# The Promise and Reality of Precision Medicine in Northern Ireland

QUEEN'S UNIVERSITY BELFAST

HSC Belfast Health and Social Care Trust

PMC PRECISION MEDICINE CENTRE OF EXCELLENCE

**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**

UNIVERSITY OF OXFORD

# The Promise and Reality of Precision Medicine in Northern Ireland

1. GLOBAL CHALLENGES TO MODERN MEDICINE
2. THE MOLECULAR PATHOLOGY PROGRAMME IN NORTHERN IRELAND
3. THE THIRD REVOLUTION IN PATHOLOGY
4. THE FUTURE

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# The Ulster Medical Society



Ulster Medical Society Programme 2019-2020

| Day and Date | Lecture | Subject | Venue | Time |
|---|---|---|---|---|
| Thursday 3rd October, 2019 | Presidential address | **Prof Mary F McMullin** *'Diagnostics in the Future'* | BCH Postgrad Centre | 20.00 hrs |
| Thursday 17th October, 2019 | UMS/QUB/NIMDTA Trainee research day | **Prof Fionnuala Ní Áinle, Dublin** *'The patient voice in collaborative academic research'* | BCH Postgrad Centre | 09.00-16.00 hrs |
| Thursday 7th November, 2019 | UMS The Robert Campbell Oration | **Prof Cecilia O'Kane, QUB** 'Advanced therapeutics for the acute respiratory distress syndrome (ARDS)' | BCH Postgrad Centre | 20.00 hrs |
| Thursday 14th November, 2019 | Joint meeting with Belfast City Hospital Medical Staff | **Prof Dr Jorg Goldhahn, Institute of Translational Medicine, Zurich** *'Artificial intelligence will make doctors obsolete?'* | BCH Postgrad Centre | 20.00 hrs |
| Thursday 28th November, 2019 | The Desmond Whyte Lecture | **Prof Manuel Salto-Tellez, QUB** *'The promise and reality of precision medicine in N. Ireland.'* | Altnagelvin Centre for Medical and Dental education | Buffet 17.00 hrs Lecture 18.00 hrs |
| Thursday 12th December, 2019 | UMS | **Prof Eileen Murphy, Professor of Archaeology, QUB** *'Life and Death in Medieval Ireland: Insights from Palaeopathology'* | BCH Postgrad Centre | 20.00 hrs |
| Thursday 9th January, 2020 | Joint meeting with Ulster Obs and Gynae Society | **Prof Basky Thilaganathan, Prof of Fetal Medicine, London** *'Preeclampsia is a placental disorder: lies, damn lies and medical science''* | BCH Postgrad Centre | 20.00 hrs |
| Thursday 23rd January, 2020 | The Gary Love Lecture Joint meeting with Ulster Society for History Medicine | **Dr Harriet Wheelock, Keeper of Collections, Royal College of Physicians of Ireland** *'Managing the heritage of Irish medicine-tales from the archives'* | BCH Postgrad Centre | 20.00 hrs |
| Thursday 6th February, 2020 | UMS | **Dr Jyoti Nangalia, Sanger Centre, Cambridge** *'Towards personalised medicine in blood cancers'* | BCH Postgrad Centre | 20.00 hrs |
| Thursday 27th February, 2020 | UMS | **Dr Brenda Moore-McCann, Dublin** *'Medical Semiotics and its influence on art, psychoanalysis and Sherlock Holmes'* and **Prof Shaun McCann, Dublin** *'Microscopes and corkscrews: a future perspective'* | BCH Postgrad Centre | 20.00 hrs |
| Thursday 5th March, 2020 | Joint meeting with Belfast City Hospital Medical Staff | **Prof Ann Mullally Harvard, USA** *'The Physician-Scientist: Rewards and Challenges. A Personal Perspective'* | BCH Postgrad Centre | 20.00 hrs |
| Thursday 19th March, 2020 | UMS Sir Thomas and Lady Edith Dixon Lecture | **Professor Irene Roberts, University of Oxford** *'GATA1, trisomy 21 and leukaemia- unravelling the link'* | BCH Postgrad Centre | 20.00 hrs |
| Friday 3rd April, 2020 | UMS | Annual Dinner | Canada Room QUB | 19.30 for 20.00 hrs |
| Thursday 7th May, 2020 | UMS | Annual General Meeting | UMS Rooms, Whitla Medical Building | 17.00 hrs |

