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Standardization and Quality Gap in Tissue Pathology?

Challenges and potential solutions

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Unmet needs in tissue diagnostics

The Standardization & Quality Gap

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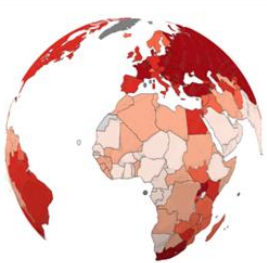
Tissue Pathology in Healthcare and Research



Demographics
Chronic disease

Drug-diagnostic co-development:
New targeted drugs and possible Companion diagnostics

Diagnostic, prognostic, and predictive:
Tissue biomarker data is a critical basis for treatment decisions

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TRANSFORMING PATHOLOGY

The Journey From Biopsy to Decisions

Main focus

Sampling Variability → Biopsy

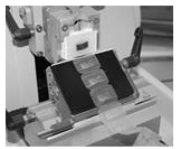
Fixatives / fixation → Fixation & embedding

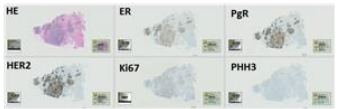
Thickness → Sectioning

Sufficiency / Quality → Staining

Inter- & intra reader variablity → Assessment

Decision





Example: Breast Panel

Challenges: Biopsies and pre-analytical steps

Shoddy biopsies deny cancer patients a shot at personalized treatment

By ELIE DOLGIN / JANUARY 22, 2016

Shoddy tumor biopsies are preventing cancer patients from receiving personalized therapies.
DAN KITWOOD/GETTY IMAGES/CANCER RESEARCH UK

Impact of delayed and prolonged fixation on the evaluation of immunohistochemical staining on lung carcinoma resection specimen

Check for updates

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Abstract
Pre-analytical factors, such as fixation time, influence morphology of diagnostic and predictive immunohistochemical staining, which are increasingly used in the evaluation of lung cancer. Our aim was to investigate if variations in fixation time influence the outcome of immunohistochemical staining in lung cancer. From lung resections, specimen with tumor size bigger than 4 cm, 10 samples were obtained: 2 were put through the standard fixation protocol, 5 through the delayed, and 3 through the prolonged fixation protocol. After paraffin embedding, tissue microarrays (TMAs) were made. They were stained with 20 antibodies and scored for quality and intensity of staining. Samples with delay in fixation showed loss of TMA cores on glass slides and deterioration of tissue quality leading to reduction in the expression of CK 7, Keratin MNF116, CAM 5.2, CK 5/6, TTF-1, C-MET, Napsin A, D2-40, and PD-L1. Prolonged fixation had no influence on the performance of immunohistochemical stains. Delay of fixation negatively affects the expression of different immunohistochemical markers, influencing diagnostic (cytokeratins) and predictive (PD-L1) testing. These results emphasize the need for adequate fixation of resection specimen.

Keywords Pre-analytical · Fixation · Immunohistochemistry · Lung adenocarcinoma

Needle Biopsy Adequacy in the Era of Precision Medicine and Value-Based Health Care

Kenneth P. H. Pritzker, MD, FRCPC; Heikki J. Nieminen, PhD

• *Context.*—Needle biopsy of diseased tissue is an essential diagnostic tool that is becoming even more important as precision medicine develops. However, the capability of this modality to efficiently provide samples adequate for diagnostic and prognostic analysis remains quite limited relative to current diagnostic needs. For physicians and patients, inadequate biopsy frequently leads to diagnostic delay, procedure duplication, or insufficient information about tumor biology leading to delay in treatment; for health systems, this results in substantial incremental costs and inefficient use of scarce specialized diagnostic resources.

Objective.—To review current needle biopsy technology, devices, and practice with a perspective to identify current limitations and opportunities for improvement in the context of advancing precision medicine.

Data Sources.—PubMed searches of fine-needle aspiration and core needle biopsy devices and similar technologies were made generally, by tissue site, and by adequacy as well as by health economics of these technologies.

Conclusions.—Needle biopsy adequacy can be improved by recognizing the importance of this diagnostic tool by promoting common criteria for needle biopsy adequacy; by optimizing needle biopsy procedural technique, technologies, clinical practice, professional education, and quality assurance; and by bundling biopsy procedure costs with downstream diagnostic modalities to provide better accountability and incentives to improve the diagnostic process.

(*Arch Pathol Lab Med.* 2019;143:1399–1415; doi: 10.5858/arpa.2018-0463-RA)

- 20% of biopsies lacking tumor cells, and/or contain necrosis / fibrosis
- Poor and non-standardized fixation impact biomarker expression / interpretation
- Artifacts: Folds, tears, debris, …
- …

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Challenges: Staining

Annual Review Issue | Open Access | Published: 26 August 2015

Proficiency testing in immunohistochemistry—experiences from Nordic Immunohistochemical Quality Control (NordiQC)

Mogens Vyberg & Søren Nielsen

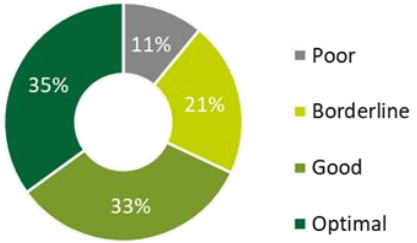
Virchows Archiv **468**, 19–29(2016) | Cite this article
3588 Accesses | **27** Citations | **2** Altmetric | Metrics

Abstract

Despite extensive use of immunohistochemistry (IHC) for decades, lack of standardization remains a major problem, even aggravated in the era of targeted therapy. Nordic Immunohistochemical Quality Control (NordiQC) is an international academic proficiency testing (PT) program established in 2003 primarily aimed at assessing the analytical phases of the laboratory IHC quality. About 700 laboratories from 80 countries are currently participating. More than 30,000 IHC slides have been evaluated during 2003–2015. Overall,

NordiQC

Staining quality



Poor staining preparations

- **One out of three pathology labs are unable to stain sufficiently well** to make a meaningful diagnostic decision
- This **could lead to incorrect choices of treatment** for patients, again at significant human and economic costs.

