ECDP 2021 Scientific Program

Accepted Abstracts (Oral Presentation & Poster)

Table of Contents

Oral Free Presentations

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OP01-1: A Comparison of Scan Profiles in Digital Cytopathology

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Introduction
The use of digital pathology in cytology is very limited by the different characteristics of these samples compared to the histological preparations. Although the use of liquid-based cytology facilitates obtaining a cell monolayer, it is common to find both cells and other elements located in different planes. Most of the scanners used are designed for histological sections or mixed use.
Material and Methods
17 slides have been selected to assess the quality of digitization and consumption of resources. The samples have been processed with BD SurePathTM with a 13mm sample area diameter. The digitization has been carried out with the Pannoramic 250 (3DHistech) scanner. Five scan profiles have been compared: 20x in a single plane; 20x with 7 layers; 20x with 5 layers; 20x with 7 layers automatically merged according to the sharpest point; and 40x with 7-layer scanning.
Results and Discussion
Single-plane images don't have an acceptable level of detail for cytological diagnosis. The images in multiple layers give an image closer to that offered by the microscope with a greater consumption of resources. Reducing the 7 to 5 scan planes slightly reduces storage, negatively affecting the level of image detail. Multilayer scanning into a single fused layer reduces storage without a significant reduction in image quality. The images acquired in multilayer with the objective of 40x require a digitization time that is not feasible in daily practice.
Conclusion
Digitization of cytological samples continues to be a challenge. It consumes a lot of resources and does not reach the level of resolution of the light microscope. It is necessary to optimize the digitization technique with a general-purpose scanner and the performance of studies that allow the incorporation of digital cytology into daily practice. The digitization of cytological preparations is a useful tool for educational purposes and in quality control programs. Broad spectrum scanning equipment needs to include specific solutions for digital cytology.

OP01-2: Quality Control Stress Test for Deep Learning-Based Diagnostic Model in Digital Pathology

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Introduction
Digital pathology provides a possibility for computational analysis of histological slides and automatization of routine pathological tasks. Histological slides are very heterogeneous concerning staining, sections' thickness, and artifacts arising during tissue processing, cutting, staining, and digitization.
Material and Methods
Nine different types of artifacts common for routine histopathology practice were computationally generated. These artifacts included focus, elastic deformation, brightness, contrast, dark spots (e.g., dust, cover glass scratches and other kinds of contamination), synthetic threads overlying tissue, contaminating squamous epithelia, greasy fingerprints on the slide surface, and hematoxylin-eosin staining scheme. In addition, three image parameters, potentially affecting performance of DL algorithm, such as jpeg compression, rotation of patch, and flipping of patch, were tested. Using six datasets from four different institutions digitized by different scanner systems, we systematically explore artifacts' influence on the accuracy of the pre-trained, validated, and high-accuracy deep learning-based model for prostate cancer detection in histological slides.
Results and Discussion
Any histological artifact dependent on severity can lead to a substantial loss in model performance. Different artifacts present with different profiles of false positive and false negative misclassification. Using similarity analysis we show morphological clusters of tissue regions most prone to misclassification. Dataset, institution, and scanner system-dependent heterogeneity may be an important contributor to misclassification.
Conclusion
Strategies for the prevention of diagnostic model accuracy losses in the context of artifacts are warranted. Stress-testing of diagnostic models using synthetically generated artifacts might be an essential step during clinical validation of deep learning-based algorithms.

OP01-3: Automated Mitosis Detection from Breast Cancer Sections Sequentially Stained with H&E and Anti-PHH3

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Introduction
To develop an AI-based mitosis detection system on H&E whole slide images (WSIs) of breast cancer cases, a reliable ground truth is essential. The manual annotation approach depends on a pathologist, which is not only time-consuming and costly but also a potential source of variability. Therefore, an antibody-supervised, high-throughput strategy for an independent ground truth was investigated.
Material and Methods
H&E slides were scanned, re-stained for PHH3 and scanned again. Tumor regions were marked by a pathologist in 5 PHH3-stained WSIs from resection specimens. PHH3-positive structures within the annotated regions were classified by a pathologist into M phase (573) and G2 phase (247). Subsequently, threshold segmentation and filtering were performed to extract all PHH3-positive structures as candidates for classification. Patches (512x512 pixels, each) were created for 3998 candidates and used to train a Convolutional Neural Network (CNN). A VGG11 architecture with batch normalization and data augmentation was used. For registration of H&E and PHH3 slides, a hierarchical patch-based registration method was implemented, involving a global coarse alignment followed by hierarchical refinement of image tiles. To compensate for displacement and orientation of the tissue, an intensity-based registration approach modeled through affine deformations is used.
Results and Discussion
A CNN was trained three times, the F1-scores for each class are: M phase 0.85, G2 phase 0.71 and other 0.97. Including the G2 phase allowed us to refine the distinction of M phase detection compared to prior works. The positions transformed by the registration diverged by a distance of up to 7µm.
Conclusion
The registration procedure allows for the detected locations to be transferred to H&E, which enables a high-throughput ground truth creation for the development of an automated mitosis detector on H&E. Further improvements of the registration method can be expected by applying a non-linear deformation model.

OP01-4: How AI Deployment Has Driven Full Scale Digitization of Pathology for Routine Clinical Workflow

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Introduction
Maccabi Healthcare Services, a large healthcare provider with a centralized pathology institute, handles some 140,000 histology accessions per year, of which approximately 700 are prostate core needle biopsies and 7000 are breast biopsies. The growing shortage in pathologists, alongside increased cancer incidence, has driven Maccabi to search for technologies to support their pathologists in their diagnostic work.
Material and Methods
We deployed AI-based diagnostic solutions Galen Prostate CE-IVD, which detects and grades prostate core needle biopsies, and Galen Breast, which detects invasive and in-situ carcinomas in breast biopsies. The underlying algorithms utilize state-of-the-art Artificial Intelligence (AI) and Machine Learning techniques, and were trained on many thousands of image samples, obtained from slides from multiple labs and geographies, and manually annotated by senior pathologists.
Results and Discussion
Both algorithms were assessed for performance on independent data from various labs and demonstrated high specificity and sensitivity with AUC >0.99, including identification of cancers missed by pathologists. The deployed solutions were applied as a quality control system on all new prostate and breast biopsies entering the lab. The system raises an alert whenever it encounters a discrepancy between the automated AI analysis and the original diagnosis, prompting a second human review.
Conclusion
The AI-based Quality Control solution was proven extremely useful for increasing diagnostic accuracy and safety. To the best of our knowledge, these are the first AI-based prostate and breast diagnostic systems running in a live clinical setting. The demonstrated utility of the AI has supported the business case for full digitization of the lab.

OP01-5: Quantifying Intra-Tumor Gene Expression Heterogeneity for Survival Prediction Using Deep Learning

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Introduction
Intra-tumor heterogeneity on the molecular level is associated with challenges for precision medicine and diagnosis of breast cancer. We hypothesized that the association between molecular characteristics and morphological patterns captured by deep learning models from hematoxylin and eosin (H&E) slides can be used to provide spatially resolved measures of intra-tumor heterogeneity, and that such heterogeneity is associated with patient outcomes (time-to-event).
Material and Methods
Spatially resolved predictions of gene expression of 50 genes in the PAM50 gene panel were generated from deep convolutional neural network (CNN) models based on H&E slides from 485 breast cancer patients. From each predicted expression pattern, 11 texture features measuring the level of spatial heterogeneity were calculated per slide. A Cox proportional hazards model with elastic net regularization was fitted to predict patients' recurrence free survival using predicted gene expression and texture features.
Results and Discussion
Based on nested cross-validation, we found that the texture based features together with slide level gene expression could classify patients into two groups with different recurrence free survival probability (P-value = 0.0184, Log-rank test) whereas gene expression alone doesn’t provide significant prognostic value (P-value = 0.2390, Log-rank test).
Conclusion
The results indicate that CNN predicted spatial gene expression patterns can be used to quantify tumor heterogeneity, which contribute to the prediction of patient survival outcomes. The proposed methodology has lower cost and is less technically demanding compared to spatially resolved molecular profiling.

OP01-6: Automatic Lung Cancer Segmentation in Histopathology Whole-Slide Images with Deep Learning

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Introduction
Automated detection and segmentation of lung cancer in digital pathology whole-slide images (WSI) using artificial intelligence (AI) can be used to automate cancer detection during diagnosis of lung biopsies and for analysis of the tumor microenvironment via segmentation. Such an AI algorithm should be capable of dealing with most lung cancer subtypes.
Material and Methods
In this paper, we present a deep convolutional neural network for lung cancer segmentation in histopathology WSIs stained with Hematoxylin and Eosin. The model was trained with slides from the Automatic Cancer Detection and Classification in Whole-slide Lung Histopathology (ACDC-LungHP) challenge, which contain multiple lung cancer subtypes, including adeno-, squamous cell carcinoma, small cell lung cancer, and non -small cell lung carcinoma, not otherwise specified (NSCLC-NOS). The model was successively fine-tuned and validated on regions of interest in lung adenocarcinoma and squamous-cell carcinoma slides from The Cancer Genome Atlas (TCGA) project.
Results and Discussion
When only trained on ACDC data and applied to the official test set of the challenge, the model achieved the 3rd best performance on the challenge's leaderboard, with an averaged Dice score of 0.7982, and achieved an area under the ROC curve (AUC) of 0.867 on TCGA data. After fine-tuning it with TCGA data, the AUC metric rises from 0.867 to 0.983.
Conclusion
The developed model can segment multiple subtypes of lung cancer in histopathology whole-slide images stained with H&E. We made the trained model publicly available as a web-based algorithm at https://grand-challenge.org/algorithms/lung-cancer-segmentation/, which can be used for automated cancer segmentation for research purposes.

OP01-7: QA Impact of Validating and Standardising Ground-Truth Colour for Digital Pathology

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Introduction
Digital pathology scanners can introduce image artefacts that perturb the ground truth of original tissue slides, with colour difference a clear variable in image analyses. Different scanners introduce variability in colour fidelity and scanners of the same model can vary in raw image colour reproducibility. There may be further effects over time, usage-intensity and service visits. Quantitative colour calibration, validation and standardisation should form an essential part of digital pathology QA.
Material and Methods
Utilising FFEI's Sierra Slide, ICC profiles and colour management software a large proportion of the WSI scanner market was quantitatively sampled for colour errors from a variety of manufacturer and end-user environments. Output image colours were cross-analysed to establish the degree of scanner-agnostic validation and standardisation it is possible to achieve by correction to ground-truth absolute colour.
Results and Discussion
Case-studies from a diverse mixture of industry, research and medical applications highlight the QA advantages of applying an independent colour management technology, whether for pathologists, pharma scientists, AI developers, WSI device manufacturers or patients. Data presented demonstrates it is possible to calibrate, quantitatively validate and standardise scanners and images to high colour fidelity irrespective of scanner model, age or service.
Conclusion
Whole slide image colour can be validated and standardised by independent, scanner-agnostic methods that are complementary to digital pathology workflow and AI analysis. Quantitative analysis and correction to absolute colour can be deployed to develop stringent QA methodologies that minimise or remove the impact of colour variation on ground-truth analysis by human or AI.

