Digital Pathology & Artificial Intelligence, the Third Revolution in Pathology (*)

(* Salto-Tellez, Maxwell and Hamilton.
Artificial Intelligence - The Third Revolution in Pathology
Histopathology. 2019 Feb;74(3):372-376

Manuel Salto-Tellez, MD (LMS), FRCPath, FRCPI
Professor and Chair of Molecular Pathology
Clinical Consultant Pathologist
Lead of the Precision Medicine Centre of Excellence

Honorary Senior Clinical Researcher, Department of Oncology, University of Oxford
DISCLOSURES

Senior Scientific Advisor & Consultant, Philips
Scientific Advisory Board, Visiopharm
Scientific Advisory Board, Targos
Scientific Advisory Board, Sonrai Analytics

Last 5 years:
Almac Diagnostics
Visiting Pathologist, Targos

Advisory boards and honoraria from:
Roche, MSD, Pfizer, Astra Zeneca, BMS
<table>
<thead>
<tr>
<th>Time</th>
<th>Session Title</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 am - 8:00 am</td>
<td>BREAKFAST</td>
<td>BALLROOM LOBBY - 2ND FLOOR</td>
</tr>
<tr>
<td>8:00 am - 8:05 am</td>
<td>Introduction to HIMA</td>
<td>Metin Gurcan, PhD - Moderator</td>
</tr>
<tr>
<td>8:05 am - 8:55 am</td>
<td>Exploring the Future of Digital Pathology in Immuno-Oncology and Companion Diagnostics</td>
<td>George Lee, PhD</td>
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<tr>
<td>8:55 am - 9:50 am</td>
<td>Opportunities for Standardization and Collaboration in Developing Histopathology Image Analysis Algorithms</td>
<td>Steven Hart, PhD</td>
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<tr>
<td>9:50 am - 10:10 am</td>
<td>REFRESHMENT BREAK</td>
<td>Ballroom Lobby - 2nd floor</td>
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<tr>
<td>10:10 am - 11:05 am</td>
<td>Breaking the Barriers of Conventional Optics: Computational Photography in the Clinical Workflow</td>
<td>Itai Hayut, PhD</td>
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<td>11:05 am - 12:00 pm</td>
<td>AI and Pathology in Training: Building and Explaining Algorithms to Medical Students</td>
<td>Scott Doyle, PhD</td>
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<tr>
<td>12:00 pm - 1:00 pm</td>
<td>LUNCH</td>
<td>Ballroom Lobby - 2nd floor</td>
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<tr>
<td>1:00 pm - 1:55 pm</td>
<td>Digital Pathology &amp; Artificial Intelligence, the Third Revolution in Pathology</td>
<td>Manuel Salto-Tellez, MD</td>
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<td>1:55 pm - 2:50 pm</td>
<td>KiNet: Single-stage Nuclear Recognition and Classification for Measuring Ki-67 Proliferation Index (PI) in Pancreatic Neuroendocrine Tumors</td>
<td>Toby Cornish, MD, PhD</td>
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<td>2:50 pm - 3:10 pm</td>
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<td>Ballroom Lobby - 2nd floor</td>
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<td>3:10 pm - 4:05 pm</td>
<td>Models for Implementing Artificial Intelligence in Pathology Practice</td>
<td>Douglas Hartman, MD</td>
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<tr>
<td>4:05 pm - 5:00 pm</td>
<td>Panel Discussion</td>
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</table>
Review

Molecular pathology – The value of an integrative approach

Manuel Salto-Tellez*, Jacqueline A. James*, Peter W. Hamilton*

*Northern Ireland Molecular Pathology Laboratory, Centre for Cancer Research and Cell Biology, Queen’s University, Belfast, Northern Ireland, UK


Integrated molecular pathology: the Belfast model

Manuel Salto-Tellez1 and Richard D. Kennedy1,2

Pathology As a Clinical discipline

“...transforming pathology of the dead into pathology of the living.”

ANATOMICAL / CLINICAL DIMENSION OF PATHOLOGY (HISTOLOGY AND CYTOLOGY)

**WHO classification of lung adenocarcinoma**

1.3.3. Adenocarcinoma
   1.3.3.1. Acinar
   1.3.3.2. Papillary
   1.3.3.3. Bronchioloalveolar carcinoma
   1.3.3.3.1. Non-mucinous (Clara / pneumocyte type II)
   1.3.3.3.2. Mucinous
   1.3.3.3.3. Mixed mucinous and non-mucinous
   1.3.3.4. Solid adenocarcinoma with mucin
   1.3.3.5. Adenocarcinoma with mixed subtypes
   1.3.3.6. Variants
   1.3.3.6.1. Well-differentiated fetal adenocarcinoma
   1.3.3.6.2. Mucinous ("colloid") adenocarcinoma
   1.3.3.6.3. Mucinous cystadenocarcinoma
   1.3.3.6.4. Signet-ring adenocarcinoma
   1.3.3.6.5. Clear cell adenocarcinoma
Cancer Taxonomy: Pathology beyond Pathology
Salto-Tellez & Cree
EJC 2019, accepted for publication

How much information holds an H&E slide?
Are pathology ground-truths a help or a hinder?

