Artificial Intelligence Driving Automated Pathology: iCAIRD and Beyond

Dr Peter Caie
Senior Research Fellow
QUAntitative and Digital (QUAD) Pathology, School of Medicine
Sir James Mackenzie Institute for Early Diagnosis
University of St Andrews

Computational Pathology Symposium, Nice, ECP 2019
Molecular Pathology: Knowledge-driven drug discovery

EGFR pathway mutation status


PDL-1 - IHC

https://www.captodayonline.com/scoring-gastric-gej-cancers-pd-l1-expression/
Molecular Pathology: Knowledge and data driven drug discovery

Genomics
- Whole genome sequencing
  - e.g. Ion torrent or Illumina

Transcriptomics
- e.g. Nanostring or Illumina
  - 800 target multiplex

Proteomics
- Tumor tissue, connective tissue, muscle layer
  - e.g. MALDI in situ mass spectrometry or RPPA

Personalised Big data Pathology

CURE
RELAPSE
METASTASIS
DEATH
Digital Pathology: Knowledge and data driven personalised pathology

Standardised object & morphology quantification, spatial interactions, pattern recognition
Hierarchical prognostic or predictive patient stratifiable signatures.

From population statistics toward personalised pathology
1. **HUMAN DRIVEN:**

**MACHINE LEARNING & IMAGE ANALYSIS:**
AUTOMATED QUANTIFICATION OF KNOWN PROGNOSTIC FEATURES

Definiens Developer XD

- Cancer cells
- Image mask

Cells In TME

- Green – panCK
- Blue – PD1
- Red – PDL1

Indica Labs HALO

- Cancer cells
- Image mask

Immune cells

- Blue – Nuclei
- Red – CD3
- Yellow – CD8
Automated Analysis of Lymphocytic Infiltration, Tumor Budding, and Their Spatial Relationship Improves Prognostic Accuracy in Colorectal Cancer

Ines P. Neachou¹, Kate Lillard², Christos G. Gavriel², Hideki Ueno³, David J. Harrison¹, and Peter D. Calie³

DOI: 10.1158/2326-6066.CIR-18-0377 April 2019

Novel prognostic score: Tumor Bud Immune Spatial Index
Tumour budding: Morphology & Molecular

Nuclei segregated into subpopulations

Mean nuclear density

\(<=1.96\)

\(>1.96\)

Mean nuclear compaction

\(>1.43\)

Tumour bud nucleus

\(\geq 1.43\)

Tumour gland nucleus

<table>
<thead>
<tr>
<th>Specificity</th>
<th>93.98%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity/Recall</td>
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<tr>
<td>Precision</td>
<td>94.29%</td>
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</table>

Beta-catenin

E-Cadherin

Ki67

MMP9

CD44

Dusp-6

Tumour gland expression

Tumour bud expression
2. HUMAN DRIVEN:

DEEP LEARNING ON DIGITAL SLIDES

DEEP LEARNING TO ACCURATELY SEGMENT TISSUE AND QUANTIFY KNOWN FEATURES

DEFINIENS®
the tissue phenomics company

RF based interpolation of CNN maps

Context RF

Epithelium - Nuc, Collab, CD3/4
Non epithelium - Nuc, Collab, CD3/4

IHC

H&E
CANDIDATE PROGNOSTIC FEATURES QUANTIFIED: MUSCLE INVASIVE BLADDER CANCER EXAMPLE

**Immune Contexture**
- CD3 / CD8 / PD-L1

ESMO 2018 - Augmenting TNM staging with machine learning-based immune profiling for improved prognosis prediction in muscle-invasive bladder cancer patients

**Cancer Morphology**
- tumour Buds

*Scientific Reports 2019* - Automated tumour budding quantification by machine learning augments TNM staging in muscle-invasive bladder cancer prognosis

**Spatial Interaction**
- tumour Buds/PDL-1/TILs/TAMs


**DEFINIENS**
the tissue phenomics company
3. HUMAN AND DATA DRIVEN:

AI ANALYSES IMAGES AND DATA

AUTOMATED SEGMENTATION OF KNOWN FEATURES & UNBIASED DATA EXTRACTION

Novel histopathologic feature identified through image analysis augments stage II colorectal cancer clinical reporting

Peter D Caie¹, Ying Zhou¹, Arran K Turnbull¹, Anca Oniscu², David J Harrison¹,²


Multi-parametric phenotypic fingerprint from image segmentation

Composite image  LVI object mask
MACHINE LEARNING WORKFLOW:

WHICH MODEL IS BEST FOR YOUR DATA?

