CytoProcessor®: A New Cervical Cancer Screening System for Remote Diagnosis

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President & Co-Founder
DATEXIM, France
I’m the President and one of the co-founder of DATEXIM SAS, the french company that manufactures CytoProcessor®.

CytoProcessor is an IVD medical device with the CE label but is not for sale in the USA. FDA approval is under investigation.
DATEXIM

- **C.N.R.S. - GREYC lab spin-off**
  - National Scientific Research Institute,
  - University Research Center for Computer science and image analysis

- **Specific skills**
  - Image processing and analysis
  - Artificial Intelligence (Machine Learning & Deep Learning)
  - Digital Pathology & Cytology

- **Team**
  - 4 PhD (Computer Sciences, Artificial Intelligence)
  - 2 Engineers (Computer Sciences & Quality Assurance)
  - 1 CytoTechnician (CT IAC)
  - 1 Sales & Marketing Director
NEW Cervical Cancer Screening system
- Artificial Intelligence for this is new ≠ Statistics and Image Processing
- Image quality with Digital Pathology brings a whole new world of data
  - Resolution 3X better than the products available on the market for clinical routine
  - Sharpness and colors are available now

for REMOTE diagnosis
- Data (slides and results) are accessed using a standard web browser
- Images are streamed providing immediate access for diagnosis

Thanks to A.I. analysis, only the areas of interest will need to be downloaded by the user
Artificial Intelligence

ARTIFICIAL INTELLIGENCE
Early artificial intelligence stirs excitement.

MACHINE LEARNING
Machine learning begins to flourish.

DEEP LEARNING
Deep learning breakthroughs drive AI boom.

Digital Pathology: an ongoing key to future

- Volume
- Sensitivity

+ 

- Time
- Cost
Overview

- What is CytoProcessor®?
- What are its performances compared to state of the art solutions on the market?
- What are the benefits of such solutions based on A.I.?
- What are the drawbacks?
- What are its possibilities?
A.I. Solution for Cervical Cancer Screening
Cervical Cancer Screening Process

- Cells Collection
- Sample Preparation
- Analysis
- Diagnosis

Gynecologist → Technician → Cyto-Technician + Artificial Intelligence → Pathologist
Innovative Cervical Cancer Screening Solution

- LBC - Slide preparation
- Slide scanner
- Automated analysis
- Local or remote access
- On screen diagnosis

CytoProcessor™
Classification steps

- Nuclei are detected
Classification steps

- Nuclei are detected
- Then classified as:
  - Abnormal
  - Intermediate
  - Superficial
  - Endocervical
  - and so on
Classification steps

- Nuclei are detected
- Then classified by:
  - Abnormal
  - Intermediate
  - Superficial
  - Endocervical
  - and so on
- Abnormal cells are sorted by “diagnostic interest”
Web-based Interface & Architecture

• Full web solution
  ➔ easy to integrate (LIS, telemedicine platforms)
  ➔ easy to maintain
  ➔ easy to collaborate
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Clinically Proven Performances

Clinical Validation in a public hospital in Cherbourg, France
- Comparative study with manual reading on NovaPrep slides
- Published in Diagnostic CytoPathology (May 2019)

Clinical Validation in a private laboratory in Lyon, France
- Comparative study with Hologic Imaging System on ThinPrep Slides
- Published in ActaCytologica (28th March 2019)
Validation Study in a private laboratory

- Non-interventional clinical study in a high throughput private laboratory
- Comparing CytoProcessor and the Hologic ThinPrep Imager
- Ground truth established by collegial review of discordance
- 9 investigators from a private laboratory

Clinical testing of a complete solution
Comparison of the 2 solutions

The same slides are diagnosed by the same cytologists, with Review Scope and CytoProcessor

Concordance?

- YES
- NO

Label « Ground Truth »

« Ground Truth » labeled by consensus

Each diagnosis in the study is then compared to the « Ground Truth »
Samples Distribution

Non-interventional clinical study in a high throughput private laboratory

Comparing **CytoProcessor** and the **Hologic ThinPrep Imager**

- Ground truth established by collegial review of discordance
- 9 investigators from a private laboratory
- Glandular lesions were also investigated

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1352 cases total</strong></td>
<td></td>
</tr>
<tr>
<td>802</td>
<td>NILM</td>
</tr>
<tr>
<td>192</td>
<td>ASC-US</td>
</tr>
<tr>
<td>231</td>
<td>LSIL (low-grade lesions)</td>
</tr>
<tr>
<td>27</td>
<td>ASC-H</td>
</tr>
<tr>
<td>87</td>
<td>HSIL (high-grade lesions)</td>
</tr>
<tr>
<td>13</td>
<td>AGC, AGC neo, and Adenocarcinoma</td>
</tr>
</tbody>
</table>
Higher Sensitivity of detection

CytoProcessor detects more abnormalities of any category, ASC-US or more severe, squamous and glandular

<table>
<thead>
<tr>
<th></th>
<th>ThinPrep Imager</th>
<th>CytoProcessor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US+</td>
<td>89 %</td>
<td>96 %</td>
</tr>
<tr>
<td>AGC+</td>
<td>100 %</td>
<td>100 %</td>
</tr>
</tbody>
</table>

CytoProcessor detects more low-grade and high-grade lesions.