OP01-8: QuPath Aided Image Analysis to Evaluate Tumor Nuclei: Application and Experience

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Introduction
Genetic testing of tumor tissue is widely used in routine clinical practice. It is known, that these methods are sensitive to the material provided: fixation, processing, tumor tissue presence are all of important significance. Current approach to estimate tumor representativeness is a semiquantitative evaluation by pathologist with high level of subjectivity and variability, which can lead to poor genetic testing results. It can be improved by computer vision technologies, using QuPath software and applying quantitative approach.
Material and Methods
We reviewed 272 cases for genomic profiling with traditional semiquantitative approach. Cases with low tumor nuclei score were digitized and analyzed by pathologist using QuPath software. The “Cell detection” analyze was applied for tumor and surrounding zones to quantify tumor and non-tumor nuclei. Scanning resolution 0.465, magnification x20. The outcome of the analysis was validated by pathologist by reviewing 5 to 10 zones and verifying quality of cell detection.
Results and Discussion
Out of 272 cases 98 (36%) were referred to QuPath aided analysis due to relatively low tumor nuclei count to eliminate subjectivity and reduce possible inadequate semiquantitative evaluation. The result of the analysis was reflected within the pathology report and provided to genetic labs. Computer analysis provided much support not only with solid pattern tumors but also with a cell chains infiltrating growth pattern and mucinous tumors, with crowed non-tumor environment. It was confirmed, that the method provides relatively objective data.
Conclusion
The computer aided approach to estimate tumor nuclei count is an adequate method for routine practice.

OP01-9: Colorectal Biopsies Assessment Using Weakly Supervised Classification of Whole-Slide Images

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Introduction
Colorectal cancer (CRC) is the third most common cancer worldwide. While it can be detected by imaging techniques, diagnosis is based on samples obtained from biopsies. In this work we propose a weakly-supervised approach to detect high-grade lesions in colorectal biopsies with high sensitivity.
Material and Methods
The dataset contains 1133 Whole Slide Images, scanned at 40x magnification, including colorectal biopsies and polypectomies. Three diagnostic categories were defined: non-neoplastic (normal colorectal mucosa, nonspecific inflammation, hyperplasia), low-grade lesions (conventional low-grade adenomas), and high-grade lesions (conventional adenomas with high-grade dysplasia and invasive adenocarcinomas). All cases were reviewed and labelled by two pathologists. If no agreement could be reached, a third pathologist reevaluated the slides. The model combines a Deep Residual Network (ResNet), Multiple Instance Learning and tile ranking, based on the expected value. Each slide is divided into 512x512 pixel patches and the one with the worst score is selected according to the ranking of the ResNet output. Since the labels are ordinal, the model optimizes a Quadratic Weighted Kappa loss, minimizing the prediction distance to the label.
Results and Discussion
The proposed method was trained on 874 cases and evaluated on the remaining 259 cases, measuring an accuracy, Quadratic Weighted Kappa and sensitivity of 84.17%, 0.795 and 93.33%, respectively.
Conclusion
Although still a very young field, these preliminary results are consistent with other computational pathology algorithms for CRC diagnosis, even the most supervised ones, indicating the promising performance of the method. Future experiments will increase the dataset and include annotated cases.

OP01-10: Training Robust Deep Learning Models for Medical Imaging Tasks with Spectral Decoupling

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Introduction
Deep learning models have been used extensively in medical imaging tasks showing impressive performance. However, the models are prone to overfit on spurious correlations which leads to poor generalisation to data generated by different centres, reliance on these correlations, and lack of robustness. These correlations can be inherent to the data or generated by the image acquisition methods. For instance, indistinguishable differences in the sharpness of the images from different scanners can degrade the performance of the model significantly.
Material and Methods
To address these challenges, we evaluate spectral decoupling (SD) in the context of medical image analysis. SD encourages the model to learn more features rather than overfitting on spurious correlations by simply adding an L2 penalty on the model's logits.
Results and Discussion
We use simulation studies to show that SD allows training on datasets with spurious correlations. Without SD, the model does not learn the original task and gives predictions based on these correlations. SD also significantly increases model robustness for data distribution shifts like differences in the sharpness of the images. To validate our findings, we train models with and without SD to detect prostate cancer on haematoxylin and eosin stained whole slide images. The models are then evaluated on prostate biopsy datasets from two different centres. The models trained with SD achieve significantly higher AUROC values in both datasets.
Conclusion
These results show that SD is a key method for training generalisable and robust models to be used across multiple centres, and recommend its use in all future medical imaging models.

OP02-1: Rapid Computer-Assisted Annotation of H&E Stains for Deep Learning

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Introduction
Deep learning has made automated analysis of conventional, low-cost H&E stains feasible. Yet, stain complexity often calls for a large annotated training set to ensure sufficient performance of the artificial neural network. This forms an extremely labor-intensive task, which often requires highly skilled pathologists. Instead, we propose a novel computer-assisted technique with virtual double stains that utilizes H&E and immunohistochemistry of exactly the same tissue section.
Material and Methods
Paraffin-embedded tissue from five melanoma patients were stained with H&E and digitized. H&E glass slides were then unmounted, re-stained with SOX10 (melanoma-cell marker), and digitized. To form virtual double stains, H&E and SOX10 images were superimposed. On SOX10 stains, thresholding classified (1) brown nuclei of melanoma cells, (2) blue nuclei of normal cells, (3) remainder tissue, and (4) unstained areas. To increase the probability of only transferring correct labels to H&E, high specificity of each classified object was sought. Automated labels were compared with manual annotations of normal and malignant cells in four random 0.1-mm^2 circles in each virtual stain.
Results and Discussion
Specificities of automated labels were 99% for both tumor and normal cells. In these small areas of comparison (in total, 2 mm^2), approximately 900 tumor cells and 600 normal cells were automatically annotated within seconds. All labels of immunohistochemistry were correctly allocated on coherent object in H&E stain.
Conclusion
With this technique, it seems manageable to create large annotated H&E training sets with high quality within a reasonable timeframe. The choice of immunohistochemistry may easily be adapted to other objects and cancer types of interest.

OP02-2: Detecting Helicobacter Pylori Using Deep Learning in H&E-Stained Histological Images

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Introduction
Identifying Helicobacter pylori (H. Pylori) on single auto-focus Haemotoxylin and Eosin (H&E) + Giemsa stained whole-slide images (WSI) using digital pathology software is a challenging, costly, and labor-intensive task. Pathology experts often need to analyze whole H&E slides in detail, which is expensive in terms of time, resources, and the diagnosis assessment may differ among experts. To alleviate these issues, we present the development and evaluation of a Computer-aided diagnosis (CAD) pipeline supported by a Deep Learning (DL)
Material and Methods
We sampled 60 WSIs from 48 different cases at 40x magnification, and using expert annotated positive regions for H. Pylori, we developed a UNET based model for segmenting H. Pylori. Among 60 H&E WSIs, 5 WSIs were selected for model training & validation, and 55 for the CAD pipeline study.
Results and Discussion
We evaluated our pipeline with the help of five pathology experts in 55 different cases. For each case, we created three evaluation scenarios - H&E, Giemsa, and H&E with the help of our pipeline, and finally, compared against Immunohistochemistry (IHC) stain as ground-truth evaluation criteria.
Conclusion
Our work confirmed that H. Pylori diagnosis suffers from suboptimal interobserver and intraobserver variability. We show that it is possible to use DL algorithms to identify H. Pylori, significantly reducing the time required for analyzing each slide and the diagnosis variance among pathologists. Hence, an opportunity for CAD emerges, showing that it is possible to improve the diagnosis process, easing the pathologist task while ensuring good qualitative results.

OP02-3: Orcaset: A Novel Dataset of OSCC Annotated Images

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Introduction
Artificial Intelligence algorithms in the Digital Pathology field are little represented compared to other branches. The lack of certified annotated datasets hampers the developmentof reliable algorithms. Several WSI datasets have being made available, mostly for challenges, or the TCGA. As far as we know, there are no oral squamous cell carcinoma annotated repository.
Material and Methods
We manually annotated four TMAs from the Surgical Unity archive ofthe University of Naples Federico II and all the WSI from the TCGA using Leica ImageScope software to generate a collection of fully annotated virtual cores. We then trained and validate four among the mostused architectures (SegNet, U-Net, U-Net with VGG16 encoder, and U-Net with ResNet50 encoder) using our dataset, composed of images sized 2250×2250 and 4500×4500, without a tiling processing.
Results and Discussion
Our first result is a publicly available dataset, called ORCA, containing annotated datafrom the Cancer Genome Atlas (TCGA) dataset, which can be used by other researchers for testing theirapproaches. Then, we trained and tested four different supervised pixel-wise segmentation methods fordetecting carcinoma areas in WSI, with a best result of a mIoU of 0.67.
Conclusion
A novel OSCC dataset is publicly available, which will allow to conduct new studies on Oral Squamous Cell Carcinoma. Moreover, although it is mandatory improve the model accuracy totranslate its usage to the bench-side, the utilisation of so large images (2250×2250 and 4500×4500) canhugely reduce time-demand for a WSI, compared to typical tiles of 224×224 or 512×512.

OP02-4: Novel Integrated AI-Based Solution for Supporting Prostate Cancer Primary Diagnosis in Routine Use

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Introduction
There is a high demand to develop clinically useful computer-assisted diagnostic solutions to bring about significant efficiency improvements for pathologists, reduce turn-around times (TATs), decrease error rates, and provide objective, reproducible, and detailed diagnoses. While several publications have demonstrated the feasibility of developing such algorithms and tools, this is the first report of a study in which pathologists perform the full diagnosis with the support of an artificial intelligence (AI)-based solution.
Material and Methods
A two-arm study in which the standard of care arm (using a microscope) was compared with an arm in which pathologist conducted the reporting using an AI-based solution workflow. Eight pathologists from six different sites in a large network of pathology labs participated in the study and reported on 2,411 slides from 320 prostate core needle biopsies (20 cases/ pathologist). Each case was reported twice, both with a microscope and with the AI-based solution randomized between pathologists. Detailed time measurements were taken for each step and compared between study arms, as was TAT. To assess the effect on the accuracy of reporting, discrepant reports were adjudicated and reviewed by a team of blinded uropathologists.
Results and Discussion
The study endpoints included accuracy of the AI-based algorithm on prostate cancer detection, grading and tumor quantitation, the efficiency of the pathologists reporting with the AI solution, turnaround time, and pathologists' satisfaction/feedback. The study demonstrated that reporting with the AI-based solution leads to >30% efficiency gains and a significant decrease of 1-2 days in TAT.
Conclusion
Significant efficiency gains are observed for the pathologist working with the integrated AI-based workflow, in addition to the potential of improving diagnosis accuracy and harmonization. Moreover, the overall user experience, as reported by pathologists, was markedly better with the AI solution compared to a microscope.

