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TURNING IMAGES INTO KNOWLEDGE

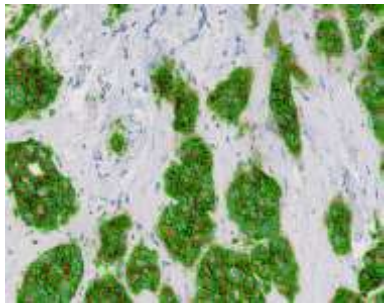
Omnyx
A GE Healthcare and UPMC Venture

HER2 Protein Expression in Breast Cancer: Membrane Morphology and Accuracy wrt. Gene Amplification

Presented by Michael Grunkin, PhD
CEO & Founder of Visiopharm
mgr@visiopharm.com

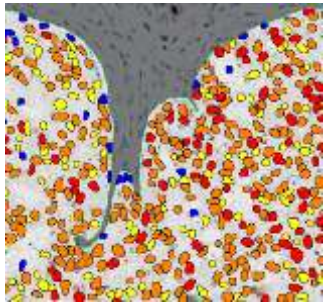
The Breast Panel

Assessment of Her2 Protein Expression



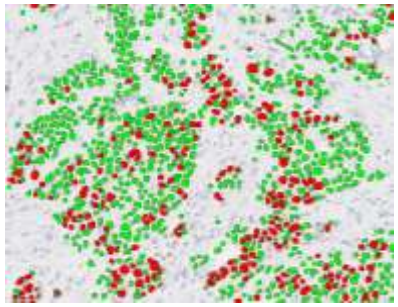
CE IVD

Hormone Receptors



CE IVD

Assessment of Ki67



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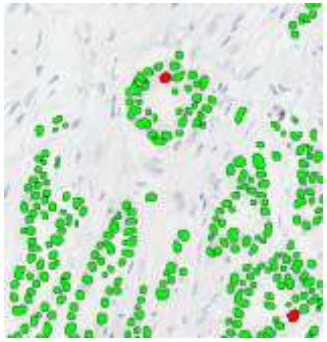
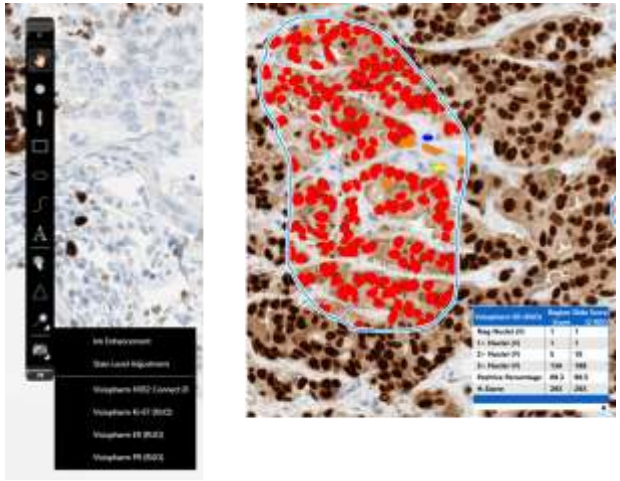
Mitotic Counting



CE IVD

Validated for Dako, Leica, and Venata stainer platforms

Omnyx & Visiopharm Partnership:



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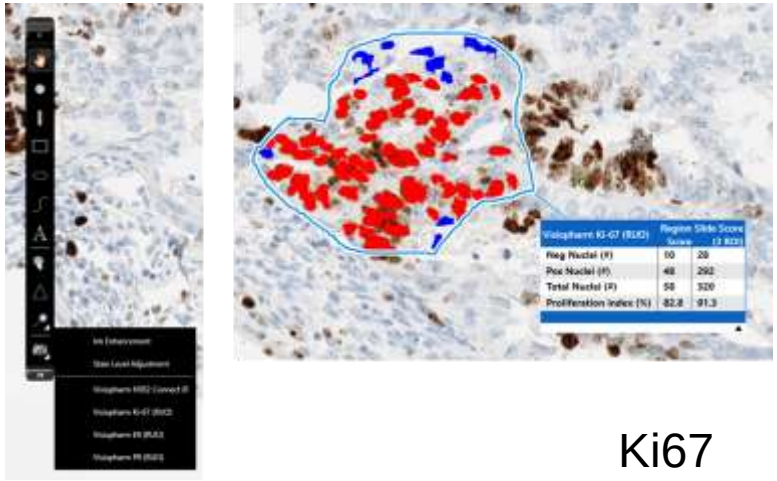
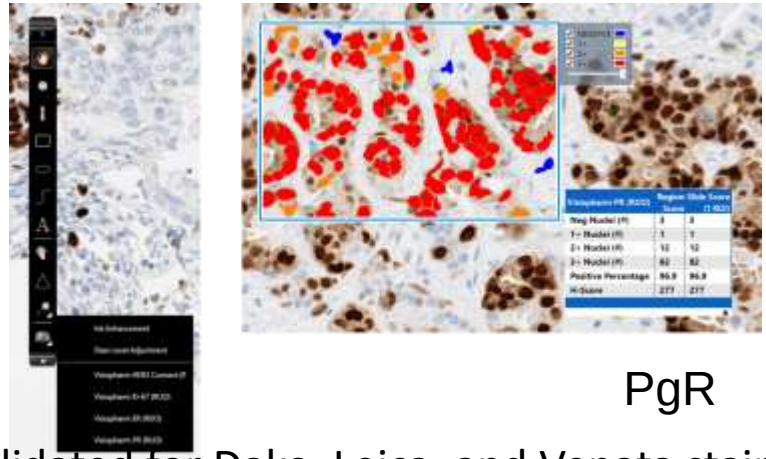
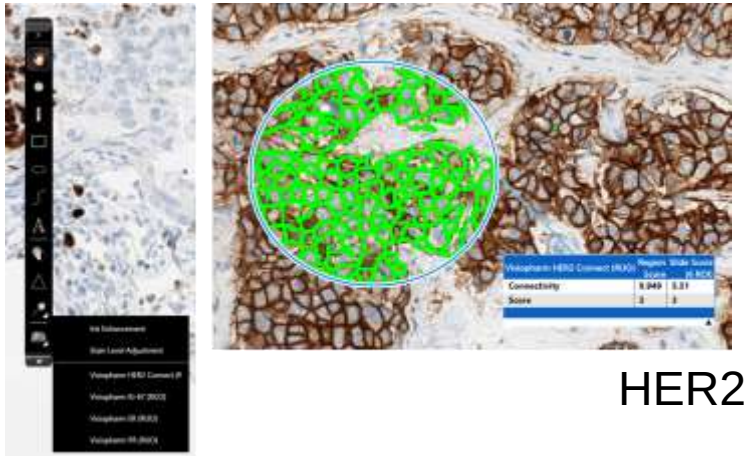


