



Project FONDEF D1111096

**FONDEF**  
Fondo de Fomento al Desarrollo Científico y Tecnológico



# Advances in Digital Pathology and its current validation in Chile

Stefan Sigle

03.05.2016



# Agenda

## Part I

- Introduction to Digital Pathology
- Architectural concept
  - Requirements engineering
  - Solucion concept

## Part II

- Image analysis validation process and results in breast cancer
- Quo vadis Digital Pathology in Chile

# An introduction to Digital Pathology

## - A jungle of definitions



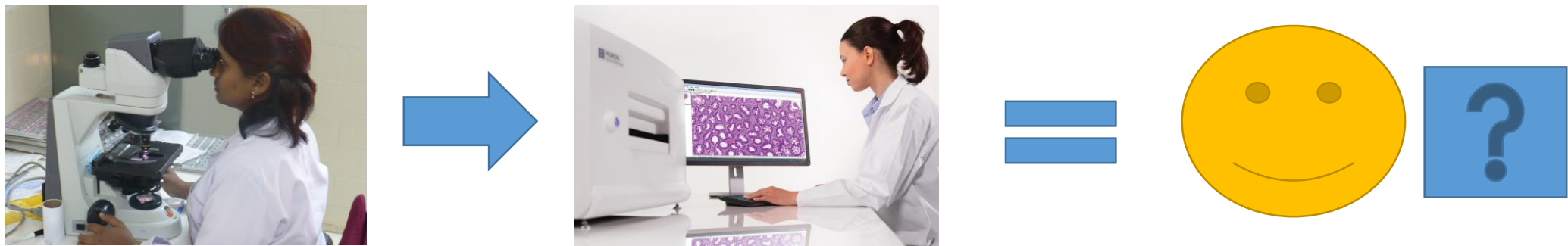
Some definitions:

- **Whole Slide Imaging (WSI):** The acquisition process of creating a virtual slide or whole slide image on a slide scanner.
- **Digital Pathology (DP):** A dynamic, image-based environment that enables the acquisition, management and interpretation of pathology information generated from a digitized glass slide. Often used interchangeably with “Virtual Microscopy.”

Source: Digital Pathology Association

# On the path to a digital workflow

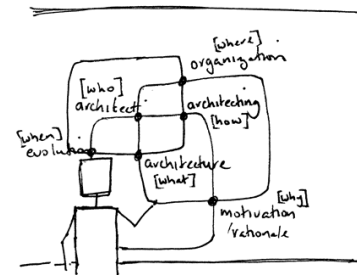
- Tissue scanners available and image acquisition is highly automatized
- Workflow in pathology is purely analog up to this day in many laboratories
- Education (in medicine) is impaired by limited access to the material
- Radiology is an successful example of the digitization process



# A target definition

An **architectural concept** for implementing the **socio-technical workflow** of **Digital Pathology** in Chile

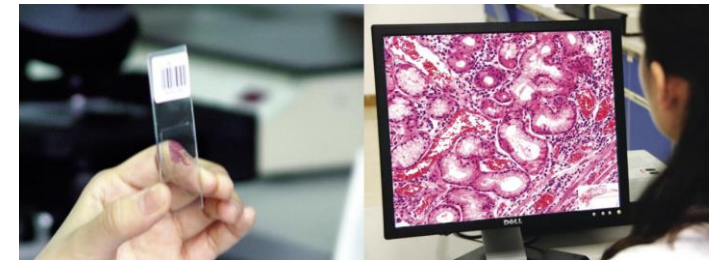
- Covers all static and dynamic IT-aspects within an organization
- Includes infrastructure and management issues



- Recognizing the user as a component in a technical system
- Joint optimization necessary



- Practise Pathology over distance
- Potential use-cases:
  - Routine consultation
  - Intra-operative section analysis
  - Interinstitutional second opinion

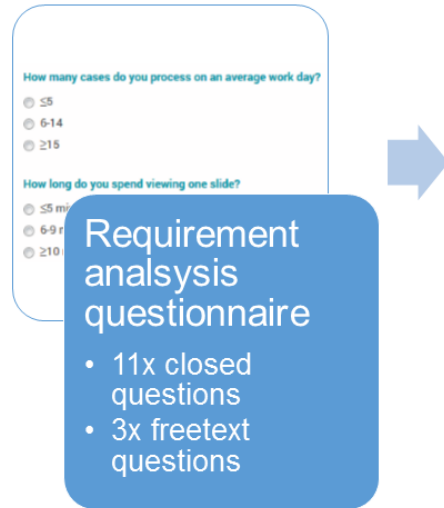


Some details about the participating pathologists (11)

Area	Min	Max
Work experience (years)	4	30
Different work-locations	1	3
Cases (per day)	10	30
Slides viewed (per day)	30	200
FISH slides (per week)	1	3
Tumor boards (per week)	1	6

Additionally 1 technician was involved.

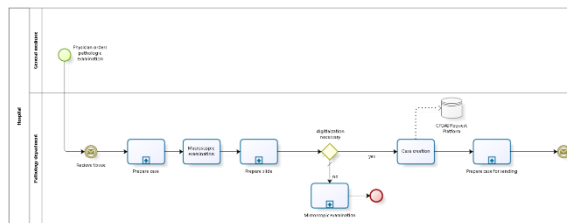
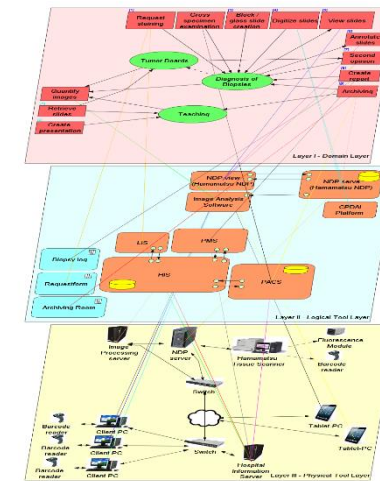
# Meta process of requirement analysis



# Solution concept

Based on reviewing the data elaborated during the meta process

- Contextual Inquiry
- Participant observation
- Models
- Evaluation questionnaire



9:50 AM

- Start of case "prostate exam"
  - Consisting of 6 slides (view time: avg. 2 min per slide)
  - Needle biopsy
- Case was positive for cancer, additional slides were ordered
  - Ordered a second opinion (from a second in-house pathologist) to ensure diagnosis
  - Annotation of the slides with ruler & pen (3 min)
    - Does not have to be "super accurate"
- Case will eventually be presented in the tumor board for its difficulty
- Dictate protocols (some of them have template in the HIS)

Tissue Scanner Project  
Questionnaire



General questions	not at all	somewhat	very
5.) How familiar are you with computers?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.) How open minded would you describe yourself towards new technology based on the internet?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7.) Do you think your work could be assisted in terms of comfort with a computer?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.) Is it possible for a digital imaging solution to complement microscopic observations?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9.) Would an automated and robust quantification help you with your daily work? (e.g. counting nuclei)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10.) Do you think your travel times can be decreased with an online platform to view and share slides?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11.) Would you be interested in participating in a study based on Digital Pathology?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Free text questions			
12.) Which information, that you do not have, would you find useful at the time of viewing a slide?			
13.) What improvements or benefits do you expect from digital pathology? (e.g. quantifying images, accessibility)			
14.) Do you have any general comments or wishes?			