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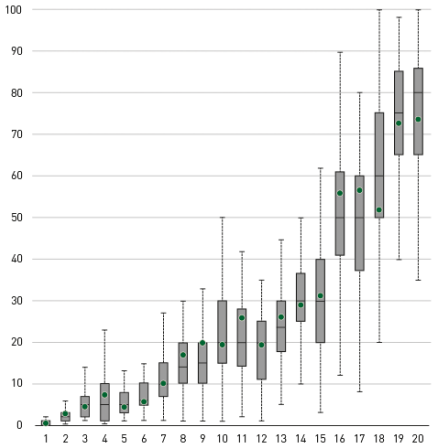
Challenges: Interpretive accuracy

Ki-67 Manual Score against Image Analysis

Median of 126 Scores



NordiQC

Original Article | Published: 26 February 2016

Digital image analysis outperforms manual biomarker assessment in breast cancer

Gustav Stålhammar ✉, Nelson Fuentes Martinez, Michael Lippert, Nicholas P Tobin, Ida Mølholm, Lorand Kis, Gustaf Rosin, Mattias Rantalainen, Lars Pedersen, Jonas Bergh, Michael Grunkin & Johan Hartman

Modern Pathology **29**, 318–329 (2016) | Download Citation ⬇

Ki67 scoring method	*Proportion misclassified*
Manual	
Cutoff ≥20%	30%
Cutoff ≥22.5%*	29%

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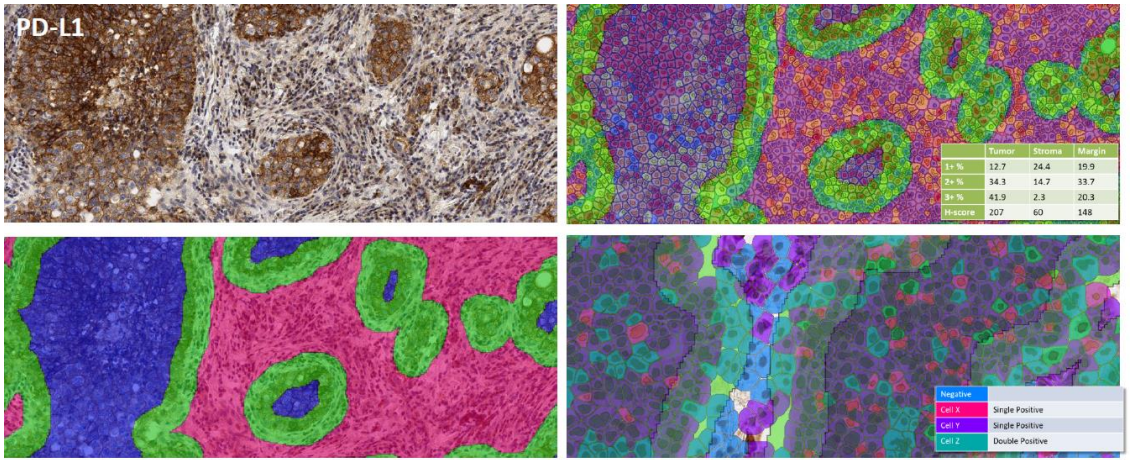
Complexity of future Dx Biomarkers



Precision medicine and financially sustainable cancer healthcare

- New companion diagnostics markers are often very complex to read & interpret
- Lack of diagnostic accuracy can result in costly, inefficient and potentially harmful treatments.
- Visiopharm's AI Driven Precision Pathology solution provides diagnostic decision support and productivity enhancements

Future Companion Diagnostic biomarkers are too complex for manual reading.

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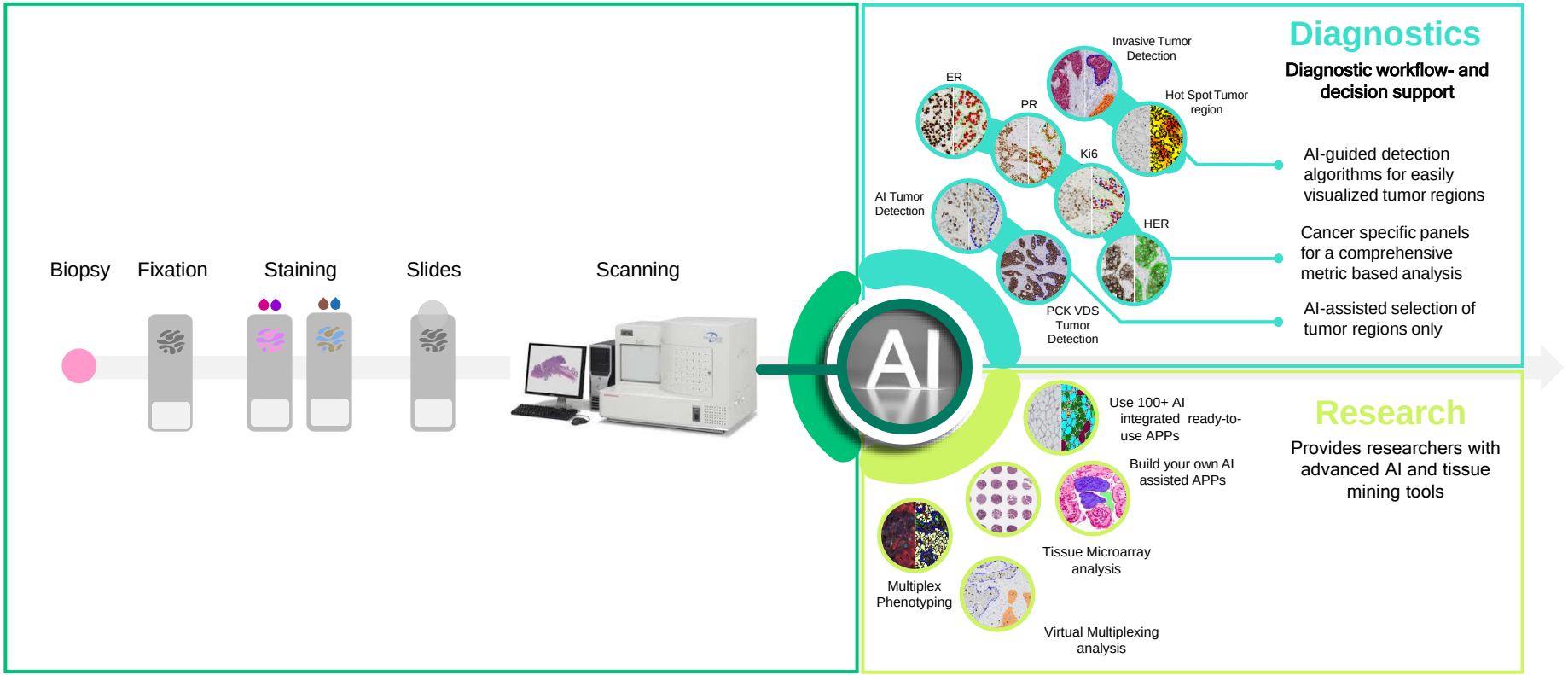
AI in Diagnostic- and Research Workflows



