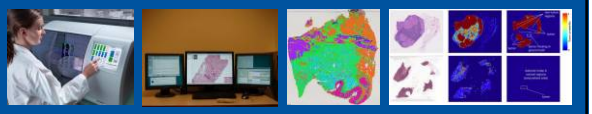
Computational pathology in breast cancer

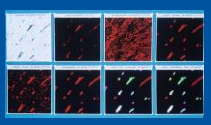


Paul J van Diest, MD, PhD
Professor and Head, Department of Pathology
University Medical Center Utrecht
The Netherlands
Professor of Oncology
Johns Hopkins Oncology Center
Baltimore, MD, USA
Visiting professor
University of Siena, Italy

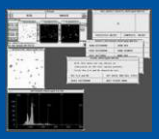
Disclosures: none

Image analysis on traditional slides

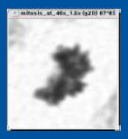
Examples of nice ñoldò image analysis applications



microvessels



DNA cytometry



mitoses

Ariol (Applied Imaging)

PAPNET

TriPath

Image analysis on traditional slides

So

image analysis raised high hopesé é

é .but not much of it made it to clinical practiceé ..

Why?

Image analysis on traditional slides

Why not the expected breakthrough?

Åslow computers
Åslow automated microscopes
Åslow cameras
Åselective approach
Åspecial stains required
Åimpractical (workflow)

Årise of immunohistochemistry
Årise of molecular pathology (gene expression arrays)

Image analysis on virtual slides

So:

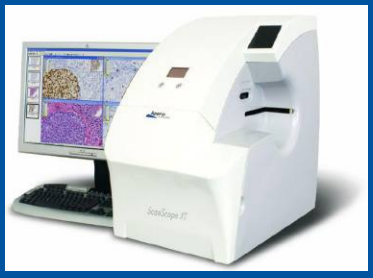
Why the revival?

Can we do better this time?

Scanners!

Fast: < 1 min
40x resolution
Fluorescence
Big slides

→ 1-4 GB files



The case for computational pathology

- Treatment of patients more dependable on pathology
- Parts of our work are not reproducible enough
- Errors are far less accepted
- Increasing workload
- Shrinking pathology crowd
- Awareness of costs/limitations of gene expression tests

The case for computational pathology

Computational pathology

- More reproducible
  → better patient care
- More efficient
  → more work with same people
- Compete better with gene arrays
  → more business
- More inspiring (less boring)
  - increased quality of life of pathologists/residents

The case for computational pathology

IBM's Watson Supercomputer May Soon Be The Best Doctor In The World

Lauren F Friedman
Apr. 22, 2014, 10:14 AM 54,746

It's based on all available medical knowledge. Human doctors can't possibly hold this much information in their heads, or keep up it as it changes over time. Dr. Watson knows it all and never overlooks or forgets anything.

It's accurate. If Dr. Watson is as good at medical questions as the current Watson is at game show questions, it will be an excellent diagnostician indeed.

It's consistent. Given the same inputs, Dr. Watson will always output the same diagnosis. Inconsistency is a surprisingly large and common flaw among human medical professionals, even experienced ones. And Dr. Watson is always available and never annoyed, sick, nervous, hungover, upset, in the middle of a divorce, sleep-deprived, and so on.

It has very low marginal cost. It'll be very expensive to build and train Dr. Watson, but once it's up and running the cost of doing one more diagnosis with it is essentially zero, unless it orders tests.

It can be offered anywhere in the world. If a person has access to a computer or mobile phone, Dr. Watson is on call for them.

The case for computational pathology

- If the world is about to change, better change it yourself!
- Opportunity, not threat
- Deliver the best quality with added value = job security
- Radiology has not been taken over by low income countries

Image analysis on virtual slides

Why the revival?

- fast computers
- fast high resolution whole slide scanners
- excellent convoluted neural network tools
- whole slides available instead of selected areas
- available on the desk/screen of the pathologist

PS: not essentially different (just larger files)!

Image analysis on virtual slides

Integration into workflow

- can slides before they leave the lab
- allow immediate analysis by pathologist

or even .