Ground-truth
(Computational pathology/artificial intelligence)

Diagnostic & Clinical Relevance

Biomarker and drug-development decisions
15 The Antibody Revolution: How ‘Immuno’ Changed Pathology

Elizabeth Soilleux and Kevin C. Gatter

Pathology As a Clinical discipline


FIRST REVOLUTION IN PATHOLOGY

IHC is introduced in Pathology with widespread adoption


QUEEN'S UNIVERSITY BELFAST
IHC

Tissue Specificity
(lineage specific)

Subcellular localization

Intensity
RUNX3, a Novel Tumor Suppressor, Is Frequently Inactivated in Gastric Cancer by Protein Mislocalization

Kosei Ito, Qiang Liu, Manuel Salto-Tellez, Takashi Yano, Kotaro Tada, Hiroshi Ida, Canhua Huang, Nilesh Shah, Masafumi Inoue, Andrea Rajanokova, Kum Chew Hiong, Bee Keeow Peh, Iwan Chour Han, Tomoko Ito, Ming Teh, Khay Guan Yeoh, and Yoshiaki Ito
Algorithmic approach to IHC diagnosis of epithelioid tumours.
Content  In this article, we would like to analyse the three distinct roles of IHC and review their individual impacts on modern diagnostic pathology: (1) diagnostic IHC; (2) genetic IHC and (3) therapeutic IHC.

Background  Immunohistochemistry (IHC) plays a central role in the histopathological classification of diseases, including cancer. More recently, the importance of immunohistochemical staining is increasing. IHC usage in diagnostics is invaluable; however, the genetic and therapeutic significance of biomarker immunostaining has become equally relevant.

Summary  Thus, we will characterise the different analytical processes that are required in the three approaches to IHC usage stated above, as well as the clinical significance and overall importance in patient management. This will allow us to hypothesise on the most appropriate laboratory environment and detection methods for the future.

well as the specific diagnostic label for a given set of histological changes. Although the IHC analysis is often interpretative and, thus, carries a reduced specificity, the identification of immunoreactivity patterns can confirm tumour type. Furthermore, when utilised in combinations (so-called immuno-panels, discussed later) and interpreted in the correct clinical context, the value of such markers is greatly enhanced.

The classic example of generic tumour markers is presented by the Cytokeratins (CKs). These are epithelial markers useful for confirming the epithelial nature of tumours and, hence, designation as carcinoma. Normally, the expression of CKs varies with epithelial cell type, extent of differentiation and tissue development; however, during malignant transformation, the CK patterns and integrity are maintained, a property that enables their use as tumour markers. Unfortunately, very
DIGITAL PATHOLOGY

ARTIFICIAL INTELLIGENCE

TISSUE-BASED QUANTITATIVE PATHOLOGY

(…)

ER
Her2
ALK
PR
PDL-1
ki67
c-MET
THE GENOMIC REVOLUTION / PERSONALISED MEDICINE

Early 20th century

1953

Discovery of the DNA double helix

1980

IHC is introduced in Pathology with widespread adoption

2004

First Molecular Tests For Solid Tumours Available

2010

NGS Becomes Widely available

2017

2019

FIRST REVOLUTION IN PATHOLOGY

SECOND REVOLUTION IN PATHOLOGY

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WHO classification of lung adenocarcinoma
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**WHO classification of lung adenocarcinoma**

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Cost, effectiveness and cost-effectiveness

125 Mut-driver genes, 71 TSG and 54 Oncogenes; 71% discovered before WES/WGS

“The outcomes of these investigations are discouraging (Table 1). Although 30 to 50% of the patients who were referred for genetic analysis of their tumors had driver mutations that were thought to stimulate tumor progression, only 3 to 13% had treatments that had been selected by individual genomic analysis.”

TMB


MSI


Sharma & Allison.
Cell 161, April 9, 2015
WE NEED NEW BIOMARKERS OF DIAGNOSIS, PROGNOSIS & PREDICTION BEYOND GENOMICS

Early 20th century

Discovery of the DNA double helix

1980

IHC is introduced in Pathology with widespread adoption

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2019

Pathology As a Clinical discipline

FIRST REVOLUTION IN PATHOLOGY

SECOND REVOLUTION IN PATHOLOGY

DIGITAL PATHOLOGY / ARTIFICIAL INTELLIGENCE

FIRST REVOLUTION IN PATHOLOGY

SECOND REVOLUTION IN PATHOLOGY

THIRD REVOLUTION IN PATHOLOGY

THE PROMISE OF ARTIFICIAL INTELLIGENCE IN HEALTHCARE DELIVERY

THE PROMISE OF ARTIFICIAL INTELLIGENCE

PREVENTION & PREDISPOSITION
DIAGNOSTIC INTERPRETATION
DIAGNOSTIC AND THERAPEUTIC DECISION PATHWAYS
EFFECT OF THE INDIVIDUAL CASE IN THE "GLOBAL HEALTH"
PRACTICAL CONSIDERATIONS FOR THE APPLICATION OF ARTIFICIAL INTELLIGENCE IN THE CONTEXT OF DIAGNOSTIC PATHOLOGY

AI-TOOL VALIDATION AS A REGULAR BIOMARKER

AI.TOOLS AS A BONA FIDE COMPANION DIAGNOSTICS
Fig. 11.1 Biomarkers in clinical practice.

AI-TOOL VALIDATION AS A REGULAR BIOMARKER

Chapter: Biomarker identification and clinical validation
Author(s): Richard D. Kennedy, Manuel Salto-Tellez, D. Paul Harkin, and Patrick G. Johnston
From: Oxford Textbook of Oncology (3 ed.)

AI-TOOLS AN BONA FIDE COMPANION DIAGNOSTICS


FDA will review targeted drugs for approval only in the context of their corresponding IVDs (biomarkers).