<table>
<thead>
<tr>
<th></th>
<th>ThinPrep Imager</th>
<th>CytoProcessor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US</td>
<td>62 %</td>
<td>66 %</td>
</tr>
<tr>
<td>LSIL</td>
<td>80 %</td>
<td>88 %</td>
</tr>
<tr>
<td>HSIL+</td>
<td>82 %</td>
<td>88 %</td>
</tr>
</tbody>
</table>
Conclusion: Better performance at every level

**Imager:** 4% of patients with a lesion were missed

54 false negatives, including 14 LSIL and 1 ASC-H

**CytoProcessor:** 1.5% of lesions were missed

21 false negatives, including 6 LSIL

=> 2.5 fold decrease!

The gain in sensitivity is attained without sacrificing specificity.

CytoProcessor had a specificity of **87%** after training with a set of 100 slides. The Imager had a specificity of **85%** for the same slides.
A few cases

This case was diagnosed « LSIL » with Imager, and « HSIL » with CytoProcessor. It has been revised to « HSIL » by consensus.
A few cases

This case was diagnosed « LSIL » with Imager, and « HSIL » with CytoProcessor. It has been revised to « HSIL » by consensus.
A few cases

These cases were diagnosed « NILM » with Imager, and « LSIL » with CytoProcessor. They have been revised to « LSIL » by consensus.
Remote Diagnosis: Workflow Time Savings

Preparation Site

- Samples
- Slide preparation and staining
- Slide scanning
- Data進: Cytologic Processor
- Slide archive
- Patient record archive
- LIS

Internet

Review Site 1

- Workstation for pathologist or cytotechnologist
- Case opened using the LIS
- Case diagnosed using Cytologic Processor
- Diagnosis entered in the LIS
- Review needed
- Diagnosis verified

Review Site 2

- Review

Review Site 3

- Review
Comparison of the workflow steps

- Time data from Renshaw et al., 2016
- Many steps are avoided thanks
  - Digital Pathology
  - Removing glass slides handling

### Table 25. Comparison of the durations of workflow steps using data from this study (1) and from Renshaw et al., 2016 (2). The means ± standard deviation are shown. Time spent by machines (no human intervention necessary) is in italics and gray. NA = not applicable. FOV = field-of-view. LIS = laboratory information system.

<table>
<thead>
<tr>
<th>Imager</th>
<th>Task</th>
<th>Duration</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Load the ThinPrep Image Processor</td>
<td>2.90 ± 0.56 s / slide</td>
<td>Load the scanner</td>
</tr>
<tr>
<td></td>
<td>Process 25 slides</td>
<td>104 ± 5 s / slide</td>
<td>Scan 25 slides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>146 ± 16 s / slide</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>152 ± 61 s / slide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transfer slides to trays</td>
<td>1.82 ± 0.17 s / slide</td>
<td>Open image in CytoProcessor</td>
</tr>
<tr>
<td></td>
<td>Transfer trays to screeners</td>
<td>0.70 ± 0.14 s / slide</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Match slides with data sheets</td>
<td>0.72 ± 0.05 s / slide</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Distribute slides to screeners</td>
<td>1.19 ± 0.07 s / slide</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Load slide on Review Scope</td>
<td>19 ± 6 s / slide</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Alignment of FOV and verification</td>
<td>27 ± 6 s / slide</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Access and Interpret patient history in LIS</td>
<td>38 ± 13 s / slide</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Screen FOV and full manual screening if required</td>
<td>155 ± 89 s / slide</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Enter diagnosis in LIS</td>
<td>Counted in step 9</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Place slide back in tray</td>
<td>Counted in step 7</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Transfer slides to pathologists</td>
<td>2.08 ± 0.71 s / slide</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Repeat steps 7-12</td>
<td>2.08 ± 1.05 s / slide</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>143 ± 84 s / slide</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.48 ± 0.36 s / slide</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Transfer slides to storage</td>
<td>2.40 ± 0.89 s / slide</td>
<td>-</td>
</tr>
</tbody>
</table>
Workflow Time Savings

- Diagnosis is 1.5 times faster with A.I. assistance

<table>
<thead>
<tr>
<th></th>
<th>Imager</th>
<th>CytoProcessor®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.6 ± 1.5 min²</td>
<td>1.7 ± 0.8 min³</td>
</tr>
</tbody>
</table>