- preanalyze scanned slides in the background
- present results at the time pathologist opens the case

Breast cancer computational pathology

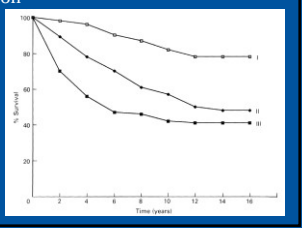
Applications

Å*objectify grading of invasive cancer*
Åobjectify grading of DCIS
Åfind lymphovascular invasion
Åquantitate immune infiltrate
Åquantitate ER, PR, HER2, Ki67
Åfinding metastases in lymph nodes
Åmolecular pathology

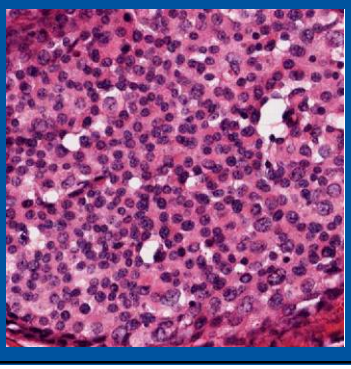
Breast cancer grading

Åprognostically strong
Åreproducibility problem

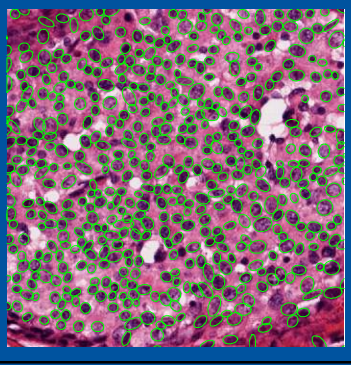
→ quantitate % tubule formation
→ quantitate nuclear size
→ quantitate mitoses



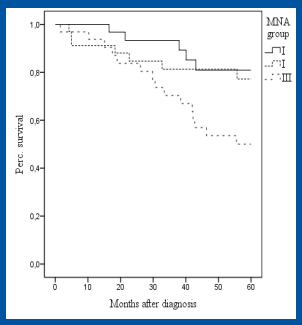
Nuclear segmentation on a breast cancer virtual slide



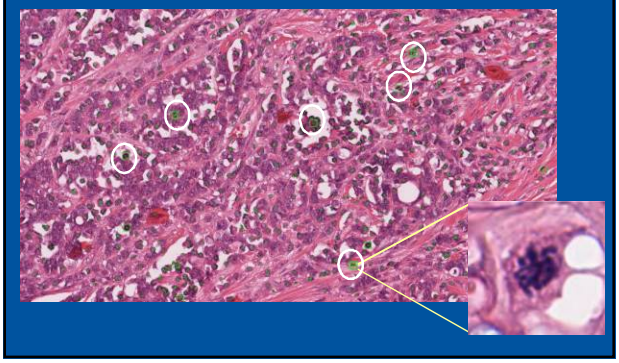
Nuclear segmentation on breast cancer virtual slides



Nuclear segmentation on breast cancer virtual slides



Mitosis segmentation on a breast cancer virtual slide



Mitoses segmentation on breast cancer virtual slides

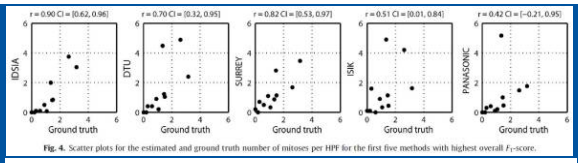


Fig. 4. Scatter plots for the estimated and ground truth number of mitoses per HPF for the first five methods with highest overall F_1-score.

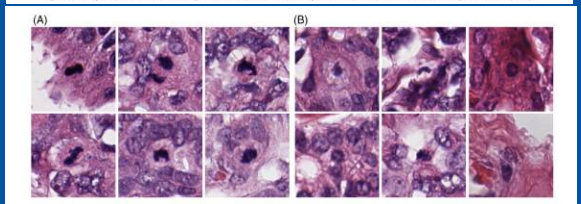


Fig. 5. Examples of the most commonly detected and missed mitotic figures. (A) Mitotic figures that were detected by most (at least ten) of the proposed methods. (B) Mitotic figures that were not detected by any of the proposed methods.

Breast cancer computational pathology

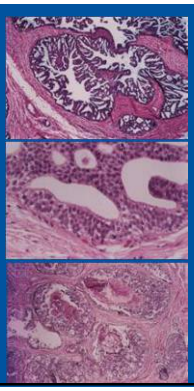
Applications

- objectify grading of invasive cancer
- *objectify grading of DCIS*
- find lymphovascular invasion
- quantitate immune infiltrate
- quantitate ER, PR, HER2, Ki67
- finding metastases in lymph nodes
- molecular pathology