Digital Pathology in Drug Development, Biomarker discovery and Stratified Medicine

Drug Development

Target Discovery

Lead Optimization

Preclinical/animal Studies

Clinical Development I

Clinical Development II

Clinical Development III

Approval

Market

Biomarker Development (Companion Diagnostics)

Biobanking
Biobanks supply high quality tissue samples and images for target and biomarker identification

Remote Biomarker Analysis and Tissue Microarrays
Digital TMA management, review and biomarker scoring for discovery and validation

Image Analysis
Quantitative automated assessment of tissue biomarkers (IHC, ISH)

Peer Review
Remote review of slides to ensure integrity of pathological interpretation and interobserver variation

Companion Algorithms
Quantitative assays to support patient stratification and therapeutic selection

Clinical Trials Enrichment
Remote review of tissue biomarkers for trial and therapeutic arm selection

Biomarker Discovery

Biomarker Validation

Assay Development

Clinical Utility Testing

Approval

Market

“The 14 Steps of Routine Tissue Diagnostics”. In Salto-Tellez, Maxwell & Hamilton; *Histopathology*, 2019 Feb;74(3):372-376
Automated tumor analysis for molecular profiling in lung cancer

Peter W. Hamilton, Yinhai Wang, Clinton Boyd, Jacqueline A. James, Maurice B. Loughrey, Joseph P. Houghton, David P. Boyle, Paul Kelly, Perry Maxwell, David McCleary, James Diamond, Darragh G. McArt, Jonathon Tunstall, Peter Bankhead, Manuel Salto-Tellez

Table:

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<td>1.8</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>5</td>
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<td>1.83</td>
</tr>
<tr>
<td>6</td>
<td>47.6</td>
<td>1.85</td>
</tr>
</tbody>
</table>
PARAFFIN BLOCK

H&E

DP/AI ANNOTATIONS

HAMiLTON et al Oncotarget 2015

NUCLEIC ACID BASED DIAGNOSIS

TISSUE HYBRIDIZATION BASED DIAGNOSIS

(MEI) QUANTITATIVE

DP/AI QUANTITATION

McCOURT et al JCP 2014

MOLECULAR DIAGNOSIS

MORPHOLOGY-LED DIAGNOSIS

QuPath
Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning

Nicolas Coudray, Paolo Santiago Ocampa, Theodore Sakellaropoulos, Navneet Narula, Matija Snuderl, David Fenyö, Andre L. Moreira, Narges Razavian and Aristotelis Tsirigos

Fig. 4 | Spatial heterogeneity of predicted mutations. a. Probability distribution on LUAD tiles for the six predictable mutations, with average values in dotted lines (n = 327 nonoverlapping tiles). The allele frequency is 0.33 for TP53, 0.25 for STK11, and 0 for the other four mutations. b-e, Heatmaps of TP53 (b,d) and STK11 (c,e) when only tiles classified as LUAD are selected (b,c), and when all the tiles are considered (d,e). Scale bars, 1 mm.
DIGITAL PATHOLOGY AT THE QUB’s PRECISION MEDICINE CENTRE

TISSUEMARK®  QuPATH  MULTIPLEXING

CD3/CD8 CRC  OVARIAN Ca  OESOPHAGEAL Ca

H&N Ca  BREAST Ca  c-MET CRC

LUNG Ca (incl. PD-L1)

TECHNICAL DEVELOPMENT

PRACTICAL APPLICATIONS
DIGITAL PATHOLOGY AT THE QUB’s PRECISION MEDICINE CENTRE

QuPATH  MULTIPLEXING  CD3/CD8 CRC  OVARIAN Ca  OESOPHAGEAL Ca

H&N Ca  BREAST Ca  c-MET CRC  LUNG Ca (incl. PD-L1)

TECHNICAL DEVELOPMENT  PRACTICAL APPLICATIONS
SAMPLE ANNOTATION AHEAD OF NUCLEIC ACID EXTRACTION AND MOL TESTING

IF YOU WISH TO APPLY NGS OF A SIGNIFICANT MAGNITUDE IN OUR ROUTINE CLINICAL SAMPLES... THERE WILL BE A SIGNIFICANT ATTRITION RATE.

NGS Failure Rates
Quantity of DNA
Quality of DNA
% Tumour cells & Total number of cells are critical

Tumour cells?

MOLECULAR PATHOLOGY PROGRAMME – GENOMICS

Ion Torrent

Illumina iScan

Affymetrix

Illumina MiSeq

Illumina NextSeq
QC fail result at varying sample cellularity

Number of genes failed at varying sample cellularity (samples run on NGS)

From: Prof. David Gonzalez de Castro
Lung Cancer: Variation in % Tumor Cell Evaluation


Colorectal Cancer: Variation in % Tumor Cell Evaluation

10 colorectal cancer cases circulated to 198 laboratories

Smits AJJ et al. Modern Pathology 27, 168-174 (February 2014)
<table>
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<th>Case No.</th>
<th>Manual</th>
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<td>1</td>
<td>213.7 1.8</td>
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</tr>
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<td>2</td>
<td>252.6 1.85</td>
<td>MUTATION NOT DETECTED</td>
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<tr>
<td>3</td>
<td>76.6 1.84</td>
<td>MUTATION NOT DETECTED</td>
</tr>
<tr>
<td>4</td>
<td>133.5 1.88</td>
<td>MUTATION EXON 21 L858R</td>
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<td>5</td>
<td>101.2 1.83</td>
<td>MUTATION NOT DETECTED</td>
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<tr>
<td>6</td>
<td>47.6 1.85</td>
<td>MUTATION EXON 19 DELETION</td>
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Deep Learning for Cellular Identification
DIGITAL PATHOLOGY AT THE QUB’S PRECISION MEDICINE CENTRE

TISSUEMARK® → MULTIPLEXING → CD3/CD8 CRC → OVARIAN Ca → OESOPHAGEAL Ca

H&N Ca → BREAST Ca → c-MET CRC → LUNG Ca (incl. PD-L1)

