Integrated Diagnostics:
The 4th Revolution in Pathology?

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Disclosure of Interests

Scientific advisor to: Mindpeak and Sonrai Analytics

Has recently received honoraria from BMS, MSD, Roche, Sanofi and Incyte.

Has recently received grant support from Phillips, Roche, MSD and Akoya, mostly in the context of government sponsored programmes.

The need for a new paradigm in biomarker discovery

Genomic Medicine

"The estimated number of patients eligible for genome-targeted therapy
… in 2006 was 28 729 of a total 564 830 patients with metastatic cancer, or 5.09%;
… by 2018, this number had increased to 50 811 of 609 640, or 8.33%.

The percentage of US patients with cancer estimated to benefit from genome-targeted therapy (ie, responders) … in 2006 was 0.70%,
… and in 2018 it had increased to 4.90%."

Marquart J, Chen EY, Prasad V. *JAMA Oncol.* 2018 Aug 1;4(8):1093-1098.

Digital Pathology & Artificial Intelligence

"The deep learning system was trained on increasing numbers of patients and evaluated on a random subset (n = 906 patients). Performance initially increased by adding more patients to the training set but reached a plateau at approximately 5000 patients."

Echle A et al. *Gastroenterology*. 2020;159:1406–1416, e1–e11

What Analytical Modalities?
What Information Technology?
What is a Synergistic Effect?

Integrated Diagnostics (multi-modal analysis):

Amalgamation of multiple analytical modalities, with evolved information technology, applied to a single patient cohort, and resulting in a synergistic effect in the clinical value of the diagnostic parts.

Multi-modal Integration: The Models

DATA MODALITIES

Unimodal Information Source	Mentions (out of 5 studies)
CLINICAL DATA/INTERPRETATION	3
HISTOPATHOLOGY	3
RADIOLOGY	3
LAB MEDICINE	2
"-OMICS"	1
ENDOSCOPY / DERMOSCOPY	1
MICROBIOLOGY/MICROBIOME	1
FUNTIONAL TESTING	1
BIOSENSORS	1
GENOMICS	1
SPATIAL TRANSCRIPTOMICS	1

ML & INTEGRATION ANALYSIS

IMAGE DATA – FEATURE-LEVEL FUSION
NON-IMAGE DATA – DECISION-LEVEL FUSION
OPERATION/SUBSPACE/ATTENTION/GRAPH/ TENSOR-BASED FUSION

SUPERVISED LEARNING (REGRESSION/ CLASSIFICATION)
UNSUPERVISED LEARNING (CLUSTERING/ DIMENSIONALITY REDUCTION)

SUPERVISED (HAND-CRAFTED VS CNN)
WEAKLY-SUPERVISED (GRAPH CNN, MLL, VIT)
UNSUPERVISED (UNSUPERVISED VS SELF-SUPERVISED)
EARLY/LATE/INTERMEDIATE FUSION

OPPORTUNITIES

PRECISION HEALTH

DIGITAL CLINICAL TRIALS
HOSPITAL-AT-HOME
PANDEMIC SURVEILLANCE
DIGITAL TWINS
VIRTUAL HEALTH COACH
(Acosta et al 2022)

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Lippi G & Plebani M. Integrated diagnostics: the future of laboratory medicine? Biochem Med (Zagreb) 2020;30(1):010501

Can Cui, et al. Deep Multi-modal Fusion of Image and Non-image Data in Disease Diagnosis and Prognosis: A Review. arXiv:2203.15588

Acosta JN, Falcone GJ, Rajpurkar P, Topol EJ. Multimodal biomedical AI. Nat Med. 2022 Sep;28(9):1773-1784

He X, et al. Artificial intelligence-based multi-omics analysis fuels cancer precision medicine. Seminars in Cancer Biology 2022.

Lipkova J, et al. Artificial intelligence for multimodal data integration in oncology. Cancer Cell. 2022 Oct 10;40(10):1095-1110.

Sammut SJ, et al.
Multi-omic machine learning predictor of breast cancer therapy response. Nature. 2022 Jan;601(7894):623-629.

Clinical, digital pathology, genomic and transcriptomic profiles of pre-treatment biopsies of breast tumours from 168 patients treated with chemotherapy with or without HER2-targeted therapy before surgery. Pathology end points (complete response or residual disease) at surgery were then correlated with multi-omic features.

Monotonical association with **pre-therapy features,** including tumour mutational and copy number landscapes, tumour proliferation, immune infiltration and T cell dysfunction and exclusion.

A multi-omic machine learning model predicted a pathological complete response in an external validation cohort (75 patients) with an area under the curve of 0.87. Here it is shown that response to treatment is modulated by the pre-treated tumour ecosystem, and its multi-omics landscape can be integrated in predictive models using machine learning

Vanguri RS, et al.
Multimodal integration of radiology, pathology and genomics for prediction of response to PD-(L)1 blockade in patients with non-small cell lung cancer. Nat Cancer. 2022 Oct;3(10):1151-1164.

