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TRANSFORMING PATHOLOGY

Artificial Intelligence and Tissue Pathology in Cancer Healthcare: Why and How?

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Visiopharm Overview & Status

Operational since: **2002**

Headquarters

Hørsholm, Denmark

Subsidiaries

Visiopharm Inc. Denver, CO, USA
Visiopharm AB/ LRI –Malmo, Sweden
Visiopharm Ltd. – London, UK & Ireland

Number of employees: **~90**

Image analysis:

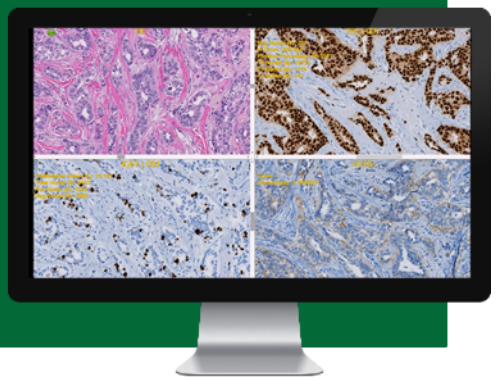
- CE-IVD for diagnostics
- Open & infinitely configurable for research
- AI & Machine Learning
- Scanner agnostic

Medical Device :

- Precision- & High throughput pathology
- CE-IVD
- ISO13485
- LIS/PACS Integration

Footprint

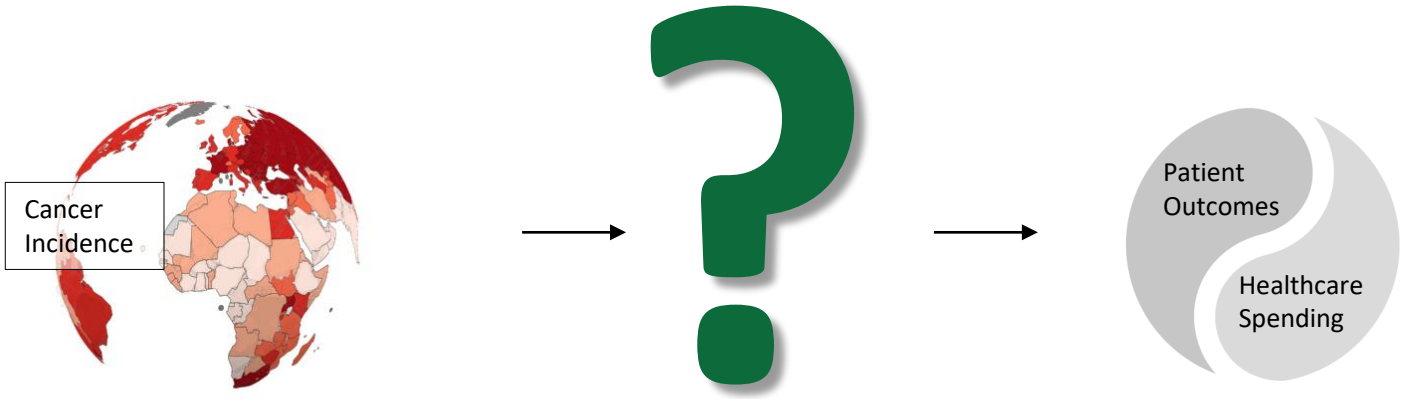
- 750 licenses sold worldwide; over 40 countries
- Countless more users
- 1,500 peer-reviewed publications since 2010