OP02-5: Correcting Differences in Multi-Scanners for Digital Pathology Images Using Deep Learning

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Introduction
In digital pathology, image-analysis algorithms can be developed to automatically quantify the expression of biomarkers of interest and provide a clinical diagnosis. When there are changes of scanning hardware or staining protocols, it is necessary to modify or re-develop algorithms due to failure in analysis and causes extra cost and time. Here, we developed deep-learning technology to convert Immunohistochemistry images across multi-scanners. As a result, we can use original legacy algorithms to analyze transformed images, which is beneficial to bypass algorithm re-development processes to minimize time and cost.
Material and Methods
We developed conditional Generative-Adversarial-Networks to transform six different biomarker-expression images (DAB, multiplex-brightfield-IHC) acquired from an updated scanner (VENTANA DP200) into new high-quality synthetic images with their image characteristics similar to those scanned using a previous-generation scanner (VENTANA iScanHT). 12,740 images with patch size of 128x128 were used as paired iScanHT/DP200 images for training, consisting of biomarker expressions CD34-aSMA, FAP/PanCK, Perforin/CD3, Ki67/CD8, FoxP3, and PD1, respectively.
Results and Discussion
The visual assessment showed that input-DP200 images were transformed to output-iScanHT images and had comparable image characteristics with target-iScanHT images. When we applied original-iScanHT algorithms to target and generated images, the evaluation of tumor-cell counts between outputs and targets resulted in Lin's concordance-correlation-coefficient of 0.86, 0.93, 0.95, 0.82, 0.80, and 0.97 for PD1, FoxP3, Ki67CD8, FAP/PanCK, CD34-aSMA, and Perforin/CD3 testing images, respectively.
Conclusion
We demonstrate the feasibility of compensating for differences in multi-scanners and show a capability in applying the legacy-iScanHT algorithms to transformed-DP200 images without re-developing algorithms. This approach has the potential to generate large datasets for future algorithm development of any new generation scanner.

OP02-6: Crowdsourcing of Deep Learning Algorithms for Diagnosis and Grading of Prostate Cancer in Biopsies

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Introduction
Prostate cancer treatment decisions rely on the Gleason grading of biopsies, which however suffers from inter- and intraobserver variability and a global shortage of pathologists. Artificial intelligence (AI) can potentially mitigate these issues by providing partial automation and decision support. We aimed at crowdsourcing the development of the next generation of AI algorithms for Gleason grading by organizing a competition open to developers around the world.
Material and Methods
We collected samples from Radboud University Medical Center and Karolinska Institutet, resulting in the largest public dataset of digitized prostate biopsies to date with 10,616 specimens from 2,113 patients for algorithm development. The competition was held on the Kaggle data science platform between April 21 and July 23, 2020. Algorithms were evaluated for concordance (quadratically weighted kappa, QWK) with uropathologist panels. During the competition, teams could receive performance estimates on a tuning set of 393 biopsies. Finally, the algorithms were evaluated on a test set of 545 biopsies, fully blinded to the participants.
Results and Discussion
In total, 1,290 developers from 65 countries contributed 1,010 algorithms. Already after the first 10 days, a QWK > 0.90 was reached, and after 33 days, the median QWK of all algorithms exceeded 0.85. Top-performing algorithms analyzed in detail showed a QWK (95% confidence interval) of 0.931 (0.918-0.944) and frequently used end-to-end training approaches and automated training label cleaning.
Conclusion
This study was the first to independently evaluate a set of AI algorithms by multiple developers for Gleason grading. Uniquely, the design of the competition allowed us to perform this validation completely independently of the algorithm developers, reducing sources of potential positive bias. These results in combination with earlier isolated studies each focusing on a single algorithm warrant evaluation of AI for prostate cancer diagnosis and grading in prospective clinical trials.

OP02-7: Transcriptome-Wide Prediction of Prostate Cancer Gene Expression from Histopathology Images

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Introduction
Gene expression profiling is a common approach for molecular phenotyping in contemporary cancer research and in molecular diagnostics. Cancer-related alterations in gene expression can cause morphological changes in tumor tissue that can be exploited to predict some molecular phenotypes directly from routine hematoxylin and eosin (H&E) stained whole slide images (WSIs) using convolutional neural networks (CNNs). In this study, we propose a computationally efficient, cluster-based approach to predict gene expression from H&E stained WSIs and conducted the first transcriptome-wide analysis in prostate cancer.
Material and Methods
The study is based on the TCGA PRAD study and includes WSIs and RNA-seq data of 15586 genes in 370 patients. Patients were split into a cross-validation (CV, n=278) and test set (n=92). First, we compared four different models in a subset of 2636 genes using CV. We then proceeded to model and predict all 15586 transcripts in CV using the best performing model. Finally, the significant associations (Spearman correlation, FDR-adjusted p-value below 0.0001) were validated in the test set.
Results and Discussion
The proposed cluster-based approach results in 1191 (45.15%) significant associations, as compared to 1030 (39.07%), 693 (26.29%) and 0 for the baseline models. In the subsequent transcriptome-wide analysis, 6618 out of 15586 (42.46%) transcripts could successfully be predicted in CV. 5419 (81.88%) of these associations could be validated in the test set.
Conclusion
These findings suggest that the proposed cluster-based model offers an inexpensive and scalable solution to predict gene expression from WSIs, providing opportunity for large-scale research studies and molecular diagnostics.

OP02-8: Digital Pathology Implementation Challenges: Scanning Issues and How to Solve Them

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Introduction
Many pathology laboratories are currently undergoing digital transformation successfully. Even so, the implementation process is not without its challenges. Scanning quality is improving each day but there are still issues to be solved and a lack of guidance on how to best perform image quality control (QC). We aim to evaluate the problems encountered when digitizing glass slides into whole slide images (WSI) and to suggest actions to address these problems.
Material and Methods
We performed quality analysis of 2963 WSIs. Errors were divided by those detected by the scanner and those detected by pathology QC (full WSI was screened at lower magnification and then zoomed in at 40x in multiple areas by pathologists/biomedical scientists). Scanning was performed in two Aperio GT450 scanners (Leica Biosystems).
Results and Discussion
Forty-six WSIs showed errors detected by the scanners (2.1% of the 2172 WSIs in which this information was available); mostly being non-read barcodes or image quality problems. During pathology QC we found 553 WSIs with issues (18.7%), of which 349 had apparent pre-scanning issues (such as small bubbles or mounting medium excess). Most commonly these corresponded only to focal blurred areas (440; 14.8%). Other problems were significant out of focus, duplicated or non-read slides.
Conclusion
We are currently implementing different measures to address these issues: the most important is to solve pre-analytical issues, such as labeling, coverslip positioning and slide cleanliness. Also relevant is the placing and cleaning of the scanners. Additionally, it would be valuable to have guidelines on the best way to perform WSI QC.

OP02-9: An International Validation Study of Automated Cancer Detection in Prostate Biopsies

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Introduction
Digital pathology provides an opportunity for computational analysis of histological slides and the standardized automation of some pathological tasks. The reporting of prostate cases is time consuming due to the large number of slides per case. In this retrospective study, we validate a deep learning-based tool for prostate cancer detection from patient biopsy samples.
Material and Methods
A prostate cancer deep learning-based detection tool was previously developed and implemented in HALO AI® and HALO AP® software (Indica Labs, Albuquerque, US). Two external validation cohorts of patients, with multifocal prostate biopsy, were analyzed from two high-volume pathological institutes: Cohort 1/Dataset 1 (Cologne, n full cases = 65, n cores = 1220) digitized by Hamamatsu S360 scanner, Cohort 2 (Wiener Neustadt, n full cases = 57, n cores = 693) digitized by Hamamatsu S360 scanner (Dataset 2) and Leica GT450 scanner (Dataset 3).
Results and Discussion
Similar high accuracy metrics were received for all three datasets implying good generalization among cases from different institutes and digitized by different scanner systems. For Datasets 1, 2, and 3, respectively, basal accuracy metrics without any forms of normalization: Sensitivity 0.97, 0.94, and 0.91, Specificity 0.93, 0.94, and 0.96, Negative predictive value 0.99, 0.98, and 0.97, and Overall accuracy 0.941, 0.942, and 0.946. Domain adaptation strategies improve the generalization and final accuracies. Several cores were detected where tumor was missed by pathologists (Cohort 1: n=7, Cohort 2: n=5). The average analysis time was 1 minute / core in Cohort 1, and 2 minutes / core for Cohort 2.
Conclusion
The prostate cancer detection tool reported high accuracy for prostate cancer detection in biopsy cases during external validation; independent of the institute or scanner used. It is fully integrated into Indica Labs' digital pathology platform and can assist pathologists in the form of pre-screening or quality control during analysis of prostate biopsy cases.

OP02-10: Design and Development of a Digital Pathology System. Experience at the 'Marques de Valdecilla' University Hospital

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Introduction
Digital pathology brings added value to diagnosis. It will be a key tool for pathology labs in the near future. Its implementation requires a careful design to meet the anticipated needs. A process of optimization of the equipment and the workflow of each laboratory is necessary.
Material and Methods
Two 3DHistech scanners have been installed. Pannoramic Desk set brings a 20x objective with capacity for one slide. It is intended for intraoperative specimen digitization. Pannoramic 250 brins20x and 40x objectives. It allows continuous workflow. It is used in the digitization of routine histological sections in selected pathologies. Storage planning is essential. We have a dedicated server with capacity to keep the images of the daily routine for 3 months and with an extension of the storage for cases of interest and teaching. The laboratory information system (GestPath) is fully connected to the digitization system. Depending on the type of sample and the technique used, the scanner performs the specific digitization for each slide. The visualization is done with the CaseViewer software through the LIS. During the implementation phase, a record of the digitized works has been made to obtain information about aspects that can be improved.
Results and Discussion
A total of 1990 slides have been digitized, including histochemical and immunohistochemical techniques. The most frequent incidents that have been detected are: samples outside the scanning area (11.3%), dirty scanned background (10.8%), focus errors (4.7%), coverslips and labels sticking out of the slide area (3.5%), soiled preparations (0.9%).
Conclusion
Previous processing of the sample is critical for obtaining an adequate digital image. It is necessary to adapt the working procedures to the technical requirements of the scanner. A limiting aspect of digital pathology is storage requirements. The integration of digital images in the LIS offers many possibilities for interaction, both for diagnosis and for graphic documentation, quickly and efficiently.