- Workflow steps requiring human intervention are 1.5-times faster with CytoProcessor

<table>
<thead>
<tr>
<th></th>
<th>Imager Total Time</th>
<th>CytoProcessor total Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technician (steps 1, 3-6,15)</td>
<td>10 sec/slide</td>
<td>4 sec/slide</td>
</tr>
<tr>
<td>Screener (steps 7, 9-13)</td>
<td>214 sec/slide</td>
<td>143 sec/slide (*)</td>
</tr>
<tr>
<td>Pathologist (steps 7, 9-12)</td>
<td>212 sec/slide</td>
<td>143 sec/slide</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>436 s / slide³</td>
<td>290 s / slide³</td>
</tr>
</tbody>
</table>

- **2.2 hours saved every 100 slides (with 5% pathologist review) based on the study**
- (*): Imager Screener time with only 40 slides experience on CytoProcessor®
- Practically, Trained Screener spend LESS than 90 sec more around 60sec !!!!

2 Time data from Renshaw et al., 2016.
3 Time data from Datexim’s clinical study using Thinprep slides.
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- What are its drawbacks (as a solution based on A.I.)?
- What are its possibilities?
Artifical Intelligence… Benefits

- A.I. for an aid in screening tasks, not for “diagnosis” tasks
  - If the human decision is difficult, it will not solve it
- Save time to use it on what really matters
  - Areas of interest instead of the whole slide
  - Slides that need a human review
- Improve diagnosis by assisting humans… BUT not replacing them!
  - Machine is sensitive, Human is specific
- Give access to state of the art technologies to a broader range of population by
  - reducing costs and human qualified resources needs
  - accessing remotely the results
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Performances rely heavily on data sets and how they are produced
- Effects of the staining reagents and protocol
- Effects of the cells preservation liquid and the technique to spread these cells
- Effects of the scanner that is used

Validation for any change in the samples processing chain
- Regulation compliance slows down the progress in the solution adaptability

The A.I. myth: “Give examples to the computer and it will solve your problems!”
- Data sets quality is of the utmost importance
- Data sets composition is also very important
- Data scientists and physicians collaboration is the key to get expected performances
- Even more true using Deep Learning technology
  - what is not learnt gives unpredictable results
Overview

What is CytoProcessor?

What are its performances compared to state of the art solutions on the market?

What are its benefits (as a solution based on A.I.)?

What are its drawbacks (as a solution based on A.I.)?

What are its possibilities?
Technology used allows to adapt without gathering millions of examples. Adaptations done and validated for other slide preparations (NovaPrep, ILSA), other staining reagents and protocols, other scanners (Leica SCN-400 & 3DHistech P250). In-house tools to adapt the solution with our partners. Annotation tools to create data sets. Pipelines to process these data and produce results to be validated. Adaptation made easy.

Adaptation made easy
Future Prospects

R&D in progress to sort automatically normal slides
- Ambition: sort 50% of the slides without missing any HSIL or worse cases
- Need many slides and diagnosis made by human to improve the results and to validate
Thank you for your attention!

VISIT OUR BOOTH #300 FOR DEMO & QUESTIONS
Scan the QR code to download the PV19 Mobile App or search for “Digital Pathology Association” in your app store.

Please visit the app to complete a brief Evaluation Survey. Your input is important and appreciated!

Presentations will be available to attendees following the conference.
Validation Study with Cherbourg Public Hospital

Ethics committee-approved non-interventional clinical study in a public hospital

- Comparing CytoProcessor and conventional screening by microscopy
- Ground truth established by collegial review of discordances
- 9 investigators from public and private laboratories
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<table>
<thead>
<tr>
<th>934 cases total</th>
</tr>
</thead>
<tbody>
<tr>
<td>655</td>
</tr>
<tr>
<td>57</td>
</tr>
<tr>
<td>107</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>90</td>
</tr>
</tbody>
</table>
Validation Study with Cherbourg Public Hospital

Challenging virtual slide images:
NOVAPREP slides with cell clusters and dark nuclei

Please see the product Technical File for the full clinical performance report.
Validation Study with Cherbourg Public Hospital

CytoProcessor detects more abnormalities of any category, ASC-US or more severe.

<table>
<thead>
<tr>
<th></th>
<th>Microscope</th>
<th>CytoProcessor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US+</td>
<td>93 %</td>
<td>95 %</td>
</tr>
</tbody>
</table>

CytoProcessor detects more low-grade and high-grade lesions. CytoProcessor detected one invasive cancer case, misdiagnosed by microscopy.

<table>
<thead>
<tr>
<th></th>
<th>Microscope</th>
<th>CytoProcessor</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSIL</td>
<td>76 %</td>
<td>88 %</td>
</tr>
<tr>
<td>HSIL</td>
<td>75 %</td>
<td>83 %</td>
</tr>
</tbody>
</table>

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