Tissue Pathology in Cancer Drug- Diagnostic Co-Development

The Healthcare Challenge of Our Time

Cancer is a major and growing healthcare challenge



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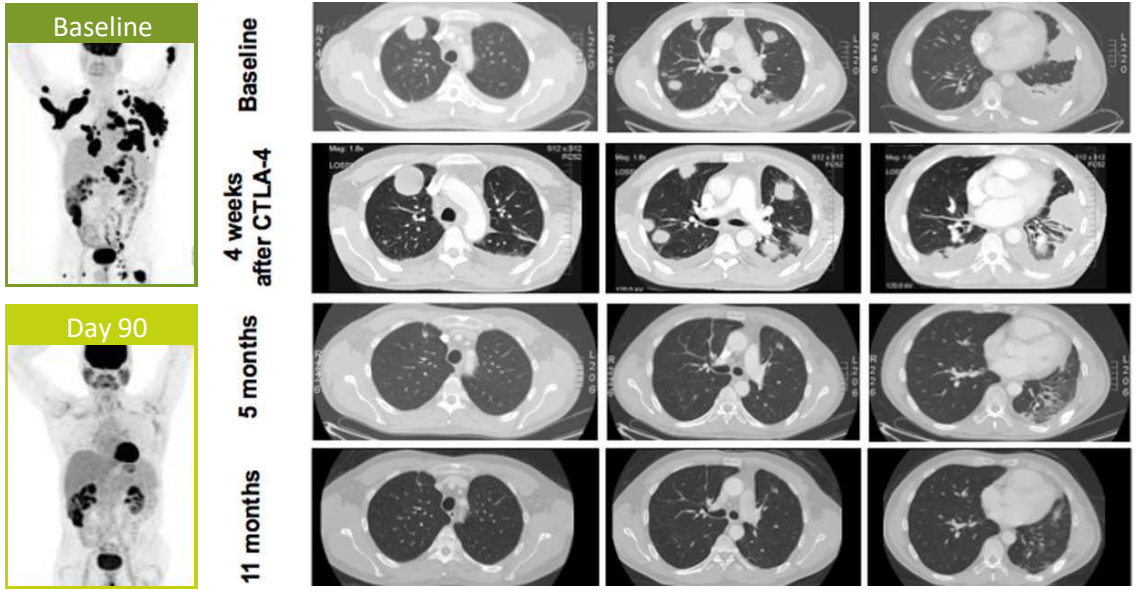
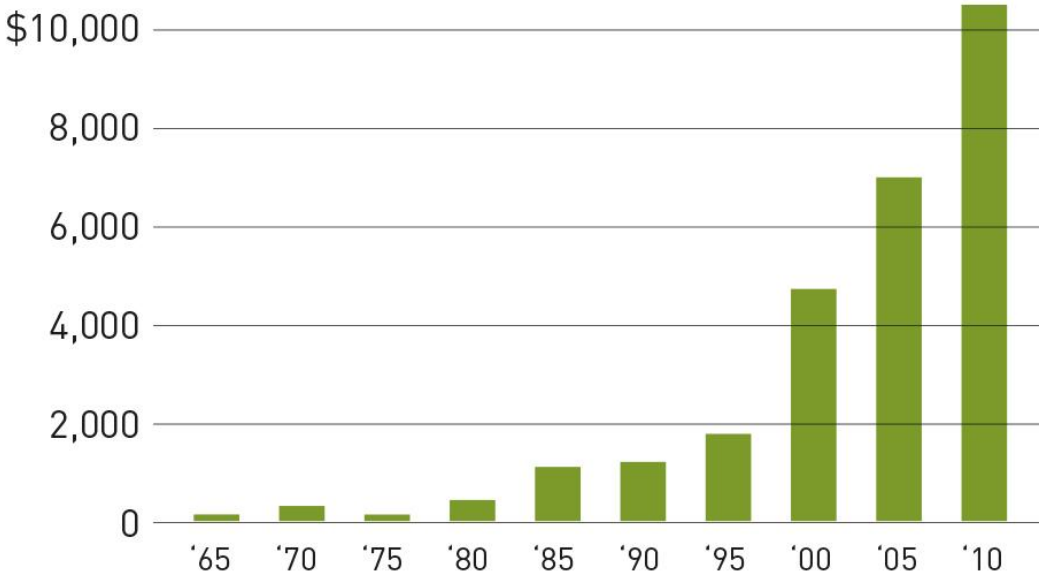
Immunotherapies: A major breakthrough in treatment



- Immunotherapies (checkpoint inhibitors) are showing promise of a cure.
- Many new drugs: Ongoing drug trials probably > 3,000
- Late stage pharma pipeline: > 600 drugs
- Targeted: They work only on a sub-population of patiens

Challenge: New Treatments and Rising Costs

A Month of Meds
Median price* of cancer drugs approved during each five-year period, for a month's supply



*Initial price upon approval, in 2014 dollars
Source: Peter Bach at Memorial Sloan Kettering Cancer Center.
The Wall Street Journal.

Cost of treatment:
Has grown above $10,000 per month

Challenge: Targeted therapies

Companion Diagnostics (CDx): Required to identify the responders to a specific treatment

Precision Medicine: Financially sustainable cancer healthcare requires that we find the right treatment for the right patient and at the right time.