Poster Presentations

P01: Upconversion Nanoparticles as Lables for Histopathological Tissue Evaluation

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Introduction
For decades, haematoxylin and eosin (H&E) stains together with a horseradish peroxidase (HRP) label and diamino benzidine (DAB) as a chromogenic substrate, have been the gold standard to visualise tissue morphology and to detect markers of interest. However, these methods suffer from a narrow dynamic range, difficulties in quantification and limited possibilities regarding multiplexing. Fluorescent IHC techniques open the possibility for a quantitative readout but suffer from photobleaching and spectral overlapping emission bands in multiplexed applications. Here we present an upconversion nanoparticle (UCNP)-based technique to visualize the breast cancer marker Her2 in tissue sections, that allows to overcome problems associated with commonly used labelling techniques.
Material and Methods
Formalin-fixed paraffin-embedded breast cancer cell line and human breast cancer tissue were sectioned and labelled. Upconversion imaging of the human tissue sections was conducted in our prototype device and compared with a standard DAB-based IHC. The combination of UCNP and H&E counterstaining on the same slide was investigated.
Results and Discussion
Images obtained with our novel device demonstrate that our UCNP bioconjugates are excellent labels for the detection of cancer markers in tissue sections. Brightfield images prove that UCNPs do not interfere with the standard tissue evaluation by a pathologist. Additionally, brightfield and luminescent images can be merged to provide a better understanding of tissue morphology.
Conclusion
Staining solutions and a novel device developed by us give hope for more accurate diagnosis by keeping the advantage of H&E staining and combining it, in one image, with the luminescent data, ideal for generating ground truth for machine learning algorithms.

P02: Augmented Reality Microscopy (ARM) Utility for Breast Tumor Measurements

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Introduction
Pathology reports about breast carcinoma require pathologists to accurately measure tumor size, distance to surgical margins, and the size of lymph node metastases. This study aimed to assess whether novel Augmented Reality Microscopy (ARM) was easier to use and more accurate to obtain these measurements compared to using a ruler with a Manual Optical Microscope (MOM) and annotation with Whole Slide Imaging (WSI).
Material and Methods
Thirty archival cases of breast cancer were reviewed including 10 invasive ductal carcinomas (IDC), 10 with ductal carcinoma in situ (DCIS), and 10 with lymph node metastases. All measurements were compared in the same manner using MOM (Olympus BX43 light microscope), ARM (Augmentiqs), and WSI (ImageScope viewer, Leica). Concordance was defined as ≤ 0.2 mm difference.
Results and Discussion
All (100%) cases showed concordance between ARM and WSI measurements, and 80% showed concordance between MOM and WSI. Measurements ≤ 0.5 mm were most challenging with the MOM method, especially at 20x magnification. At low magnification (2x and 4x), WSI measurements were most challenging. MOM measurements were the most time-consuming, while ARM was the fastest method, followed by WSI.
Conclusion
ARM required no prior digitization of slides, was easy to use and quicker than MOM and was as accurate as WSI when measuring breast tumor size, distance to margins, and size of lymph node metastases.

P03: Microscope HD Video Streaming in University Pathology Teaching through YouTube and Twitch

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Introduction
Pandemic situation has forced a rapid adaptation of theoretical-practical university teaching. Videoconferencing systems, have replaced most of the face-to-face classes without special problem. Pathology practical teaching has required an adaptation in which digital pathology has intensified even more learning models with remote diagnosis.
Material and Methods
Our practical teaching based on scanned digital microscope slides has been complemented with HD Video streaming technology. We have installed a HD camera with 1080p video output (Hayear) in a trinocular microscope connected with a video capture device to a computer and broadcast images with OBS (Open broadcasting software) of routine daily cases. Video transmission was directed to YouTube and Twitch and students access these platforms to watch the images and follow the explanations of the teachers. The dialogue and questions interaction was maintained in a videoconference with Microsoft Teams.
Results and Discussion
HD video image quality is very high, analogous to direct viewing under the microscope. Students already familiar with scanned digital microscopic sides have acquired a new view of pathological diagnosis. The practice model maintains the selected cases of each type of representative pathology lesions, and incorporates the direct view of the real diagnosis. Professors transmit in real time their diagnostic activity, while explaining the morphological criteria or the additional techniques by immunohistochemistry or molecular pathology that the microscopic patterns suggest for confirmation or targeted therapy.
Conclusion
High definition video transmission in real time brings for university students the most direct approach to the diagnostic pathology and to the knowledge of the morphological patterns of each entity. For them it represents the understanding in a much more exact way the work of attending pathologists and the importance of their role in the hospital management of patients and the learning of prognostic and therapeutic orientation of lesions.

P04: Analysis of Paraffin-Embedded Slides of Esophageal Carcinoma After Different Treatments Using QuPath

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Introduction
The microscopic tumor extension during or after radiochemotherapy and its correlation with the tumor microenvironment are presently unknown. Therefore, we analyzed resection specimen of esophageal carcinoma patients having undergone neoadjuvant radiochemotherapy followed by resection (NRCT+R) or resection (R) alone.
Material and Methods
Esophageal resection specimen [n=20; five NRCT+R and five R from each, squamous cell carcinoma (SCC) and adenocarcinoma (AC)] were analyzed in QuPath-Version.0.2.3. Paraffin-embedded tumor sections were stained with hematoxylin/eosin, or with antibodies specific for HIF-1alpha (hypoxia), Ki67 or p53. After the whole slide scan, trained cell classifiers enumerated tumor positive cells (TPC). TPC were quantified by QuPath and two independent observers. Ki67 and p53 within hypoxic region were quantified to estimate tumor cell proliferation and mutational status, and results were correlated with the respective treatment. Statistical analyses were performed using one-sided Wilcoxon signed-rank test and Bland-Altman analysis [OriginPro®9.8 (OriginLab corporation)].
Results and Discussion
The mean difference in TPC between QuPath and manual quantifications was -2.1 [SD ±1.96]. In tumor resection of patients with SCC, the Ki67- or p53-TPC overall were statistically significantly lower in the NRCT+R than in the R cohort (Ki67: p=0.01, p53: p=0.03). Conversely, Ki67- or p53-TPC within hypoxic region were statistically significantly lower in patients with AC receiving NRCT+R compared to R (p = 0.01).
Conclusion
QuPath provides accurate and reproducible quantification of TPC from resection specimens compared to manual counting. Changes in the tumor microenvironment induced by NRCT were detected in both SCC and AC. A larger study is planned to validate these preliminary results.

P05: Instant Digital Pathology for Rapid Evaluation of Thyroid Cytology: A Pilot Study and Molecular Test

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Introduction
Confocal Laser Fluorescent microscopy (CFM), known as instant digital pathology, is emerging tools for fast imaging from fresh unfixed tissues. It requires minimal preparation avoiding material damage or loss. FCM VivaScope-2500 is used to accelerate intraoperative evaluation of surgical margins. No data are still available for its use in thyroid cytology. Aims: assess the Vivascope performance for rapid adequacy evaluation and, whenever possible, for morphological immediate diagnosis; explore feasibility of molecular analysis on these samples.
Material and Methods
Twenty patients undergoing fine needle aspiration (FNA) of thyroid nodules, having US EU-TIRADS risk ≥ 3, and with indication for surgery were enrolled. Cellular material from first FNA pass was delivered on foam-like scaffolds while the second pass was smeared for routine cytology. Scaffolds were freshly observed with VivaScope to obtain H&E-like images and then submitted for permanent sections and molecular analysis. Pathologists skilled in thyroid diseases evaluated in blind Vivascope images, paired routine FNA and final surgical histology.
Results and Discussion
CFM allowed satisfactory digital images; adequacy was confirmed in all cases. Architectural changes (papillary or microfollicular structures) and morphological details were evaluable from fresh cellular specimens in a new visual modality. Concordance between FCM evaluation and routine FNA diagnosis reached 75% Concordance between VivaScope and final histological diagnosis from surgical specimen was 85%. Feasibility of molecular analysis on post VivaScope material was demonstrated.
Conclusion
Instant digital pathology using cell-capturing scaffolds allows fast adequacy assessment of cytological samples and supports morphological evaluation; molecular analysis may be added. CFMs represent innovative tools for management of patients with thyroid nodule.

P06: Physical Color Calibration of Scanners for Deep Learning Based Diagnosis of Prostate Cancer

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Introduction
It has been observed that there exists a drop in performance on deep learning based diagnosis of prostate cancer caused by the technical instability introduced by whole slide images (WSIs) acquired using different scanners in various institutions. To solve this problem, Sierra slide from FFEI is introduced to estimate the color profiles of scanners and transfer the color of the corresponding images to a standard profile.
Material and Methods
A total of 3,653 biopsies scanned by Aperio ScanScope AT2 were used for training, while 100 tuning and 230 testing slides were scanned with a Hamamatsu NanoZoomer S360 C13220 01. One Sierra slide is scanned on both scanners to estimate their scanner-specific ICC color profiles for the color transformation, where the profile of standard RGB has been chosen as the target. Ensembles of Inception V3 DNNs are used for patch level training and prediction, and gradient boosted trees implemented in Xgboost for WSI level prediction of cancer presence. The DNNs are trained and evaluated both with and without calibration and their corresponding prediction performances will be compared. Approximate annotations of malignant regions and Gleason grading were performed by a single pathologist (L.E.).
Results and Discussion
As a preliminary result, we have successfully applied color calibration on several images, resulting in visually more natural colors. By evaluating the results of the prediction by the two models in terms of AUC compared to the pathologist's diagnosis, we expect to observe if color calibration using the Sierra slide improves the performance of deep learning for prostate cancer detection and Gleason grading on WSIs.
Conclusion
Color variances between original images from different scanners can been standardized using the Sierra color calibration slide. As an ongoing project, we aim to confirm if color calibration using Sierra slides is an effective tool for improving the generalization of AI-assisted cancer diagnosis algorithms across scanner platforms.

P07: A Python Application Programming Interface for Accessing Philips iSyntax Whole Slide Images

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Introduction
Scanner vendors store Whole Slide Images (WSI) in different proprietary formats, complicating algorithm development. Vendor-neutral libraries such as OpenSlide lack support for the iSyntax format used by the Philips IntelliSite scanner, gaining in popularity due to FDA approval. While Philips recently released a Software Development Kit (SDK) for accessing iSyntax, challenges remain. Firstly, the SDK represents a relatively low-level interface requiring familiarity with the iSyntax format. Secondly, due to lack of integration in vendor-neutral libraries, developers cannot rely on a single, consistent application programming interface (API). We present a Python API facilitating seamless access to iSyntax data, requiring minimal changes to applications designed to rely on OpenSlide.
Material and Methods
The API enables access to: (1) a label image for slide identification, (2) a low-resolution macro image of the slide, and (3) the WSI scanned at high resolution. Compatible metadata attributes are provided as DICOM tags, and other metadata adhering to the OpenSlide generic properties format. The API enables both reading the entire WSI at a desired level of resolution, and extracting rectangular regions from any desired pyramid level utilizing the efficiency of the iSyntax Discrete Wavelet Transform scheme. The names and input parameters of the methods adhere to the OpenSlide API, allowing developers to use existing code developed on top of OpenSlide without modifications.
Results and Discussion
We scanned prostate needle biopsies from the Stockholm-3 trial on the Philips scanner for testing the API. We verified that our API can successfully interface the iSyntax format with a previously developed artificial intelligence system for Gleason grading.
Conclusion
The presented API serves as a powerful interface between algorithm developers and the iSyntax format. On top of the API, developers can easily build algorithms while spending minimal effort on dealing with the proprietary format or on modifying existing applications.

