Antibodies to Artificial Intelligence

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Agenda

- Introduction to Leica Biosystems
- Pre-analytical Variables Discussion
- Artificial Intelligence (AI) Introduction
- Potential Applications of AI
- Observations & Conclusions

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Advancing Cancer Diagnostics, Improving Lives

Don’t wait another day!

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Our Mission
Advancing cancer diagnostics, Improving lives
Because Time is of the Essence...

Don’t Wait Another Day
Aligning and integrating the workflow to enable same day diagnosis

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Striving Towards Vision24

Enabling clinicians to efficiently provide patients a highly confident diagnosis within 24-hours from biopsy

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Bringing you Global Innovations

With the most relevant technologies from wherever they are

- 1,500 Patents*
- 460 Research and Development Experts
- 3,000 Associates

*TIncludes patents granted and patents filed.
Beginning to End Integration
A Holistic System-wide Approach to the Lab

1. Only company to own the workflow from biopsy to diagnosis
2. Dedicated consumables for our instruments
3. Enabling control of the lab through IT solutions

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.

Leica Biosystems – Confidential
Real World Example

Breast Cancer Testing Scandal Shines Spotlight on Black Box of Clinical Laboratory Testing

By Karyn Hede

Yrs. 1997 – 2005

400 out of 1000 Breast Cancer Cases Incorrect ER Status

100 patients have since died

Ineffective treatment been given to patients

Findings: “Overworked pathologists and a lack of Standards”

$17.5M settlement in flawed cancer tests


Karyn Hede

JNCI: Journal of the National Cancer Institute, Volume 100, Issue 12, 18 June 2008, Pages 836-844, https://doi.org/10.1093/jnci/djn200

Published: 18 June 2008

Quality and standards matter

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.

Leica Biosystems – Confidential
Every Step Affects the Slide Quality

Variability will exist without any artifacts. Standardization is the best path forward.

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Pre-analytical Variability

- Greatly affects downstream Image Interpretation
- Design out image artefact issues at the pre-analytical stage & design in quality
- Don’t use software to make up for sub-standard input
- Like drinking water from a dirty glass
## Pre-analytical Variability Impact

<table>
<thead>
<tr>
<th>Pre-analytical Variability</th>
<th>Artifacts</th>
<th>Impact to Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixation</td>
<td>Chatter</td>
<td>Higher scan failure rate</td>
</tr>
<tr>
<td>Section Thickness</td>
<td>Loss of tissue</td>
<td>Increased need for slide QC</td>
</tr>
<tr>
<td>Microtome technique</td>
<td>Folded Tissue</td>
<td>Substandard quality images</td>
</tr>
<tr>
<td>Water bath temperature</td>
<td>Non specific staining</td>
<td>Missed Information in images</td>
</tr>
<tr>
<td>Antigen retrieval</td>
<td>Variance in “Color”</td>
<td>Increased analysis time due to need to have software elimate artifacts</td>
</tr>
<tr>
<td>Staining Protocol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Examples of Histological Artifacts

Utilizing software to correct for poor preparation is a mistake

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Results

Liver tissue from the same tissue block stained with H&E at six different laboratory locations across North America.

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Role of AI in the Future of Pathology

Quicker Decisions

Better Decisions

Enable Pathology to focus on critical few

Early stage research AI is in the innovation phase of the adoption curve

- The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Applications of AI in Medicine

Radiology

Artificial Intelligence may help diagnose Tuberculosis in remote areas.

AI to identify TB on chest X rays

Ophthalmology

An AI Ophthalmologist shows how machine learning may transform medicine.

Eye scanning algorithm to detect a form of blindness

Cardiovascular

MRI – measuring blood flow through the heart.

FDA cleared

Range of applications in medicine, majority of which are in the research phase

- The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
## AI Horizons of Applications in Pathology

<table>
<thead>
<tr>
<th>Treatment Decisions</th>
<th>Diagnosis</th>
<th>True Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Human guided Image Analysis</td>
<td>• Fit for purpose classifiers</td>
<td>• Classifiers with general knowledge of the application field</td>
</tr>
<tr>
<td>• Algorithms quantify biomarker expression &amp; features</td>
<td>• Algorithms can find tumor</td>
<td>• Assimilate disparate data to derive conclusions</td>
</tr>
<tr>
<td>• Aid in treatment decisions</td>
<td>• Computer aided diagnosis</td>
<td>• Guides the pathologist where to look</td>
</tr>
<tr>
<td>• Examples: Circulating tumor cells, HER2 quantification</td>
<td>• Examples: Identify tumor and improve quantitation</td>
<td>• Example: Screening cases and bring unique patterns to pathologist attention</td>
</tr>
</tbody>
</table>

### General AI

- The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.