Medical imaging + histopathologic + genomic features
Aiming to predict immunotherapy response

n=247 patients with advanced NSCLC

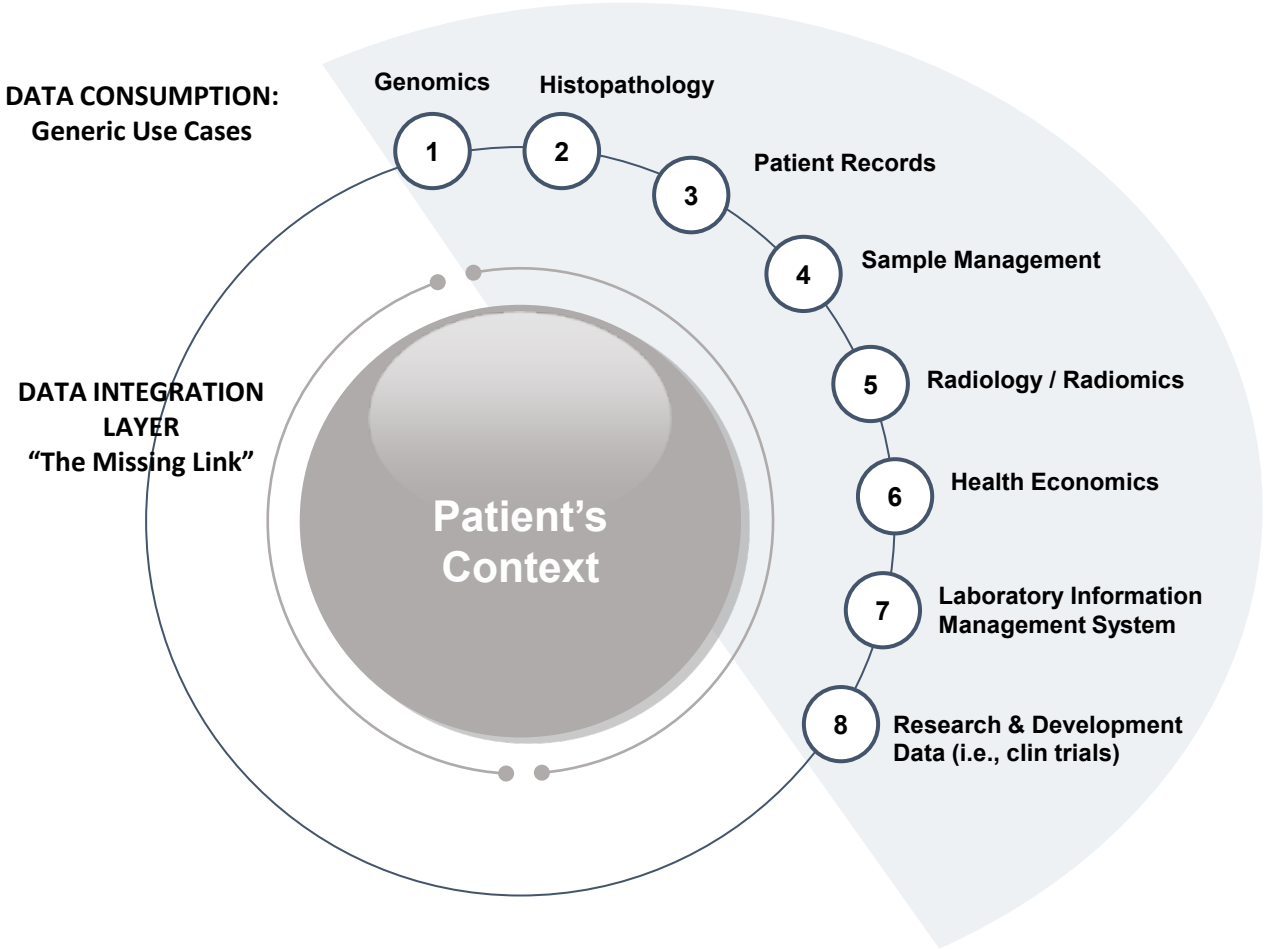
- computed tomography scan images,
- digitized programmed death ligand-1 IHC slides and
- known outcomes to immunotherapy.

Computational workflow to extract patient-level features and a ML approach to integrate multimodal features into a risk prediction model.

The multimodal model outperformed unimodal measures, including tumor mutational burden and programmed death ligand-1 immunohistochemistry score

What is IDD? Integrated Discovery & Diagnostics for RMH & ICR

The Royal Marsden and the ICR have a longstanding and successful partnership and together are recognised as one of the world-leading comprehensive cancer centres



Integration:

IDD (Integrated Discovery & Diagnostics) is a joint strategic initiative by the Institute of Cancer Research (ICR) and the Royal Marsden Hospital (RMH) aimed at accelerating oncology discovery and patient diagnostics through advanced data analytics. Key to this solution is the provision of integrated genomic, histologic, radiologic and clinical data to our world leading scientists and clinicians.