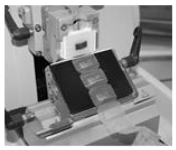
Challenges in achieving Precision Pathology

Tissue-base Cancer Diagnostics

The Journey From Biopsy to Decisions

Main focus

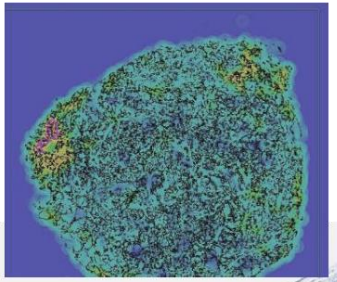
Sampling Variability	Fixatives / fixation	Thickness	Sufficiency / Quality	Inter- & intra reader variablity	
Biopsy	Fixation & embedding	Sectioning	Staining	Assessment	Decision



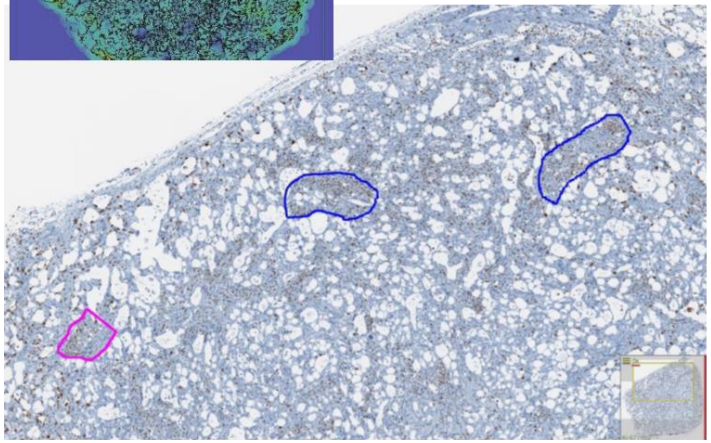
Example: Breast Panel

Cognitive challenges and limitations in Dx reading

Where to read

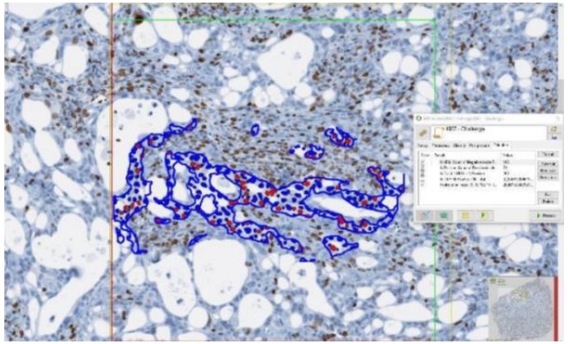


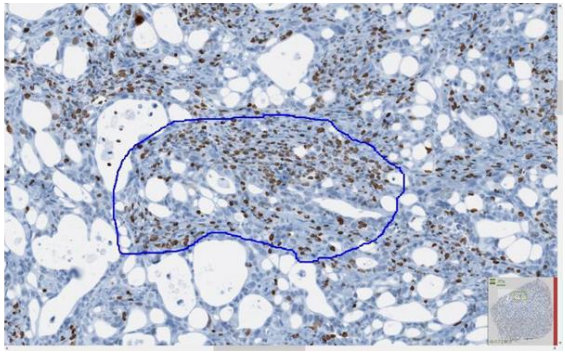
< 50% of pathologists are able to correctly identify the ”hot-spot” required for correctly assessing location and rate of cancer growth.