Ki67

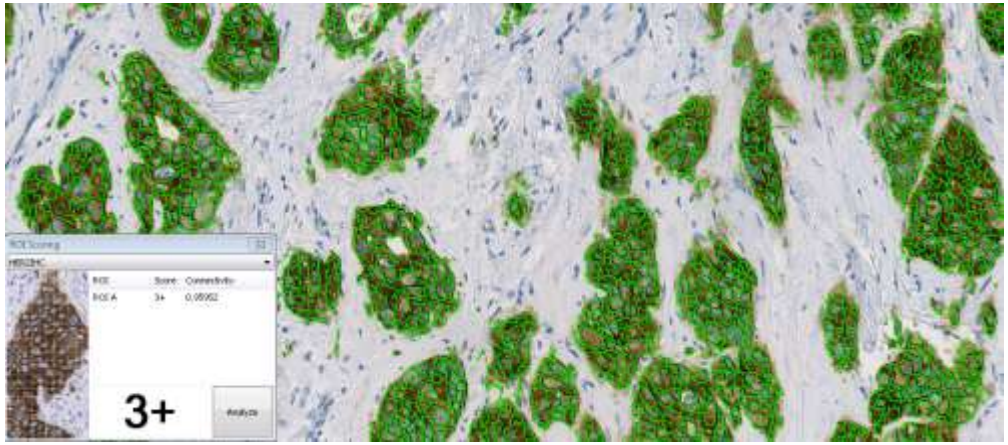


PgR



HER2

Validated for Dako, Leica, and Venata stainer platforms



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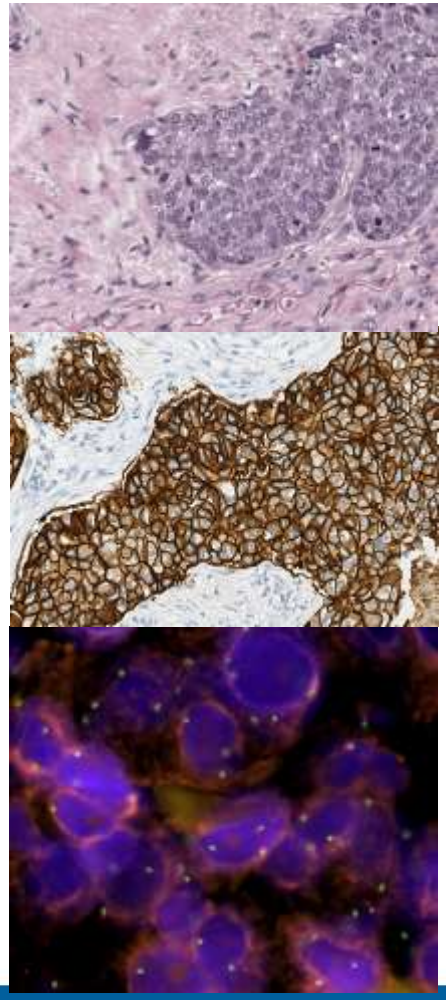
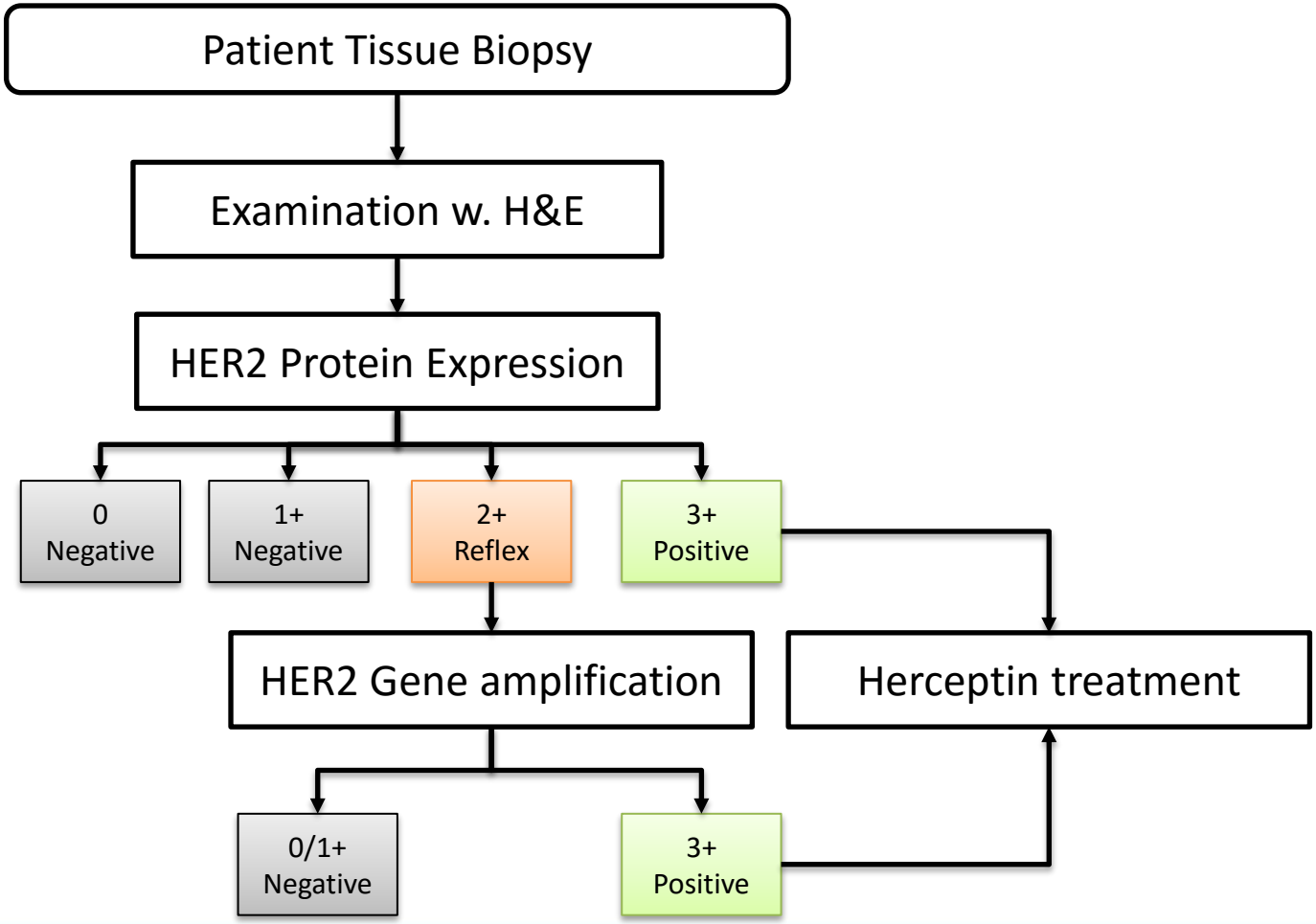
HER2: Why do we need another algorithm?

On the importance of HER2 testing





VOLUME 31 · NUMBER 31 · NOVEMBER 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update

Antonio C. Wolff, M. Elizabeth H. Hammond,* David G. Hicks,* Mitch Dowsett,* Lisa M. McShane,* Kimberly H. Allison, Donald C. Allred, John M.S. Bartlett, Michael Bilous, Patrick Fitzgibbons, Wedad Hanna, Robert B. Jenkins, Pamela B. Mangu, Soonmyung Paik, Edith A. Perez, Michael F. Press, Patricia A. Spears, Gail H. Vance, Giuseppe Viale, and Daniel F. Hayes**

Author affiliations appear at the end of this article.

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*Steering Committee member

American Society of Clinical Oncology Clinical Practice Guideline Committee approval: April 26, 2013; College of American Pathologists approval: June 21, 2013.

Editor's note: This article summarizes the Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American

ABSTRACT

Purpose

To update the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guideline recommendations for human epidermal growth factor receptor 2 (HER2) testing in breast cancer to improve the accuracy of HER2 testing and its utility as a predictive marker in invasive breast cancer.

Methods

ASCO/CAP convened an Update Committee that included coauthors of the 2007 guideline to conduct a systematic literature review and update recommendations for optimal HER2 testing.

Results

The Update Committee identified criteria and areas requiring clarification to improve the accuracy of HER2 testing by immunohistochemistry (IHC) or in situ hybridization (ISH). The guideline was reviewed and approved by both organizations.