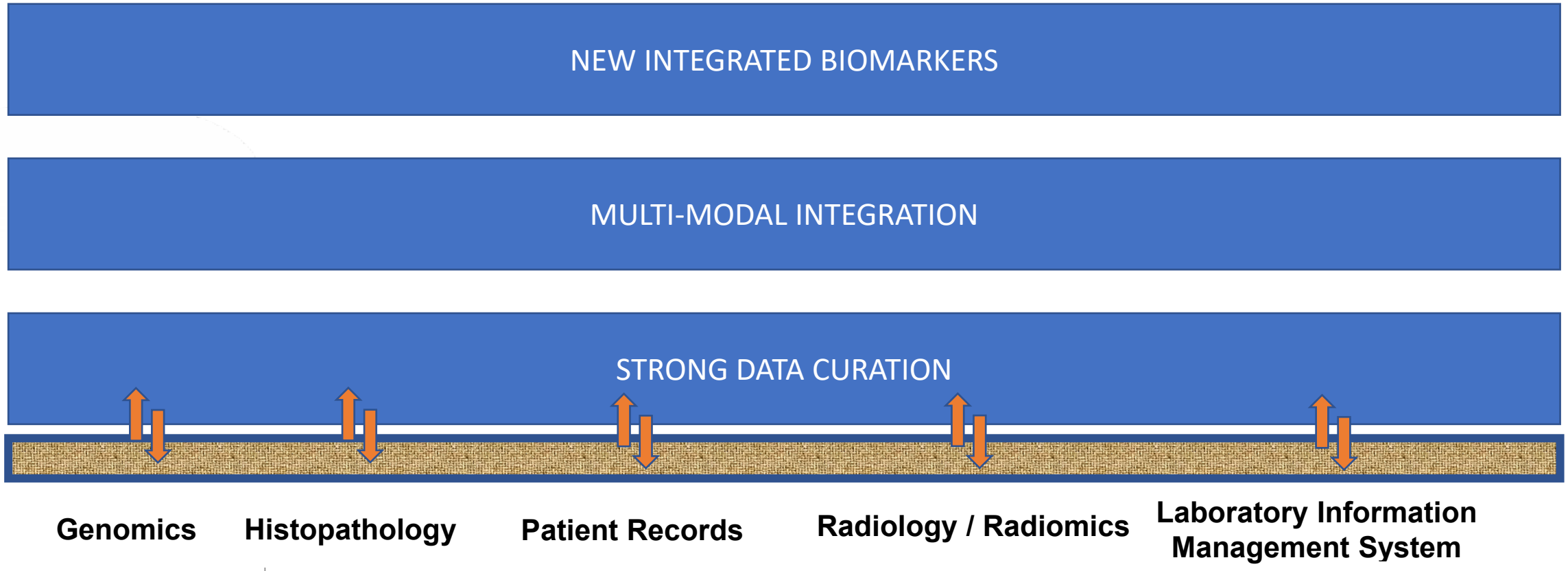
Our **guiding hypothesis** is that integrated, multi-modal data will drive the next generation of oncology discovery and patient care and that modern technology will enable this to be achieved at scale and speed.

IDD has three main objectives:

1. **Develop a high quality, integrated, multi-modal data platform to manage 20,000 cancer patients a year that is available to all ICR/RMH scientists and clinicians** which is technically excellent and financially sustainable
2. **Develop intuitive digital solutions (eg. data visualisations, AI)** to optimise oncology research and patient care
3. **Develop strategic partnerships to accelerate the delivery of innovative solutions to cancer patient**

IDD Challenge: Curation versus “Direct from Source”

The Royal Marsden and the ICR have a longstanding and successful partnership and together are recognised as one of the world-leading comprehensive cancer centres



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IDD Challenge: Curation versus “Direct from Source”

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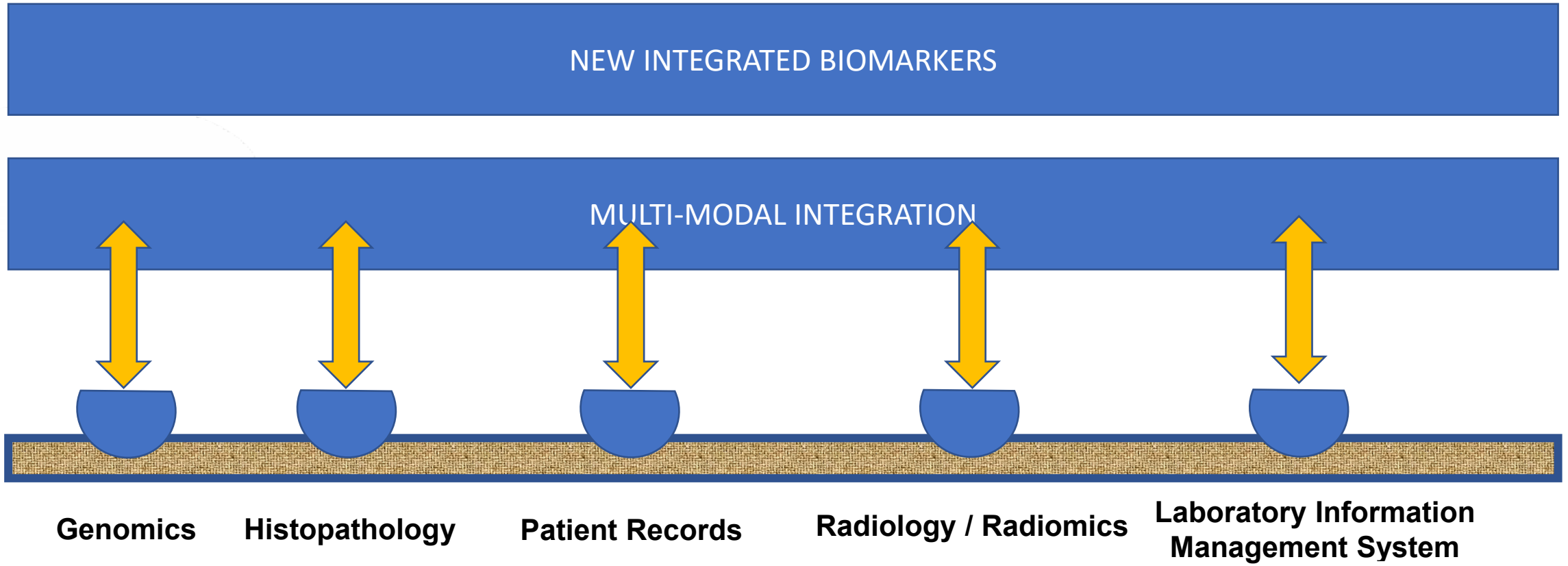