DCIS grading

- prognostically strong
- reproducibility problem

→ quantitate architecture
→ quantitate nuclear size
→ quantitate necrosis



Breast cancer computational pathology

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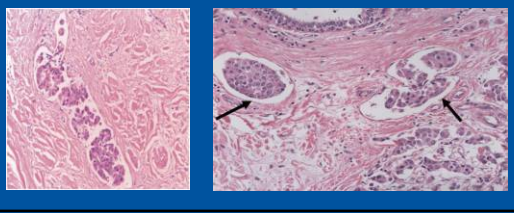
- molecular pathology

Detecting lymphovascular invasion

- important risk factor for radiation oncologist
- not always easy to find without IHC



Breast cancer computational pathology

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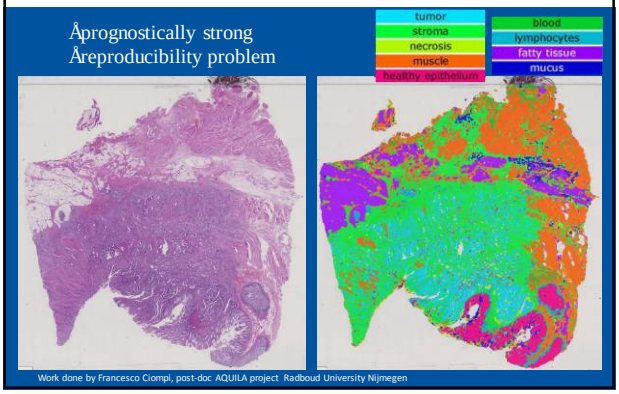
- molecular pathology

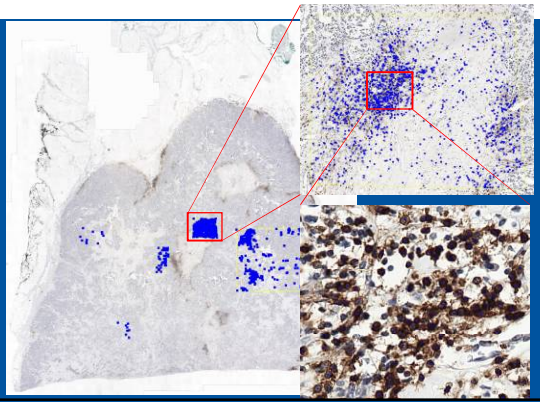
Immune infiltrate quantitation

- prognostically strong
- reproducibility problem



Work done by Francesco Ciompi, post-doc AQUILA project Radboud University Nijmegen

Immune infiltrate quantitation



Breast cancer computational pathology

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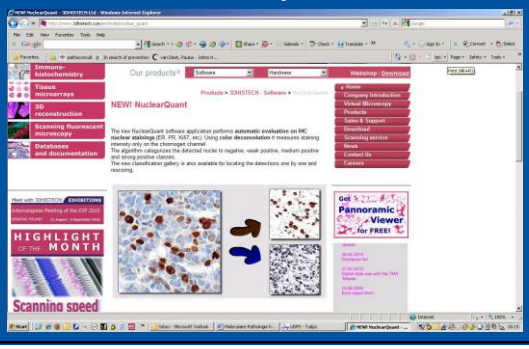
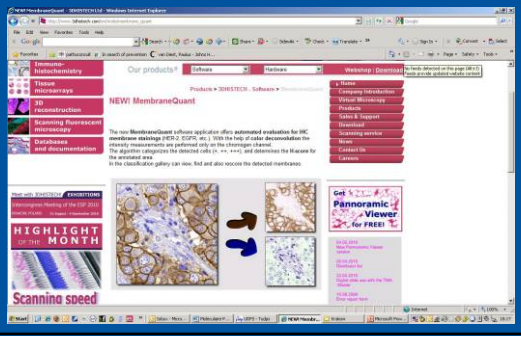
ER/PR/Ki67 quantitation in breast cancer