P08: Automatic Segmentation of Tumor Infiltrating Lymphocytes in Breast Histopathology Slides

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Introduction
Tumor-infiltrating lymphocytes (TILs) are connected with improved prognosis in breast cancer patients and play an essential role in mediating response to chemotherapy. We aim to provide an automatic workflow, allowing for quantification of TIL and stromal area.
Material and Methods
Two whole breast histopathology images, provided by the Pathomorphology Department University Hospital, have been selected and divided into smaller images, of which 281 representative samples were segmented into 3 categories: TIL, neoplasm and stroma, using the criteria defined by the International Working Group for TILs in Breast Cancer (2014). The resulting masks were subsequently used to train a segmentation residual network model – ResNet34 in the Python environment.
Results and Discussion
The final classifier was then used to segment a new dataset of 22 images. Resulting masks were compared with human created segmentations based on the ratio of TIL area to the sum of TIL area and remaining stromal area (as approximated based on pixel count in each mask). Our predicted ratios correlate with ratios based on human selection with $r = 0,94$, $p<0,001$.
Conclusion
We have successfully created a segmentation algorithm that can approximate lymphocyte infiltrate in breast cancer images. Next we would like to apply it to breast histopathology slides to support traditional pathological assessment of TILs.

P09: Normal and Neoplastic Salivary Gland Segmentation Using Machine Learning – A Pilot Study

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Introduction
The advent of digital pathology and the availability of whole slide images (WSI) has allowed the application of artificial intelligence (AI) and machine learning (ML) to pathology, supported by advancements in computing power and technology. Numerous studies have used AI/ML to differentiate between normal and cancerous tissues, such as breast cancer, but its usefulness in salivary gland tumours remains unexplored. The aim of this pilot study was to use ML for differentiation between normal salivary gland tissue and salivary gland tumours.
Material and Methods
Normal salivary gland tissue and benign and malignant salivary gland tumours (SGT) were used. 30 WSI were used for initial training and testing, including 20 WSI of normal glands and 10 WSI of SGT including pleomorphic adenoma and adenoid cystic carcinoma. An open-source image analysis software (QuPath) was employed, and the representative areas classified into three different classes including normal serous gland, normal mucous gland and tumour. Nine unseen WSI (3 of each class), including both gland types (serous and mucous) as well as tumours, were used to test and validate the classifier and perform automated analysis.
Results and Discussion
Our 'black-box' classifier within this small cohort showed good differentiation between normal serous and mucous glands as well as tumours. The detection accuracies were 98%, 76 % and 67% for serous, mucous gland and tumour detection respectively.
Conclusion
Our novel pilot data shows that ML can be used for analysis and differentiation between normal salivary glands and SGT. A larger cohort needs to be analysed to determine the true significance of these findings.

P10: An Approach to Resource Saving Histology Dataset Expansion

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Introduction
Annotated datasets are still a bottle neck for artificial intelligence in pathology. We report an approach to expand existing histology datasets with less efforts from pathologists.
Material and Methods
Previously published dataset of breast lesions (104 cases, 23 k tiles), 57 new cases to expand dataset and 50 new test cases. Classification groups: non-specific invasive cancer differentiated, non-specific invasive cancer low-differentiated, lobular invasive cancer, non-invasive ductal carcinoma, fibroadenoma, fibrocystic changes, papilloma and background. Initial convolutional neural network model was trained with published dataset and applied to new cases on a tile-by-tile bases. Two kinds of resulting tiles were captured for further steps. Confident tiles with classification probability 80% and more (overall 46 k tiles). And doubt tiles, which included two competing categories, each not less than 40% probability (overall 28 k tiles). The third group was a summary of two groups (overall 50 k tiles). These groups were added to published dataset. Based on the expanded datasets three new models were trained and tested with test cases. The analysis results were evaluated by a pathologist.
Results and Discussion
We identified, that models trained on dataset with doubt tiles outperformed initial model and model with confident tiles in malignant vs benign tissue, though the quantity of doubt images added less than 20% to initial published dataset.
Conclusion
To form a new training dataset based on existing one, one should include controversial or imperfect tiles. It improves model learning even with fewer image quantities.

P11: Neural Network Analysis Visualization Approach for Diagnostic Pathology

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Introduction
Neural network (NN) analysis is getting wider for both research and diagnostic pathology. Currently pixel-by-pixel classification approach is the leading one, though it demands comparatively huge computational resources. We developed an approach for pathologists to interact with a whole slide image (WSI) NN analysis.
Material and Methods
We used a server-based software (SaaS) to upload WSI, analyze it with NN model on a tile-by-tile basis for primary breast lesions and cancer metastases. The classification task analysis is typically represented with probabilities for each of the categories. We used the category with the highest probability for each tile to color the tile, provide classification category and the probability. Pathologist can apply cut-off for the probability and observe only those tiles with probability higher than the chosen. Additionally, tiles quantity for each classification group were provided with corresponding probability.
Results and Discussion
The approach and its application to routine diagnostic process were verified by 5 qualified pathologists. Testing sample included 57 cases of primary breast lesions and 30 cases with 137 lymph nodes, 77 positives. Colored tiles and text information with the highest probability were recognized as convenient approach for WSI NN analysis. It was identified, that in 40 to 50% cases pathologists used additional information to review statistical data on tiles quantity with different probability.
Conclusion
We developed an approach and a software tool for pathologists to interact with WSI NN analysis, which includes visual information, statistical data and ability to adjust it to a demanded level of classification confidence.

P12: QuPath-Based Approach to Evaluate Liver Parenchyma Status: Preliminary Data

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Introduction
Liver parenchyma condition is important for evaluation dead donor organ status. Current approach is based on visual evaluation and semi-quantitative estimation of hepatocyte with fat degeneration. The approach is a semi-quantitative and subjective. The aim of the study was to develop an approach using QuPath software and whole-slide images to objectively evaluate dead donor parenchyma changes comparing to normal liver
Material and Methods
17 needle biopsy samples from potential alive donors (AD), 15 surgical biopsy samples from dead donor (DD). Hematoxylin and eosin stained slides were scanned with x20 magnification and 96 dpi. Computer analysis of the whole slide image was performed with QuPath software, using cell detection applied to the whole section, only liver parenchyma selected with no portal tracts. ANOVA analysis was applied to distinguish two groups.
Results and Discussion
We identified following significantly distinguished features. Quantity of cells per sq mm: DD 23% less than AD. Quantity of cells per sq mm with nucleus circularity >0.9: DD 50% less than AD. Mean nucleus circularity for all evaluated cells was 5% lower at DD group.
Conclusion
We propose an approach, which allows objective evaluation of liver parenchyma status and identify features, distinguishing dead donor liver changes. The study is ongoing with the focus on finding objective criteria to evaluate liver parenchyma status and potential transplantation outcome.

P13: Primary and Metastatic Tumor Tissue Datasets to Train Neural Network Model for Metastasis Detection

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Introduction
Traditional methods of detecting lymph node metastases stained with hematoxylin and eosin are labor-intensive, time-consuming and routine. Convolutional neural network (CNN) can help pathologists to reduce or eliminate human factor, but annotated datasets are of limited availability. The aim of the study was to identify if initial tumor samples applicable to train models to identify metastases
Material and Methods
We prepared three datasets and trained three corresponding CNN models. The first dataset and model: 6 cases, 126 lymph nodes, 91 with metastases, 16048 tiles. The second: primary breast cancer: 41 cases, 12943 tiles. The third is a summary of the first and the second. Models were trained with efficintnetB0 and the outcome was tested with 137 newly collected lymph nodes, including 77 with breast cancer metastases.
Results and Discussion
Model 1 demonstrated higher sensitivity than model 2 and 3: 86.3%, 74.7% and 67.9%, respectively. NPV: 80.4%, 70.4%, 63.4%, respectively Although group 3 had almost two times image quantity comparing to 1 and 2, model 3 demonstrated the lowest sensitivity of all models. The specificity and PPV did not differ significantly in all CNN models and had a range 67.2-74.6% and 75.3-78.5%, respectively.
Conclusion
CNN model trained with metastases outperformed CNN trained with primary tumor samples, though having lower dataset size. It was demonstrated on a limited dataset with only breast cancer metastasis and needs further research to confirm.

P14: Semiautomated Workflow for Tissue-Microarray Analysis on Tumors of the Central Nervous System

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Introduction
Meningiomas are the most common primary intracranial neoplasms. They are classified into 3 grades of aggressiveness but even benign meningiomas also recur in up to 30% of the cases. Their diagnosis relies on well-established histological criteria but it suffers from inter-observer variability and lack of quantitative information. The use of state-of-the-art methodologies for automated image analysis combined with data science approaches in large series of samples may provide new markers for decision support systems in the management of these tumors.
Material and Methods
In this work, we developed methods and pipelines for semiautomated analysis of digitalized hematoxylin-eosin from 37 meningiomas included in tissue microarrays (TMA) with a large follow-up. We designed and explored multiple parameters in order to reflect cell populations and morphology distributions in the tissues. Image, statistical and machine-learning analyses were performed using in-house MATLAB scripts.
Results and Discussion
Principal Component Analysis (PCA) and Partial Least squares Discrimination Analysis (PLS-DA) models were built for exploring data structures and for discrimination between clinically relevant groups. Automated TMA de-arraying and identification of samples were achieved. The analysis showed associations with recurrence and clinical characteristics for several parameters. Specifically, we found associations with the most frequent nuclei size and with other properties of nuclei morphology distribution in the sample.
Conclusion
Our results suggest that the semiautomated analysis of whole digitalized slides from TMAs combined with multivariate predictors may help in the decision-making process in the management of meningioma (funding from GV/2020/048).

P15: Detection and Segmentation of Lymph Nodes within Large H&E Datasets Using Explainable Features

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Introduction
The analysis of resected Haematoxylin-Eosin (H&E) stained lymph nodes (LNs) is currently limited to establish if they contain metastatic tumours. Automatic analysis of the microarchitecture is difficult partially due to the lack of annotated LNs for machine learning. We hypothesize that machine learning is able to (1) find digital H&E slides containing LNs by generating probability maps via deep learning and using shape and statistical features extracted from the maps, and (2) segment LNs in those images.
Material and Methods
We used 759 H&E slides containing LNs delineated by an expert pathologist, and 1018 without LNs, from oesophageal cancer patients recruited into the OE02 trial. The dataset was randomly divided into training (80%) and test (20%) sets. With our innovative method, a UNet architecture was used to generate pixel-wise predictions for LN presence, from which handcrafted features were extracted. These features trained an optimized xgboost model which predicted if the region truly contained a LN.
Results and Discussion
All results reported were evaluated on the test set. The accuracy of automatically detecting images with LNs was 0.95, compared to an accuracy of 0.91 obtained using the current state-of-the-art method (thresholding). For LN segmentation, our model achieved an overall Dice score of 0.78 (image-level) and 0.71 (LN-level).
Conclusion
The first part of our workflow can be used in a routine diagnostic setting; the second part would allow large-scale investigations of LNs, identifying new clinically relevant biomarkers that might lead to personalized treatment. External validation on other LN H&E datasets from various cancer types is necessary before clinical implementation.

