Advances in Digital Pathology and its current validation in Chile

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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 djungle 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 a 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)

<table>
<thead>
<tr>
<th>Area</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work experience (years)</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>Different work-locations</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cases (per day)</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Slides viewed (per day)</td>
<td>30</td>
<td>200</td>
</tr>
<tr>
<td>FISH slides (per week)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Tumor boards (per week)</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

Additionally 1 technician was involved.
Meta process of requirement analysis

Requirement analysis questionnaire
- 11x closed questions
- 3x freetext questions
Solution concept

Based on reviewing the data elaborated during the meta process

- Contextual Inquiry
- Participant observation
- Models
- Evaluation questionnaire
Allocation of features to different expansion stages

Stage 1: digitalization and remote access

Stage 2: online services and slide transportation

Stage 3: full implementation in the clinical routine
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.
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

- Negativo (0/1+)
  - Therapy anti-her2

- Equivocal (2+)
  - FISH

- Positive (3+)
  - Treatment
  - Adverse effects
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 HercepTestTM IHC or fluorescence in situ hybridization (FISH) by a central testing facility.


**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)

(2002)

**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

- 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
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

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

12 virtual slides as training set (108 ROIs)
14 virtual slides as validation set (126 ROIs)

234 ROIs Clasificados
78 Clasificaciones finales
ROIs size and location vary
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:

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

- 80% Sensitivity - 0,86 Connectivity
- 20% Sensitivity - 0,05 Connectivity
Defining the sensitivity value

Sensitivity connectivity 0/ 1+
Defining the sensitivity value
Defining the sensitivity value

**Sensitivity connectivity 3+**

![Graph showing sensitivity connectivity 3+ relationship](image_url)
Defining the sensitivity value

Sensitivity connectivity combined

HER2 – Connectivity Range

1+  2+  3+
0-? 1-? 2-? 3-?

Connectivity

Sensitivity
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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