A new auto-annotation method and machine learning strategy for detection and annotation of cancer areas in prostate biopsies

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Prostate cancer

- The second most common cancer in men worldwide
- 1/7 men will be diagnosed with prostate cancer
- 1.3 million patients in Europe and 1 million in the US undergoing biopsies every year
- Inter-observer variability in Gleason scoring is high

→ Major bottleneck in pathology workflow
→ Risk of therapeutic decision errors
Challenge

Implementation of an automated image analysis algorithm to serve as a decision support tool for pathologists.

Aim of study

Develop a strategy for highly specific detection and outlining of cancer areas in clinical biopsy whole slide images (WSI’s), which will serve as training material for Machine-Learning algorithms.
INIFY™ - Prostate

NOTE; INIFY™ Prostate is an investigational device, not yet CE-marked for clinical use
Why use a decision support tool?

Potential:

1. Reduce time for diagnosis
2. Minimize intra- and inter-individual variation
3. Increase accuracy and precision
4. Reduce Overall Work load for the Pathologist
Ground truth for training of algorithm?

When the intra- and inter-individual variation is high

In machine learning, the term "ground truth" refers to the accuracy of the training set's classification for supervised learning techniques.
Inter-individual variations in annotation

Goodman et al
Frequency of disagreement and error in Gleason scores, the kappa values reflecting agreement between the pathology reports and the “gold standard,” were 0.61 for biopsies (0 = pure chance 1= complete agreement 0.80 =very good agreement)

Brimo et.al
A major discrepancy in Gleason score was present in 14.7%, defined as a change to a different risk category
High-throughput immunostaining

Human prostate cancer sections

Secondary antibody

Primary antibody

Tissue

Alexa 488
Alexa 555
Alexa 633

KRT5/6 (basal cells)
KRT8/18 (epithelial cells)
AMACR (cancer marker)
Workflow

High-throughput immunostaining of prostate cancer sections

Immunofluorescence scanning

Detachment of coverslip High-throughput H&E staining

Brightfield scanning
Fluorescence image

DAPI (blue), KRT8/18 (green), KRT5/6 (orange) and AMACR (red)
Difficult area for marking epithelial cells
Immunofluorescence with KRT8/18
Use immunostaining as a mask
Cut out only epithelial cells
Basal cells detected with KRT5/6
Neoplastic cells detected with AMACR
Train neural network on cancer vs. benign
Verification by pathologists

Automated generated MasterAnnotation

Pathologist 1

Pathologist 2
Development of a decision support tool

**Master annotation**
Multiplex IF + H&E

**Method comparison**
Master annotation vs pathologist

**Mask for machine learning**
Master annotation verified by pathologist

**Verification**
Independent WSIs

**Product**
Decision support tool for pathologists
Separation of slides containing cancer
Automatic Gleason grading

More accurate diagnosis
Speed up decision process
Prioritize worst slides first
Segmenting Potentially Cancerous Areas in Prostate Biopsies using Semi-Automatically Annotated Data

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MIDL Paper, results

- The model produced promising predictions for the test biopsies
- The model performed on par with three pathologists
- The model even found missed, by the pathologists, areas in a few biopsies
Examples of heatmap predictions and the annotated ground truth

- HE slide
- Annotated by pathologist

Predictions
- M1pr
- M1,2pr
- M1bi
- M1,2bi on both 1 mpp and 2 mpp
- M1pr,bi and M1,2pr,bi were trained on prostatectomies first and then tuned on biopsies at 1 mpp and then both 1 and 2 mpp.

NOTE: This is a concept description, the product is not yet CE-marked for clinical use
Conclusion

• We have developed a robust and powerful method (master annotation) for specific and objective visualization of cancer areas in prostate biopsy whole slide images

• This forms the basis for machine learning to generate a highly accurate decision support tool for pathologists.
Project team

Medical technology software company specialized in image analysis and artificial intelligence

www.contextvision.com

Antibody-based proteomics for mapping the entire human proteome in normal tissue, cancer and cell lines

www.proteinatlas.org

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Exhibit booth #36
Dr Filippo Fraggetta,
Ospedale Cannizarro,
Catania, Italy

ContextVision installation

007 18:45–19:00
Implementation of the ContextVision INIFY™ tool for the automatic detection of prostatic cancer in a fully digital routine workflow
Filippo Fraggetta, Italy
S. Lionti, G. Giuffrida, C. Emmanuele, P. Pepe

NOTE This prototype was installed for research use only.