TECHNICAL DEVELOPMENT → PRACTICAL APPLICATIONS
QuPath
Quantitative Pathology

Whole slide viewing
Fast, flexible image viewer capable of displaying whole slide images (often > 30 GB uncompressed) using dynamic colour transforms (e.g. stain separation) & tracking slide navigation

Accurate biomarker quantification
Nuclear, cytoplasmic & membranous biomarkers can all be quantified quickly using unique, automated segmentation algorithms combined with trainable cell classification

Tissue Microarray support
Automated de-masking of Tissue Microarrays & ability to view related cores side-by-side

Sophisticated tumour identification
Powerful tumour identification algorithms can be applied directly to slides of interest - including slides stained for immune cells - without the need to stain for a separate tumour marker

Fast analysis
Large image regions are split into tiles where necessary & these tiles analysed in parallel with efficient algorithms - giving fast results without requiring specialist hardware

Flexible object classification
Apply object classification with the default 'out-of-the-box' random forest classifier, or create highly customised algorithms by tuning the choice of classifier, parameters & features used

Interactive tools
Extensive tools for slide navigation, annotating areas, exporting image regions or manually counting cells

Stain estimation
Analytical analysis can be tailored to different stains & scanners using advanced stain estimation, visualisation & optimisation tools

Data exchange
Exchange data with open source tools (e.g. ImageJ), or read images from a variety of sources, including cloud-based hosting (e.g. via PathAI)

Visualisation
View measurements in context by colour coding objects according to their features, e.g. to identify hotspots or visualise cell distributions for immuno-oncology applications

User-friendly automated analysis
Workflows provide guided analysis for common tasks, or users can devise their own approaches by running commands in any order, which are automatically tagged for reproducibility

Scripting
Experienced users can enter commands & write scripts to perform sophisticated, highly-customised analysis using QuPath’s powerful, efficient hierarchical data structures

Analytics & export
Create interactive results tables, histograms, scatterplots & survival curves directly within QuPath, or export results in standard formats to import into other software if required

Versatility
QuPath has been developed as a cross-platform application that runs on Windows, Mac OS X and Linux to support a wide range of applications & image types

Bankhead P et al (Salto-Tellez & Hamilton), 2018
https://qupath.github.io
More than 28,000 downloads, used by both academia and industry. Presented QuPath at the European Congress of Pathology in Amsterdam, and training courses in Barcelona, Heidelberg, Uppsala and Zurich.

Applied in more than 100 publications (Google Scholar) so far:

### Table 3. Socio-demographic characteristics of surgically resected Stage 2 and 3 colon adenocarcinoma patients diagnosed in Northern Ireland (NI), 2004-2008.

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<th>Characteristic</th>
<th>NIBiBank remit (n=746)</th>
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<th>NIBiBank retrieved (n=561)</th>
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<td>Year of diagnosis</td>
<td></td>
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<tr>
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<td>121 (16.4)</td>
<td>83 (24.1)</td>
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<td>155 (20.4)</td>
<td>99 (25.8)</td>
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<td>2006</td>
<td>198 (26.4)</td>
<td>120 (30.7)</td>
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<td>2007</td>
<td>154 (20.8)</td>
<td>81 (21.8)</td>
<td>141 (25.1)</td>
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<td>2008</td>
<td>174 (23.5)</td>
<td>101 (25.4)</td>
<td>162 (28.9)</td>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Male</td>
<td>398 (53.9)</td>
<td>200 (51.0)</td>
<td>358 (64.2)</td>
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<tr>
<td>Female</td>
<td>348 (46.1)</td>
<td>279 (49.0)</td>
<td>233 (35.8)</td>
<td>0.55</td>
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<tr>
<td>Age at diagnosis, years</td>
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<tr>
<td>Mean ±SD</td>
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<td>&lt;50</td>
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<td>151 (20.4)</td>
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<td>32 (40.5)</td>
<td>394 (69.6)</td>
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<td>III</td>
<td>314 (42.4)</td>
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<td>378 (51.3)</td>
<td>60 (36.2)</td>
<td>318 (55.1)</td>
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<tr>
<td>2</td>
<td>47 (6.4)</td>
<td>5 (3.6)</td>
<td>42 (7.4)</td>
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<tr>
<td>3-4</td>
<td>35 (4.9)</td>
<td>9 (5.5)</td>
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<tr>
<td>Unknown</td>
<td>202 (27.3)</td>
<td>35 (22.2)</td>
<td>167 (29.8)</td>
<td>0.99</td>
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</tbody>
</table>

*Chi-squared or t-tests comparing patients with and without Biobank remit v. patients with non-retrieved samples.

**Area-based measure of socio-economic status, derived from post-code or usual address at time of colon cancer diagnosis.