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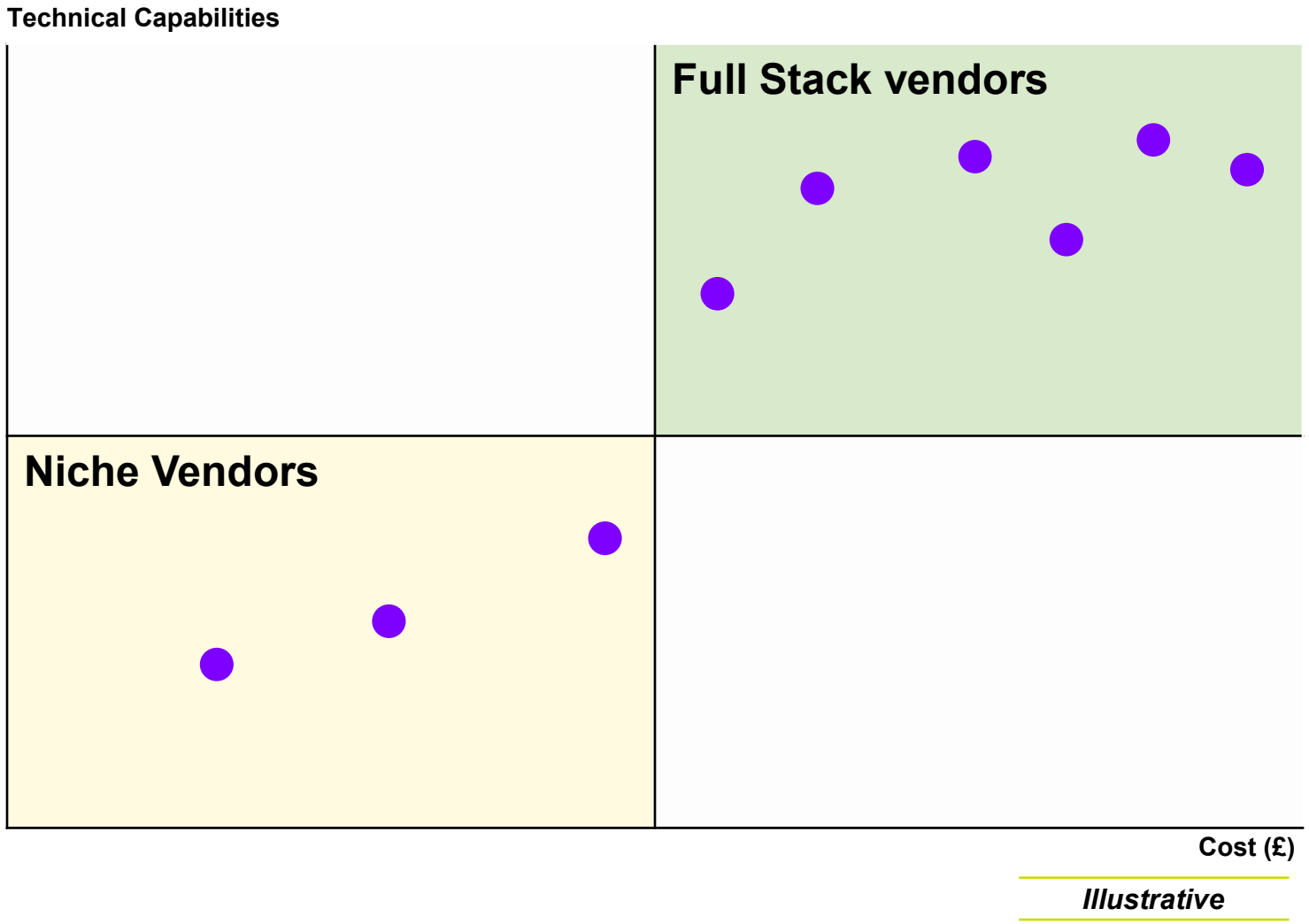
Vendor Technical Assessment - Executive Summary