Nuclear Quant



HER2 quantitation in breast cancer

MembraneQuant



FISH quantitation in breast cancer

FISH Quant

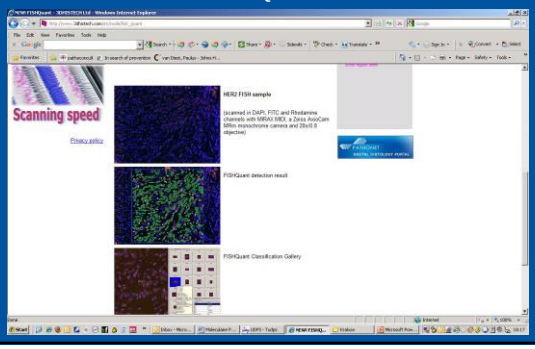


Image analysis on virtual slides: certification

Table 1 FDA 510k Approved Automated Image Analysis Systems and their performance

Manufacturer	System	Approved use	Assay	Sample size	Automated vs manual score % concordance
Genetix	Ariol	HER-2	DAKO HercepTest	124	[a]
		HER-2 (FISH)	Abbott Vysis PathVysion DNA Probe kit	82	98
		ER	Kisight nuclear IHC	75	93.2–98.6[b]
		PR	Kisight nuclear IHC	75	84.4–96.1[b]
TriPath Imaging	VIAS	HER-2	Ventana PATHWAY anti-HER-2/neu (clone cb11)	201	77
		HER-2	PATHWAY (4B5)	206	86
		PR	Ventana anti-ER	210	88.2–94.1[b]
		ER	Ventana anti-PR	210	94.6–98.5[b]
		P53	Ventana CONFIRM anti-p53	204	86–98[b]
		Ki67	Ventana anti-Ki-67	207	88.4–97[b]
Chromavision	ACIS	HER-2	DAKO HercepTest	90	75
		ER&PR	No data	No data	No data
Cell analysis	QCA	ER	DAKO Cytomation (1D5)	192	85.15
BioImagene	PATHIAM	HER-2	DAKO HercepTest	176	80.4
Aperio	ScanScope XT System	HER-2	DAKO HercepTest	180	86.5

[a] In general, the likelihood of the image analysis systems to produce a consistent score on a given slide is as likely as the pathologists are to agree with each other

[b] Depending on cut-off thresholds of pos ≥1, 5 or 10% positive stained tumour cells

Conway et al. Histochem Cell Biol 2008

Breast cancer computational pathology

Applications

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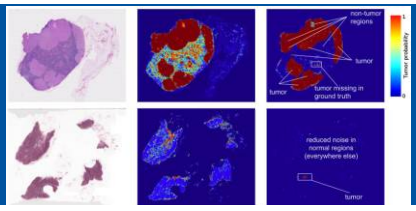
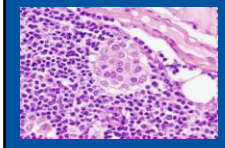
- Åfind lymphovascular invasion
- Åquantitate immune infiltrate
- Åquantitate ER, PR, HER2, Ki67
- Å*finding metastases in lymph nodes*
- Åmolecular pathology

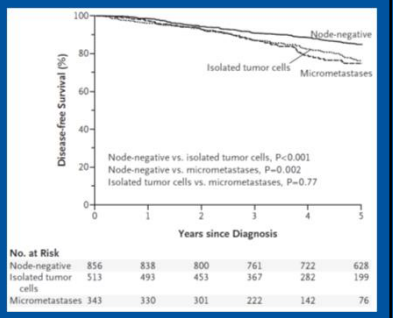
Detecting lymph node metastases



Input & model size	Validation FROC	Validation @8FP	Validation AUC	Test FROC	Test @8FP	Test AUC
40X	98.1	100	99.0	**87.3** (83.2, 91.1)	**91.1** (87.2, 94.5)	**96.7** (92.6, 99.6)
40X-pretrained	99.3	100	100	**85.5** (81.0, 89.5)	**91.1** (86.8, 94.6)	**97.5** (93.8, 99.8)
40X-small	99.3	100	100	**86.4** (82.2, 90.4)	**92.4** (88.8, 95.7)	**97.1** (93.2, 99.8)
ensemble-of-3	-	-	-	**88.5** (84.3, 92.2)	**92.4** (88.7, 95.6)	**97.7** (93.0, 100)
20X-small	94.7	100	99.6	**85.5** (81.0, 89.7)	**91.1** (86.9, 94.8)	**98.6** (96.7, 100)
10X-small	88.7	97.2	97.7	79.3 (74.2, 84.1)	84.9 (80.0, 89.4)	**96.5** (91.9, 99.7)
40X+20X-small	94.9	98.6	99.0	**85.9** (81.6, 89.9)	**92.9** (89.3, 96.1)	**97.0** (93.1, 99.9)
40X+10X-small	93.8	98.6	100	82.2 (77.0, 86.7)	87.6 (83.2, 91.7)	**98.6** (96.2, 99.9)
Pathologist [1]	-	-	-	73.3*	73.3*	**96.6**
Camelyon16 winner [1,23]	-	-	-	80.7	82.7	**99.4**