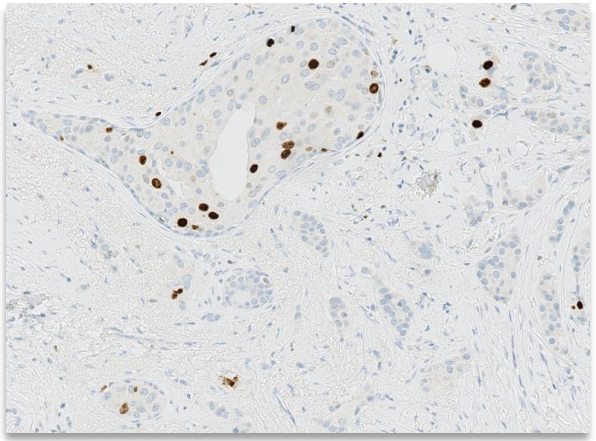
What to read

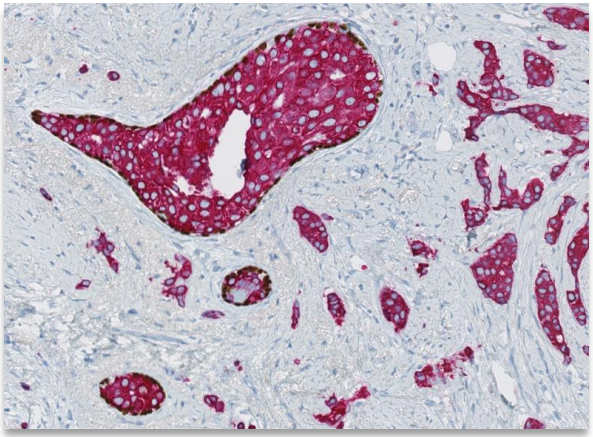
Pathologists are often unable to visually exclude tumor-infiltrating lymphocytes (and pre-invasive cells), resulting in inaccurate diagnostic assessments.

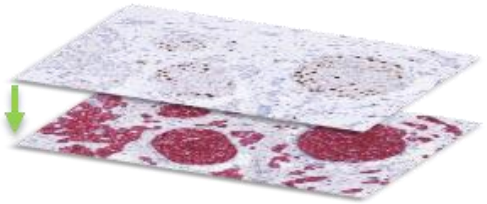




Cognitive challenges and limitations in Dx reading

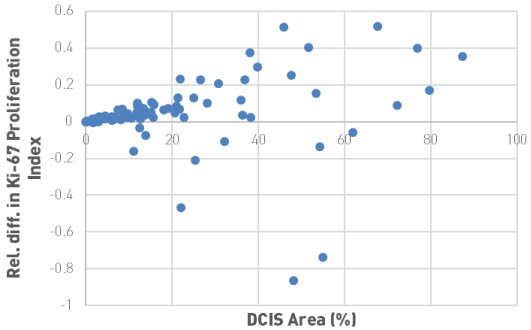






Where & What to read

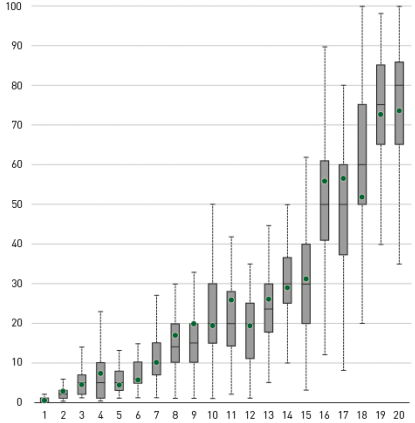
Discriminating between invasive- and pre-invasive tumor is a problem for interpretive accuracy, as well as for molecular diagnostic methods



Challenge: Interpretive Accuracy

Ki-67 Manual Score against Image Analysis

Median of 126 Scores



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

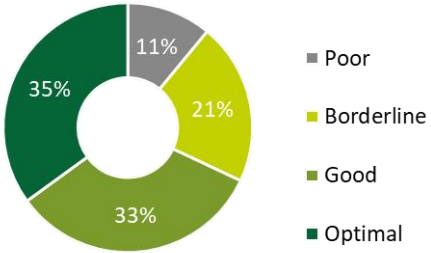
Modern Pathology **29**, 318–329 (2016) | Download Citation

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

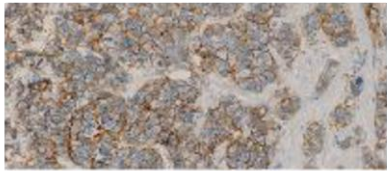
Select 20 tumors: Varying degrees of Ki67 expressions → Create TMA → Selection & stain: Optimized & standardized staining protocol → Scan all 20 Sections (tumors) → Send to 126 pathologists for reading (Global & Hot-spot) → Collect dataset for analysis

Insufficient staining quality is surprisingly common

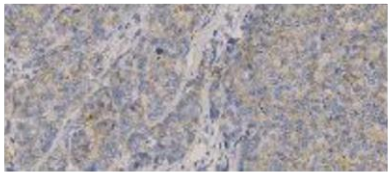
Staining quality



LAB A: Sufficient staining



LAB B: Insufficient staining



Two sections from same breast cancer patient, stained with HER2 at two different labs.