IDD & Pathology: Laboratory Integration

The unmet clinical need in Early Detection of Recurrence in CRC

Some CRC patients stage II high-risk may be cured, while low-risk patients can relapse without adjuvant chemotherapy

High-risk patients treated the same as low-risk patients with stage III disease

Tie J et al. Sci Transl Med 2016, H Elsaleh et al. Lancet 2000 355:1745–50

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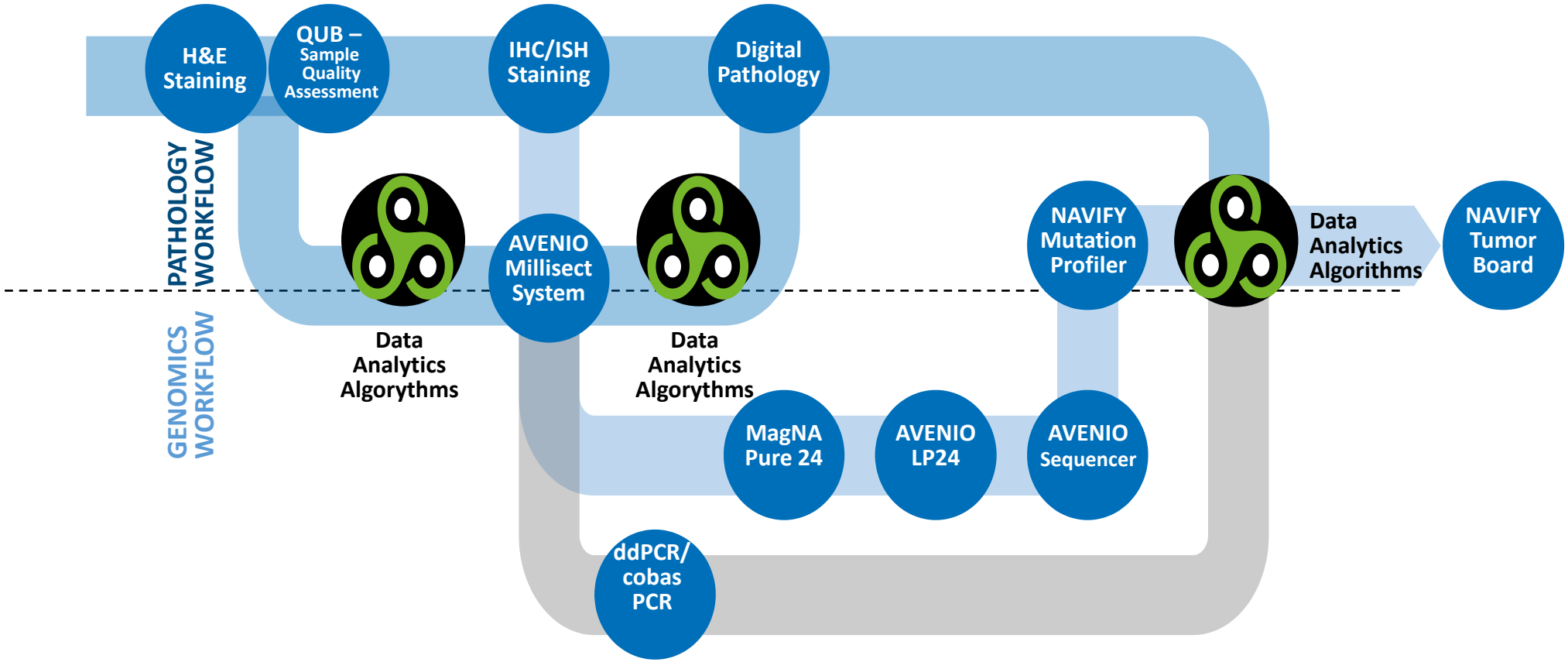
SONRAI ANALYTICS

Roche

Integrated workflow



Work Package 2: Algorithm Development to Interface H&E with AVENIO Millisect and Inform Molecular Testing

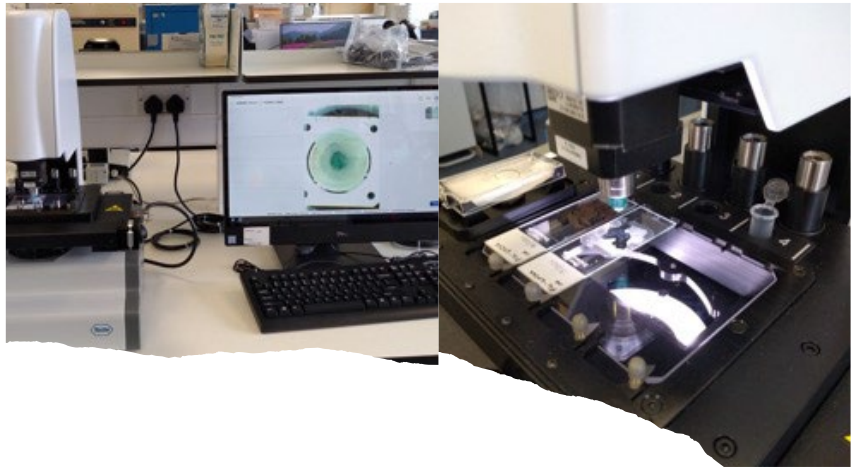
Start date: 03/02/2020 Anticipated total man-days: 295
End date: 30/04/2023
Work Package Leader: QUB and Sonrai