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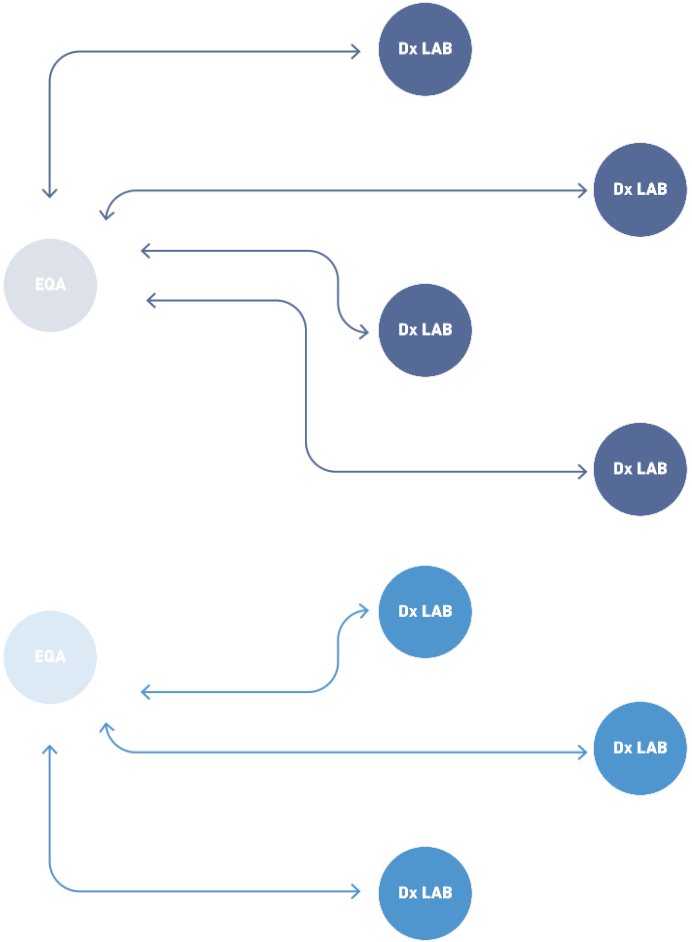
Needs, Technology and Infrastructure

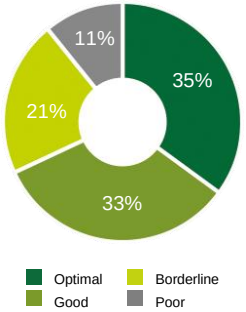
Focus: Stain Quality Management

DIAGNOSTIC PATHOLOGY LABS

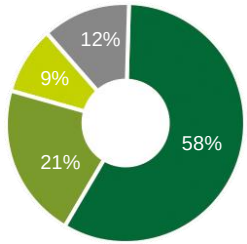
- **Lab Fail rate:** More than 30% of all labs fail in providing sufficient staining quality for Dx purposes
- **Participation in Quality Schemes:** Most participate in Quality Schemes with External Quality Assurance Organizations.
- **Number of Biomarkers:** Modern pathology labs are routinely using 80-120 tissue diagnostic biomarkers
- **Number of Labs:**
  - ~8-9000 Dx pathology labs in US, Europe, and Japan
  - ~10,000 labs in China
- **Frequency of Quality Runs:** Just a few per year per marker, given the current lack of scalability. The need is higher.