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.

In-sufficient manually staining may lead to

- Diagnostic inaccuracy
- Ineffective/harmful treatment
- Ineffective healthcare spending

Problems: Impact on Interpretive Accuracy

Multiplicative error!

<70% pass rate

<70% correct Dx classification

Main focus

Sampling Variability → Biopsy

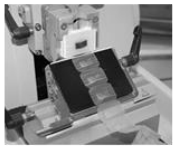
Fixatives / fixation → Fixation & embedding

Thickness → Sectioning

Sufficiency / Quality → Staining

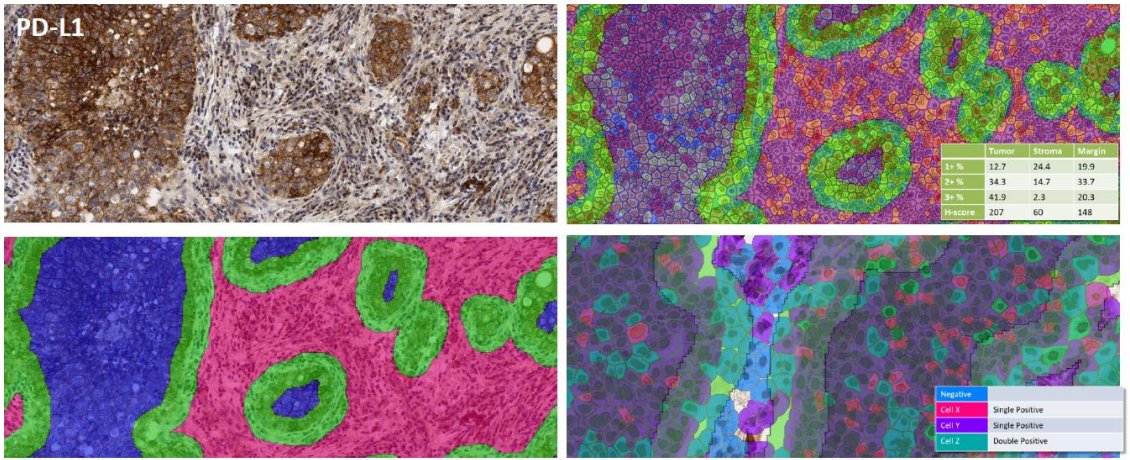
Inter- & intra reader variablity → Assessment

Decision



Example: Breast Panel

Complexity of future Dx Biomarkers will be overwhelming



- Targeted therapies are costly (fx.: AstraZenca's Imfinzi cost > MDKK 1.0 million/patient for one year's treatment).
- Complexity of new companion diagnostics will be a challenge to manual reading & interpretation
- Lack of diagnostic accuracy can result in costly, inefficient and potentially harmful treatments.

Future Companion Diagnostic biomarkers are too complex for manual reading.

Tools for precision pathology will be critical to precision pathology and, as such, a pre-requisite to sustainable healthcare in the future of targeted therapies

Artificial Intelligence & Diagnostic Decision Support

Augmenting Pathologists

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Artificial Intelligence

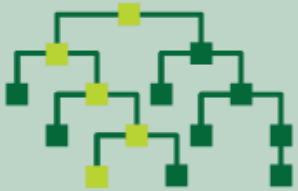
An overview

Artificial Intelligence

Any technique that enables computers to mimic human behavior.

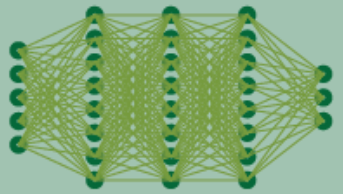
Machine Learning

The ability to learn without directly being programmed.