### Table 4. Risk factors associated with survival in all Stage 2 and 3 colon adenocarcinoma patients diagnosed in Northern Ireland, 2004-2008, and retrieved by Northern Ireland Biobank (n=661).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Alive (n=354)</th>
<th>All Deaths (n=908)</th>
<th>Hazard ratio (95% CI)</th>
<th>CRC Deaths (n=212)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Male</td>
<td>194</td>
<td>194</td>
<td>1.00</td>
<td>1.00</td>
<td>0.99 (0.72-1.23)</td>
</tr>
<tr>
<td>Female</td>
<td>160</td>
<td>144</td>
<td>0.98 (0.78-1.22)</td>
<td>1.00</td>
<td>0.91 (0.72-1.23)</td>
</tr>
<tr>
<td>Age at diagnosis, years &lt;50</td>
<td>26</td>
<td>12</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>50-60</td>
<td>42</td>
<td>21</td>
<td>0.72 (0.53-1.00)</td>
<td>1.00</td>
<td>0.64 (0.40-0.97)</td>
</tr>
<tr>
<td>60-70</td>
<td>119</td>
<td>61</td>
<td>0.79 (0.51-1.25)</td>
<td>1.00</td>
<td>0.77 (0.50-1.21)</td>
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<tr>
<td>70-80</td>
<td>123</td>
<td>119</td>
<td>0.95 (0.51-1.78)</td>
<td>1.00</td>
<td>0.94 (0.52-1.74)</td>
</tr>
<tr>
<td>80+</td>
<td>45</td>
<td>97</td>
<td>1.62 (0.85-3.08)</td>
<td>1.00</td>
<td>1.15 (0.57-2.32)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>II</td>
<td>219</td>
<td>159</td>
<td>1.00</td>
<td>1.00</td>
<td>0.94 (0.60-1.49)</td>
</tr>
<tr>
<td>III</td>
<td>125</td>
<td>142</td>
<td>2.02 (1.55-2.63)</td>
<td>1.00</td>
<td>2.74 (1.90-3.78)</td>
</tr>
<tr>
<td>Tumour grade</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Well differentiated</td>
<td>307</td>
<td>250</td>
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</tr>
<tr>
<td>Poorly differentiated</td>
<td>44</td>
<td>46</td>
<td>1.44 (1.02-2.04)</td>
<td>0.94 (0.60-1.52)</td>
<td>1.58 (1.06-2.36)</td>
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<td>0</td>
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<td>Adjuvant chemotherapy receipt</td>
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<td>1.00</td>
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<tr>
<td>No</td>
<td>126</td>
<td>60</td>
<td>0.47 (0.23-0.97)</td>
<td>1.00</td>
<td>0.51 (0.25-0.97)</td>
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<td>Family history of colorectal cancer</td>
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<tr>
<td>No</td>
<td>185</td>
<td>135</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>187</td>
<td>178</td>
<td>1.08 (0.73-1.60)</td>
<td>1.00</td>
<td>1.15 (0.73-1.79)</td>
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<tr>
<td>Unknown</td>
<td>107</td>
<td>138</td>
<td>1.43 (1.11-1.83)</td>
<td>1.00</td>
<td>1.48 (1.09-2.01)</td>
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<td>ECOG performance status</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>196</td>
<td>142</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>27</td>
<td>1.43 (0.93-2.20)</td>
<td>1.00</td>
<td>1.47 (0.86-2.46)</td>
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<tr>
<td>3-4</td>
<td>11</td>
<td>19</td>
<td>1.63 (0.84-3.10)</td>
<td>1.00</td>
<td>2.02 (1.18-3.56)</td>
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<td>Unknown</td>
<td>132</td>
<td>119</td>
<td>1.11 (0.66-2.16)</td>
<td>1.00</td>
<td>1.00 (0.73-1.36)</td>
</tr>
</tbody>
</table>

All results mutually adjusted – we recommend all models are adjusted for (except adjustment for): age (in categories), gender, year of diagnosis (as a continuous variable), grade, MSI status, ECOG performance status, family history of colorectal cancer, adjuvant chemotherapy use (within three months of surgery) and stage.

### Characteristics (N=293)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td><strong>Tumour grade</strong></td>
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</tr>
<tr>
<td>G1</td>
<td>5</td>
<td>2%</td>
</tr>
<tr>
<td>G2</td>
<td>119</td>
<td>41%</td>
</tr>
<tr>
<td>G3</td>
<td>169</td>
<td>58%</td>
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<tr>
<td><strong>pN stage (Nodal involvement)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>127</td>
<td>43%</td>
</tr>
<tr>
<td>N1mi</td>
<td>4</td>
<td>1%</td>
</tr>
<tr>
<td>N1</td>
<td>95</td>
<td>32%</td>
</tr>
<tr>
<td>N2</td>
<td>38</td>
<td>13%</td>
</tr>
<tr>
<td>N3</td>
<td>29</td>
<td>10%</td>
</tr>
<tr>
<td><strong>pT stage</strong></td>
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<tr>
<td>T1</td>
<td>65</td>
<td>22%</td>
</tr>
<tr>
<td>T2</td>
<td>181</td>
<td>62%</td>
</tr>
<tr>
<td>T3</td>
<td>41</td>
<td>14%</td>
</tr>
<tr>
<td>T4</td>
<td>6</td>
<td>2%</td>
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<td><strong>Histological type</strong></td>
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<tr>
<td>Ductal NST</td>
<td>230</td>
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<tr>
<td>Lobular NST</td>
<td>31</td>
<td>11%</td>
</tr>
<tr>
<td>Mixed ductal and lobular</td>
<td>25</td>
<td>9%</td>
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<tr>
<td>Other</td>
<td>7</td>
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<tr>
<td><strong>ER status (at diagnosis)</strong></td>
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<tr>
<td>Positive</td>
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<td>60%</td>
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<tr>
<td>Negative</td>
<td>115</td>
<td>39%</td>
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<td>1%</td>
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<td><strong>PR status (at diagnosis)</strong></td>
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<tr>
<td>Positive</td>
<td>115</td>
<td>39%</td>
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<tr>
<td>Negative</td>
<td>139</td>
<td>47%</td>
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<tr>
<td>Unknown</td>
<td>39</td>
<td>13%</td>
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</table>

### HER2 status (at diagnosis)

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<thead>
<tr>
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<tr>
<td>Positive</td>
<td>75</td>
<td>26%</td>
</tr>
<tr>
<td>Negative</td>
<td>192</td>
<td>66%</td>
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<tr>
<td>Unknown</td>
<td>26</td>
<td>9%</td>
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### Lymphovascular invasion