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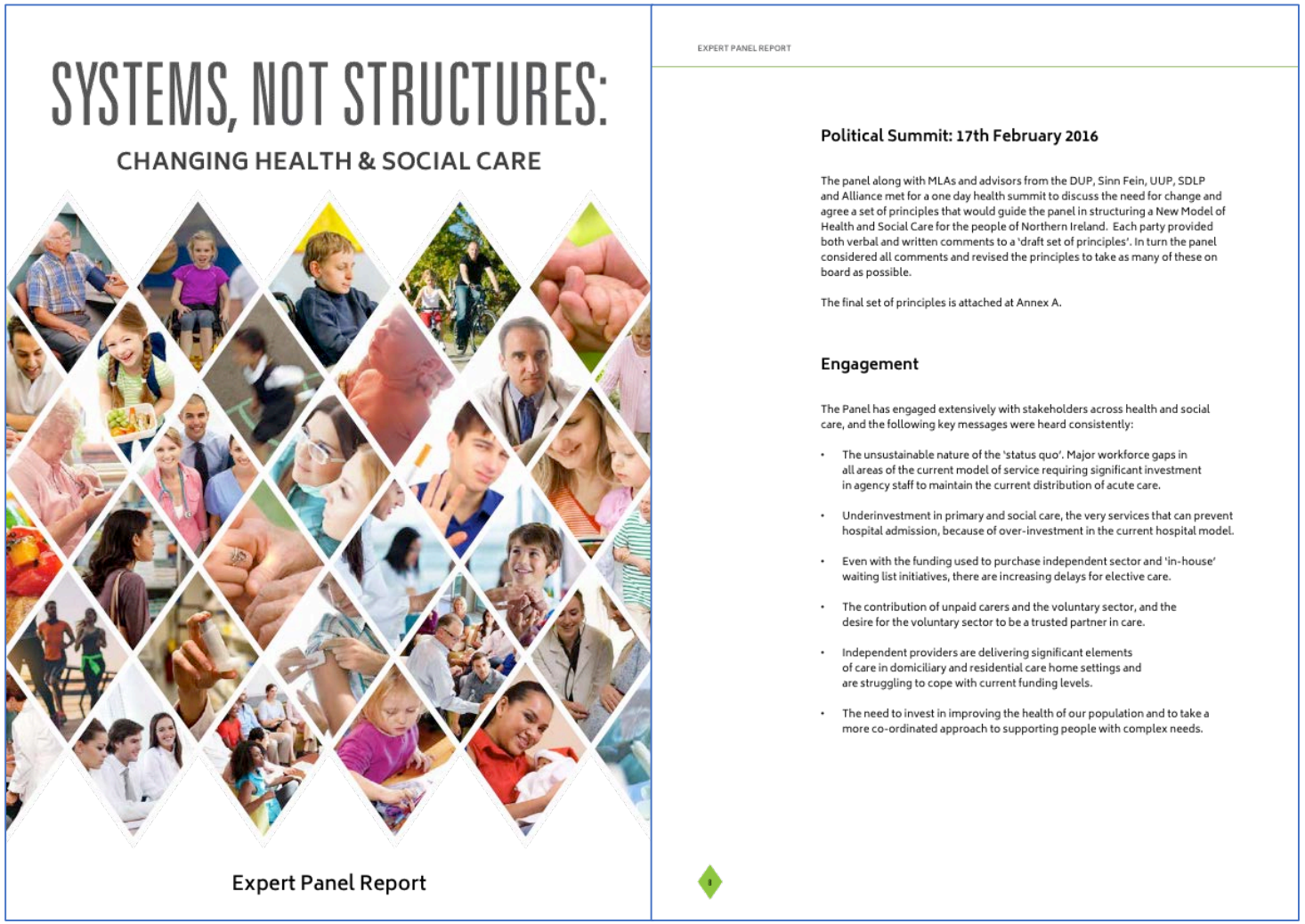
*“MAY YOU LIVE IN INTERESTING TIMES”*

CHINESE CURSE

Frederic R. Coudert at the Proceedings of the Academy of Political Science, 1939

# 1. THE UNSUSTAINABILITY OF THE CURRENT HEALTH & SOCIAL CARE SERVICE



SYSTEMS, NOT STRUCTURES:

CHANGING HEALTH & SOCIAL CARE

Expert Panel Report

EXPERT PANEL REPORT

**Political Summit: 17th February 2016**

The panel along with MLAs and advisors from the DUP, Sinn Fein, UUP, SDLP and Alliance met for a one day health summit to discuss the need for change and agree a set of principles that would guide the panel in structuring a New Model of Health and Social Care for the people of Northern Ireland. Each party provided both verbal and written comments to a 'draft set of principles'. In turn the panel considered all comments and revised the principles to take as many of these on board as possible.