P16: Reducing the False Negative Prostate Biopsies Using Deep-Learning Assessment of Benign Biopsies

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Introduction
Transrectal ultrasound guided systematic prostate biopsy is common to establish a prostate cancer diagnosis. The 10-12 prostate core biopsies only sample a minority of the prostate volume and tumour tissue between biopsy cores can be missed, leading to low sensitivity to detect clinically relevant cancers. We examined whether a deep-learning model can detect prostate cancer associate morphological patterns in benign core biopsies.
Material and Methods
We included 6,985 whole slide images from 893 men with prostate cancer and 8,246 images from 712 benign men, digitized at 20X magnification, down-sampled by a factor of two and split into image tiles of 299×299 pixels with 50% stride (14,674,954 tiles). A deep convolutional neural network was optimized using 1013 men for training and 254 men for validation for a binary classification of benign cores from benign men versus benign cores from men with prostate cancer. Classification performance was evaluated in an internal test set (316 men) using Receiver Operating Characteristics (ROC) and Area Under the ROC curve (AUC). Sensitivity on patient level prediction was evaluated at specificity of 0.99 and 0.95.
Results and Discussion
We observed a tile level AUC=0.702, a slide level AUC=0.727, and a patient level AUC=0.739. Sensitivity on patient level classification was 0.043 and 0.224 at specificity of 0.99 and 0.95, respectively.
Conclusion
We demonstrated that, with low false positive rate (specificity=0.95), over 20% of cancer patients were detected based on benign core biopsies, suggesting that the false negatives caused by sparse sampling in routine diagnostics could be improved.

P17: Using Deep Learning to Predict Gene Expression-Based Breast Cancer Proliferation Score from H&E WSIs

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Introduction
Introduction: Breast cancer (BC) is the most common cancer in women. Routine BC pathology classification only provides limited risk stratification of patients. Recently, novel risk scores based on biomarker panels are emerging as a potential improvement, but requires lab-based assays that are costly and time-consuming. The aim in this study is to determine if deep convolutional neural networks (CNNs) can be applied to predict a gene expression-based proliferation score from routine H&E whole slide images.
Material and Methods
Material and Methods: WSIs and RNA-sequencing data from N=991 surgically treated invasive BC patients were included from Clinseq and TCGA datasets. A deep CNN model was optimised to predict a continuous proliferation score from WSIs using RNA-sequencing as ground truth, and assessed using Spearman correlation. Prognostic performance was assessed through Cox proportional hazard modelling, estimating hazard ratios (HR) with 95 % confidence intervals of recurrence-free survival.
Results and Discussion
Results: The RNA-seq estimated proliferation score could be predicted from WSIs using the CNN model with a Spearman correlation of 0.691 ($p<0.001$). A high proliferation score, RNA-seq and predicted by the CNN, was significantly associated with higher risk of recurrence or death in univariate analysis HR=1.5 (95 % CI 1.0-2.1) p=0.028 and HR=1.5 (95 % CI 1.0-2.1) p=0.039.
Conclusion
Conclusion: The results suggest that the gene expression-based proliferation score could be predicted from BC morphology captured in routine H&E stained WSIs using a CNN model, with comparable prognostic performance to the RNA-seq based proliferation score.

P18: The Effectiveness of Whole Slide Imaging in Assessing the Invasive Breast Carcinoma Cases

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Introduction
Nowadays, especially with the pandemic and restriction rules due to infection with SARS-CoV-2, digital pathology is gaining more and more ground. The purpose of the present study is to assessed the efficacy and the utility of WSI obtained from selected cases of breast invasive carcinoma, including both hematoxylin-eosin (H&E) and immunohistochemical slides obtained in our pathological department.
Material and Methods
Our study includes 100 invasive breast carcinoma cases, each case being composed of one H&E-stained glass slides and four immunohistochemical stained slides with estrogen receptor, progesterone receptor, KI67 and HER2-neu biomarkers. All the slides were assessed by two experienced pathologists: firstly, at light microscopy and secondly, after nine weeks of washout period, the WSI of the same cases. All the slides were scanned with HuronTissueScope 4000XT slide scanner and the assessment of the immunostain of the WSI were done using the free QuPath program. SPSS version 26.0 was used to perform the statistical analysis in order to evaluate the concordance and agreement between the diagnosis of the two specialists. Intra- and inter – observer agreement between the results of light microscopical and WSI assessment were realized using Cohen κ statistics
Results and Discussion
An excellent agreement was recorded for H&E stain diagnosis on light microscopy and WSI, but a less value was obtained when immunostains were evaluated by the two methods. An excellent concordance and reproducibility were noticed when only the WSI were used.
Conclusion
Our research provides further evidence of the high efficacy of WSI especial in the evaluation of immunohistochemical expression of immunohistochemical biomarkers, which are essential for establishing a tailored therapy for the patients with invasive breast carcinoma.

P19: Automated Removal of Pen Ink on Whole Slide Images Using Weakly-Supervised Deep Neural Networks

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Introduction
Pathologists commonly use pen ink to indicate malignant regions. Deep learning models can erroneously learn that ink is evidence of malignancy. We trained a weakly-supervised attention-based neural network under a multiple-instance learning paradigm to detect and remove pen ink on a slide.
Material and Methods
We gathered whole slide images (WSIs) of H&E-stained malignant skin (240 WSIs) and prostate (465 WSIs) specimens, half with and half without pen ink present. The dataset was randomly partitioned into 70%/15%/15% train/validation/test sets. Each WSI was divided into 128x128 pixel tiles to train the model to classify each WSI as positive or negative for pen ink. Ink-containing regions were identified by iteratively predicting on a WSI with high-attention tiles removed until the prediction became negative, automatically excluding pen ink from the image.
Results and Discussion
The ink-detection model achieved 98% balanced accuracy on 106 withheld test WSIs. To demonstrate the efficacy of removing ink tiles in downstream modeling, we trained a malignancy-detection model on prostate WSIs with and without pen ink excluded. The model without pen ink removed erroneously focused on ink tiles to achieve strong performance. With ink removed, model performance increased, with +3% balanced accuracy and +3% precision by focusing on regions of malignancy, reducing false positives.
Conclusion
Our technique for pen ink removal requires no annotations and performs on both skin and prostate images. It is not color-dependent and requires no handcrafted or heuristic features to select inked regions. We demonstrate the importance of removing such seemingly innocuous artifacts from machine learning datasets.

P20: Predicting Genetic Intra-Tumor Heterogeneity From Digital Histopathology Slides

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Introduction
Genetic intra-tumor heterogeneity (ITH) results in therapeutic failure and drug resistance in cancer treatment. It can be quantified by genomic sequencing. Yet, it may not be applicable for all patients since it is expensive or there is not enough tissue sample. Histopathology, however, is a routine diagnostic tool and cheaper than genomic sequencing. This study explores predicting genetic ITH from hematoxylin and eosin (H&E) stained whole-slide-images (WSIs) to provide clinicians with new tools to plan treatments and/or monitor therapeutic response without additional cost.
Material and Methods
We downloaded sequencing data and WSIs data of the Lung Adenocarcinoma cohort from The Cancer Genome Atlas. The number of clones within a tumor obtained by processing sequencing data was used as the genetic ITH metric. We developed a novel multiple instance learning model to classify patients as low ITH (1-4) vs high ITH (8-15) directly from WSIs. Each patient was represented as a bag of patches cropped over the WSIs of the patient and the genetic ITH label of the patient was used as the bag label.
Results and Discussion
There were 63 (34/29) and 23 (11/12) patients in the training and test sets, respectively. Our model was trained end-to-end on the training set. Then, the trained model was tested on the hold-out test set. We obtained the area under receiver operating characteristics curve value of 0.727 (95% CI:0.485 - 0.938).
Conclusion
Our model produced promising results to explore further genetic intra-tumor heterogeneity prediction from WSIs as a new tool.

P21: Deep Learning Model for Metastasis Risk in Colon Cancer Patients Based on Binary Tumor Images

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Introduction
The goal of this study was to develop a CNN-based model to stratify colon-cancer patients in two risk-groups regarding the occurrence of distant metastasis. To achieve this a model based on InceptionResNetV2 was trained on binary, histological images.
Material and Methods
We considered 291 patients with pT3- and pT4 adenocarcinoma, of no special histological type and without metastasis at diagnosis. For every patient a representative tumor section was chosen, stained with Cytokeratin AE1/AE3, and transformed to binary images using ImageJ. To avoid overfitting, the images were augmented during training and dropout layers were added to the model.
Results and Discussion
The trained model was able to discriminate patients of a validation collective (n=128) according to occurrence of metastasis (AUC: 0.842 95%-CI: 0.774-0.911). Comparing Kaplan-Meier curves of the risk groups, the high-risk group showed a substantially worse progress (log-rank test: $p<0.001$). Additionally, using multivariate Cox-regression we were able to prove risk-classification a prognostic factor (HR=5.4; 95%-CI: 2.5-11.7; $p<0.001$), even when adjusting for age, sex, and other pathological variables. The stratification showed good results for both UICC subgroups. In the UICC III subgroup (n=53) 80% of the high-risk group developed metastasis, whereas this was only the case for 4% of the patients in the low-risk group.
Conclusion
These results support usage of deep learning models for stratification of colon cancer patients. The fact that the images used for the model are of binary nature and only resemble the architecture of the tumor is an interesting aspect of this study and shall be further investigated.