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<tbody>
<tr>
<td>present</td>
<td>176</td>
<td>60%</td>
</tr>
<tr>
<td>possible</td>
<td>7</td>
<td>2%</td>
</tr>
<tr>
<td>not present</td>
<td>106</td>
<td>36%</td>
</tr>
<tr>
<td>unknown</td>
<td>4</td>
<td>1%</td>
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</table>

### Nottingham Prognostic Index

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<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>&lt;=3.4</td>
<td>3</td>
<td>1%</td>
</tr>
<tr>
<td>&gt;3.4 but &lt;=5.4</td>
<td>195</td>
<td>67%</td>
</tr>
<tr>
<td>&gt;5.4</td>
<td>95</td>
<td>32%</td>
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### Primary treatment

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Total mastectomy</td>
<td>155</td>
<td>53%</td>
</tr>
<tr>
<td>Wide local excision</td>
<td>138</td>
<td>47%</td>
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### Trastuzumab

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<tbody>
<tr>
<td>Yes</td>
<td>54</td>
<td>18%</td>
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<tr>
<td>No</td>
<td>239</td>
<td>82%</td>
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### Hormone Therapy

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<tbody>
<tr>
<td>Anti-oestrogen</td>
<td>152</td>
<td>52%</td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>25</td>
<td>9%</td>
</tr>
<tr>
<td>None</td>
<td>116</td>
<td>40%</td>
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### Adjuvant radiotherapy

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<tr>
<td>Yes</td>
<td>245</td>
<td>84%</td>
</tr>
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<td>No</td>
<td>44</td>
<td>15%</td>
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<tr>
<td>unknown</td>
<td>4</td>
<td>1%</td>
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### Local recurrence or new primary at follow up

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<tbody>
<tr>
<td>local recurrence</td>
<td>3</td>
<td>7%</td>
</tr>
<tr>
<td>new contralateral primary</td>
<td>6</td>
<td>2%</td>
</tr>
<tr>
<td>residual ipsilateral axillary disease</td>
<td>3</td>
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<tr>
<td>none</td>
<td>276</td>
<td>94%</td>
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### Distant metastatic disease at follow up

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<tbody>
<tr>
<td>None</td>
<td>214</td>
<td>73%</td>
</tr>
<tr>
<td>One site</td>
<td>68</td>
<td>23%</td>
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<tr>
<td>Multiple sites</td>
<td>11</td>
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### Survival at follow up

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<tr>
<td>Yes</td>
<td>220</td>
<td>75%</td>
</tr>
<tr>
<td>No</td>
<td>72</td>
<td>25%</td>
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</table>

### Progression/Recurrence

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</thead>
<tbody>
<tr>
<td>Yes</td>
<td>98</td>
<td>33%</td>
</tr>
<tr>
<td>No</td>
<td>193</td>
<td>66%</td>
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</table>

### Age

<p>| | | |</p>
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<tr>
<td>Mean</td>
<td>52</td>
<td>25-78</td>
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</table>
Integrated tumor identification and automated scoring minimizes pathologist involvement and provides new insights to key biomarkers in breast cancer.
Detection of TGFB1 RNAscope and AE1-AE3 and CD3 IHC. Tissue architecture maintained, no fragmentation.
DIGITAL PATHOLOGY AT THE QUB’s PRECISION MEDICINE CENTRE

TISSUEMARK®

QuPATH

MULTIPLEXING

CD3/CD8 CRC

OVARIAN Ca

OESOPHAGEAL Ca

H&N Ca

BREAST Ca

c-MET CRC

PRACTICAL APPLICATIONS
Role of the PD-1 Pathway in Cancer

- Programmed death 1 (PD-1) pathway is an immune checkpoint pathway that is expressed on the surface of activated T cells.

- One of its ligands, PD-L1, is highly expressed on the surface of tumor cells.

- Binding of PD-1 with PD-L1 inhibits T cell activation, allowing immunosuppression and neoplastic growth.

Pardoll DM.
The blockade of immune checkpoints in cancer immunotherapy.
Most of these discrepancies were around the <1% - 3% threshold, Some around the 45%-55% threshold.

Humphries, Craig, (Salto-Tellez). JTO 2019
DIGITAL PATHOLOGY AT THE QUB’s PRECISION MEDICINE CENTRE

TECHNICAL DEVELOPMENT

TISSUEMARK® QuPATH MULTIPLEXING

H&N Ca BREAST Ca c-MET CRC LUNG Ca (incl. PD-L1)

PRACTICAL APPLICATIONS

Craig, Humphries, Alderdice et al (Salto-Tellez) 2019 (under review)
New cases of bowel cancer, 2015, UK

Deaths from bowel cancer, 2016, UK

Survive bowel cancer for 10 or more years, 2010-11, England and Wales

Preventable cases of bowel cancer, UK

https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer#heading-Four
QuPath

Patients with untreated, primary colorectal cancer
n=1895 (100%)

Patients with complete sets of immune biomarker results
n=1582 (83.5%)

Discovery cohort of consecutive stage II and III CRC patients reported in Northern Ireland (2004-2008)
n=555

Validation cohort of stage I-III CRC patients obtained through the Grampian Biorepository (1994-2009)
n=711

Chemotherapy cohort of CRC patients enrolled in MRC FOCUS obtained through S-CORT consortia
n=316

Craig, Humphries, Alderdice et al (Salto-Tellez) 2019 (under review)
Craig, Humphries, Alderdice et al (Salto-Tellez) 2019 (under review)
Craig, Humphries, Alderdice et al (Salto-Tellez) 2019 (under review)
DIGITAL PATHOLOGY AT THE QUB’s PRECISION MEDICINE CENTRE