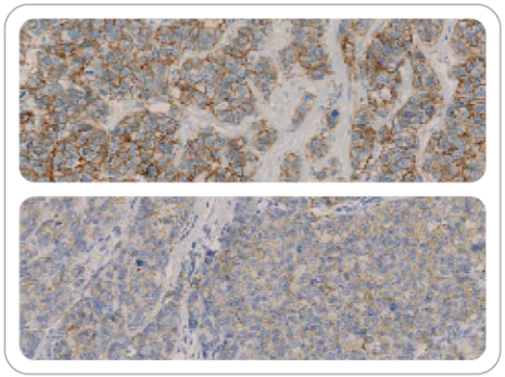


General module
~19,000 slides stained for ~85 markers



Breast cancer module
~8,000 slides stained for ~5 markers





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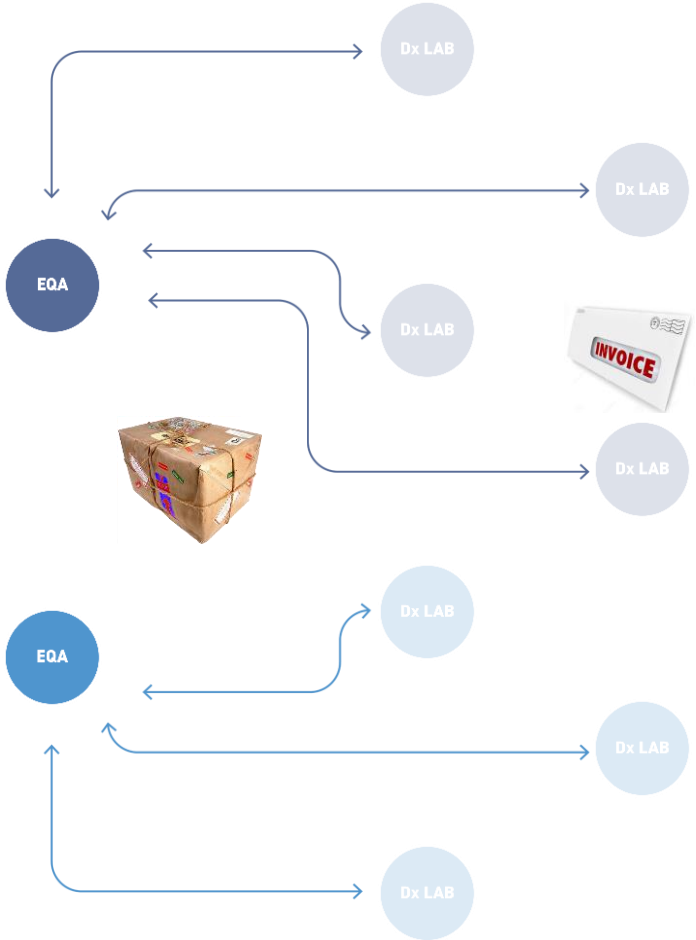
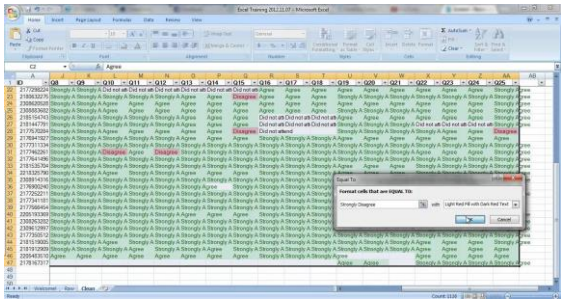
QUALITY SCHEMES & SCALABILITY:

- **Purpose of EQA:** External Quality Assurance (EQA) Organizations exist to promote standardization and quality of staining with IHC & ISH tissue diagnostic assays.
- **Quality Runs and Proficiency Testing**: Unstained test slides are sent out to participating labs. Slides are stained and sent back to the EQA for assessment of quality
- **Not a scalable model:** The current workflows are highly manual, labor- intensive, and hard to scale.





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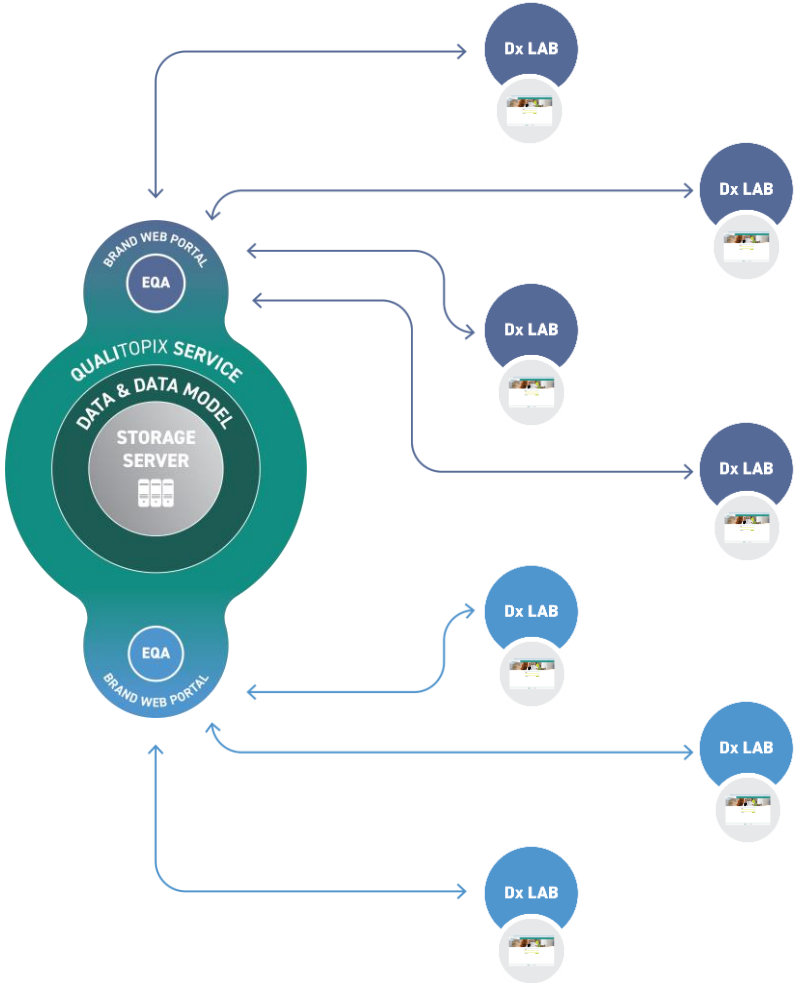
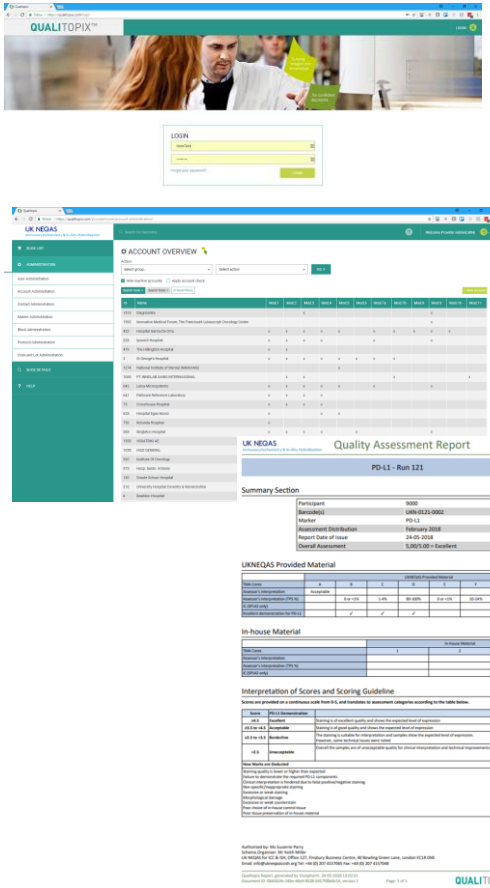
Introducing an Administration Platform for EQA.