P22: Automated Identification of Different Tissue Regions in H&E and IHC Slides Using Deep Learning

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Introduction
Identifying different tissue regions and characterizing their spatial relationships in the tumor microenvironment (TME) can add prognostic value in a clinical practice. It also enables further analysis of TME, by studying spatial location of different cell types in different tissue regions which can support new biomarker discovery for drug development. The manual annotation of different tissue areas across Whole Slide Images (WSIs) is an error-prone and time-consuming task. Herein, we developed two automated algorithms for segmentation of tumor, stroma, necrosis, and other (background, blood, nerve, muscle, etc) in Hematoxylin and Eosin (H&E) and Immunohistochemistry (IHC) slides.
Material and Methods
The deep learning architecture that we employed for both algorithms is U-Net. One dataset consists of WSIs of colorectal tumor sections stained with H&E is used to train the H&E segmentation model. Another dataset consists of colorectal tumor sections stained with Ki67/CD8 is used to train the IHC segmentation model. On both datasets, within the tumor area, different tissue regions are annotated by a pathologist and ground truth segmentation masks are generated. We used 108 WSIs (77 for training, 31 for testing) for H&E model, and 87 WSIs (60 for training, 27 for testing) for IHC model. We used image patches of fixed size (512x512 pixels) as the input to the U-Net model and ground-truth masks as the corresponding mask labels.
Results and Discussion
For both models, we were able to achieve acceptable mask segmentation predictions both quantitatively and visually for all four classes. The average dice similarity coefficient on the validation set was 0.71 for H&E model and 0.75 for the IHC model, and the average intersection over union was 0.70 for H&E model and 0.82 for the IHC model.
Conclusion
Automated segmentation of different tissue types in the tumor environment by deep learning algorithms potentially enables faster and more reliable assessment of WSIs by eliminating the need for manual annotation from pathologists.

P23: Quantitative Morphological Characterization of Pancreatic Islets in HE-Stained Slides

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Introduction
Pancreatic islets represent a network of endocrine cells that play an essential role in the maintenance of homeostatic processes. Aging and genetic mutations can interfere with the endocrine pancreas morphology and functional activity. However, little is known about the relationship between islet structure alterations and their functional activity. Additionally, the pancreatic islet morphological characterization is often performed in a qualitative manner. Here we propose an image analysis workflow for the extraction of quantitative data concerning the morphological characterization of pancreatic islets in hematoxylin and eosin (HE) stained whole-slide images. This workflow was applied for characterization and discrimination of age and genotype-associated changes in the islets morphology.
Material and Methods
HE stained pancreas slides were scanned using NanoZoomer2.0HT (Hamamatsu) at 40x magnification with a resolution of 226nm/pixel. A deep learning algorithm was trained in HALO® (IndicaLabs) for the segmentation of pancreatic islets. The segmentation output was post-processed in Fiji and a set of measurements was extracted for the morphological characterization of pancreatic islets.
Results and Discussion
The pancreas endocrine percentage, islet average area, the fit ellipse minor and major axis, the Feret diameter, and minimum Feret features presented differences among age groups. The fit ellipse minor and major axis, and Feret diameter allowed the discrimination between different genotypes.
Conclusion
The quantitative morphological characterization of pancreatic islets can help to identify age- and genotype-associated changes, allowing to reduce the subjectivity associated with this analysis.

P24: New Cytomine Open-Source Software Architecture and Modules for AI in Digital Pathology

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Introduction
The open-source Cytomine web software tool (https://www.cytomine.org) can be installed on servers and it enables remote visualization and collaborative annotation of WSIs using a web browser. While it was delivered with machine learning-based image recognition algorithms since (Marée et al., Bioinformatics 2016), its architecture was not flexible enough to seamlessly integrate heterogeneous algorithms.
Material and Methods
Cytomine architecture was refactored to enable the reproducible remote execution of image analysis and AI workflows. Our new architecture is based on a rich workflow description schema (incl. input, output, parameters, default values) and on the encapsulation of each workflow with its original software environment into a software container. Workflows can be built and versioned in the cloud whenever a new release is triggered from their associated source code repositories (using GitHub and DockerHub automated builds). They can be launched through Cytomine web user interface and run on high-performance computing or multiple server architectures using Singularity containers and SLURM scheduling system.
Results and Discussion
We successfully integrated tens of workflows including ImageJ/Icy/CellProfiler/ilastik/Octave scripts or Python scripts leveraging Scikit-learn, Keras, or PyTorch (Rubens et al., Cell Patterns 2020). This list is not limited as any computer/data scientist is able to add other software as long as they fulfill minimal requirements. In this talk, we will illustrate the benefits of this architecture with studies performed at ULiège (https://uliege.cytomine.org) to quantitatively compare various deep learning algorithms (incl. StarDist, NuClick, U-Net,...) for cell counting and tissue area delineation (incl. glands, bronchi, tumors,...) in multiple digital pathology datasets.
Conclusion
Our developments are a further step towards truly collaborative and reproducible digital pathology. To ease their adoption, Cytomine documentation was significantly improved (https://doc.cytomine.org/).

P25: Assessment of Prostate Carcinoma Architecture through Fractal Analysis in Correlation with Gleason and Srigley Grading Systems

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Introduction
The aim of the study is to assess the existence of possible connections between tumor cell architecture (GO) and vascular network architecture (VN) in relation with two different grading systems of prostate carcinoma (PC) described by Gleason and Srigley using the fractal dimension (FD) analysis.
Material and Methods
435 prostatic tissue fields with different individual PC patterns according to the above mentioned grading systems were selected and stained on three serial sections with: H&E for grading and Gömöri technique and CD34 immunomarker for assessment of tumour cells (GO) and vascular network (VN) architecture respectively. Images were binarized using color focus for CD34 and intensity focus for Gömöri stainings. The FD was computed for each binary image using a box-counting algorithm. Values tending to “1” meant a more “Linear type” distribution (Lt-D), while those to “2” meant a more “Area/Surface type” distribution (At-D). The averages (AV) of the two values were clustered and classified using “k-nearest neighbor” approach.
Results and Discussion
GO AVs had a more ordered smooth ascending trend towards At-D (FD > 1.5) in Srigley system than in Gleason system while VN AVs had a clear Lt-D (FD < 1.5) with a descending trend towards high-grade patterns in both systems. Both AVs had a direct correlation (Pearson’s test p value < 0.001 with CM=0.180), evolving either towards At-D or Lt-D together.
Conclusion
VN follows GO when related one to the other, but they are evolving smoothly divergently in relation with the degree of differentiation especially in Srigley system.

P26: Assessment of E-Cadherin Expression in Prostate Carcinoma in Correlation with Gleason and Srigley Grading System

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Introduction
E-Cadherin (ECHAD) is a transmembrane cell adhesion protein correlated to the formation and growth of epithelial malignancies. The aim of this study is to assess the correlation between the expression of ECHAD and two different grading systems of prostate carcinoma described by Gleason and Srigley.
Material and Methods
A series of 435 prostatic tissue areas with individual patterns of the two grading systems were immunohistochemically (IHC) stained with ECHAD and images were evaluated through a proprietary computational algorithm. The algorithm marked the pixel where the red channel was more intense than the other channels. Then the overall color intensity of the previously selected mask was inverted and considered as the value for the intensity of the IHC staining, larger values meaning more intense staining. Mean values (AV) distributions were stratified on each of the grading systems. ECHAD expression location was also stratified: 01M=Membrane, 02MC=Membrane+Cytoplasm, 03C=Cytoplasm.
Results and Discussion
ECHAD expression AVs had downward trend from the well differentiated (WD) to most poorly differentiated (PD) patterns in both grading systems more clearly outlined and stabilizing in Srigley system. ECHAD expression site evolved from predominantly 01M in WD patterns towards 03C in PD patterns, the trend being statistically validated by chi-square test ($p < 0.0001$) in both systems.
Conclusion
The degree of intercellular adhesion revealed a decreasing trend in both grading systems, from the WD to the PD patterns. The developed computational algorithm allowed an accurate assessment of ECHAD expression in correlation with the differentiation patterns of the two grading systems.

P27: Digital Experience on Practical Cytopathology Online Course Using Whole Slide Imaging

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Introduction
Digitization is a reality in surgical pathology as primary diagnosis but a challenge in cytology. The aim of this study is to explain our experience in an "ongoing" practical course using whole slide imaging digitalized cytological cases.
Material and Methods
The course has 6 monthly sessions of different topics and 5 cytological cases each. We digitized their slides using the DP200 scanner and uploaded the images to the Vector platform (both Ventana, Roche) for viewing before and after the virtual review with the expert through Cisco Webex platform. 102 participants have enrolled in it. We ask them about their satisfaction in the images quality, virtual teaching method and individual practical sessions using Google Forms.
Results and Discussion
From 41 responses (63.4% cytotechnicians, 17.1% pathologists, 9.8% cytotechnician students and 7.3% pathology residents) 65.9% declare having experience in viewing digitized cases and value the images quality as excellent (45%) and good (45%). Their satisfaction with the digitized slide screening is good (57.5%) and excellent (22.5%). They are satisfied with the virtual format of the course (58.5% excellent and 39% good) as well as with the specialist's guided session (59% excellent and 35.9% good). Respondents value the access to cases before and after it (100%) and would repeat the edition and format of the course (95.1%).
Conclusion
Digitization of cytology is useful to encourage and disseminate knowledge among different professional levels. The virtual teaching method is an effective and comfortable modality for teaching at a practical (cases visualization) and theorical level (cases discussion).

P28: Identification of Biomarkers Using DeePathology STUDIO AI Platform

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Introduction
The MMR examination is an important indicator for treatment with Kytruda for patients various types of cancer. It is done on PFFE biopsies which are IHC stained with 4 Antibodies for proteins that generate the complex responsible for correcting DNA mutations. In case one of these proteins is not expressed, a mutation examination is done in order to identify the change in the DNA sequence. Eligibility for the Kytruda treatment requires identifying a mutation at least in one of these genes or proteins. The MMR examination is done on IHC platforms such as Ultra Bench Ventana using fixed reagents and antibodies. However, the differences in the tissue processing, procedures and between the antibodies batches lead to inconsistent results. This calls for an objective rule for the screening.
Material and Methods
An AI solution was created to check whether at least one cancerous nuclei was positively stained. 10 cases were screened using the DP200 slide scanner. The WSIs were analyzed using the DeePathology STUDIO, a Do It Yourself platform that allows the creation of AI solutions for various problems in Pathology.
Results and Discussion
We present the process of creating an AI solution for this challenging problem and the results on its application to real life cases.
Conclusion
Identification of solely weakly stained cancerous nuclei is very demanding and usually requires the analysis of highly trained senior pathologists and high resolution and magnification microscopes. The ability to create and deploy an AI solution to this problem greatly simplifies this procedure.

P29: Systematic Review and Meta-Analysis of Automated Tools for HER2, ER and T-cell Scoring in Cancer Biopsies

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Introduction
Computer assisted scoring (CAS) in pathology should improve standardisation, reproducibility, and throughput. This review assesses the validation approaches and performance of CAS tools developed for HER2, ER and T-cell scoring in tumour tissue to provide a baseline to judge new algorithms and identify attributes needed for clinical adoption.
Material and Methods
PubMed, Web of Science, and IEEE Xplore Digital Library were queried to retrieve peer-reviewed studies quantitatively validating CAS tools. Study quality was assessed using standardised criteria (protocol CRD42019139688). The algorithms and validation approaches were described. Agreement of CAS with pathologists was assessed in random effects meta-analysis; studies reporting Cohen's κ of agreement against manual ER Allred scoring and manual HER2 scoring (0/1+, 2+, 3+) were included.
Results and Discussion
Moderately good agreement with manual scoring was observed for HER2 (κ = 0.75, 95% CI: 0.70-0.81) and ER algorithms (κ = 0.74, 95% CI: 0.66-0.83). Automated and pathologist generated scores agreed at least as well as those between pathologists for HER2 and T-cells, but not ER. Multiple pathologists providing annotations improved performance for HER2. CAS increased inter-observer agreement compared to manual scoring, however, it did not reduce the need for confirmatory HER2 fluorescent in-situ hybridization testing.
Conclusion
Validation of CAS should not only demonstrate agreement with pathologists, but also a benefit over conventional scoring practice, by improving reproducibility, robustness to staining variability or correlation to patient outcome. As study heterogeneity and lack of context description can hinder adoption, we suggest there is a need for reporting guidelines for validating of such tools.