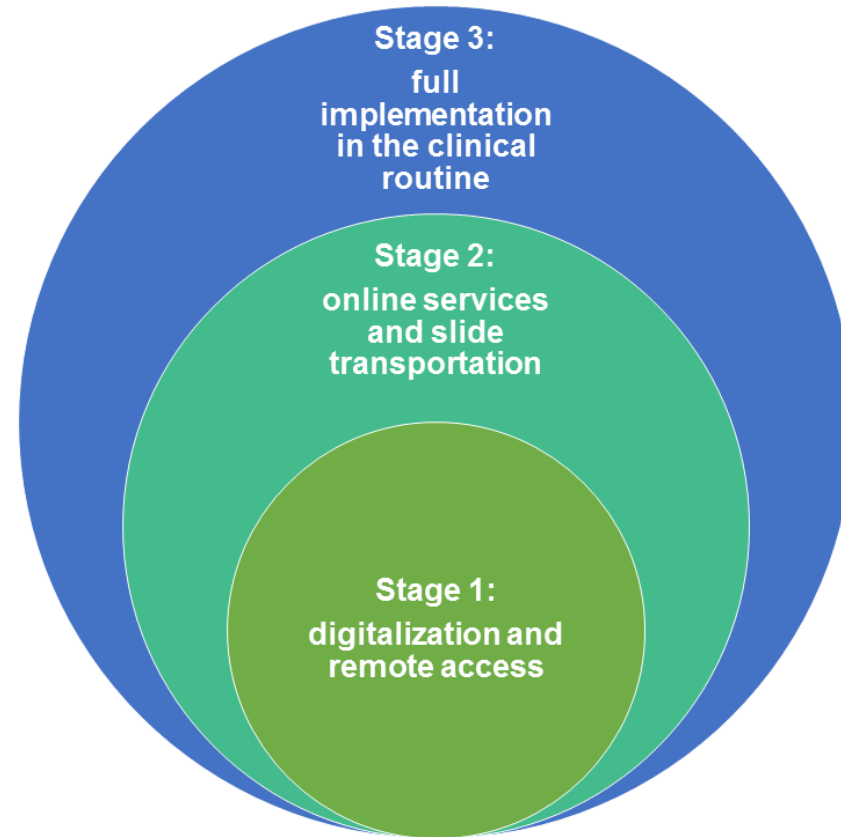
Thank you very much for your cooperation!

20.04.2014



# Solution concept

Allocation of features to different expansion stages

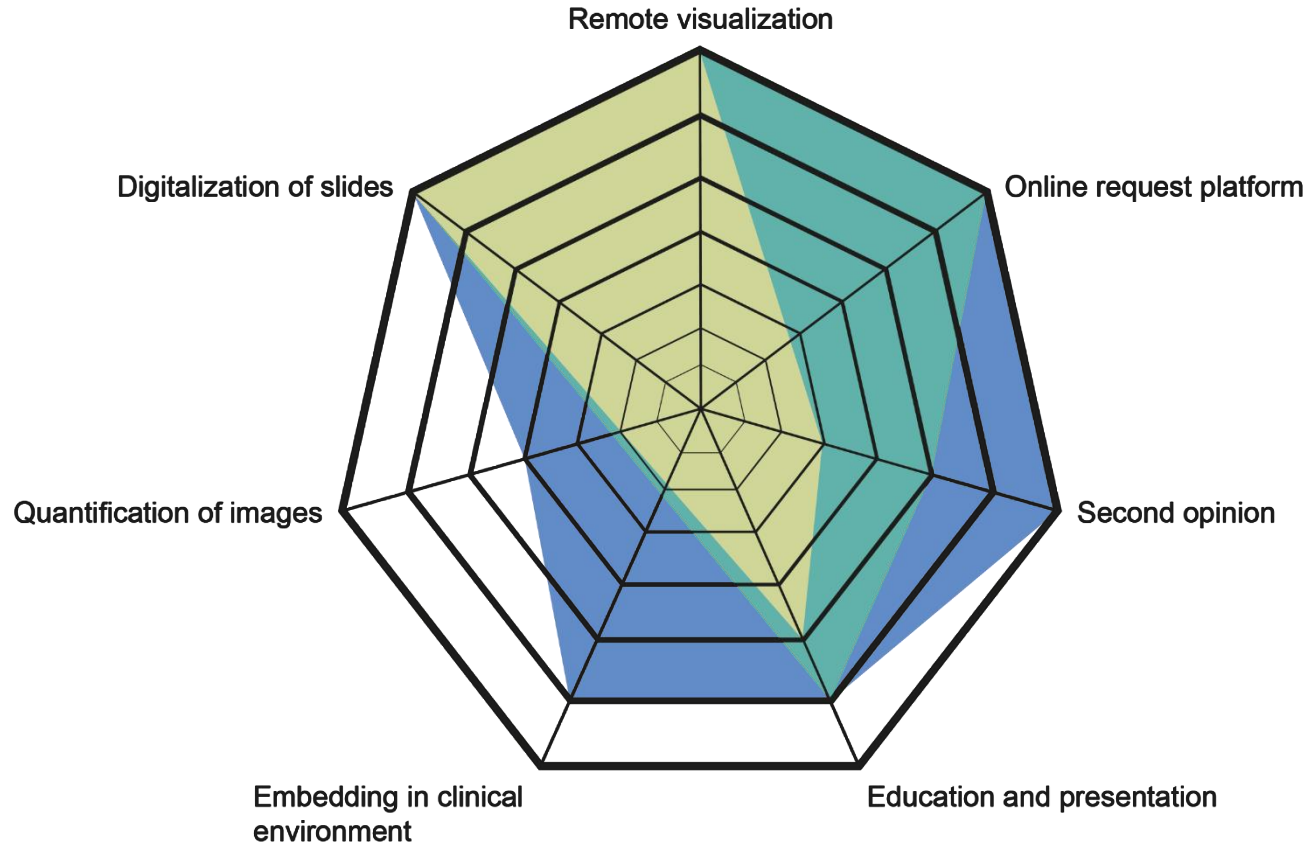


# Solution concept

The following 7 essential features have been extracted:

1. Digitalization of slides,
2. Remote visualization,
3. Online request platform,
4. Second opinion,
5. Education and presentation,
6. Embedding in clinical environment,
7. Quantification of images.

# Solution concept




Stage 1 - digitalization and remotely accessible digital slides

Stage 2 - online service for digitalization and transportation

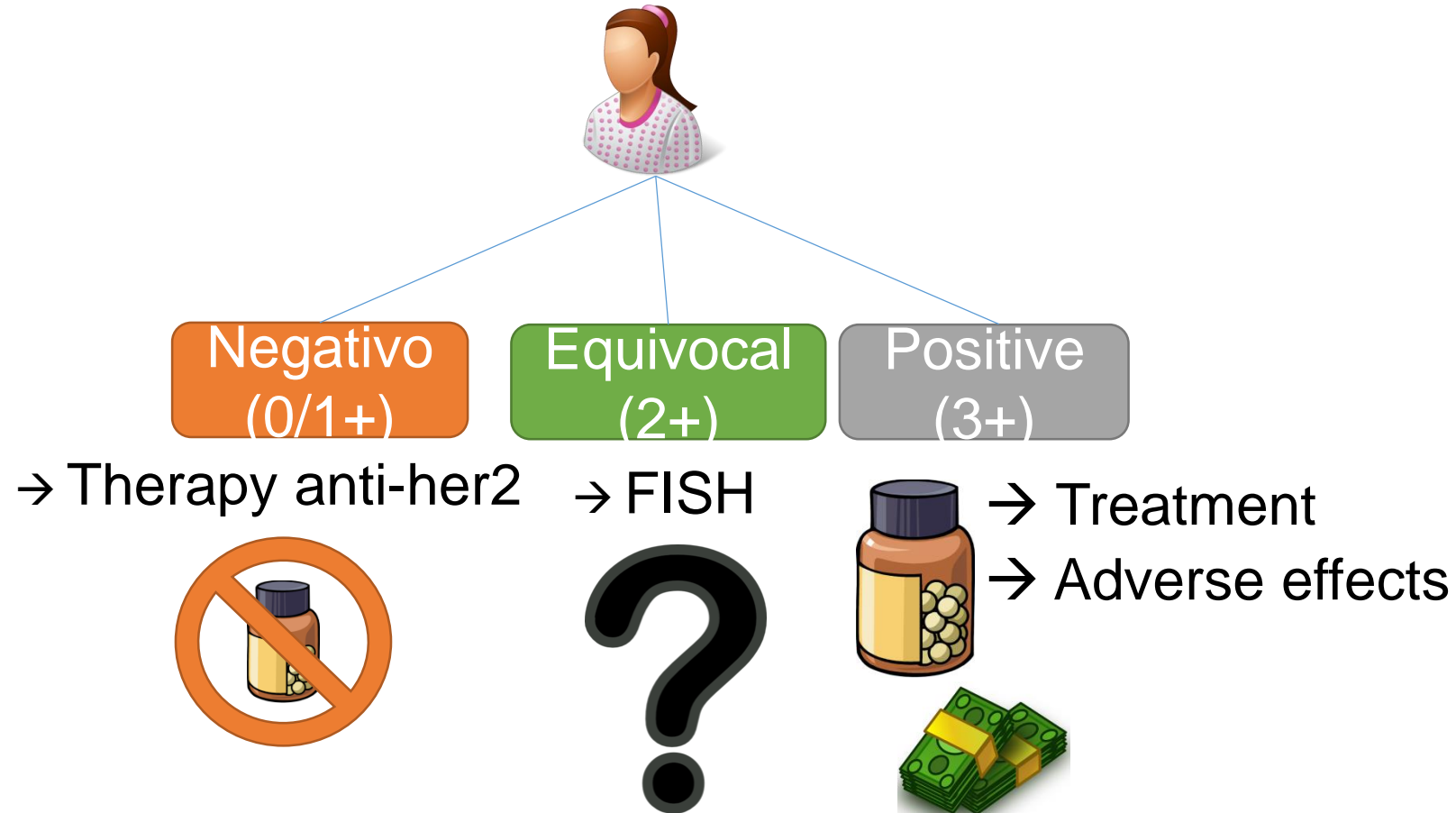
Stage 3 - full implementation of digital pathology within clinic routine