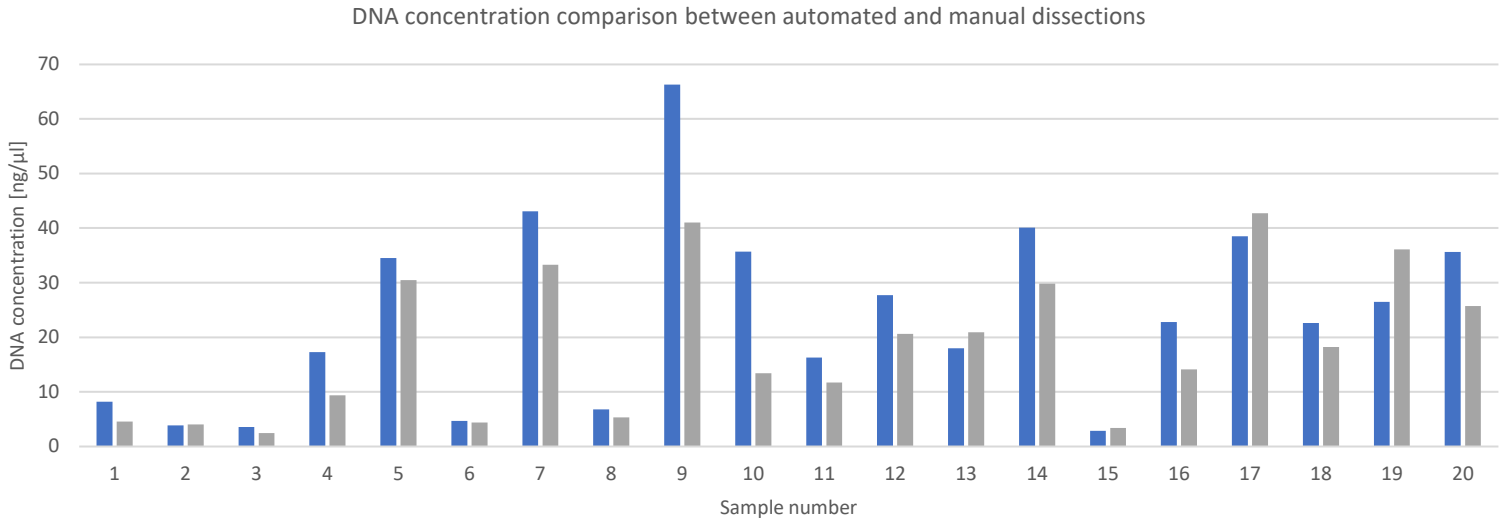
Work Package Objectives:

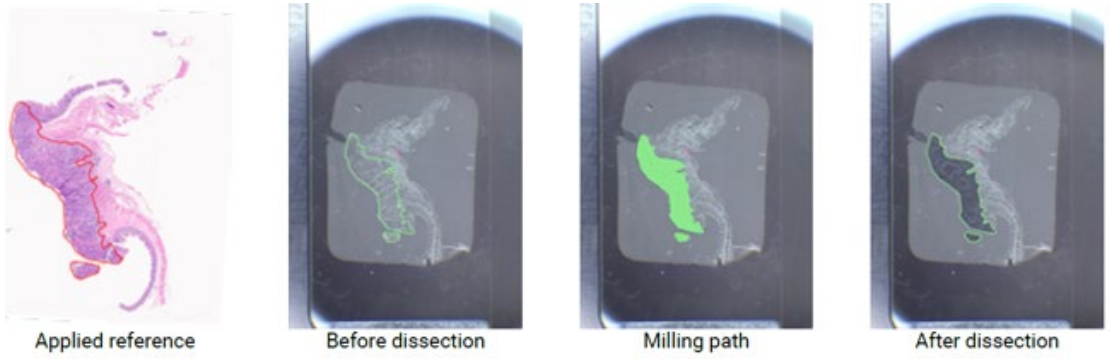
- To optimise the selection of tumour material via H&E DP algorithms (HE 600, DP 200)
- To reduce NGS technical failures and ensure robust detection of relevant genomic alterations.
- Develop metrics and algorithms to predict expected DNA yield and mutant allele frequencies from digital H&E images