RF  SVM  KNN

WHAT DATA IS IMPORTANT IN YOUR MODEL?

No Free Lunch
A principled machine learning framework improves accuracy of stage II colorectal cancer prognosis

Neofytos Dimitriou, Ognjen Arandjelovic, David J. Harrison and Peter D. Cale

N= 180 CRC patients
70% training/30% test sets

DATA DRIVEN: 123 IMAGE BASED FEATURES

Parameter reduction: Sequential floating forward search
Sequential floating backward search

Hyperparameters: Set by HYPEROPT

<table>
<thead>
<tr>
<th>Classifier</th>
<th>Hyperparameter</th>
<th>Distribution</th>
<th>Values</th>
</tr>
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<td>C</td>
<td>Log-uniform</td>
<td>In(1e-5), In(1e-3)</td>
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<tr>
<td>SVM, RBF kernel</td>
<td>C</td>
<td>Log-uniform</td>
<td>In(1e-5), In(1e-3)</td>
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<tr>
<td>Class weight</td>
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<td>Balanced or none</td>
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<tr>
<td>Gamma</td>
<td>Log-uniform</td>
<td>In(1e-3)</td>
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<tr>
<td>T stage</td>
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<tr>
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<td>Log-uniform</td>
<td>[10, 1000]</td>
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<tr>
<td>Cokiner</td>
<td>Categorical</td>
<td>Gini or entropy</td>
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<td>Maximum features</td>
<td>Categorical</td>
<td>Biased</td>
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<td>Maximum depth</td>
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<td>Integer</td>
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<tr>
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<td>Weights</td>
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<td>Uniform, or Euclidean distance</td>
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<tr>
<td>Metric</td>
<td>Balanced or none</td>
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Differentiation (0.62)
TNM stage (0.65)
KNN model (0.94)

AUROC

The experiments were performed by 20 times repeating tenfold cross-validation on training data.
Beyond augmentation? “I have bladder cancer – do I really need a repeat cystoscopy?”

**BladderLight**: Fully automated, non-invasive urinary bladder cancer surveillance test: >95% sensitivity ensuring under 5% false negatives.

A. Automatic image analysis of IF labelled patient sample

- Nuclear and cell segmentation
- Biomarker based cell classification

- 125 continuous data measurements: shape, extent & texture, of every individual nucleus and cell, co-registered to biomarker classifications

B. Clinical & image analysis parameters as input for machine learning

- Low Risk
- High Risk

- Patient urine sample is collected and fixed using a disposable device at point of care: e.g. local GP
- Automated decision made to refer to hospital or remain home (risk of cancer or no risk of cancer)

**Results:**
- 624 patients (75 cancer positive) recruited from NHS Fife (no patient exclusion)
- Saving unnecessary cystoscopies
- Sensitivity: 97%, specificity 75%
4. DATA DRIVEN

UNDIRECTED/UNLABELLED BY HUMANS
Beyond augmentation? Automatically identified morphological features

Colorectal Cancer Outcome Prediction from H&E Whole Slide Images using Machine Learning and Automatically Inferred Phenotype Profiles

Xingzhi Yue, Neofytos Dimitriou, Peter D. Caie, David J. Harrison, and Ognjen Arandjelović
School of Computer Science & School of Medicine
University of St Andrews, UK

N=75 stage I and II CRC patient samples

Figure 1: Chromatic normalization examples (left & right: original & normalized tiled strips).

<table>
<thead>
<tr>
<th>Patch level</th>
<th>Cluster level</th>
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<tbody>
<tr>
<td>Accuracy</td>
<td>F1</td>
</tr>
<tr>
<td></td>
<td>Accuracy</td>
</tr>
<tr>
<td>Ph5-CNN-SVM</td>
<td>0.68</td>
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<tr>
<td>Ph10-CNN-SVM</td>
<td>0.70</td>
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Figure 2: Training corpus augmentation by synthetically generated imagery. Shown is an original image (far left) and four examples of synthetic images generated from it (the remainder).

Figure 3: (a) Distribution of patch memberships (left) across different information ratio based clusters and the corresponding visual examples (right). (b) An example of a WS1 (left) and sample patches (right) from the different phenotype based clusters inferred automatically.