Web based

- Designed to manage all interactions between EQA's and participating labs
- Provides services for EQA's and participating Labs
- Multi-tenant web platform, with EQA branded front end.
- Private Log-in for:
  - EQA's
  - External assessors
  - Participating Lab's





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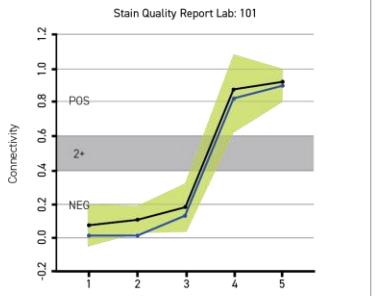
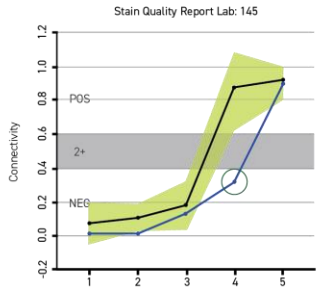
Measuring and Reporting Staining Quality

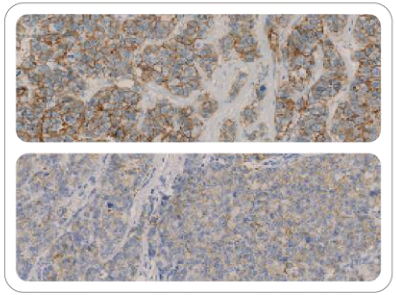
Patented methods for IA/AI based Proficiency Testing APPs.