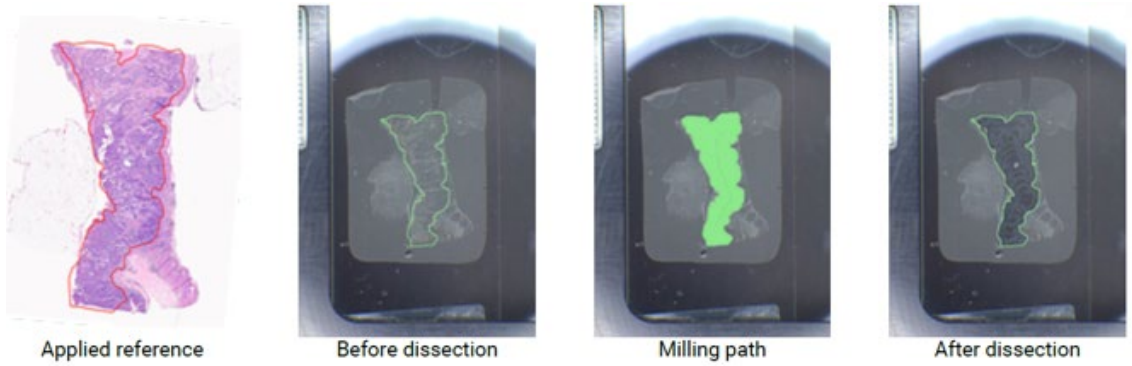
Automated AI-assisted macro-dissection

AVENIO® MilliSect System









Work Package 3: Early Detection (Risk Stratification) of Recurrence

Start date: 01/06/2021 Anticipated total man-days: 615

End date: 30/04/2023

Work Package Leader: QUB and Sonrai

Work Package Objectives:

WP3C – CRC Risk Stratification Testing Set (E2E):

- ***n=371***
- ***IHC (CD3, CD8 and PDL1),***
- ***FFPE AVENIO,***
- ***PBMC AVENIO***
- ***plasma AVENIO (x2) sequencing.***
  - ***Carried out with the full end to end (E2E) workflow***
  - ***At the end of this phase the integrated algorithm will be validated and/or further developed if required.***