# Resumé CPDAI (after 1 year of operations):

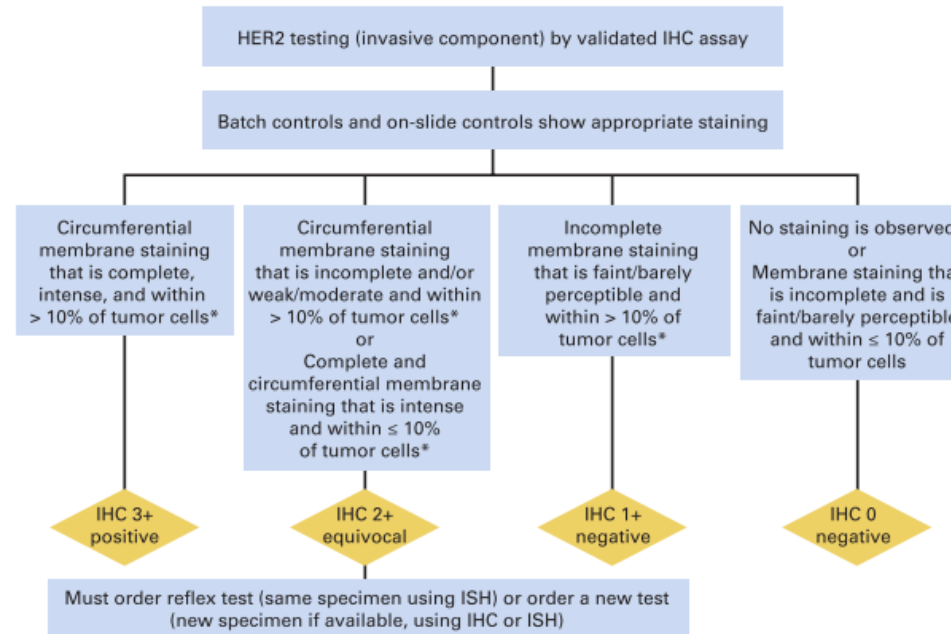
- 
- 900 slides digitalized
  - Memory consumption: (32 Terabyte)
  - Network connections: 10 GBps fibre optic to the slide server
  - Internal traceability system (TRACPad)
  - 20 National laboratories (investigation, clinics, academic)
  - 2 international institutions (El Salvador, Colombia)
    - Uruguay? 😊
  - Most used use-case: interconsulting, teaching

## Part II: (automated) Image analysis, validation process and results in breast cancer

# The problem of HER2 receptor status detection and treatment



# Guidelines



The Ministry of Health in Chile adopted these recommendations in “Manual de Recomendaciones de Anatomía Patológica para Tumores Malignos”, 2013



# HER2 variability – no improvement over the last decade

## Real-World Performance of HER2 Testing—National Surgical Adjuvant Breast and Bowel Project Experience

...  
We found that 18% of the community-based assays, which were used to establish the eligibility of patients to participate in the B-31 study, could not be confirmed by HercepTest™ IHC or fluorescence *in situ* hybridization (FISH) by a central testing facil-

(2002)

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

### Results

Approximately 20% of current HER2 testing may be inaccurate. When carefully validated testing is performed, available data do not clearly demonstrate the superiority of either immunohistochemistry (IHC) or *in situ* hybridization (ISH) as a predictor of benefit from anti-HER2 therapy.

(2007)

Constant World-wide variability: 20%  
→ But how is it in Chile?

Paik et al., Journal of the National Cancer Institute, 2002  
American Society of Clinical Oncology and College of American Pathologists, 2007



# HER2 variability in Chile

## Variabilidad en la determinación del estado de HER2 por inmunohistoquímica en Chile

Luis Contreras-Melendez <sup>a,+</sup>, Antonio Piottante-Becker <sup>a</sup>, María Contreras-Seitz <sup>b</sup>,  
María Garmendia-Flores <sup>a</sup> y Jorge Levican-Asenjo <sup>a</sup>

<sup>a</sup> Servicio de Anatomía Patológica, Clínica Las Condes, Santiago, Chile

<sup>b</sup> Interno de Medicina, Universidad Andres Bello, Santiago, Chile

Recibido el 9 de julio de 2012; aceptado el 19 de septiembre de 2012

Disponible en Internet el 13 de noviembre de 2012

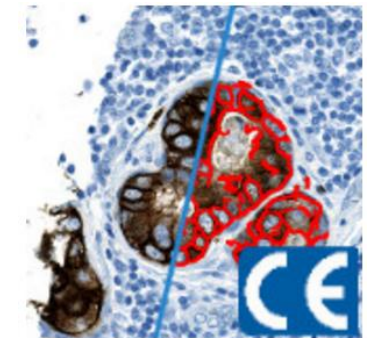
- 41 National laboratories
- 221 Biopsies
- Variability: 19,7% comparing IHQ
- Variability: 25,6% comparing FISH
- But: no informations about the sources of variability are given

Rev Esp Patol. 2013;46(1):33-39

# Motivation

Provide a tool to aid the diagnostic process by automated image quantification.