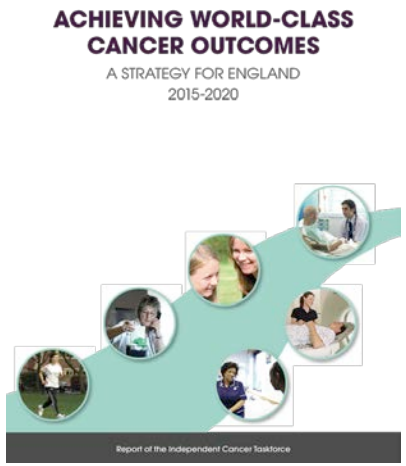
The final set of principles is attached at Annex A.

**Engagement**

The Panel has engaged extensively with stakeholders across health and social care, and the following key messages were heard consistently:

- The unsustainable nature of the 'status quo'. Major workforce gaps in all areas of the current model of service requiring significant investment in agency staff to maintain the current distribution of acute care.
- Underinvestment in primary and social care, the very services that can prevent hospital admission, because of over-investment in the current hospital model.
- Even with the funding used to purchase independent sector and 'in-house' waiting list initiatives, there are increasing delays for elective care.
- The contribution of unpaid carers and the voluntary sector, and the desire for the voluntary sector to be a trusted partner in care.
- Independent providers are delivering significant elements of care in domiciliary and residential care home settings and are struggling to cope with current funding levels.
- The need to invest in improving the health of our population and to take a more co-ordinated approach to supporting people with complex needs.

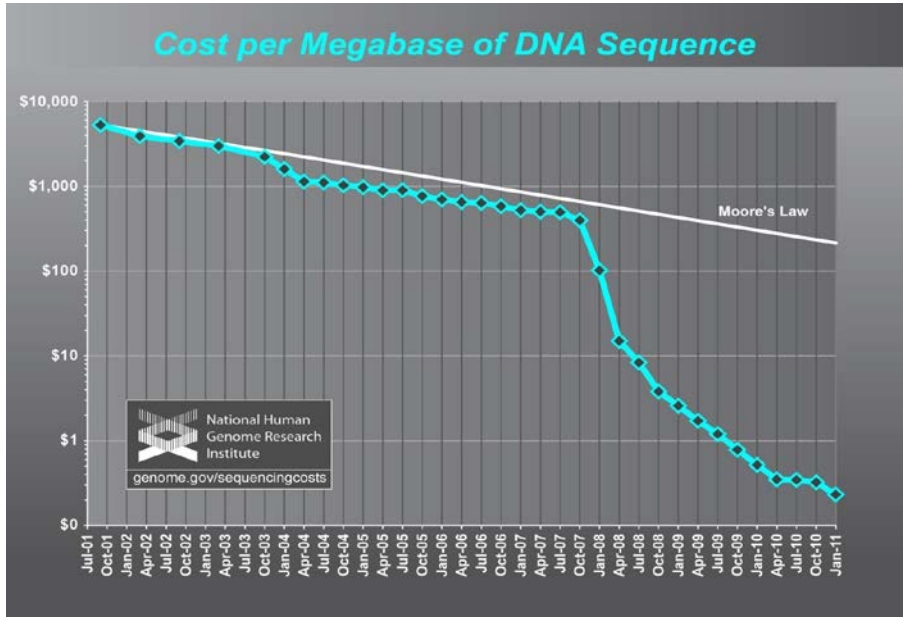
## 2. THE RESEARCH-DIAGNOSTIC BOUNDARIES ARE FAR FROM CLEAR-CUT