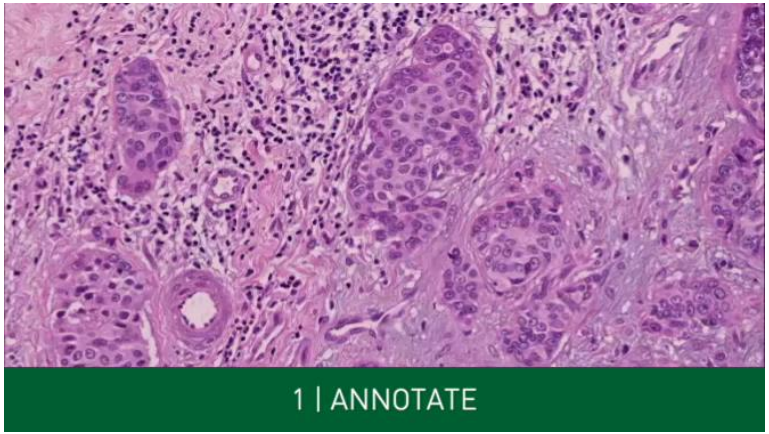
Deep Learning

The learning of underlying features in data using deep neural networks.

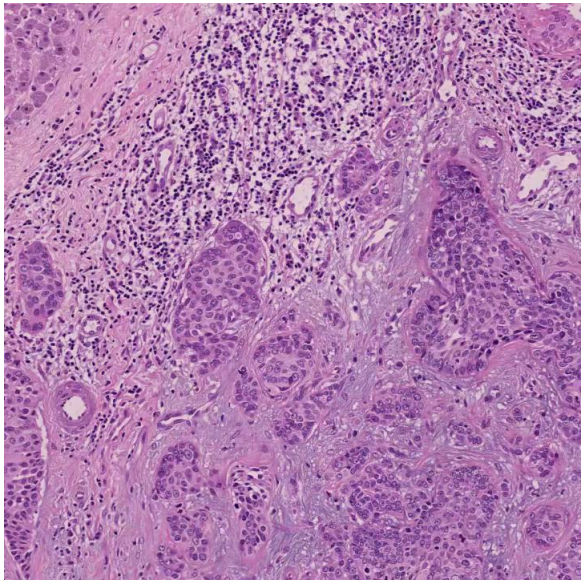


Artificial Intelligence & Deep Learning in Image Analysis

Teach by example



Training



Calculation/estimation of probability map

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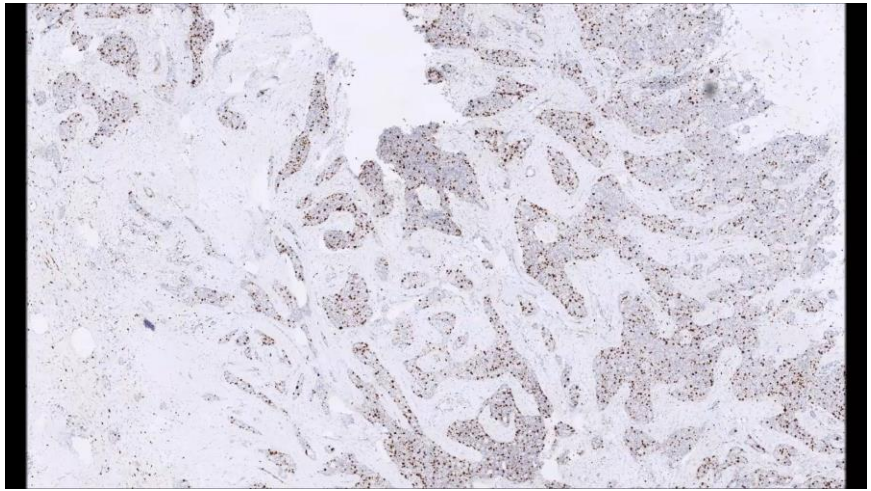
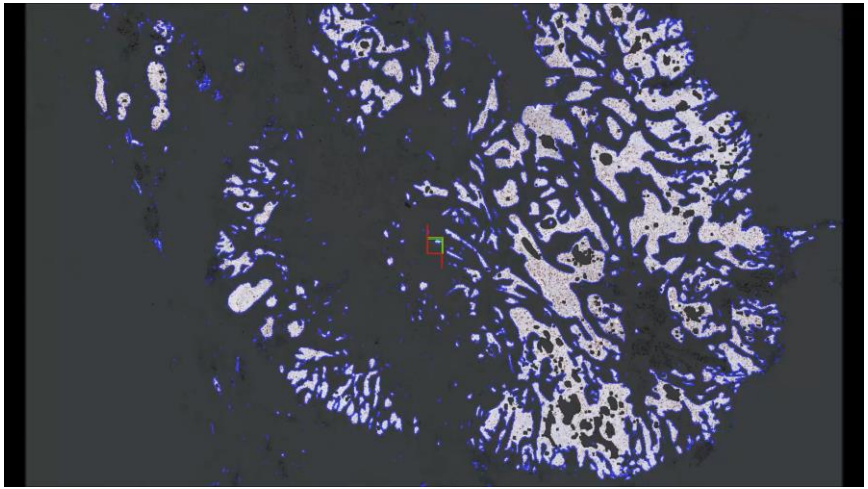
Automated identification of invasive components & hot-spots