P30: Pathologist-Led Definition of Generalizability for Clinical AI Ensures Patient-Relevant Performance and Clinical Usability

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Introduction
Artificial intelligence (AI) applied to diagnostic workflows promises accuracy and efficiency gains, and AI-based systems are available in the market for use today. “Generalizability” describes the ability for algorithms to perform across broad populations and on data from different laboratories, without refitting or calibration. Attaining and validating generalizability is not only a technical data problem but has clear clinical and patient safety implications.
Material and Methods
An AI-driven prostate cancer detection system was developed by Paige, using multiple-instance learning, that detects and indicates tissue suspicious for invasive cancer. The system was developed on diverse and clinically representative data from a single institution from >33,000 slides, >6770 patients.
Results and Discussion
First, the system was validated on a validation set from >800 laboratories which included highly challenging cases. Additional validation confirmed performance across images acquired from different scanners. Then, the system was tested by independent pathologists at independent sites. On unseen data, without any site-specific calibration, the prostate cancer detection system performed with near-perfect sensitivity and high specificity, and was demonstrated to increase the diagnostic accuracy of pathologists.
Conclusion
While the development and initial in-silico validation was essential to creating the algorithm’s technical ability to generalize, the performance on unseen prostate core biopsy data, from independent sites in different parts of the world, demonstrated the most relevant attributes of generalizability. A pathologist-led definition of generalizability and standardized criteria should be used to test new clinical AI applications in pathology. This will ensure that patient safety considerations are at the forefront of the clinical validation efforts for powerful but reliable AI applications.

P31: Deep Learning with Transfer Learning on Basal-Cell Carcinomas Subtype Automated Classification

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Introduction
Deep-learning algorithms are an emerging approach in medical image classification due to their performance, and, through them, a new concept arose - transfer learning. This implies replacing the final layers of a trained network and retraining it for a new task, while keeping the weights from the imported layers.
Material and Methods
Addressing the pathology of basal-cell carcinomas we have designed and trained a deep-learning convolutional network capable of classifying ten different subtypes. Transfer learning from a well-known general-purpose image classification network – AlexNet – was used. 2520 patches with basal-cell carcinomas, were independently labeled by two pathologists as infiltrating (36), with adnexal differentiation (480), micronodular (660), sclerosing (morphea-like) (12), nodular (120), nodular adenoid variant (60), nodular keratotic variant (96), nodular nodulocystic variant (240), pigmented (492), superficial (324). 85% of the data were used for training and 15% for testing on 100 independent training sequences. Each of the 100 resulted networks independently labeled the whole dataset.
Results and Discussion
Mean and standard deviation accuracy (ACC) for the networks was of 85±17, while for the area under the receiver operating characteristic (AUC) was 0.87±0.15. The normal distribution of the classification error shows that the network reached a maximum classification rate on the dataset. Supposing a larger dataset would slightly increase the classification ACC the resulted classifier could assist pathological diagnosis, providing first or second opinion and thus aiding the pathologist into making an accurate and reliable diagnosis.
Conclusion
Having a relatively small and unbalanced dataset, we conclude that the resulted networks show promising ACC and AUC, and in turn, this proves that transfer learning from AlexNet can be successfully used on histological images.

P32: Inking Cellblocks Improves Scanner Detection for Primary Diagnosis

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Introduction
Cellblock transforms liquid-based cytology in a pellet-cone to be processed and used for immunohistochemistry (IHC). Cellblock's matrix is transparent and often hard to be automatically detect by the scanner (ADS), generating incomplete whole slide images (WSIs).
Material and Methods
Tests were designed to evaluate if inking cones after bronchus cytology facilitates ADS. First test: 15 cellblocks were sectioned, one half inked green (1HG) and the other inked black (1HB). One haematoxylin-eosin (HE) slide was produced from each half-cone. Second test: 15 cellblocks were sectioned, one half inked black (2HB) and the other left unstained/null (2HN). HE and AE1AE3 IHC slides were produced from each half-cone. Slides were evaluated by 3 pathologists.
Results and Discussion
First test: all sections were ADS; one 1HG was rescanned (6.7%)(p=0.317), scanning 1HBs was faster (mean±sd;62.3±19.7s vs 72.1±21.5s)(p=0.022) and lighter to archive (367.3±81.4Mb vs 400.2±99.0Mb)(p=0.041) than 1HGs; WSI quality was similar regardless the colour; ink interference at the limits of the section was frequent in 1HGs (p<0.0001). Second test: all HEs were ADS; two 2HNs were rescanned (13.3%)(p=0.157), scanning time (75.8±14.4s vs 69.5±21.0s)(p=0.125) and archive consumption (373.8±63.6Mb vs 351.2±79.3Mb)(p=0.164) was similar for 2HBs and 2HNs, respectively; WSI quality was similar regardless inking; ink interference was not relevant (p=0.063). In IHC, one 2HB (6.7%) and 8 2HNs (53.3%) were not ADS (p=0.016), scanning 2HNs was faster (76.1±13.7s vs 81.3±18.0s)(p=0.001) and lighter to archive (165.7±58.1Mb vs 369.7±140.8Mb)(p=0.001) than 2HB's; WSI quality was equivalent regardless inking; ink interference was recorded(p=0.001).
Conclusion
Inking cellblocks improves scanner detection and allows the production of quality WSIs for diagnosis.

P33: Automated Quantification of Ki-67-Positive Cells on Whole-Slide Images in Pediatric High-Grade Glioma may Have More Prognostic Value than WHO Grade

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Introduction
The WHO adult glioma grading system may not be suitable for pediatric high-grade gliomas. However, a clinical, radiological or biological characteristic of these tumours having a prognostic value is of outmost importance.
Material and Methods
Each one of our set of 114 patients suffering pediatric high-grade gliomas of WHO grades III and IV had a whole-slide image (WSI) of a biopsy sample. Using an automated computer procedure with the same values of the few parameters for each WSI, we quantified the area fraction of tissue occupied by Ki-67-positive cell nuclei. We statistically compared the resulting index with the overall survival during follow-up (which last between 0.03 and 46.8 months, with median 24.1 months).
Results and Discussion
According to a global review of the automatic segmentation of the Ki-67-positive cells on each of the WSI by a human observer, the results were of very good quality, except for 7 images which had to be excluded of the study because of technical problems (insufficient sample or image quality, or artefact cytoplasmic staining by the Ki-67 immunomarker). Furthermore, our quantitative index was significantly correlated with the overall survival (a 10% increase of Ki-67 index was associated with a hazard ratio of 1.53). In contrast, WHO grade and other biomarkers did not show significant prognostic value.
Conclusion
For pediatric high-grade gliomas, WHO grade is not reliable for prognosis. In contrast, our automatic WSI quantification provides a useful alternative. In addition, it consumes less human specialist's time and is devoid of inter-specialists variability, and does not require any machine training phase.

P34: Establishing Qualitative Image Analysis Methods for Tumour Microenvironment Research

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Introduction
Tumor microenvironment (TME) evaluation requires combination of many cellular and spatial information. Hepatocellular carcinoma (HCC) is the most common primary liver tumor however the correlation between TME features and prognosis remains still unclear. With implementing computational pathology workflow, we aim to define morphological, immunological characteristics of HCC TME as well as their relationship with clinicopathological features.
Material and Methods
The workflow includes 4 parts. Firstly, we collected liver resection tissue blocks and slides from 98 patients. Digitalised H&E slides were evaluated for the amount of tumor infiltrating lymphocytes in different locations (intratumoral, tumur stromal and tumor margins). Secondly, consecutive slide cuts of tumors were stained with panel of TME markers and digitalised. Tumoral regions were annotated manually for one set of stainings. Background tissue, tumor centre, and outer and inner tumor margin annotations were generated automatically. Thirdly, two AI models were trained to detect and classify stroma vs tumor and inflammation vs other cell types. For cell detection pre-trained StarDist models were used. Fourthly, after registration of slides, the generated annotations have been carried through all the IHC slides of each tumor tissue. QuPath was used for all the digital workflow.
Results and Discussion
The accuracy of inflammatory cells detected, and classification were 98% on H&E and 92% on IHC slides. The stroma detection accuracy was 95% for IHC slides.
Conclusion
We present a pipeline which implements effectively open-source solutions for research and enhances the collected data effectively. The semi-automatized computational pathology workflow is able to discover tumour specific spatial TME features.

P35: AI-Power to the Pathologist - IHC Guided Annotations Improved the Resolution Performance of the Algo Compared to Manual Annotated whole Slide Images

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Introduction
Prostate biopsies represent a fair amount of the pathologist workload and in addition the diagnosis is subjective and suffers from high intra- and inter-observer variability. To improve the consistency and objectivity in the grading and evaluation of prostate core needle biopsies, we have developed an AI-based decision support tool for pathologists to detect and outline neoplastic glandular tissue. To improve the consistency and objectivity in the grading and evaluation of prostate core needle biopsies, we have developed an AI-based decision support tool for pathologists to detect and outline neoplastic glandular tissue.
Material and Methods
To reduce the turnaround time and improve the quality and objectivity of our training data, we developed a patented multiplex staining method to train our algorithms to detect and outline glandular tissue without basal cells (WOB). Pathologists manually annotated WOB areas, as well as areas with intraductal cancer, in scanned H&E whole slide images as suspicious for cancer, assisted by aligned immunofluorescence images. The semantic segmentation algorithm, inspired by DeepLabv3+, in INIFY® Prostate Screening (ContextVision, Sweden) was developed within a deep learning framework developed in-house at ContextVision.
Results and Discussion
The algorithm was evaluated on 58 prostate biopsies, stained at five different laboratories and scanned on three different scanners brands (Leica Aperio, 3DHistech and Hamamatsu). It achieved a median pixel-level sensitivity and specificity of 98.4% and 97.5%, respectively, on cancer images, and a specificity of 99.0% on benign images, using a tolerance of 3 pixels (or approximately 21 µm).
Conclusion
Using this training methodology, we have developed INIFY® Prostate Screening, a CE marked AI-based software that a clinical setting, predicts, outlines, and quantifies suspected cancer areas in prostate biopsy H&E whole slide images.