TECHNICAL DEVELOPMENT

TISSUEMARK® QuPATH MULTIPLEXING CD3/CD8 CRC OVARIAN Ca H&N Ca BREAST Ca c-MET CRC LUNG Ca (incl. PD-L1)

PRACTICAL APPLICATIONS

Humphries, Craig, et al (Salto-Tellez) 2019 (under review)
New cases of oesophageal cancer, 2015, UK

Deaths from oesophageal cancer, 2016, UK

Survive oesophageal cancer for 10 or more years, 2010-11, England and Wales

Oesophageal cancer cases are preventable, UK, 2015

Optimised biomarkers staining for the immune and immune checkpoint proteins quantified. Each TMA core (10x) shows a cases where staining was clear and quantifiable. Each panel contains a magnified view of the staining at 40x.
Adaptive immune biomarker expression impact on five-year patient survival.

Dichotomisation was based on the cut-off calculated using a ROC curve. Cases falling into the high group are represented by the red line with the blue line representing low expression. Log-rank p values are shown for each graph.

Humphries, Craig, et al (Salto-Tellez) 2019 (under review)
Immune checkpoint biomarker expression impact on five-year patient survival.

Dichotomisation was based on the cut-off calculated using a ROC curve. IDO-1 was dichotomised based on expression of the biomarker in tumour, stroma or both, while PD-L1 was grouped based on clinically established cut-off points (<1%, 1-49% and >50%). Cases falling into the high group are represented by the red line with the blue line representing low expression for ICOS and PD-1. For IDO-1 and PD-L1 the dichotomisation is represented in the key for each biomarkers respectively. Log-rank p values are shown for each graph.

What do we think about combining these two figures 3/4 in to one figure for both adaptive and checkpoint markers?

\textit{Humphries, Craig, et al (Salto-Tellez) 2019 (under review)}
Correlation matrix displaying spearman rank.

Positive correlation is represented in blue. The size of the circle corresponds to the magnitude of the correlation.
Five-year survival of patients expressing CD45RO+/ICOS+ vs CD45RO-/ICOS- only.

Table below displays number of patients in each group at specified time points, in brackets is the number of censored patients.
Multiplex co-expressing case displaying dual cell CD45RO+/ICOS+ expression. A) TMA core multiplex image with an exploded view of a tumour and stromal region via individual fluorescence channels with dual labelled cells identified in the composite. B) and C) Assessment data for both ICOS and CD45RO, respectively, in both the tumour and stroma for both ‘immune hot’ and ‘immune cold’ groups. D) Cellular co-expression of CD45RO+/ICOS+ cells within tumour and stroma for both ‘immune hot’ and ‘immune cold’ groups. P values are two tailed t-tests.
“Greg Clark, UK Secretary of State for Business, Energy and Industrial Strategy (BEIS), has confirmed today (Tuesday 6 November) that UK Research and Innovation will invest £14 million PathLAKE as part of the Industrial Strategy Challenge Fund.”

PathLAKE
Pathology image data Lake for Analytics, Knowledge and Exploration
Partners in computational pathology excellence
The Design Paradigm

NHS On-Premise Data Sources
- Philips SDK, DeID
- Site Data Pond

PathIS
- kyto
- Glencoe Software

PathLEAD Data Lake & the Analytics Engine

Middleware
- HDR UK
- Genomics England
- ISCF Centres

Use Cases
- Oxford Cancer Biomarkers
- Sonrai

Middleware
- Perspectum Diagnostics
The PathLAKE Exemplars:
Improving pathology practice & patient outcome in the NHS

**Diagnostic Efficiency AI**

- **COLON & PROSTATE CANCER**
  - Automated reporting of colon biopsies
  - Automated prostate cancer detection
  - Automated IHC requesting for prostate
  - NHS savings pathologist time (35 and 200 hrs/1000 biopsies respectively), error reduction, reduced turn-around (24hrs).

**Prognostic AI**

- **BREAST & PROSTATE CANCER**
  - AI assisted breast cancer prognostic index and prostate cancer grading
  - Patients get better prognostication and consistency.
  - Better management decisions
  - Better outcomes.

**Predictive AI**

- **CD3/CD4/CD8 SCORING TOOLS**
  - CD3/CD4/CD8 scoring in colorectal cancer
  - Improved selection of targeted therapy
  - Accuracy and reproducibility
  - More cost-efficient for the NHS
  - Better outcomes for patients

“...improve diagnosis and deliver precision treatments”. Across the NHS
The Future of DP/AI:

- **Early 20th century**: Pathology as a Clinical discipline
- **1953**: Discovery of the DNA double helix
- **1980**: IHC is introduced in Pathology with widespread adoption
- **2004**: First Molecular Tests For Solid Tumours Available
- **2010**: NGS Becomes Widely available
- **2017-2018**: First digital Scanner is Cleared by FDA
- **Artificial Intelligence In Pathology Solutions**

**FIRST REVOLUTION IN PATHOLOGY**

**SECOND REVOLUTION IN PATHOLOGY**

**THIRD REVOLUTION IN PATHOLOGY**

*Salto-Tellez, Maxwell and Hamilton. Artificial Intelligence - The Third Revolution in Pathology*  
*Histopathology. 2019 Feb;74(3):372-376*
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>2001</td>
<td>Sarcoma Translocation</td>
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<tr>
<td></td>
<td>Lymphoma Translocations</td>
</tr>
<tr>
<td></td>
<td>Clonality Testing (MSI)</td>
</tr>
<tr>
<td></td>
<td>ER, PR, Her2</td>
</tr>
</tbody>
</table>

Example 1

Example 2

2007
Lung Adenocarcinoma

2016-17
Cancer Immunotherapy
Pembrolizumab
1st line in met NSCLC
PD-L1 testing by IHC

2019
?