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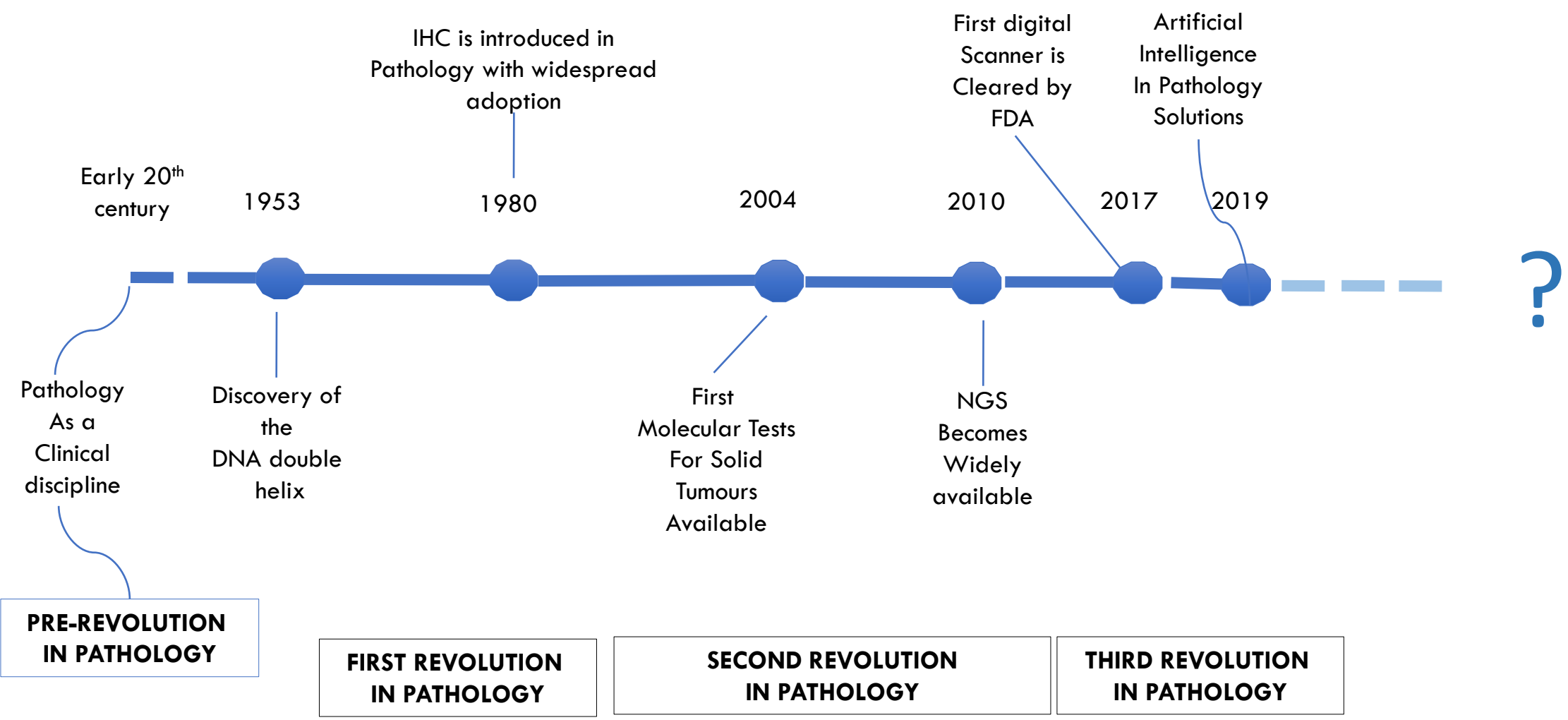
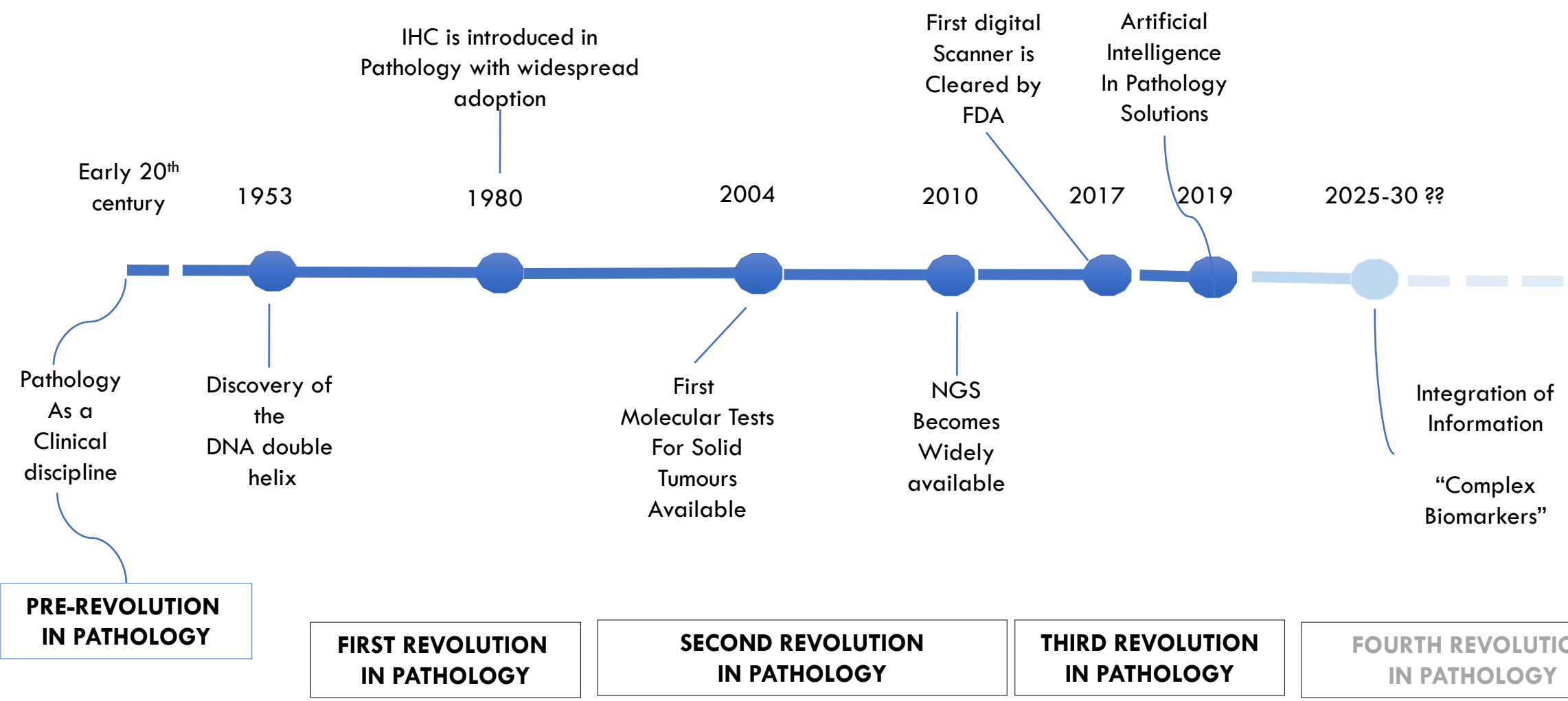

IHC is introduced in Pathology with widespread adoption
First digital Scanner is Cleared by FDA
Artificial Intelligence In Pathology Solutions
Early 20th century
1953
1980
2004
2010
2017
2019
?
Pathology As a Clinical discipline
Discovery of the DNA double helix
First Molecular Tests For Solid Tumours Available
NGS Becomes Widely available
PRE-REVOLUTION IN PATHOLOGY
FIRST REVOLUTION IN PATHOLOGY
SECOND REVOLUTION IN PATHOLOGY
THIRD REVOLUTION IN PATHOLOGY



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Adapted from:
Salto-Tellez, Maxwell and Hamilton. Histopathology. 2019 Feb;74(3):372-376

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Thank you!
Leads: Adrian Cottrell & Lewis Butler

Accenture project (Gang of 10)
Mike Hubank
Nick James
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PathLAKE Computational Pathology Excellence

UKRI UK Research and Innovation