- Whole Slide Imaging
- Visiopharm for image analysis
  - 12 years of experience
  - Used in 10 Nordic hospitals



HER2

1

VISIOPHARM®

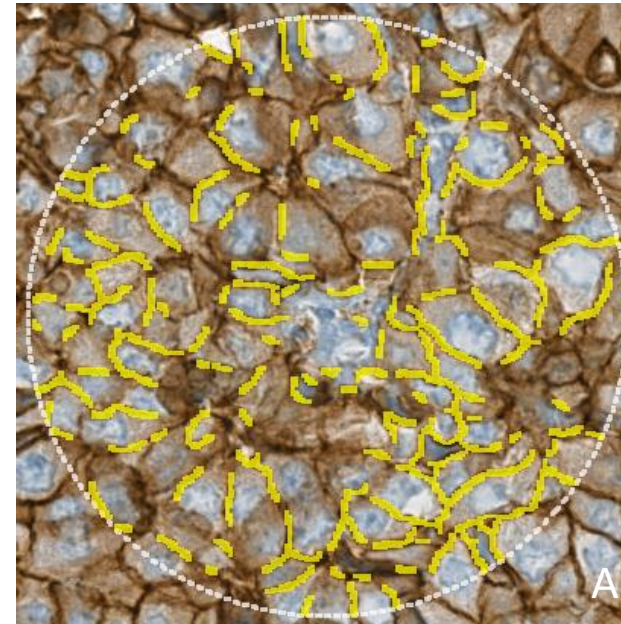
<http://www.visiopharm.com/blog/tag/pathology/page/2/>

# How Visiopharm quantifies HER2 expression

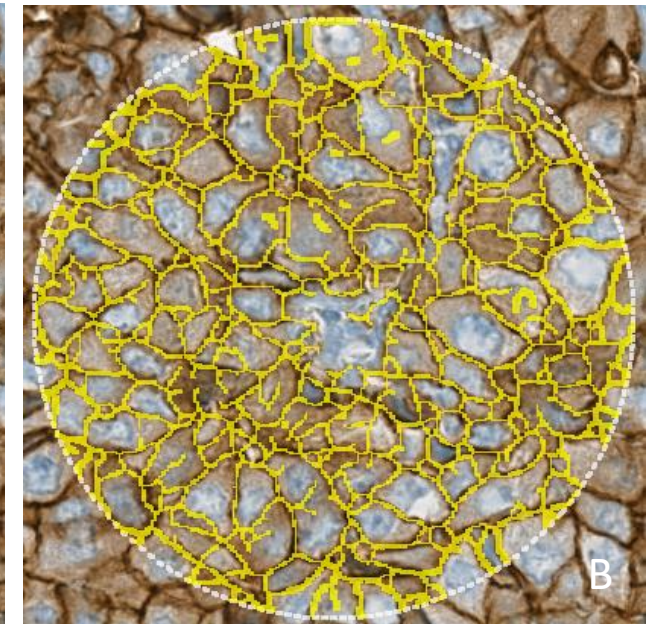
## 3 Steps:

1. Selection of a **Region of Interest (ROI)**
2. Select **Sensitivity** (finds cell membranes)
3. Calculate **Connectivity** (calculates distribution of HER2 stained membrane fragments)

→ The connectivity value is then mapped to the ASCO/CAP scoring



- 20% Sensitivity  
- 0,05 Connectivity

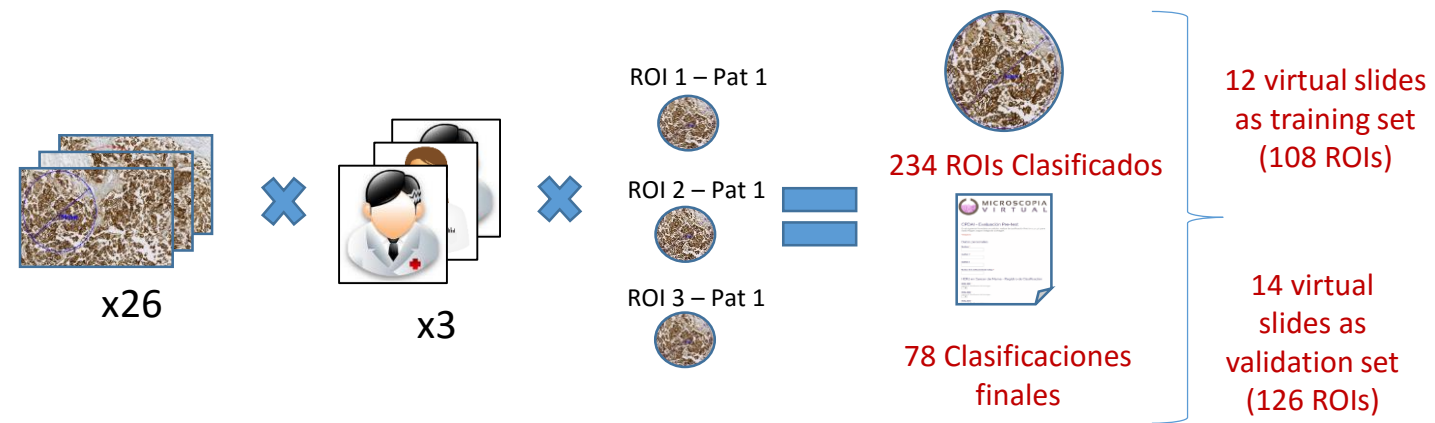


- 80% Sensitivity  
- 0,86 Connectivity

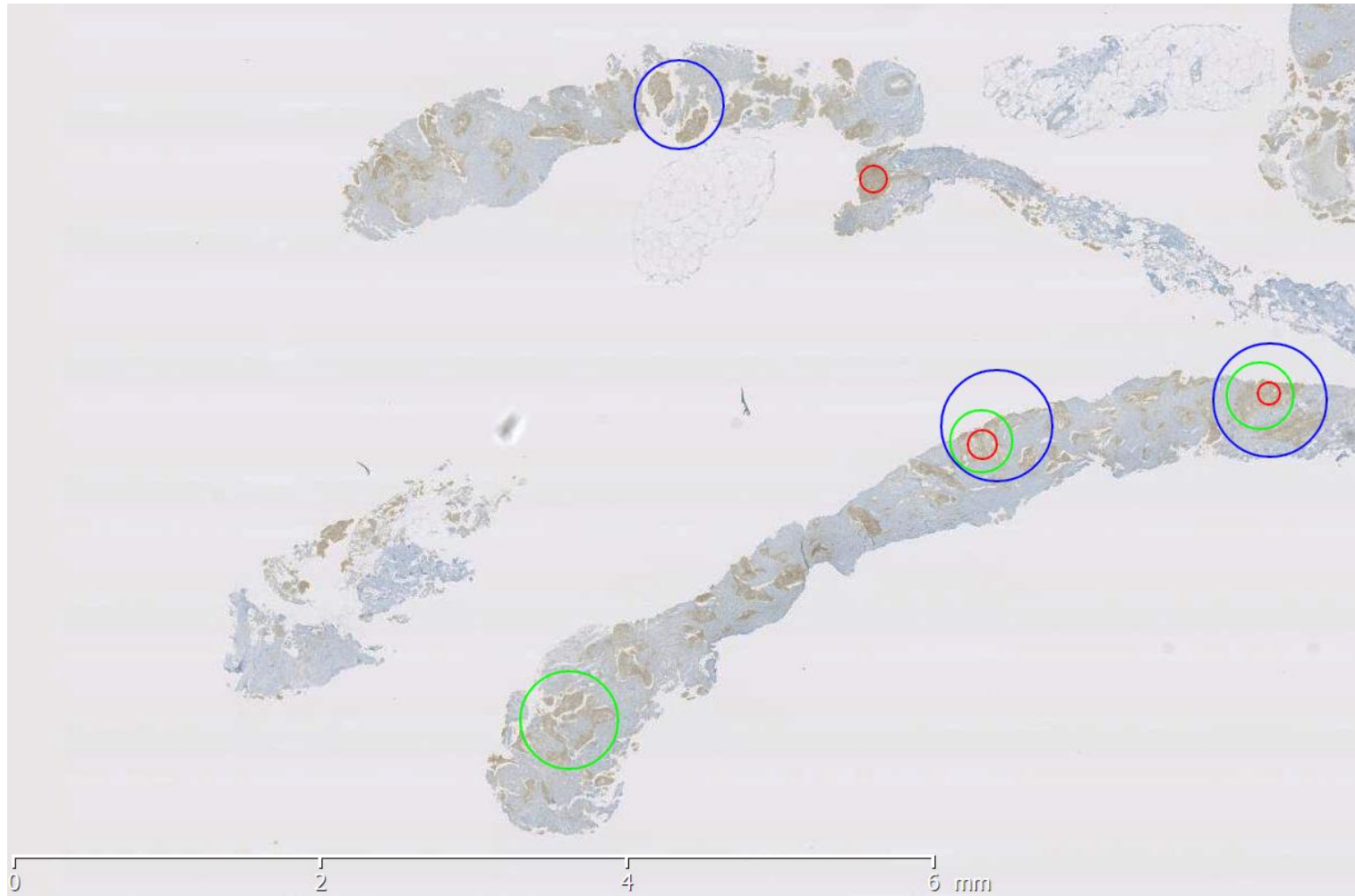
# What about ROIs?