---

**Quantitative IA**

**Narrow AI**

**General AI**
Companies using AI Today

In 2016, companies invested $26B to $39B in artificial intelligence

Speech recognition & computer vision are the most common adopters

- Siri. Your wish is its command.
- TESLA MOTORS
- Amazon
- NETFLIX
- Pandora

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Artificial Intelligence (AI)

- Term was coined by John McCarthy in the 1955 proposal for the 1956 Dartmouth.

- Human intelligence exhibited by machines:
  - Narrow AI (face recognition, speech recognition, self-driving)
  - General AI (not there yet)

“We propose that a 2 month, 10 man study of artificial intelligence be carried out during the summer of 1956 at Dartmouth College in Hanover, New Hampshire. The study is to proceed on the basis of the conjecture that every aspect of learning or any other feature of intelligence can in principle be so precisely described that a machine can be made to simulate it. An attempt will be made to find how to make machines use language, form abstractions and concepts, solve kinds of problems now reserved for humans, and improve themselves. We think that a significant advance can be made in one or more of these problems if a carefully selected group of scientists work on it together for a summer.”

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Machine Learning (ML)

- 1st mention by Arthur Samuel, an IBM scientist, in 1959 three years after the definition of AI

- ML gives software the ability to change when exposed to new data

- It is a tool that is used in the development of AI.

- Deep learning, support vector machines (SVM), decision trees, Bayesian networks are some of the many machine learning techniques.

- Best used for problems for which input and output data is available but no algorithm to match input to output exists.

“Field of study that gives computers the ability to learn without being explicitly programmed”
Machine Learning: not new to Leica Biosystems

Aperio GENIE
Powerful Histology Pattern Recognition

Aperio GENIE is an interactive image analysis tool for digital pathology that automatically identifies regions of interest for research, e.g. differentiating tissue classes of interest in H&E, IHC, Immuno-fluorescence, or Special Stain slides.

POWERSFUL TISSUE CLASSIFICATION FOR BIG DATA
- User-defined classes and input images/annotations
- Iterative, pixel-by-pixel learning across the training set
- Classifiers can be easily tested for accuracy, and are readily retrained at any time
- Differentiate tissue classes of interest in H&E, IHC, Immuno-fluorescence or Special Stain slides

Aperio GENIE trained to identify and quantify Tumor, Struma and non-tissue
Aperio GENIE mark-up, with user-defined color-coded classification

Recalls table shows output: frequency of classes expressed as % of pixels

Aperio GENIE is an RUO product, for machine learning, and not suitable for Clinical Use

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
<table>
<thead>
<tr>
<th>Oncology</th>
<th>Toxiology</th>
<th>Neurodegenerative Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Biomarker Evaluations for prognostics, prediction, therapeutics</td>
<td>o Identification of Disease and Normal</td>
<td>o Neuropathology presentation of Alzheimer’s</td>
</tr>
<tr>
<td>o H &amp; E identification and assessments: Breast, Colorectal, Ovarian, Prostate, Gastric</td>
<td>o Xenograft evaluations</td>
<td>o Cerebral multi-morbidity assessments</td>
</tr>
<tr>
<td></td>
<td>o Applications for: Liver, Lymph, Lung, Lymphoid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrology</td>
<td>Validation or QC</td>
<td>Inflammation</td>
</tr>
<tr>
<td>o Identification of Glomeruli</td>
<td>o Biobank Quality: Skin, Bone, Lymphatic</td>
<td>o Brain Injury assessment</td>
</tr>
<tr>
<td>o Enumeration of podocytes</td>
<td>o Staining Quality: IHC, ISH, IF, FISH, H&amp; E</td>
<td>o Inflammatory dilated cardiomyopathy</td>
</tr>
<tr>
<td>o Assays including: H&amp;E, PAS, MAS, etc</td>
<td>o Digital Pathology vs Microscope assessments</td>
<td>o Immuno infiltrates in colorectal cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.</td>
</tr>
</tbody>
</table>

Leica Biosystems – Confidential
Example of using GENIE to evaluate histological standardization

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
H & E Verified with Cytokeratin