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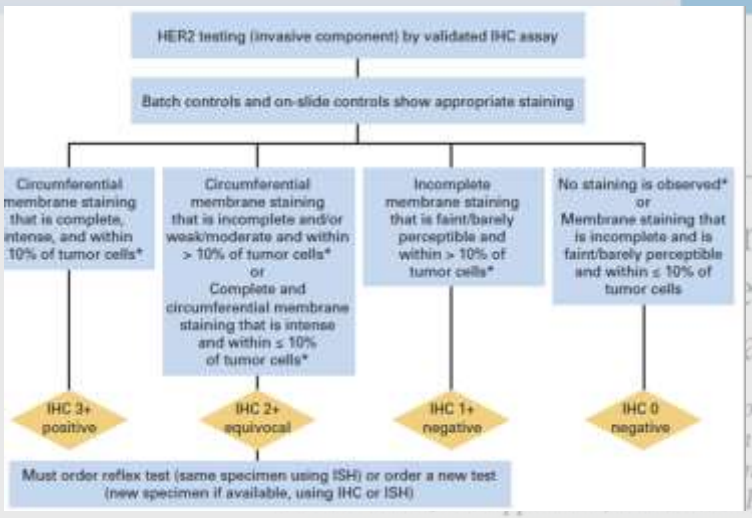

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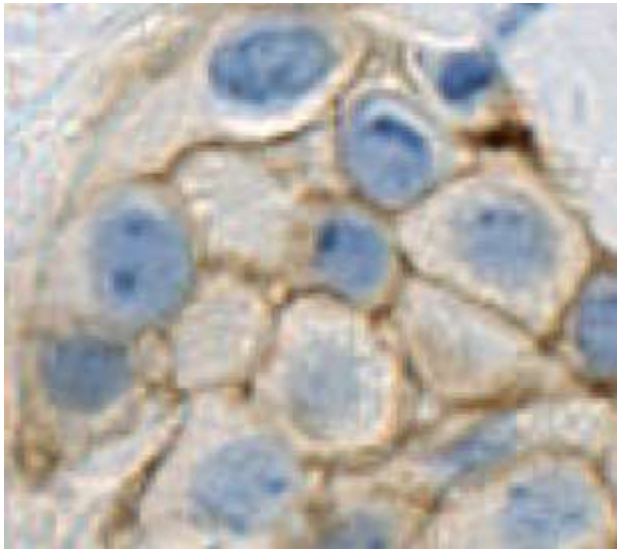
HER2 SCORE ~ INTENSITY + MEMBRANE COMPLETENESS

Intense
Moderate
Weak
Faint /Barely perceptible

Complete
Incomplete

Unanswered Questions of Relevance to IA and Standardization

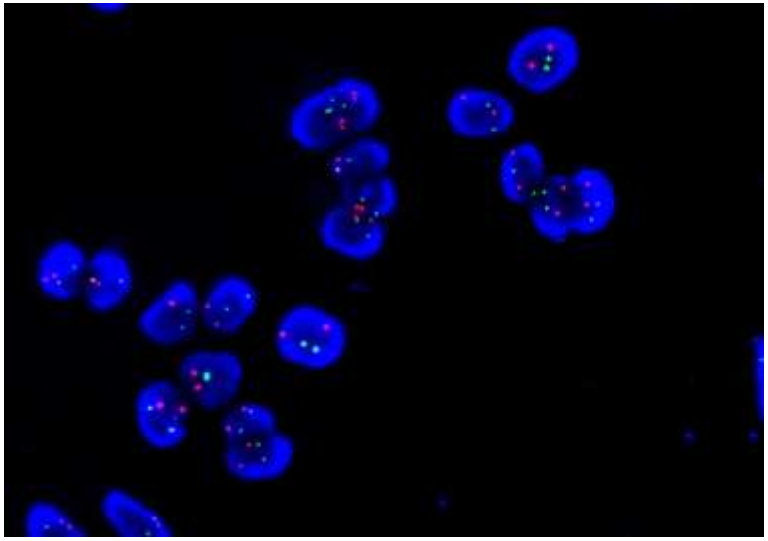
- How and how much does the evaluation criteria **Intensity** and **Completeness** contribute to a correct classification of a patient as Her2 negative or positive (proteine overexpression or gene amplification)?
- How do we achieve standardization of intensity measurements and define **Intense**, **Moderate**, and **Weak**?
- How do we achieve standardization of **Completeness** of positive membrane staining, and especially level of **Completeness**
- How do we handle positive membrane objects with no associated nucleus?



Limitations of Commerical IVD Algorithms

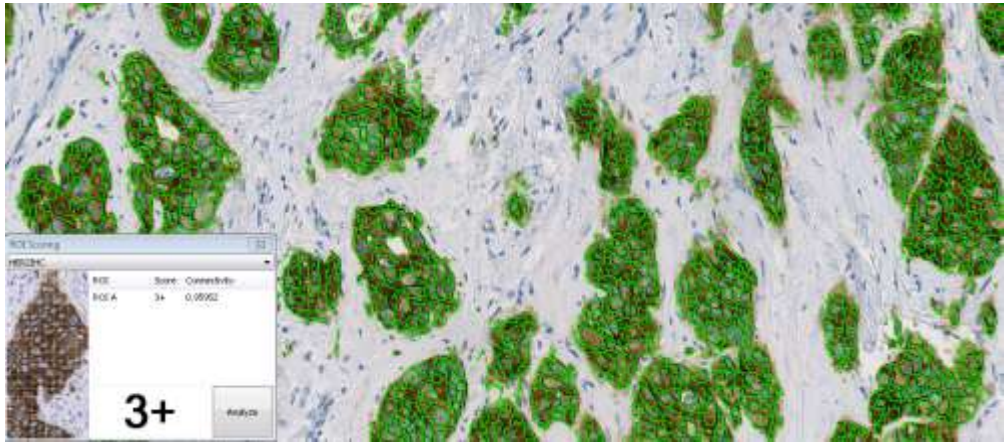
- Based mainly on intensity, and not membrane morphology (except Dobson et al)
- Validated against manual reading rather than HER2 gene amplification (which is current gold standard)
- Most algorithms require careful manual outlining of tumor cells/regions, which is tedious, time consuming, and labor intensive
- Often only validated for one reagent vendor