We investigated

- Size
- Location
- Classification



# ROIs size and location vary

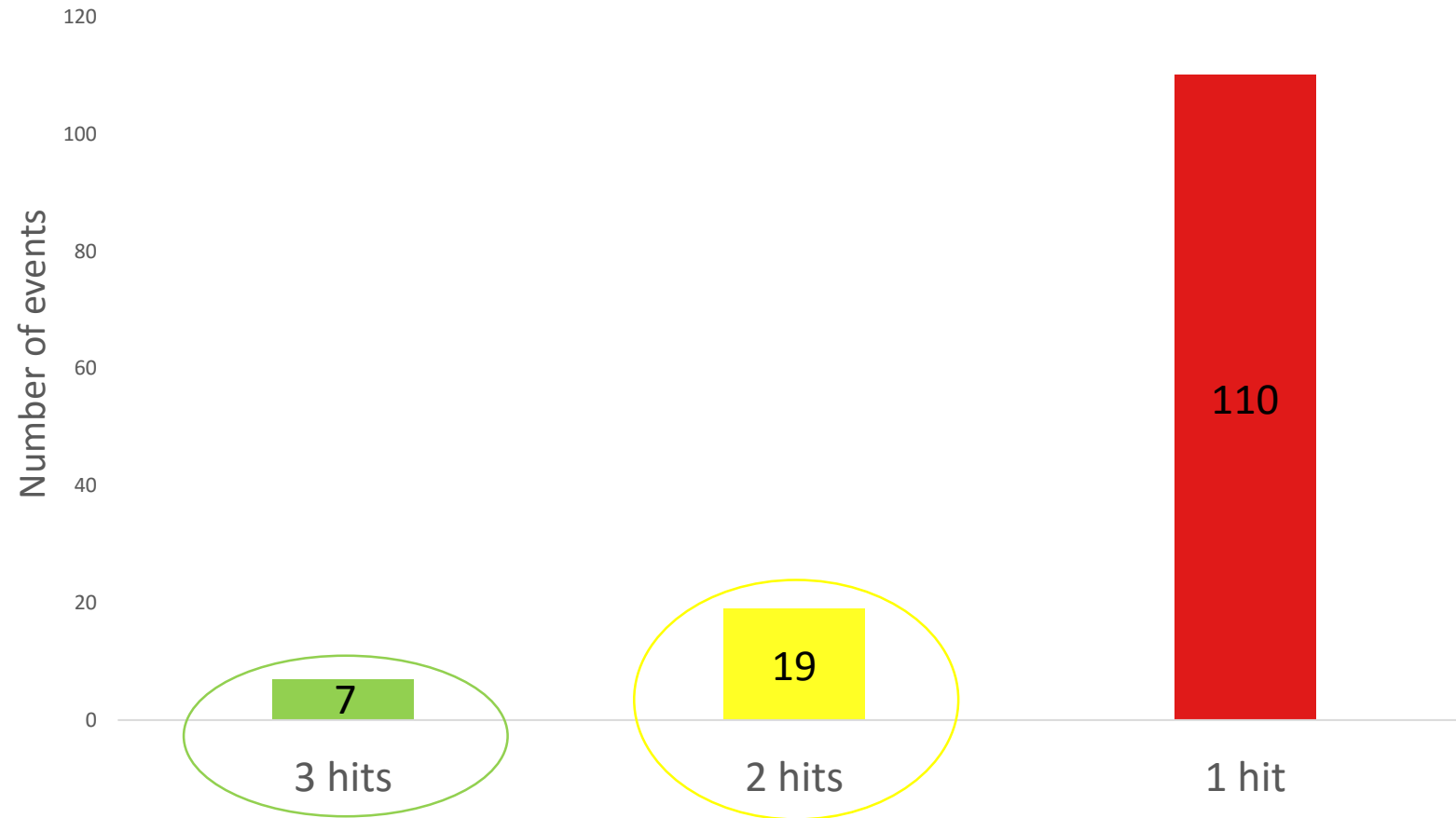


○ Pathologist 1

○ Pathologist 2

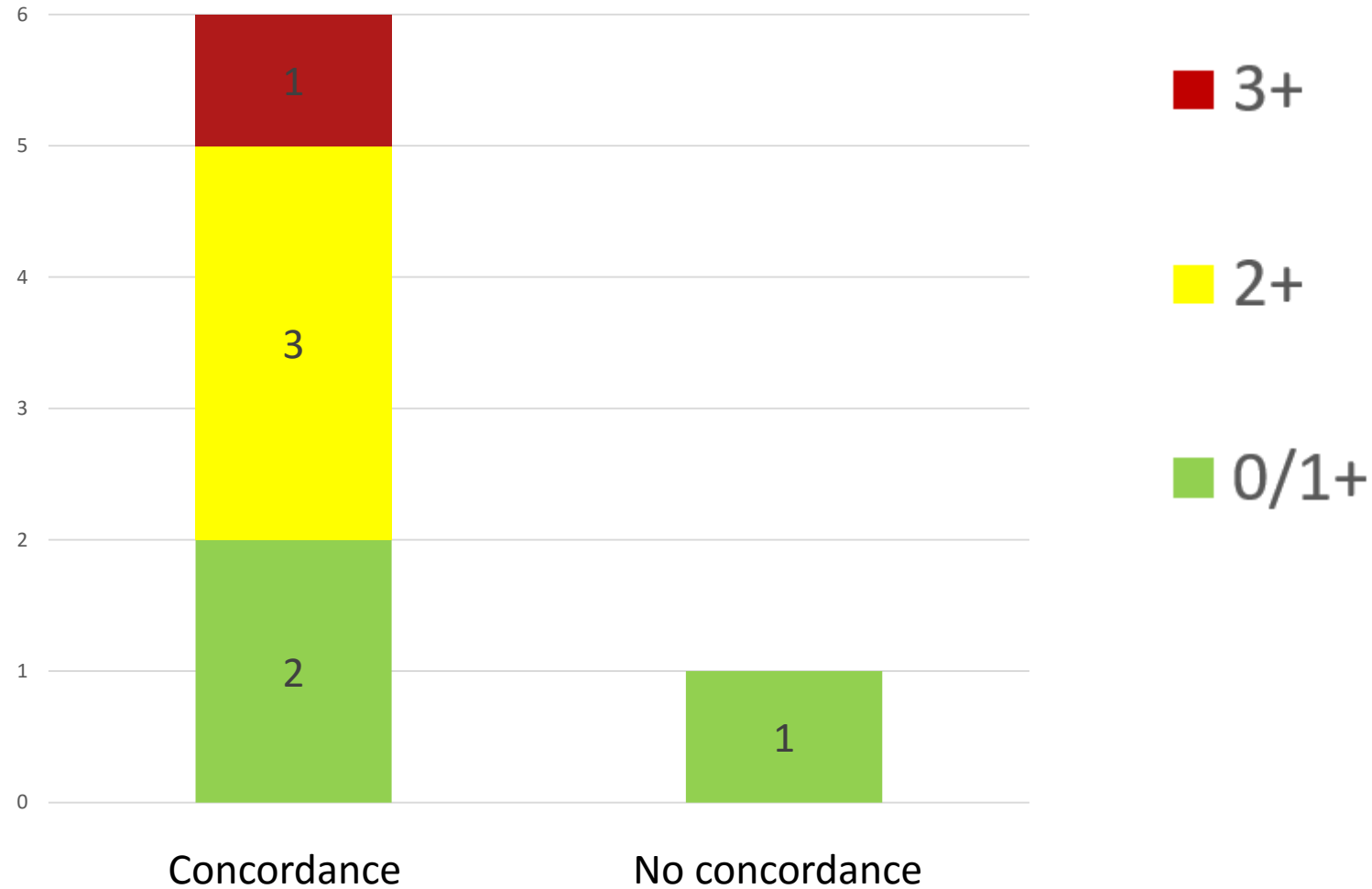
○ Pathologist 3

# Little concordance in ROI location



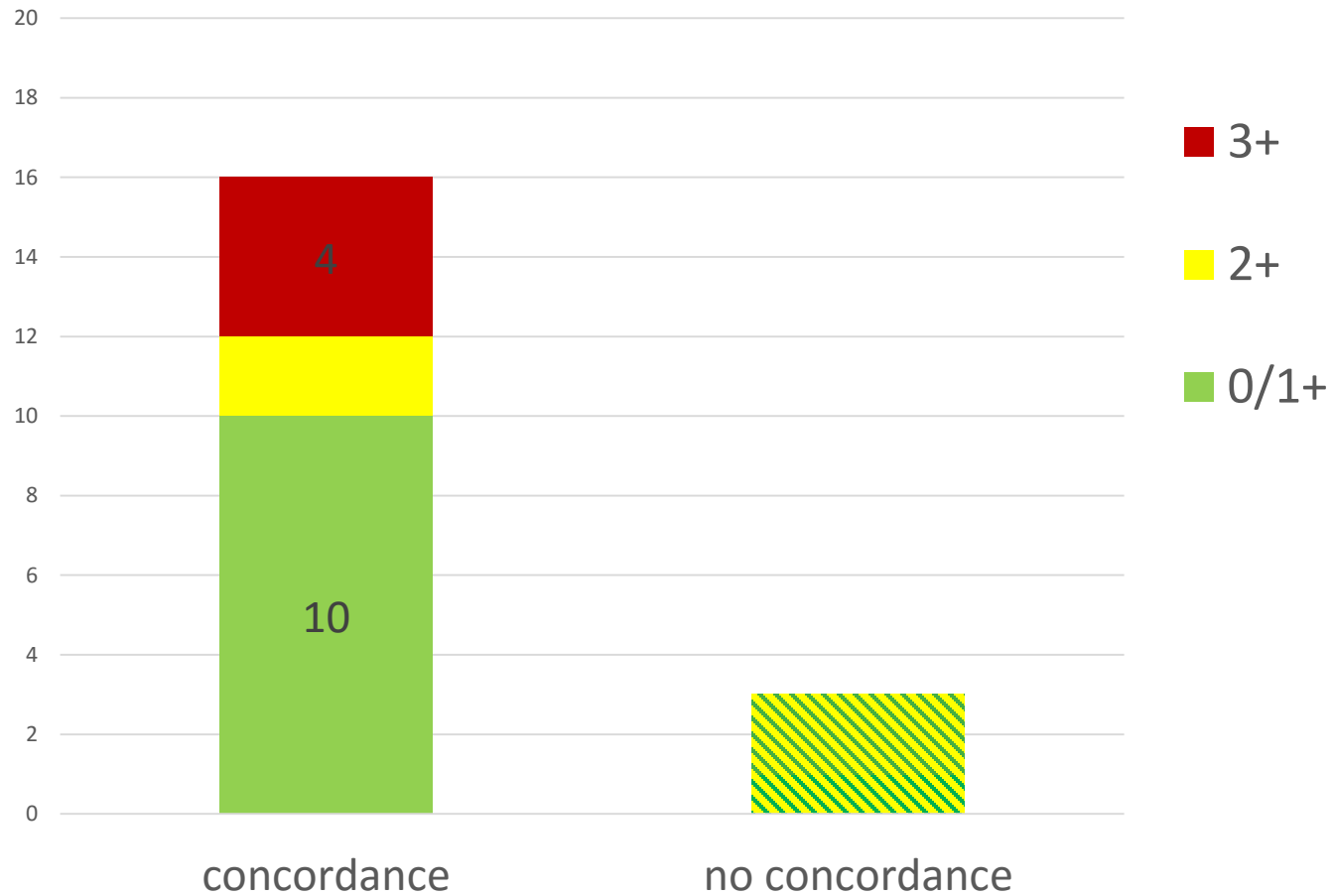
How similar are the classifications in ROIs with 2 hits and 3 hits local concordance?