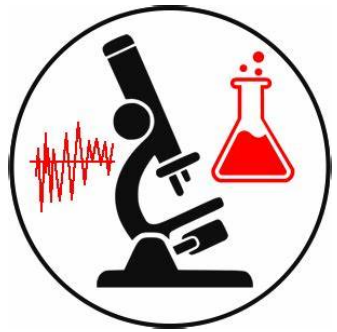



5.8.1 Supportive environment for research –

Recommendation 50: NHS England should ensure commissioners and providers are incentivised to maintain the UK's world-leading position in cancer studies and applied health research. ***This should ensure that as many patients as possible have the opportunity to be part of a study, including in smaller stratified trials.***

Recommendation 51: By the end of 2015, NHS England should publish clear guidance ***that commissioners must meet excess treatment costs for clinical trials accepted on to the NIHR portfolio as part of routine business***. ETCs for radiotherapy trials should be distributed through a national fund held by NHS England to ensure high quality clinical trials are developed and delivered optimally.



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# 3. THE LACK OF RELEVANCE OF TRANSLATIONAL RESEARCH

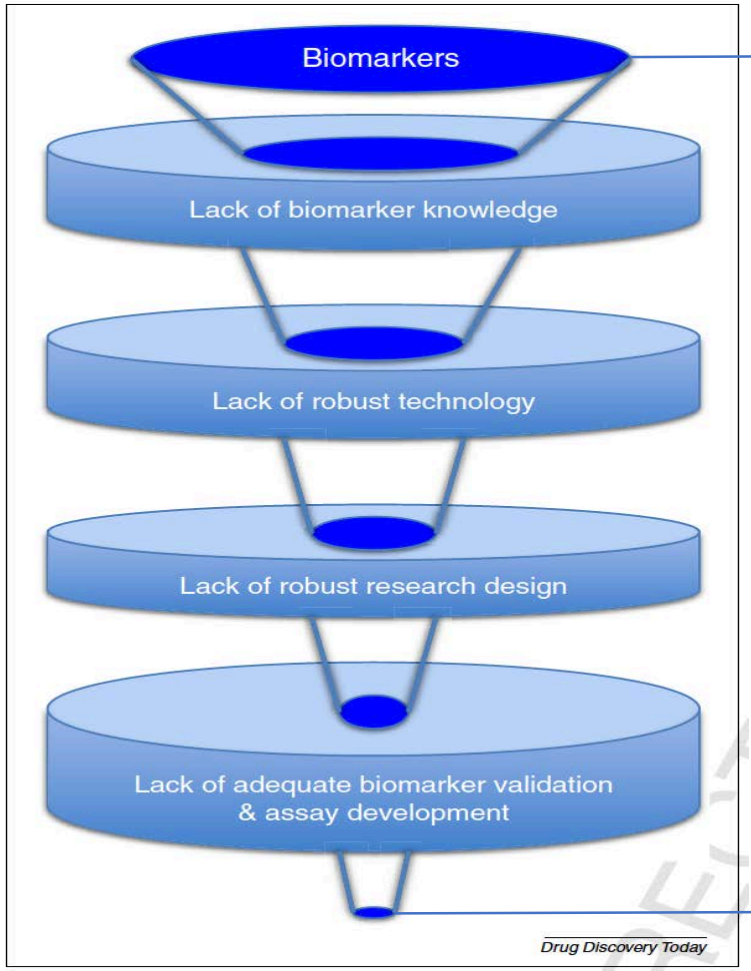



FIGURE 1

*Salto-Tellez & Kennedy.*
*Drug Discovery Today, 2015*

**100%**

**Kern SE.**
**Why your new cancer biomarker may never work: recurrent patterns and remarkable diversity in biomarker failures.**
**Cancer Res. 2012 Dec 1;72(23):6097-101**