Automated & standardized biomarker quantification



Solutions: Impact on Interpretive Accuracy

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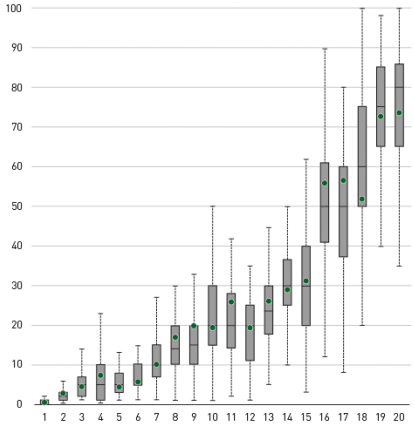
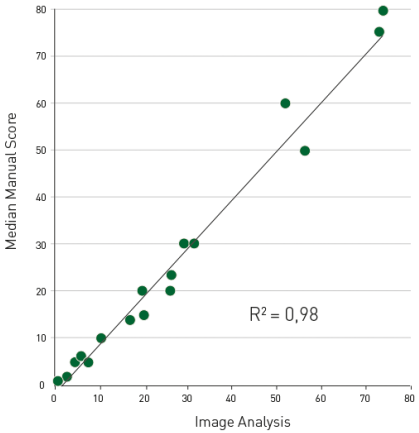
Median of 126 Scores





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

% mis-classifiction dropped from ~30% to at least 19% using IA

KAROLINSKA INSTITUTET ANNO 1810

NordiQC

Select 20 tumors: Varying degrees of Ki67 expressions → Create TMA → Selection & stain: Optimized & standardized staining protocol → Scan all 20 Sections (tumors) → Send to 126 pathologists for reading (Global & Hot-spot) → Collect dataset for analysis

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Diagnostic Digital Pathology

Documented Performance Improvements

Automated and correct elimination of stromal- and

MODERN PATHOLOGY (2016), 1–12

Digital image analysis outperforms manual biomarker assessment in breast cancer

Gustav Stålhammar[1,2], Nelson Fuentes Martinez[1,3], Michael Lippert[4], Nicholas P Tobin[5], Ida Mølholm[4,6], Lorand Kis[7], Gustaf Rosin[1], Mattias Rantalainen[8], Lars Pedersen[4], Jonas Bergh[1,5,9], Michael Grunkin[4] and Johan Hartman[1,5,7]

[1]Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden; [2]St Erik Eye Hospital, Stockholm, Sweden; [3]Södersjukhuset, Stockholm, Sweden; [4]Visiopharm A/S, Hoersholm, Denmark; [5]Cancer Center Karolinska, Stockholm, Sweden; [6]Department of Applied Mathematics and Computer Science, Technical University of Denmark, Kongens Lyngby, Denmark; [7]Department of Clinical Pathology, Karolinska University Hospital, Stockholm, Sweden; [8]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden and [9]Department of Oncology, Karolinska University Hospital, Stockholm, Sweden

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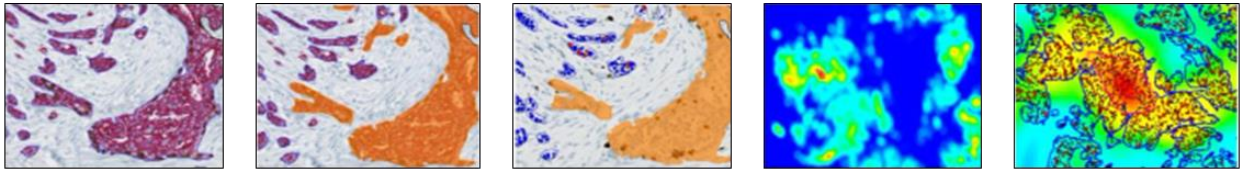
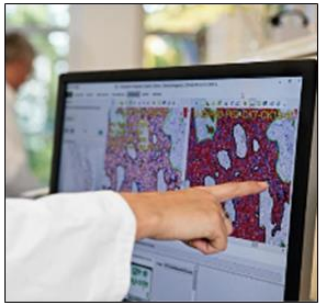