Optimal

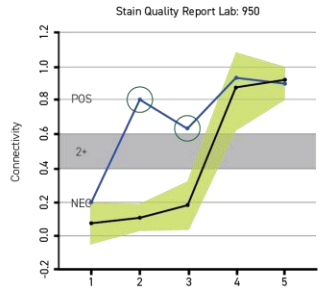


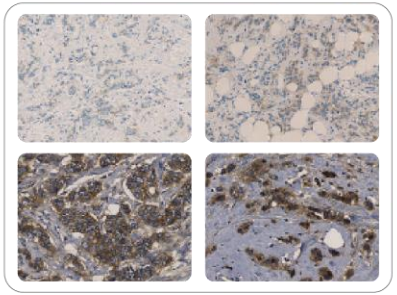
Poor



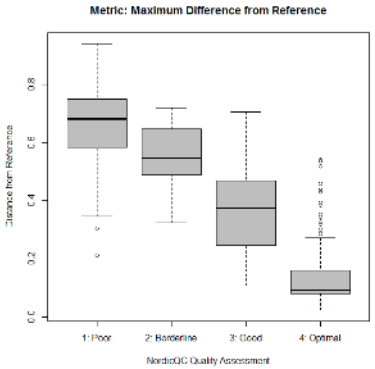


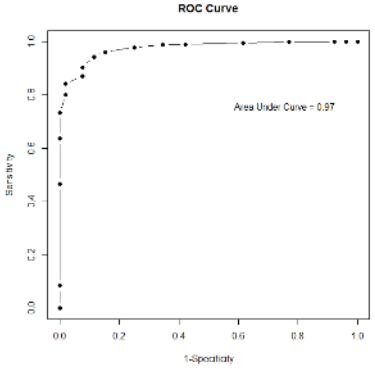
Borderline





Concordance w. EQA





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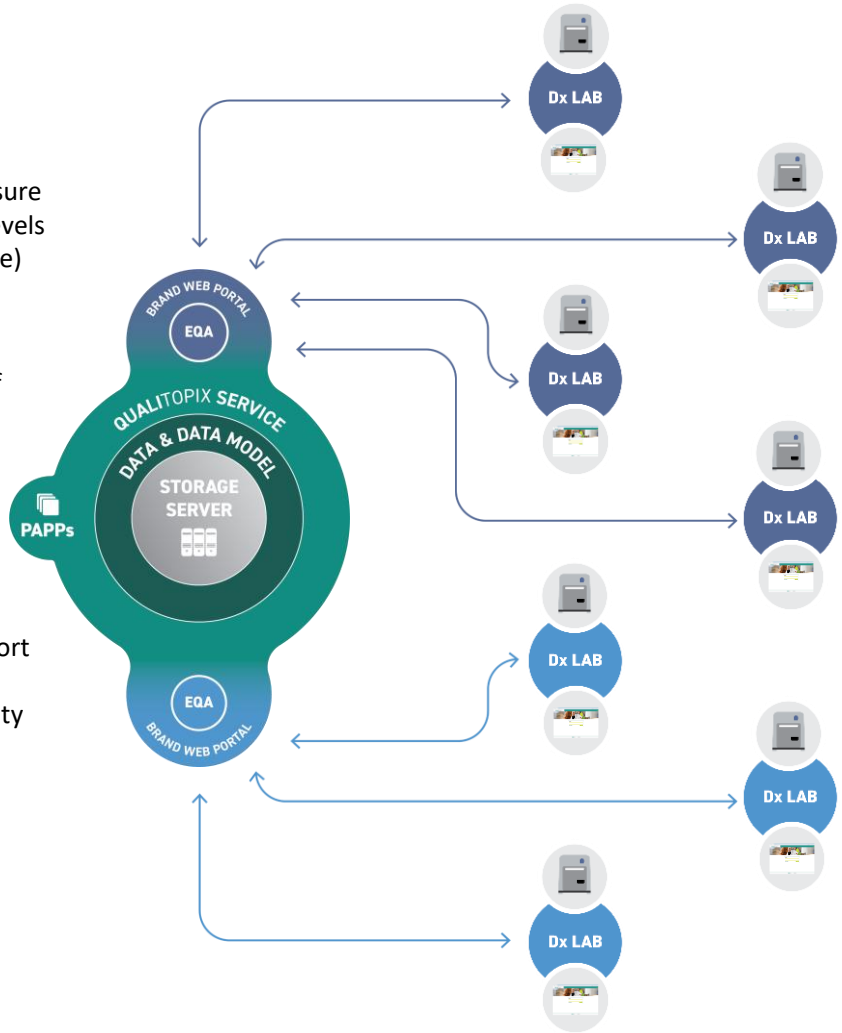
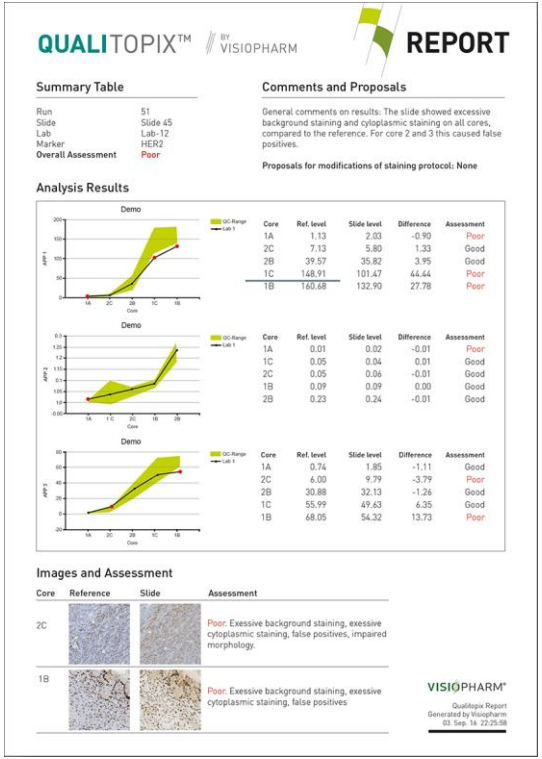
Proficiency testing APPs (PAPPs):

- **Expression levels:** Measure biomarker expression levels on test-slides (multi-core)
- **Distance metric from reference:** Provides a quantitative measure of stain quality
- **Decision support:** Support assessors in providing a grading of staining quality and support a pass/fail decision.





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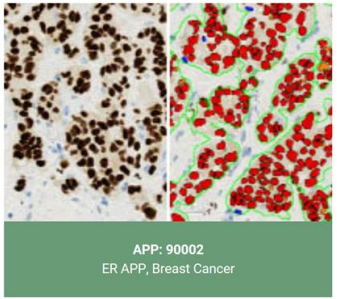
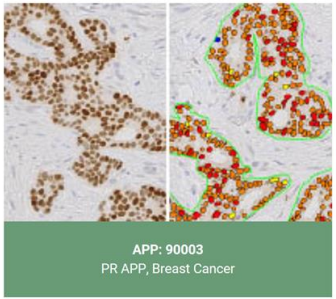
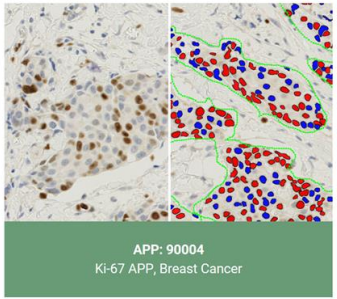
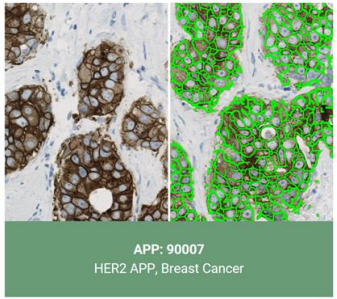
Existing Proficiency Testing APPs (prototypes)









Validated for:	ER	PR	KI67	HER2
Reagents	Dako, Leica, Roche	Dako, Leica, Roche	Dako, Leica, Roche	Dako, Leica, Roche
Scanners	Hamamatsu, Aperio, 3DHistec, Leica, Philips	Hamamatsu, Aperio, 3DHistec, Leica, Philips	Hamamatsu, Aperio, 3DHistec, Leica, Philips	Hamamatsu, Aperio, 3DHistec, Leica, Philips
Types	Tissue & cell	Tissue & cell	Tissue & cell	Tissue & cell