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
HER-2 FISH Assessment on Tumor Cells

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Deep Learning (DL)

- 1965 – 1st deep learning model was developed by Alexey Grigoryevich Ivakhnenko and Valentin Grigorevich Lapa

- DL is a form of ML

- DL refers to neural networks, specifically neural networks with large numbers of hidden layers

  - 1985 - First mention of the term “DL” in the machine learning field in a paper by Rina Dechter
  - 2011 - DL network by Cireșan et al. outperforms humans in traffic sign recognition contest
  - 2012 – Deep learning network halves error rate in Imagenet competition

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Deep Learning (DL) Explained

Deep-learning algorithms take many forms. Steve Finkbeiner’s lab used a convolutional neural network (CNN) such as this one to identify, with high accuracy, dead neurons in a population of live and dead cells.

**INPUT**
The network is trained using several hundred thousand annotated images of live and dead cells.

**TRAINING AI**
Over multiple iterations, the network discovers patterns in the data that can distinguish live from dead cells. Convolutional layers identify structural features of the images, which are integrated in fully connected layers.

**APPLICATION**
Challenged with unlabelled images, the network assigns each cell as alive or dead with high accuracy.

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.

Ref: Jeremy Linsley/Drew Linsley/Steve Finkbeiner/Thomas Serre
How does DL differ from ML?

<table>
<thead>
<tr>
<th>Disadvantage</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ It is something of a black box</td>
<td>▪ Solves problems that can’t be solved with traditional techniques</td>
</tr>
<tr>
<td>▪ Requires more data than traditional techniques</td>
<td>▪ Can use additional data to improve results</td>
</tr>
<tr>
<td>▪ May be fooled by carefully crafted adversarial examples</td>
<td>▪ It can “see” patterns that people can’t</td>
</tr>
<tr>
<td></td>
<td>▪ Can outperform humans on certain tasks</td>
</tr>
<tr>
<td></td>
<td>▪ Sensitivity and specificity higher than other techniques</td>
</tr>
</tbody>
</table>

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Deep Learning Considerations

Tumor in the Slide Stack

Annotate Everything

*Reference Garry Larson, The Far Side

Good Data is hard to come by. Well annotated data is VERY hard to come by

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Aperio AI Research & Development

Pathologist Input Annotations

Detailed Labelled Output

Hundreds of Slides Processed

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Deep Learning Examples

Deep learning can be used to identify patterns & across entireSlides

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Deep Learning Examples

Deep learning can be used to identify patterns

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Deep learning can be used at the cell level or even at subcellular level.

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Research & Development in AI is Exploding

>100 Companies in the AI space

No clinically approved AI Solution on market

Getting Started is easy. Going all the way with AI requires expertise in many areas

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
## Considerations to Create a Scalable Solution

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology Variance</strong></td>
<td>Samples sourced from a <strong>minimum</strong> of 3 sites: staining instruments, processors</td>
</tr>
<tr>
<td><strong>Training Set Biases</strong></td>
<td>Source training set data tagged by a <strong>minimum</strong> of 5 qualified pathologists</td>
</tr>
<tr>
<td><strong>Digital Scanner Impact</strong></td>
<td>Source digital images from more than one scanner model. Use the same models for training &amp; test sets</td>
</tr>
<tr>
<td><strong>Clinical Ground Truth</strong></td>
<td>Verification on a test set of Pathologist Scores is inherently flawed. Test sets should be compared to clinical output</td>
</tr>
<tr>
<td><strong>Scalable &amp; Integrated Solution</strong></td>
<td>The classifier has to exist within the Pathologist environment &amp; must be scalable to enable acceptable performance</td>
</tr>
</tbody>
</table>

**Challenge is to make 1 AI Classifier apply to (m)any Datasets**

---

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
Enabling the Future of AI in Pathology

Collaboration
- Plethora of AI frameworks and deep learning toolkits out there
- Meaningful applications require deep collaboration between Pathologist & Engineering
- Neither discipline can do it alone

Performance
- Large amounts of good quality data is key
- How best to verify?
- What is the acceptable performance standard?

Benefit
- Application needs true “value add” to the user and ultimately the patient
- Has to be more accurate or more reproducible than Pathologist reviews
- Has to be easy to use and easily fit within the Pathologist’s workflow

As an aid to the Pathologist

The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.
The clinical use claims described in the information provided have not been cleared or approved by the U.S. FDA nor are the products available in the United States.