Example with Ki67 marker: Automated detection of invasive tumor cells, elimination of pre-invasive / stromal cells, identification of invasive tumor front ant hot-spots, quantification of sub cellular biomarkers

Precision pathology: Providing automated, accurate and verifiable diagnostic decision support for standardizing tissue morphometry and biomarker assessment

High Throughput pathology: Automation in diagnostic workflows, resulting in shorter turn-around times at lower cost

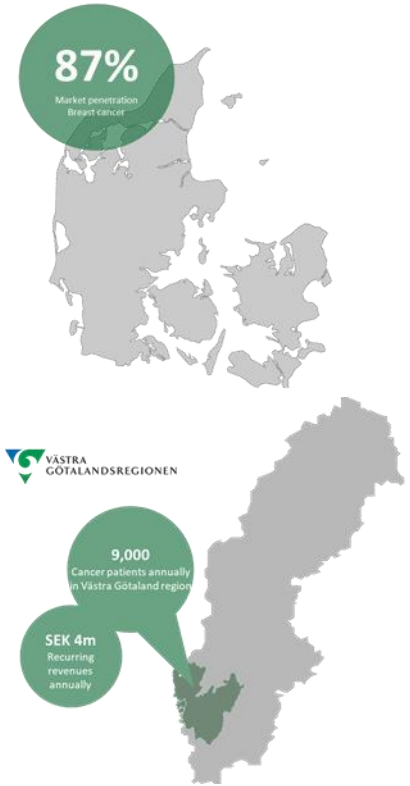
Plug-in to existing workflows: seamless integration to data management and workflow systems at the pathology lab (LIS and PACS systems)

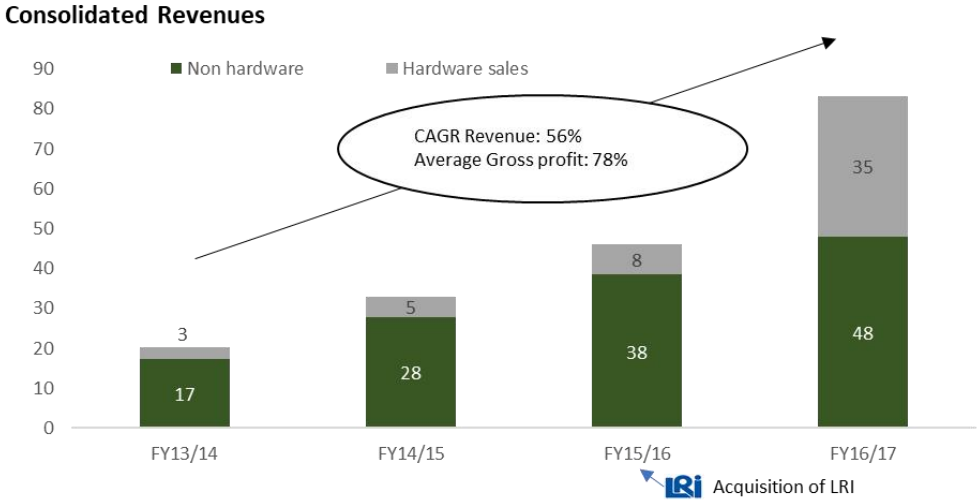


Powered by patented & cutting edge image analysis and artificial intelligence technology

Growth in Research & Diagnostic Applications

Breast cancer: 15% of all cases





"We feel the system is robust and mature enough to be used in the routine", says **Dr. Eva Balslev**, Senior Pathologist at Herlev University Hospital

"We have been able to document improved reproducibility and diagnostic accuracy of diagnostic readings", says **Professor Mogens Vyberg**, Chief Consultant of the Pathology Department at Aalborg University Hospital

"We are lacking pathologists and have to use our time in the best possible way making the diagnosis in the most optimal way and at the lowest cost" says **Dr. Anne Marie Bak Jylling**, Associate Prof. at Odense University Hospital