Molecular Subsets of Lung Cancer Defined by Driver Mutations

Frequency of Driver Mutations in NSCLC, %

<table>
<thead>
<tr>
<th>Driver</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>2-7</td>
</tr>
<tr>
<td>BRAF</td>
<td>1-3</td>
</tr>
<tr>
<td>EGFR</td>
<td>10-20</td>
</tr>
<tr>
<td>HER2</td>
<td>2-4</td>
</tr>
<tr>
<td>KRAS</td>
<td>10-25</td>
</tr>
<tr>
<td>MEK1</td>
<td>1</td>
</tr>
<tr>
<td>NRAS</td>
<td>1</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>1-3</td>
</tr>
<tr>
<td>RET</td>
<td>2-2</td>
</tr>
<tr>
<td>ROS1</td>
<td>1</td>
</tr>
</tbody>
</table>

Unknown
(...) Ten years ago, the idea that all of the genes altered in cancer could be identified at base-pair resolution would have seemed like science fiction.

Today, such genome-wide analysis, through sequencing of the exome or of the whole genome, is routine. (…) Vogelstein et al. Science. 2013; 339(6127): 1546–1558.
“Never make predictions, especially about the future.”
Yogi Berra
The Future of DP/AI:

**FIRST REVOLUTION IN PATHOLOGY**
- Early 20th century
- Discovery of the DNA double helix
- Pathology as a Clinical discipline

**SECOND REVOLUTION IN PATHOLOGY**
- 1953
- IHC is introduced in Pathology with widespread adoption
- Pathology

**THIRD REVOLUTION IN PATHOLOGY**
- 1980
- First Molecular Tests For Solid Tumours Available
- 2004
- NGS Becomes Widely available
- 2010
- First digital Scanner is Cleared by FDA
- Artificial Intelligence In Pathology Solutions

The Future of DP/AI:

1. AI – the ultimate purpose of AI?

2. AI – the ultimate tool for integration?

3. AI – the ultimate challenge to Pathology?
The Future of DP/AI:

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Philips IntelliSite Pathology Solutions

IntelliSite Ultra Fast Scanner
High throughput slide scanner designed for routine use in high volume labs and integrated pathology networks

IntelliSite Image Management and Viewing System
IntelliSite Image Management System (IMS) aims to improve the efficiency and effectiveness of the pathology lab. Our viewer is designed to get pathologists through cases as fast as possible.

Largest Non-Inferiority Trial in Digital Pathology

<table>
<thead>
<tr>
<th>Pivotal FDA Study</th>
<th>Study Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of sites</td>
<td>4</td>
</tr>
<tr>
<td>(Cleveland Clinic, University of Virginia, Miraca Life Sciences and Advanced Pathology Associates)</td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>2,000</td>
</tr>
<tr>
<td>(cross-tissue/H&amp;E/IHC)</td>
<td></td>
</tr>
<tr>
<td>Number of reads</td>
<td>16,000</td>
</tr>
<tr>
<td>Number of reading pathologists</td>
<td>16</td>
</tr>
<tr>
<td>(4 per site)</td>
<td></td>
</tr>
<tr>
<td>Number of adjudicating pathologists</td>
<td>3</td>
</tr>
</tbody>
</table>
Cancer Taxonomy: Pathology beyond Pathology
Salto-Tellez & Cree
EJC 2019, accepted for publication

HOW MUCH INFORMATION HOLDS AN H&E SLIDE?
ARE PATHOLOGY GROUND-TRUTHS A HELP OR A HINDER?

GROUND-TRUTH (COMPUTATIONAL PATHOLOGY/ARTIFICIAL INTELLIGENCE)

DIAGNOSTIC & CLINICAL RELEVANCE

BIOMARKER AND DRUG-DEVELOPMENT DECISIONS
The Future of DP/AI:

1. AI – the ultimate purpose of AI?
2. AI – the ultimate tool for integration?
3. AI – the ultimate challenge to Pathology?
<table>
<thead>
<tr>
<th></th>
<th>ACCURACY</th>
<th>TAT</th>
<th>NEW INSIGHTS</th>
<th>TRULY TRANSFORMATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAMILTON</td>
<td>+++</td>
<td>+?</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BEJNORDI</td>
<td>+++</td>
<td>+/+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HUMPHRIES</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>COUDRAY</td>
<td>?</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>INTEGROMICS</td>
<td>?</td>
<td>?</td>
<td>+++</td>
<td>++++++ +++++++++++++</td>
</tr>
</tbody>
</table>

*Fridman (Galon). Nat Rev Cancer 2012*
The Future of DP/AI:

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http://www.keywordhungry.com/cGF0aG9sb2d5IHJlcG9ydA/

FINAL TISSUE-BASED DIAGNOSIS
FINAL TISSUE-BASED DIAGNOSIS

SURGICAL PATHOLOGY REPORT

PREOPERATIVE DIAGNOSIS: Gynaecological Ultrasound Bladder

POSTOPERATIVE DIAGNOSIS: Same

FINAL MICROSCOPIC DIAGNOSIS:
- Endometrium, squamous
- Endometriosis, adenofibroma
- Endometriosis, adenofibroma, FSG grade 2
- Invasive into muscular wall
- Abundant squamous metaplasia present

COMMENT: This case was reviewed by Dr. James Cross, and he agrees with the initial diagnosis.

http://www.keywordhungry.com/cGF0aG9sb2dSIHJlcG9ydA/