Detecting lymph node metastases





Workflow integration

Example of fully integrated mitoses recognition algorithm

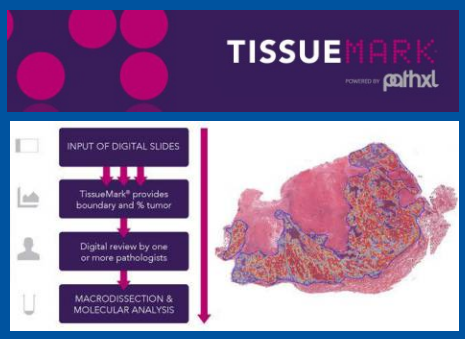
- Automatic kick in based on data mining of LMS and PALGA
- Runs in the background
- Finds the slides containing tumor
- Segments the tumor
- Finds possible mitoses
- Shows heat map of possible mitoses
- Visually confirm most mitoses rich area
- Visual check or count in defined area

Breast cancer computational pathology

Applications

- Åobjectify grading of invasive cancer
- Åobjectify grading of DCIS
- Åfind lympohovascular invasion
- Åquantitate immune infiltrate
- Åquantitate ER, PR, HER2, Ki67
- Åfinding metastases in lymph nodes
- *Åmolecular pathology*

Molecular pathology



Business case

No extra money for digital pathology?

Åalgorithms must be cheap

Åpay reasonable amount per view

Åclear gain in efficacy

Business case

The case for ER

Å60% = 100% positive
Å30% = 0% positive

→ Quantitation useful in ~ 10% of cases
→ Volume of 200 / year ~ 20 cases eligible
→ Algorithms must be cheap
→ Pay per view?

Business case

The case for HER2

Å75-80% = 0-1+
Å10% = 3+

→ Quantitation useful in ~ 10-15% of cases
→ Volume of 200 / year ~ 20-30 cases eligible
→ Algorithms must be cheap
→ Pay per view?

Business case

The case for finding lymph node metastases

Ågoing through slides takes~15 min
ÅIHC if negative
Åwith deep learning ~5 min

→ 10 min pathologistôs time could be saved = ~ 13-24 euro
→ Volume of 200 / year ~ 200 cases eligible ~ 4,000 euro
→ IHC saved in 10% of cases = ~ 250 euro ~ 2,500
→ Purchase becomes interesting

Conclusions

Ågrowing gamma of deep learning algorithms in breast pathology

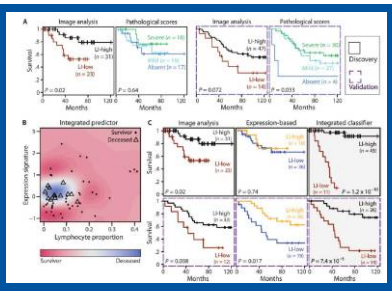
Åimprove the quality of work of the pathologist

Åimproves diagnosis and treatment of (cancer) patients

Åworkflow integration is crucial

Åbusiness case needs to be worked out

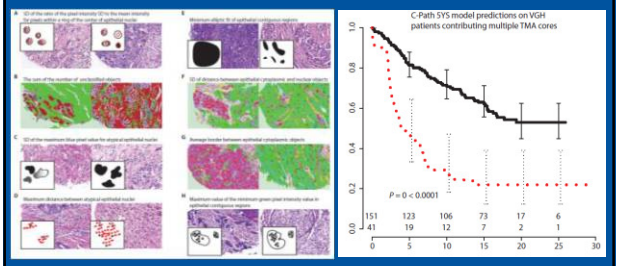
Global image analysis



Quantitative Image Analysis of Cellular Heterogeneity in Breast Tumors Complements Genomic Profiling

Yinyin Yuan,[1,2,+] Henrik Failmezger,[3,4‡] Oscar M. Rueda,[1,2‡] H. Raza Ali,[1,2‡] Stefan Gräf,[1,2‡] Suet-Feung Chin,[1,2] Roland F. Schwarz,[1,2] Christina Curtis,[5] Mark J. Dunning,[1] Helen Bardwell,[1] Nicola Johnson,[6] Sarah Doyle,[6] Gulisa Turashvili,[7,8] Elena Provenzano,[6,9] Sam Aparicio,[7,8] Carlos Caldas,[1,2,9,10] Florian Markowetz[1,2,*]

Global image analysis



Systematic Analysis of Breast Cancer Morphology Uncovers Stromal Features Associated with Survival

Andrew H. Beck,[1,2,*] Ankur R. Sangoi,[1,2] Samuel Leung,[2] Robert J. Marinelli,[2] Torsten O. Nielsen,[3] Marc J. van de Vijver,[4] Robert B. West,[5] Matt van de Rijn,[5] Daphne Koller[1,2]