Review of methods by Dobson et al, Histopathology 57:27-38, 2010



Concordance with manual reading & mostly intensity based:

- Aqua by HistoRx 70%
- ACIS by Dako/Chromavision 75%
- Pathiam by BioImagene 81%
- VIAS by Ventana/Tripath Imaging 86%
- Scanscope XT by Aperio 86%
- (Tissue IA by SlidePath 91%)



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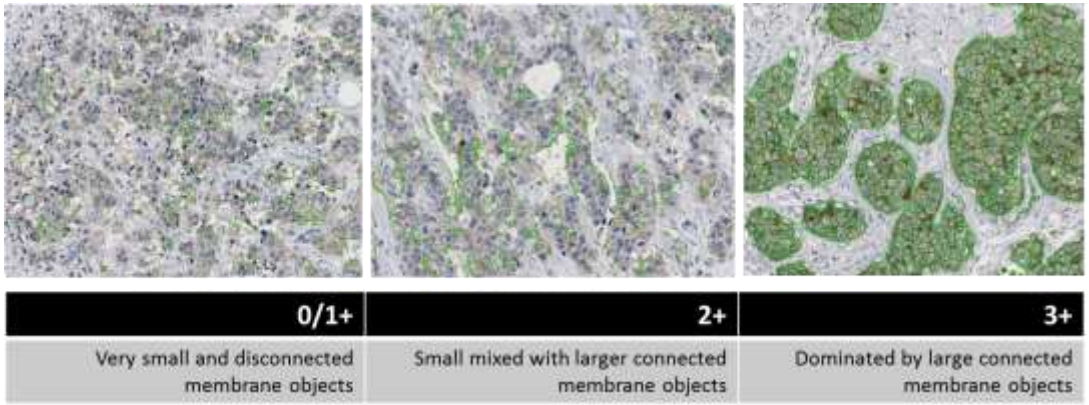
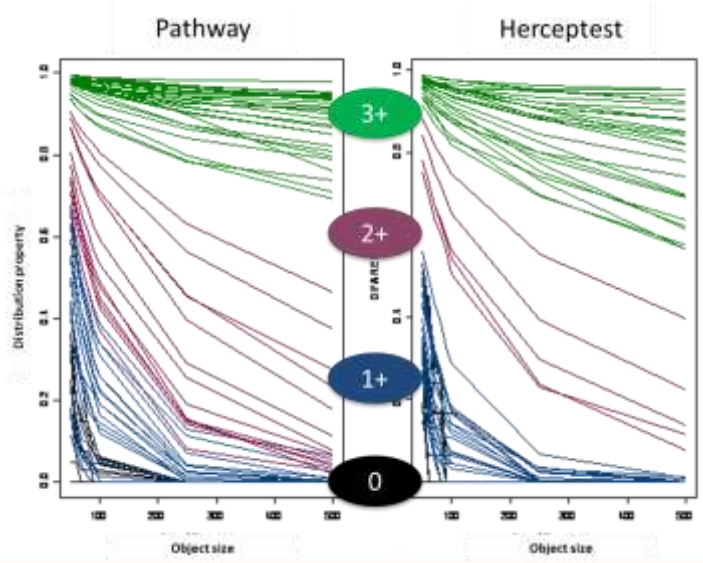
HER2: How does the HER2-CONNECT Work?

Connectivity: Generalized Membrane Completeness





The size distribution of membrane objects are different for different levels of protein expression

Size distribution can be quantified as Area Under Curve = Connectivity

Connectivity is a continuous number btw 0 and 1

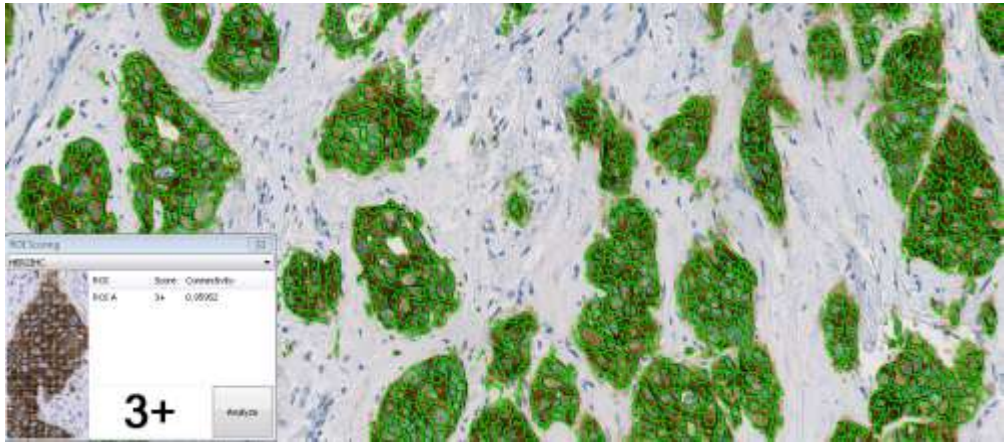
Connectivity can be translated (gated) into classical scores og 0, 1+, 2+, and 3+

Connectivity makes intensity irrelevant:

HER2-FISH ~ INTENSITY + CONNECTIVITY

Intensity of the positive membranes above the detection threshold does not contribute statisitically independent information that contributes to explain either Manual Scoring or Her2-FISH amplification.