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Next steps

Monitoring & Calibration

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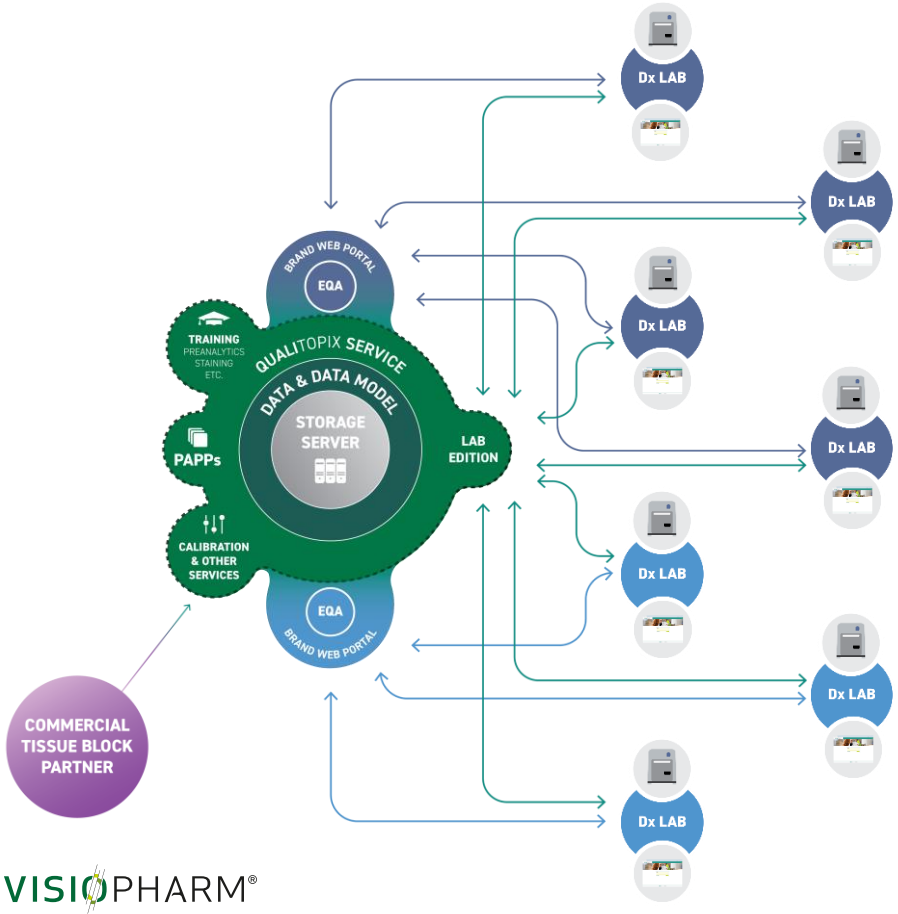
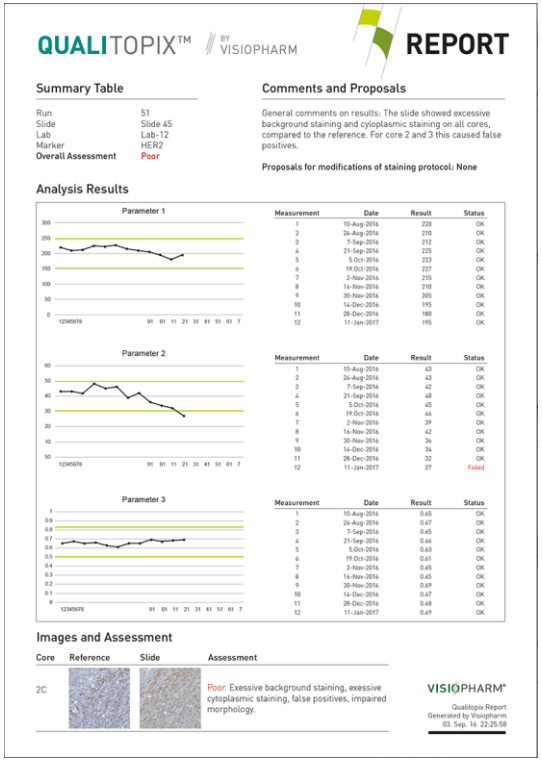
Stain Quality Management: Monitoring?