**1%**

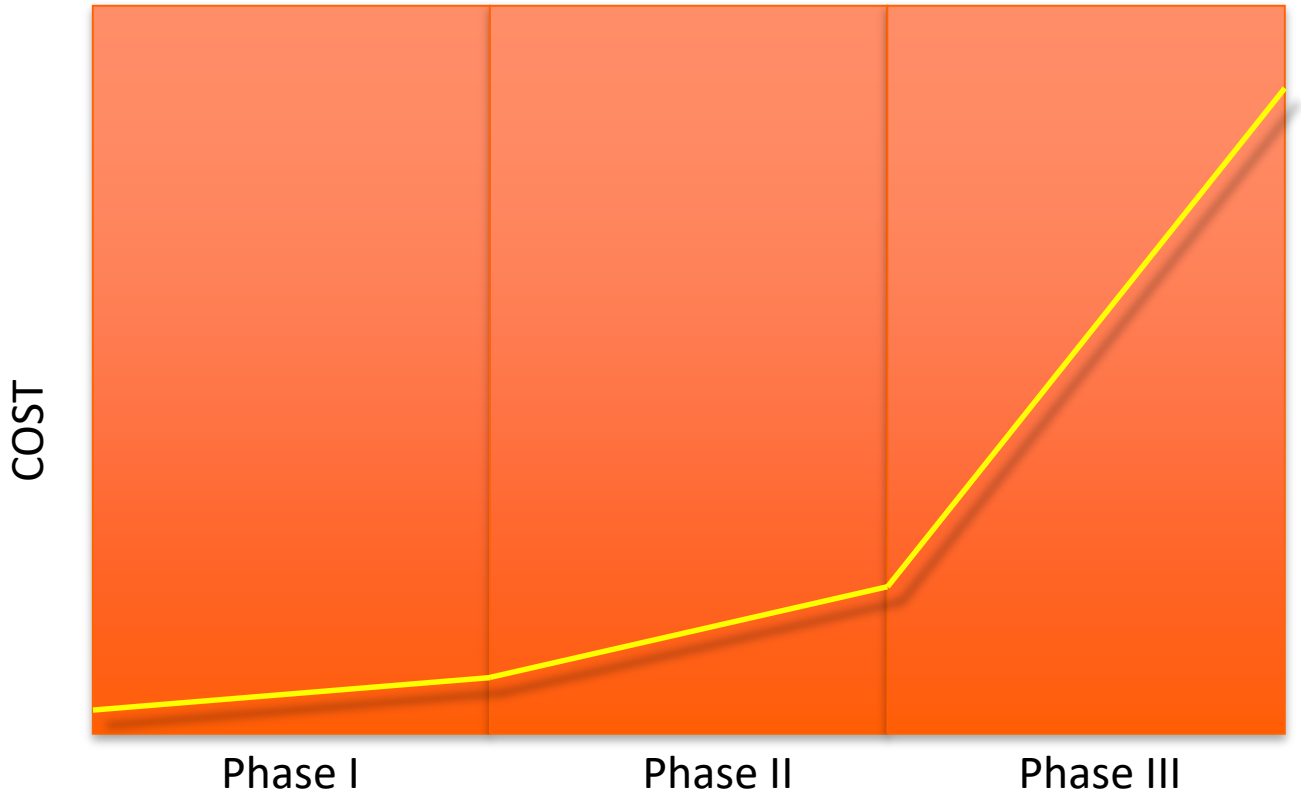
# 4. THE CONUNDRUM OF DRUG DEVELOPMENT

## Delivering affordable cancer care in high-income countries

Richard Sullivan, Jeffrey Peppercorn, Karol Sikora, John Zalcberg, Neal J Meropol, Eitan Amir, David Khayat, Peter Boyle, Philippe Autier, Ian F Tannock, Tito Fojo, Jim Siderov, Steve Williamson, Silvia Camporesi, J Gordon McVie, Arnie D Purushotham, Peter Naredi, Alexander Eggermont, Murray F Brennan, Michael L Steinberg, Mark De Ridder, Susan A McCloskey, Dirk Verellen, Terence Roberts, Guy Storme, Rodney J Hicks, Peter J Ell, Bradford R Hirsch, David P Carbone, Kevin A Schulman, Paul Catchpole, David Taylor, Jan Geissler, Nancy G Brinker, David Meltzer, David Kerr, Matti Aapro

### Panel 5: Cost of pharmaceutical innovation

A recent study by the Tufts Centre for the Study of Drug Development in the USA estimated that the average cost of a new medicine (including clinical trial outlays, spending on failed molecules, and interest payable on research and development investments, but excluding other costs and all profit contributions) is roughly US$1·3 billion.[175] Anticancer drug development costs are likely to be more because of high failure rates and above average premarket development periods.[176]