Eliminating a component that makes standardization very hard



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HER2: Clinical Performance Data and Publications

Breast Cancer Res Treat
DOI 10.1007/s10549-011-1514-2

PRECLINICAL STUDY

Digital image analysis of membrane connectivity is a robust measure of HER2 immunostains

Anja Brügmann · Mikkel Eld · Giedrius Lelkaitis · Søren Nielsen · Michael Grunkin · Johan D. Hansen · Niels T. Foged · Mogens Vyberg

Received: 18 February 2011 / Accepted: 8 April 2011

Abstract The purpose of this study was to develop and validate a new software, HER2-CONNECT™, for digital image analysis of the human epidermal growth factor receptor 2 (HER2) in breast cancer specimens. The software assesses immunohistochemical (IHC) staining reactions of HER2 based on an algorithm evaluating the cell membrane connectivity. The HER2-CONNECT™ algorithm HER2-CONNECT™ can discriminate between amplified and non-amplified cases with high accuracy and diminish the equivocal category and thereby provides a promising supplementary diagnostic tool to increase consistency in HER2 assessment.

Keywords Breast cancer · HER2 · Image analysis

Breast Cancer Res Treat
DOI 10.1007/s10549-011-1514-2

PRECLINICAL STUDY

Digital image analysis of membrane connectivity is a robust measure of HER2 immunostains

Herceptest

DR by 5 pathologists

Pathway

I A P	0/1+	2+	3+	
0/1+	110	17	0	127
2+	0	7	4	11
3+	0	5	72	77
	110	29	76	215

Percent agreement: 87.9%
Cohen's Kappa: 0.79

I A P	0/1+	2+	3+	
0/1+	125	9	0	134
2+	0	6	4	10
3+	0	0	71	71
	125	15	75	215

Percent agreement: 94.0%
Cohen's Kappa: 0.88

Sensitivity/Specificity when compared to HER2 FISH: 99.2%/100%

Data from >170 laboratories

	Sensitivity	Specificity	Inconclusive (2+)	HER2 IHC Test	Scanner	Site
HER2-CONNECT	100% (77/77)	100% (127/127)	5% (11/215)	HercepTest	NanoZoomer	Aalborg Hospital (cores)
Manual	100% (73/73)	97.3% (100/113)	13% (29/215)			
HER2-CONNECT	100% (71/71)	100% (134/134)	5% (10/215)	Pathway HER2	NanoZoomer	Aalborg Hospital (cores)
Manual	100% (75/75)	100% (125/125)	7% (15/215)			
HER2-CONNECT	63.9% (63/83)	98.1% 406/414)	2% (8/504)	Pathway HER2	ScanScope	Vilnius University Hospital (cores)
Manual	65.4% (51/78)	98.3% (393/400)	5% (27/505)			
HER2-CONNECT+ Pathology Review	100% (64/64)	81% (17/21)	41% (59/144)	HercepTest	ScanScope	Intermountain Central Laboratory (tissue)
Manual	100% (61/61)	0%[1] (0/15)	47% (68/144)			
HER2-CONNECT	98.2% (333/339)	99.4% (505/508)	4% (33/880)	Multiple	NanoZoomer	176 labs (cores)

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HER2-CONNECT™

CE

EU: For in vitro diagnostics use

INTENDED USE

HER2-CONNECT is intended for use with digital images as an accessory to *in vitro* diagnostic test for analysis of HER2 receptor protein for the detection and semi-quantitative measurement of HER2/neu (c-erbB-2) in formalin-fixed, paraffin-embedded normal and neoplastic breast tissue.

It is indicated as an aid to the pathologist in the assessment of breast cancer patients for whom treatment with trastuzumab is being considered.

SUMMARY AND EXPLANATION

In breast cancer patients, overexpression of the HER2 protein is an individual prognosticator of breast cancer and a predictive marker of response to targeted treatment with trastuzumab and other medications and vaccinations directed against HER2 (1, 2).

Correct assessment of the HER2 protein overexpression or gene amplification is crucial for proper treatment, and the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) has issued guidelines that are used worldwide (3). Despite efforts to standardize assay techniques and interpretation, scoring remains time-consuming and subjective with inherent observer variability (4-6).