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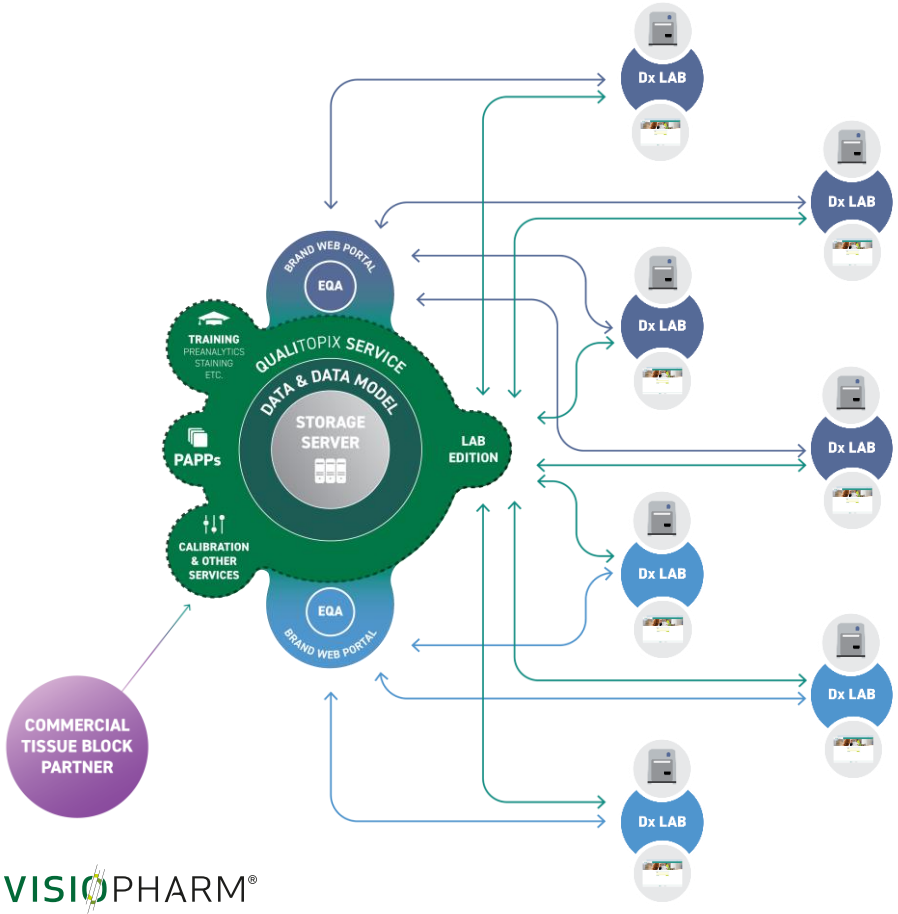
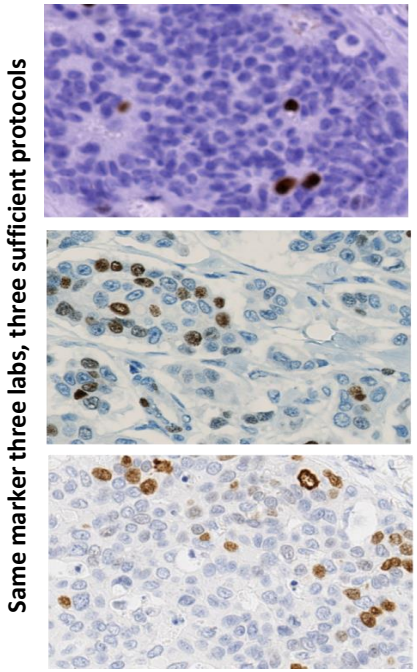
APP Calibration: The missing link?





- **APP Calibration:** Even with optimal stain quality, there are significant differences in the visual appearance of tissue stains. Image analysis APPs require calibration to provide optimal performance.

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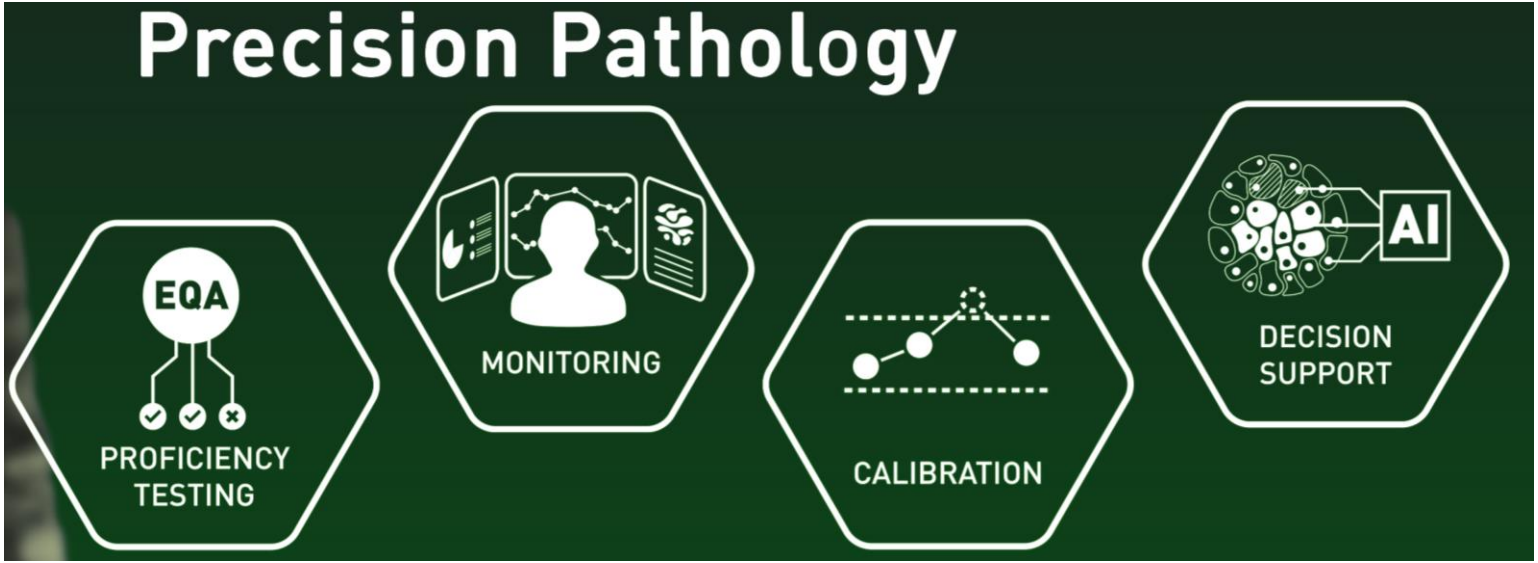

Scalability in Proficiency Testing
Solution for External Quality Assessment organizations requiring true scalability for Quality Schemes and Proficiency Testing.

Continuous Monitoring of Stain Quality
Solution for labs requiring on-demand / continuous measurement of stain quality for monitoring of trends or fluctuations.

APP Calibration
Solution for digitized labs using IA, to ensure optimized performance of IA-APPs wrt to local staining protocols

Decision Support
Solution for digitized labs using IA for cell/region identification, quantification of morphology, subcellular biomarker expression, automated phenotyping

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