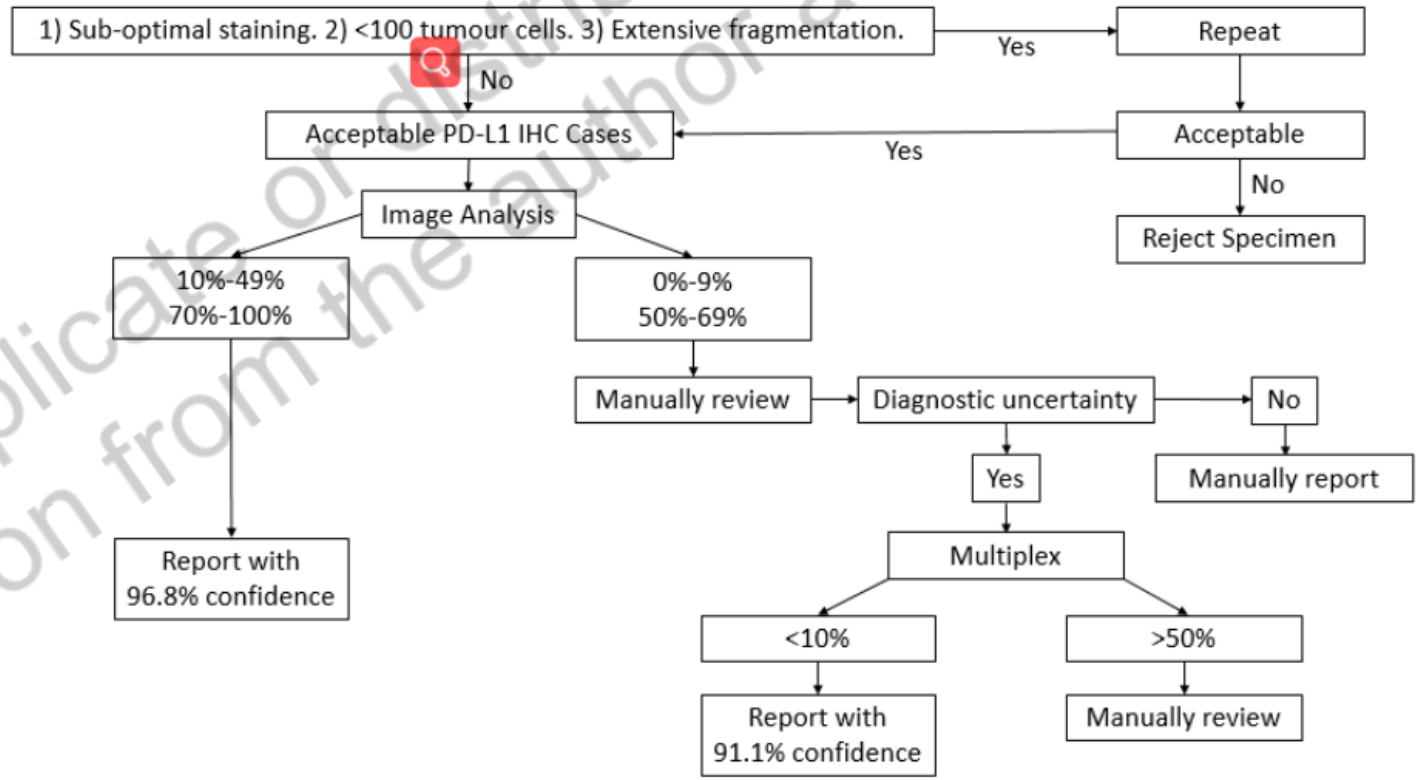

Figure S2. A diagnostic decision tree proposing the most beneficial application of image analysis and multiplex to appropriately triage PD-L1 diagnostic cases.

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PD-L1 Analysis by Digital Quantitation… … why is it not SoC?

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- ***Understanding the limitations*** of AI and ML is essential for physicians as they begin to integrate them in clinical practice, as well as to assist with continued development of these tools[1]

Key challenges of diagnostic AI in pathology[1,2]

Access to large well-annotated data sets
Context switching between workflows
Algorithms are slow to run
Algorithms require configuration
Properly defined protocols for training evaluation
Algorithms are not properly validated
Lack of health economics
No clear evidence of added value in everyday clinical decision-making
Possibility of false negative results or missed diagnosis

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AI, artificial intelligence; ML, machine learning.

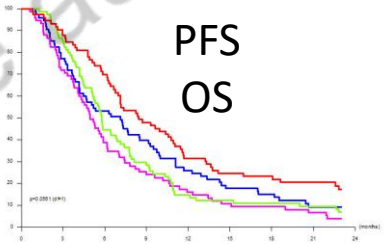
1. Pucchio A et al. *Nat Biotechnol*. 2021;39:388–389.
2. Serag A et al. *Front Med (Lausanne)*. 2019;6:185.

BIOMARKER STRATIFICATION

STRATIFICATION THROUGH RANDOMIZATION

The computer randomly assigns patients to two or more groups, helping to prevent bias

Investigational group receives new treatment



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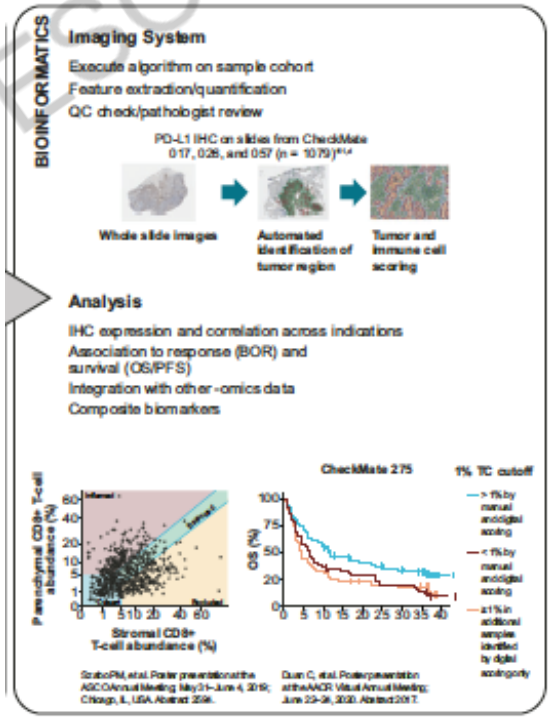

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Conclusion

- The development, validation, and adoption of ML/AI algorithms represents the most important challenge of tissue pathology facing our generation

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