Figure 4: Examples of clustering results. Each block of four images comprises the original WS1 (top left), and the corresponding information density (top right) and phenotype based (k = 5 and k = 10 respectively bottom left and bottom right) clustering labels, colour coded.
iCAIRD The Industrial Centre for Artificial Intelligence Research in Digital Diagnostics.

A pan-Scotland collaboration of 15 partner organisations.
- Academic
- NHS
- Industrial

£15.8m funding:
Centred at the University of Glasgow’s Clinical Innovation Zone at the Queen Elizabeth University Hospital.

Teams across Scotland, including St Andrews.

- Create infrastructure to develop and apply AI in digital diagnostics within both pathology and radiology
- Fast-track digitisation of Scottish NHS pathology data to create the largest fully digital pathology laboratory network in Europe.
- Work with partner Philips to establish an HDRUK national pathology image archive of anonymised disease cases within the National Data Safe Haven
- Create AI algorithms for reporting of gynaecology samples that fits into the Digital pathologist’s daily workflow
The Industrial Centre for Artificial Intelligence Research in Digital Diagnostics.

Key features
• Tried & tested partnerships
• NHS NSS Board
• Safe havens & HDRUK
• SINAPSE
• Direct link to clinicians
Democratising AI: Reducing Barriers to Entry

1. The Domain Barrier

Without an existing product line and an established clinical collaborator network it's hard for SMEs to know where to focus.

2. The Data and Annotation Barrier

Machine learning solutions require huge amounts of data to generalise well. It's hard for SMEs to get access to that scale of data and harder still to annotate it accurately.

3. The Clinical Validation Barrier

Without a product already integrated into the clinical workflow it's difficult for SMEs to validate algorithms in a real-world multi-centre setting and generate the evidence needed to demonstrate their clinical effectiveness.

4. The Regulatory Barrier

Healthcare AI has stringent requirements on safety and effectiveness. These can daunt SMEs wanting to enter the market.

5. The Channel to Market Barrier

Without an established global sales and marketing organisation it's difficult for SMEs to access a large enough customer base, and without an established reputation it is equally hard to form commercial partnerships with established vendors.
**AI in Gynaecological pathology**

**Work in St Andrews: 5000 samples/App**

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**Endometrial AI Pathology App**

**Why?**
- 42% of gynaecological specimens are endometrial
- Exclusion of neoplasia is key pivot
- Only 3% of endometrial biopsies show adenocarcinoma
- >95% of biopsies are benign

**Perfect setting to develop AI to reduce NHS workload**

**Technically challenging**
Benign patterns show considerable heterogeneity in pattern due to endogenous and exogenous hormonal influence.

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**Cervical AI Pathology App**

**Why?**
- 26% of gynaecological specimens are cervical biopsies
- Accurate assessment of cervical intra-epithelial neoplasia (CIN)
- exclusion of invasive squamous or adenocarcinoma.

**Perfect setting to develop AI to reduce NHS workload**

**Technically challenging**
Requires contextual image mapping at multiple resolutions to distinguish CIN from invasive cancer.

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**2 approaches compared:**

**HUMAN DRIVEN (pathologist): Morphology and slide annotations**

**DATA DRIVEN: AI algorithms developed with just slide level annotations**

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If these targets are achieved there would be an 85% time saving in consultant time across these specimen types. This would result in a saving of £185,650 per annum for NHS GGC which is 54% of reporting time in gynaecological pathology. Extrapolated across the UK, this would equate to a saving of £9.3 M per annum.
iCAIRD Interoperability and Impact

Scotland
- Durable, collaborative networks
- Leverage other funds and support
- Three helix approach: Barrier reduction
- Sustainability

Global
- Interoperable platform technologies
  - SHAIP
  - Open access pathology images,
  - Associated molecular and patient data
  - Platform agnostic AI

iCAIRD Data lake
Multiple Disease types

- Molecular
- Clinical
- TB – image analysis
- TIL/TAM – image analysis
- PDL-1 analysis

Platform agnostic and multiscale AI solutions
Main challenges in IF imaging overcome by AI

Local variations of IF intensity, Unspecific staining of necrotic regions, Staining and slide preparation artefacts, Variability of epithelium-associated patterns and of cell-associated patterns, etc...

Inter and Intra-image variability of IF signal

Unspecific staining (e.g. Necrosis)

A lot of different phenotypes (e.g. nuclei)