# high concordance in 3 hit areas



→ In 85% of the cases the pathologists agree completely  
 → In 15% of the cases only 2 out of 3 pathologists agree

# high concordance in 2 hit areas



→ In 85% of the cases the pathologists agree in classification  
 → In 15% the pathologists do not agree

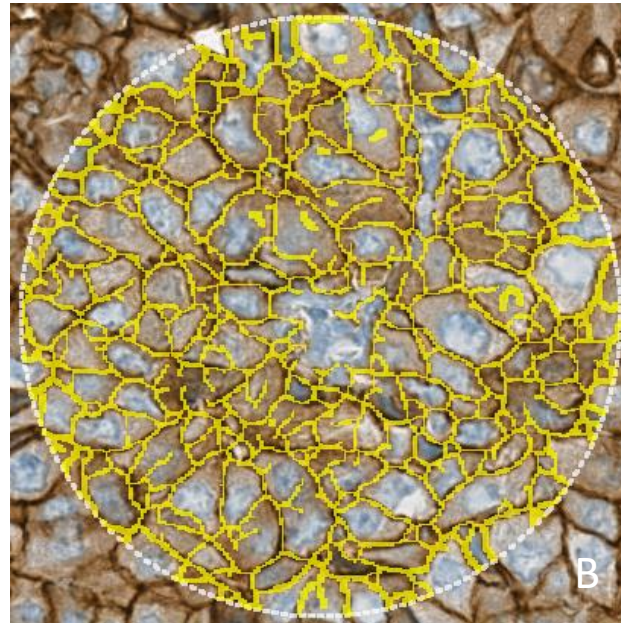


# About Sensitivity and ROIs

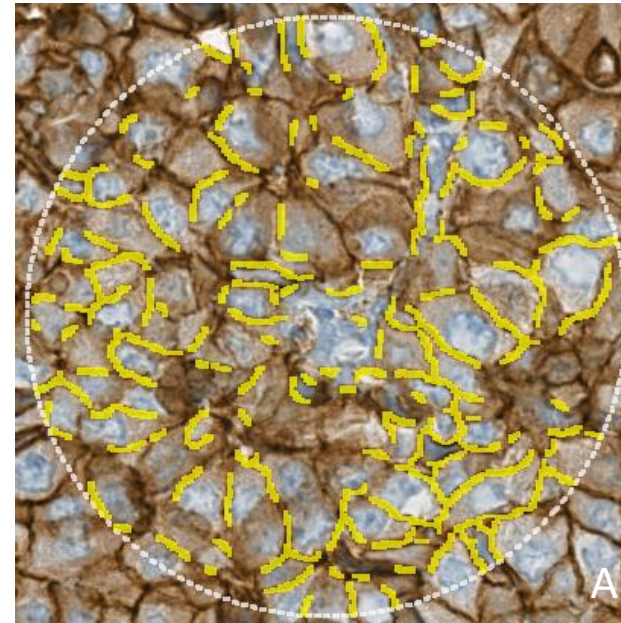
## 3 Steps:

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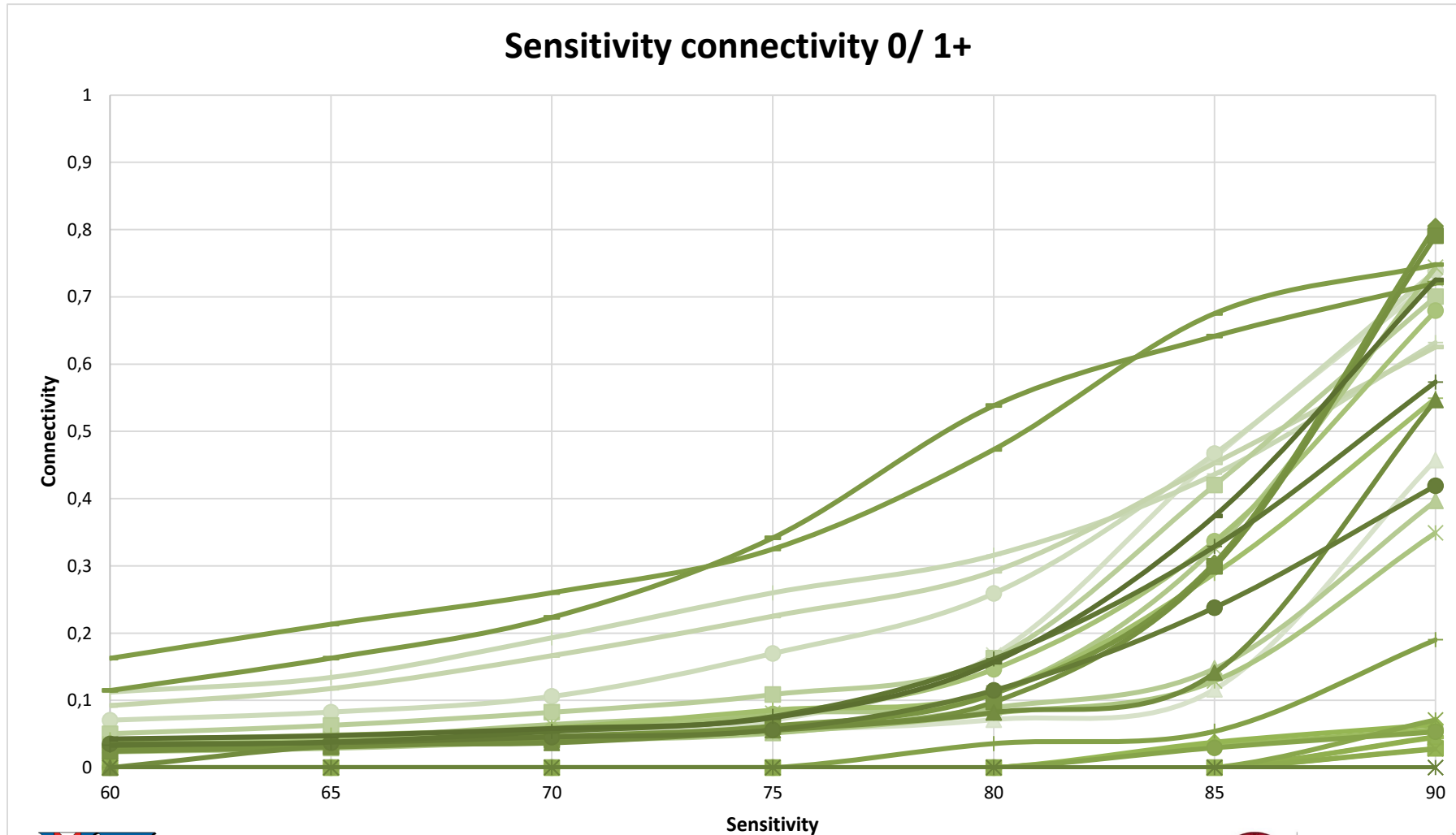