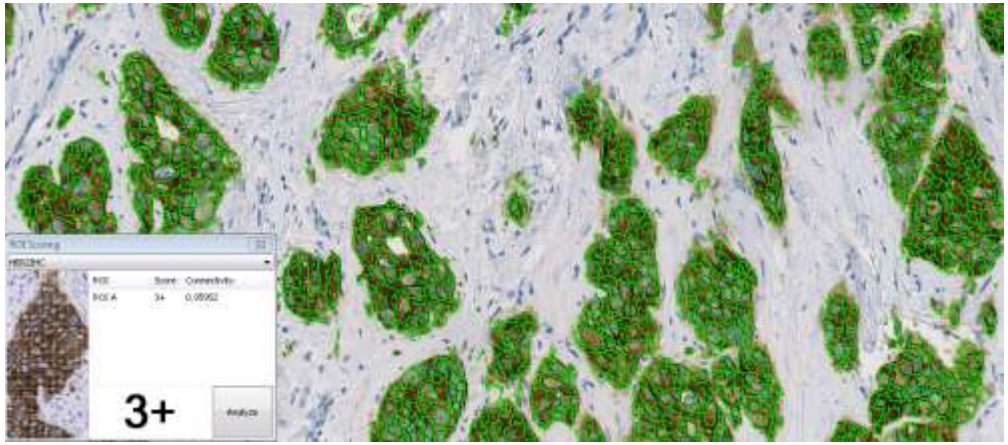
HER2-CONNECT is an image analysis software module, which offers automated and objective analysis of whole slide digital images acquired by scanning of breast cancer tissue slides stained by HER2 immunohistochemistry (IHC). HER2-CONNECT is unaffected by the presence of stromal and other non-tumor tissue, and the outlining of tissue regions of interest suitable for analysis is therefore simple (7, 8). HER2-CONNECT provides a supplement to manual and subjective scoring, and it reduces the number of inconclusive (2+) results without compromising the diagnostic sensitivity and specificity. The score provided by HER2-CONNECT must be confirmed by manual review of the image by a qualified pathologist.

Overview of the procedure (described in details in the chapter "Operating Procedure"):

- Open the VIS program
- Open the whole slide image to be analyzed

Package insert for CE marked HER2-CONNECT algorithm.

- Validated for Dako, Leica, and Ventana stainer platforms
- Validated across scanner platforms
- Allow diagnostic pathology labs to always choose best-of-breed solution components



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HER2: What are Pathologists Asking For (other than science)?

Most common answer:

Improved Sensitivity/Specificity wrt HER2-FISH

Site IV, Ireland		HER2-CONNECT			
		NEG	2+	3+	TOTAL
Manual Reading	NEG	44			44
	2+	8	3	3	14
	3+			3	3
TOTAL		52	3		61
N		61			
%Agreement		81.97%			
95% C.I.		70%-91%			

Out of 61 cases, a total of 14 (23%) were read manually as 2+
A total of 3 (5%) were read 2+ by HER2-CONNECT

The Her2-Connect re-classified:

- 8 cases as Negative – they were all FISH negative
- 3 cases as 3+ - they were all FISH positive

Reduction in inconclusive cases: 79%

Unpublished data

Site III, Denmark		HER2-CONNECT			
		NEG	2+	3+	TOTAL
Manual Reading	NEG	217			217
	2+	46	5	2	53
	3+	0	1	41	42
TOTAL		263	6	43	312
N		156		2 cores per patient	
%Agreement		84.29%			
95% C.I.		80%-88%			

Out of 312 cores, a total of 53 (17%) were read manually as 2+
A total of 6 (1,9%) were read 2+ by HER2-CONNECT

The Her2-Connect re-classified:

- 46 cores re-classified as Negative: All were FISH negative
- 2 cores re-classified as 3+ - Both were FISH positive

Reduction in inconclusive cases: 89%

Unpublished data provided by: Prof. Ben Vainer and Henrik Holm Rossing, Rigshospitalet

Potential for cost savings

Reagent Cost: Average list price for fx the INFORM© Her2-FISH test in estimated at EUR 170, according to Jeffrey Emch, senior marketing manager of molecular lifecycle management at Ventana Medical Systems. Average sales price is probably lower but varies from lab to lab.

Labor cost: Approximately EUR 70 (excluding overheads etc)