- 80% Sensitivity  
- 0,86 Connectivity

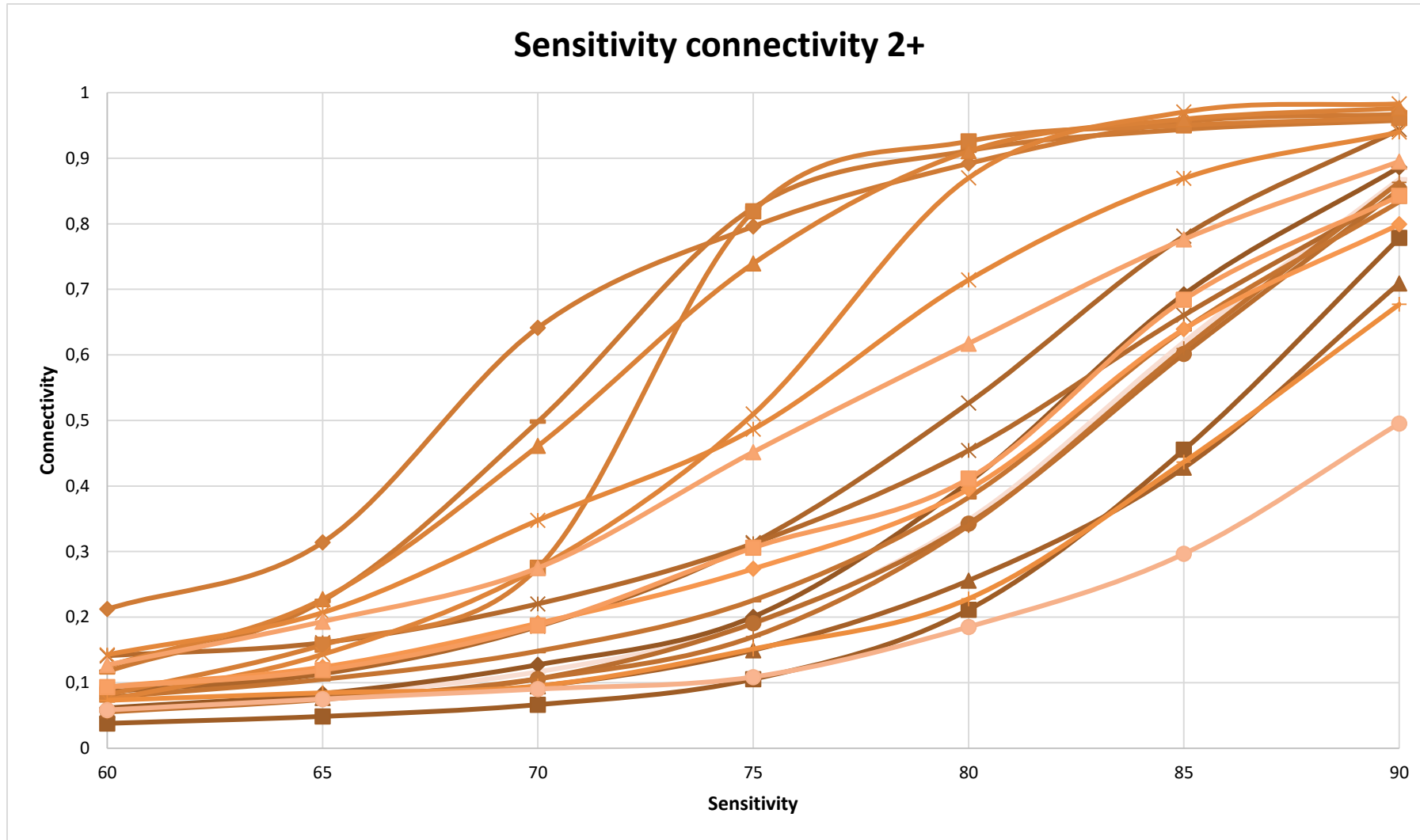


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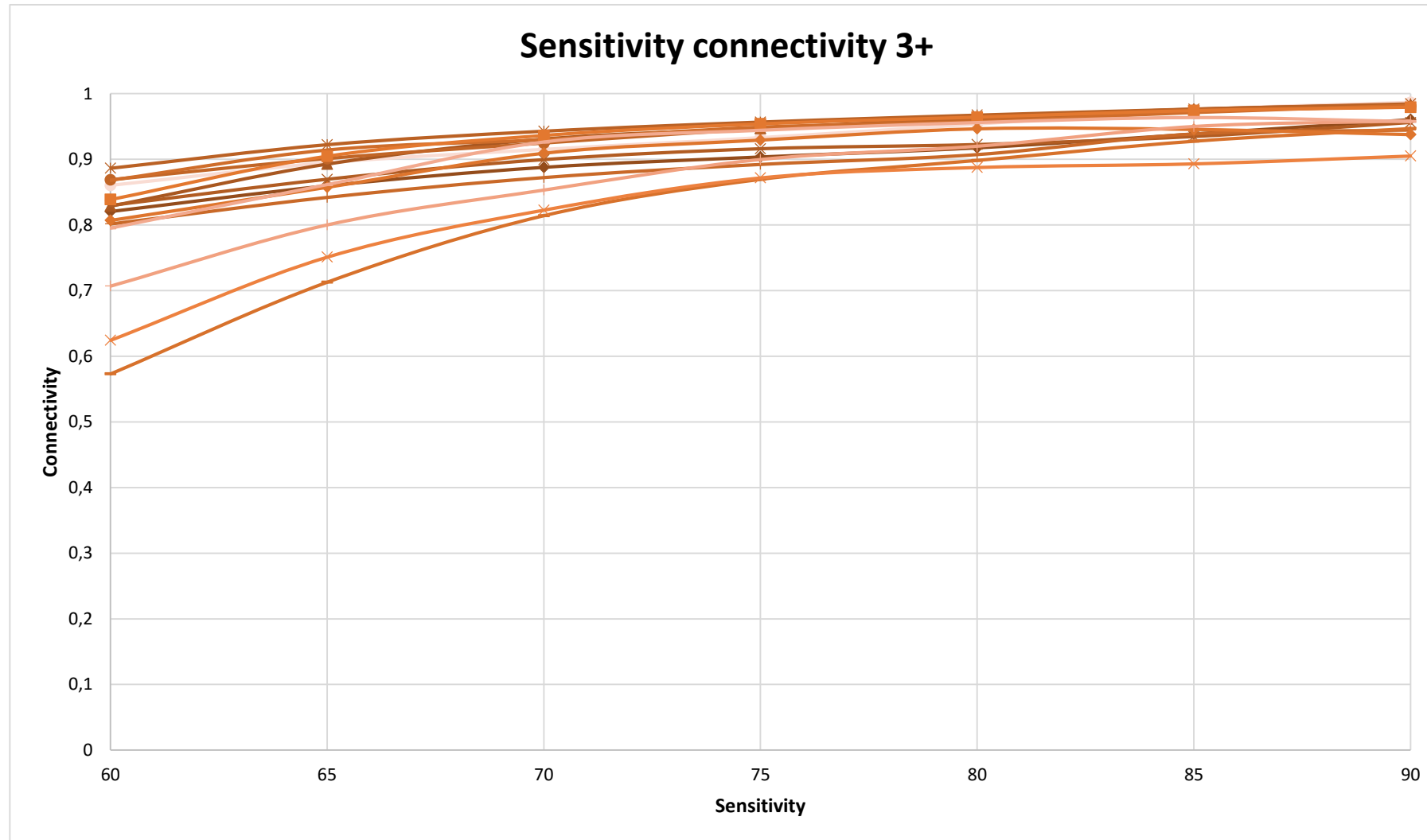
# Defining the sensitivity value



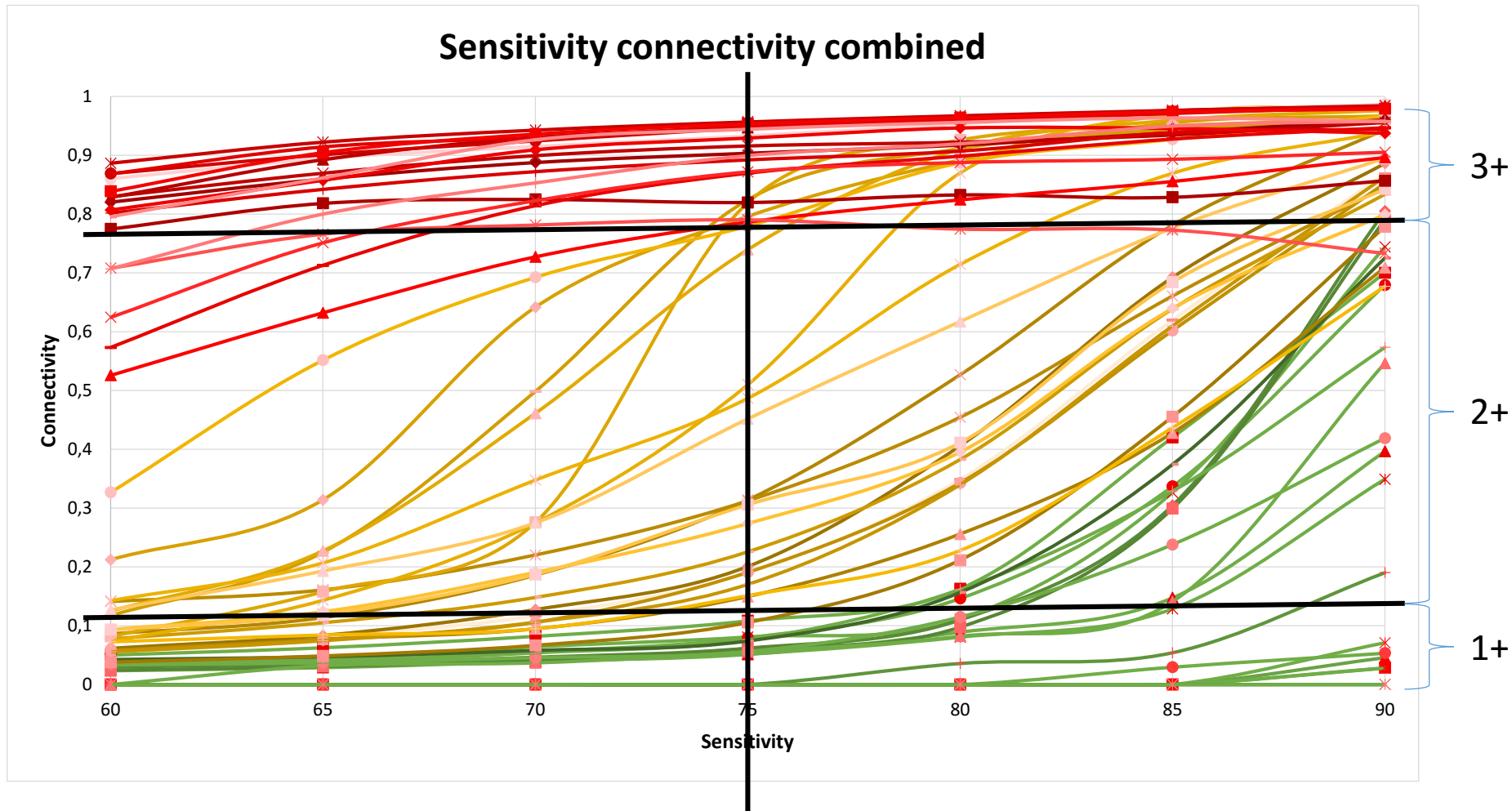
# Defining the sensitivity value





# Defining the sensitivity value



# Defining the sensitivity value



 College of American Pathologists  
 American Society of Clinical Oncology


**HER2 – Connectivity Range**

1+	?-?
2+	?-?
3+	?-?

## Future Work

- Applying machine learning algorithms to clearly define 2+ cases
- Validate the results with FISH reflex tested tissue samples
- Validation of Estrogen- and Progesteron receptors

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- 
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  - Most used use-case: interconsulting, teaching



CENTRO DE PATOLOGIA DIGITAL ASISTIDO POR INTERNET

Thanks to:



Dr. Steffen Härtel



Dra. Eugenia Díaz



MSc. Alejandra García



Dr. Gonzalo Rojas



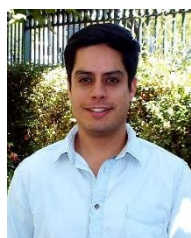
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Dra. Andrea Matura



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MSc.(c) Jimena López



MSc. Stefan Sagle



MSc.(c) Luis Briones



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- Dra. Marisol Guerero
- Dra. Claudia Ramis





Thank you for your attention!

Vista Cerro Manquehue, Santiago