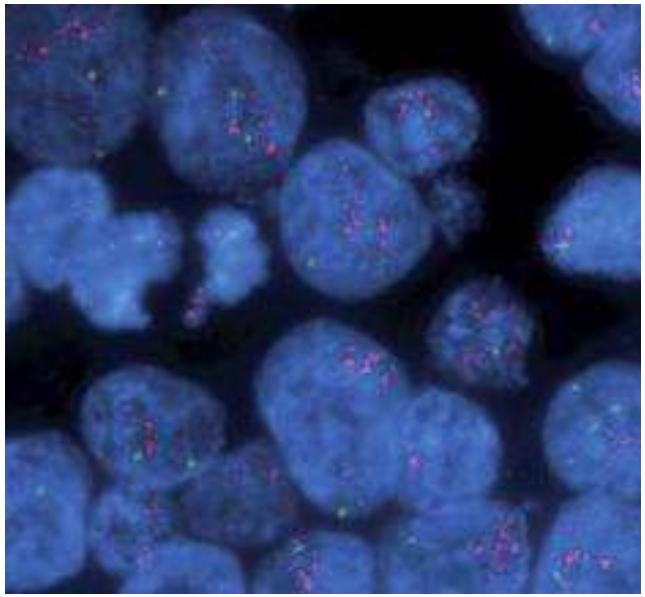
Total cost per test (at least): EUR 240

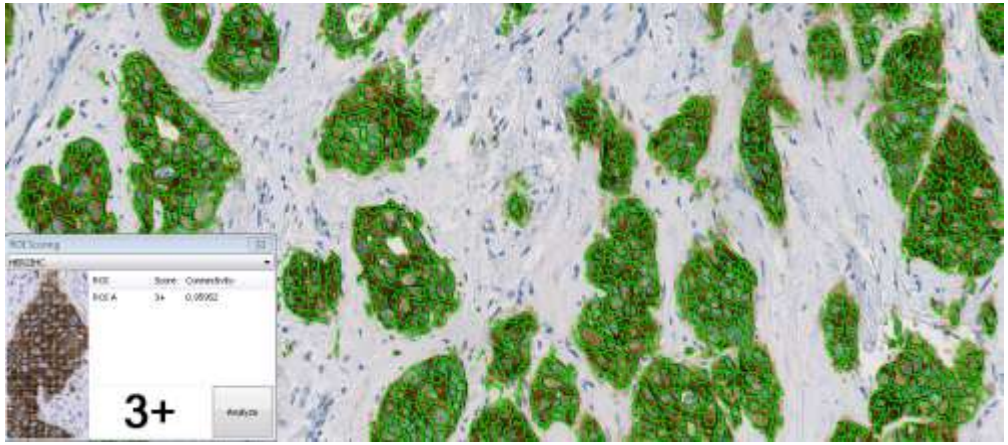
Fraction 2+ cases: ~20%

Reduction in 2+ cases using HER2-CONNECT: >=75% (depending on lab)

Average saving per 100 patients: 100 cases x20% x 75% x EUR 240 EUR / case = EUR 3600

NOTE: Calculations for TMA setup's are more complex and depends on the number of cases per block/slide and cores per patient.





CE

IVD

Where is it used today?

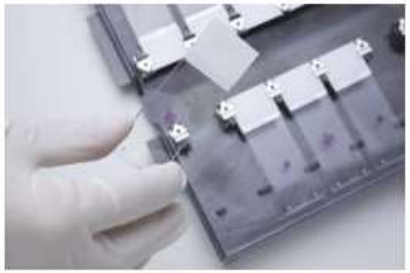
Tuesday, June 4, 2013

Danish Pathologists Embrace New Standards in Cancer Diagnostics on a National Scale

Over the last twelve years, Visiopharm has worked closely with leading Danish and International cancer researchers and pathologists to develop diagnostic software capable of improving and standardizing diagnostic reading, while automating key steps in the diagnostic workflow. This software is now being deployed at central pathology labs across Denmark.

Hoersholm, Denmark (PRWEB) June 04, 2013

There is a pressing need to improve and standardize the diagnostic work on cancer in order to optimize patient care. In Denmark, the healthcare system and pathology departments, face major challenges. These include too few experienced pathologists, a growing volume of diagnostic tests, demands to reduce turnaround times, and overall costs of pathology.



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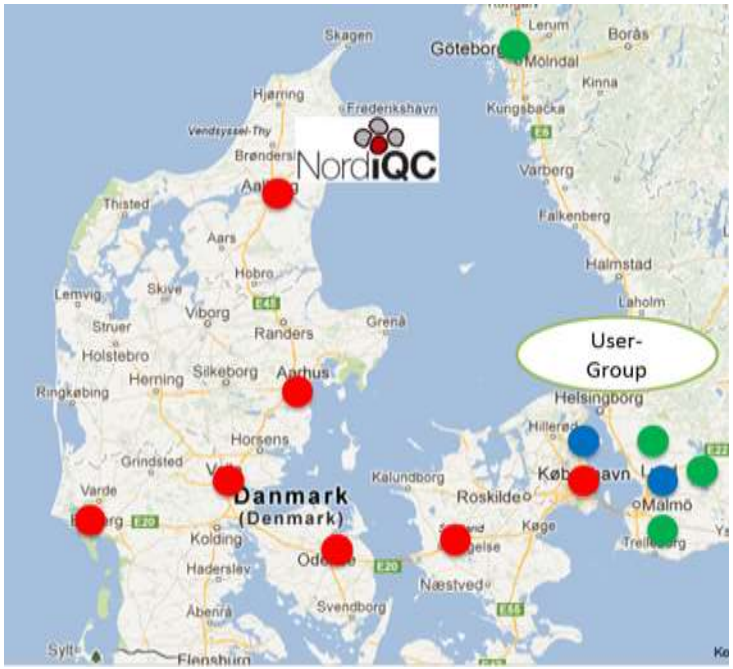
Last year Visiopharm released its first CE-marked, in-vitro diagnostic (IVD) software module. Several other CE-marked software modules are close to being released, providing a complete set of software modules for diagnosis and classification of breast cancer. Software for other tumor panels is also in Visiopharm's development pipeline.

> "The new approaches we have developed with Visiopharm are important steps towards standardizing, and potentially further improving breast cancer diagnostics."

These software modules have been developed and validated on all major staining and scanning platforms in close collaboration with, among others, Aalborg



- Herlev Hospital ⇦
- Aarhus
- Aalborg/NordiQC ⇦
- Odense
- Rigshospitalet ⇦
- Slagelse/Næstved
- Vejle
- Esbjerg

Thank You for Your Attention

Contributions from:

Prof. Mogens Vyberg, NordiQC
Dr. Anja Brügmann, Aalborg University Hospital
Prof. Ben Vainer, Copenhagen University Hospital
Dr. Henrik Holm Rossing, Copenhagen University Hospital
Dr. Beth Bjerregaard, Herlev University Hospital
Dr. Eva Balslev, Herlev University Hospital
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Johan Doré, Visiopharm
Thomas Ebstrup, Visiopharm
Michael Lippert, Visiopharm
Martin Kristensson, Visiopharm

For additional questions, feel free to email:
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Delivery of Quantitative Digital Pathology for In-Vitro Diagnostics

Challenges and Solutions