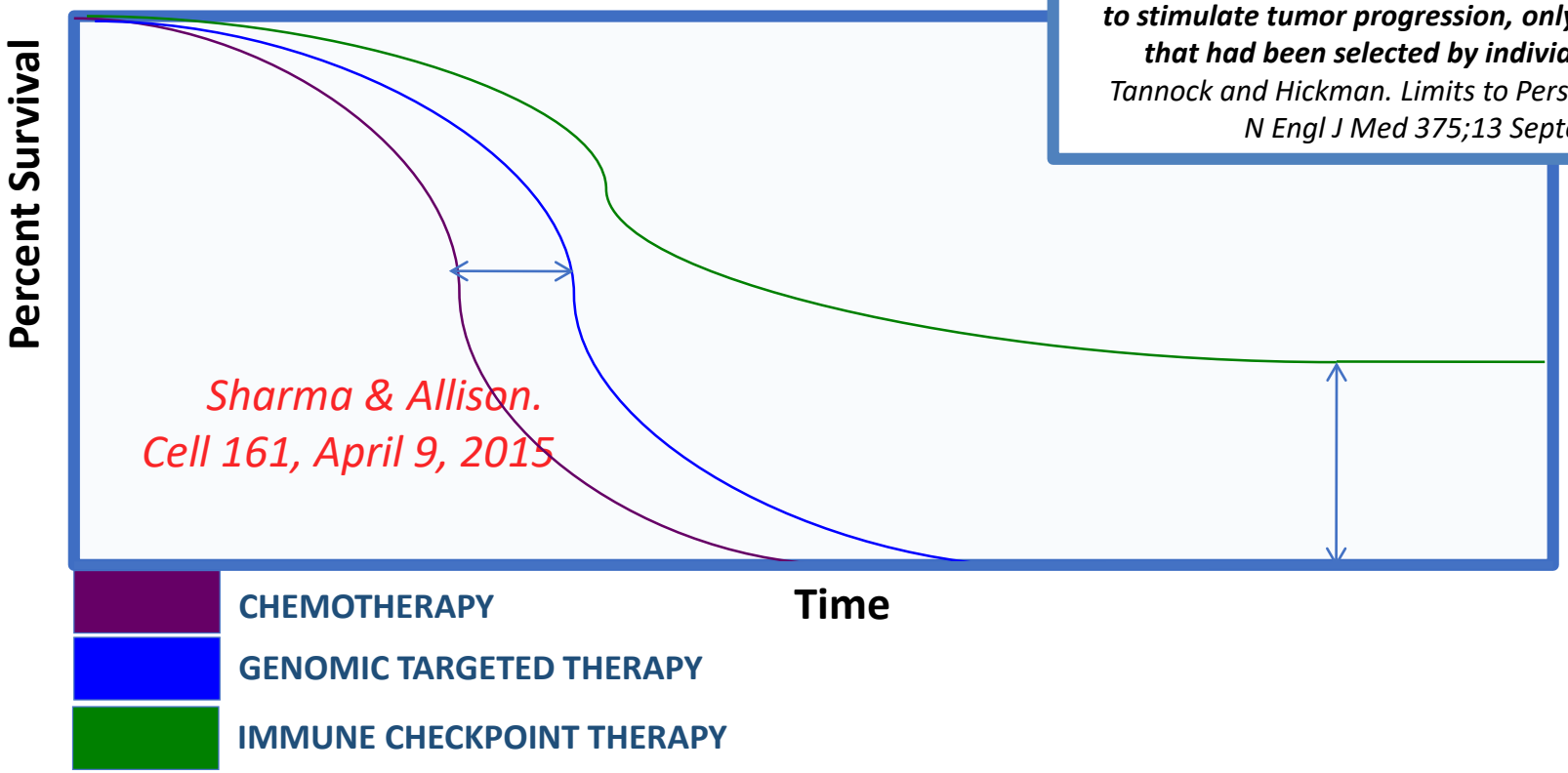



**Adapted from: Phasing out phase III trials? How much evidence do we need if the target is clearly hit?** Jaap Verweij, Erasmus University Medical Center, Daniel Center, Rotterdam, The Netherlands
*AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics November 12-16, 2011 • San Francisco, CA*

# 5. THE RELATIVE RELEVANCE OF PERSONALISED MEDICINE

***"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."***

*Tannock and Hickman. Limits to Personalized Cancer Medicine. N Engl J Med 375;13 September 29, 2016*

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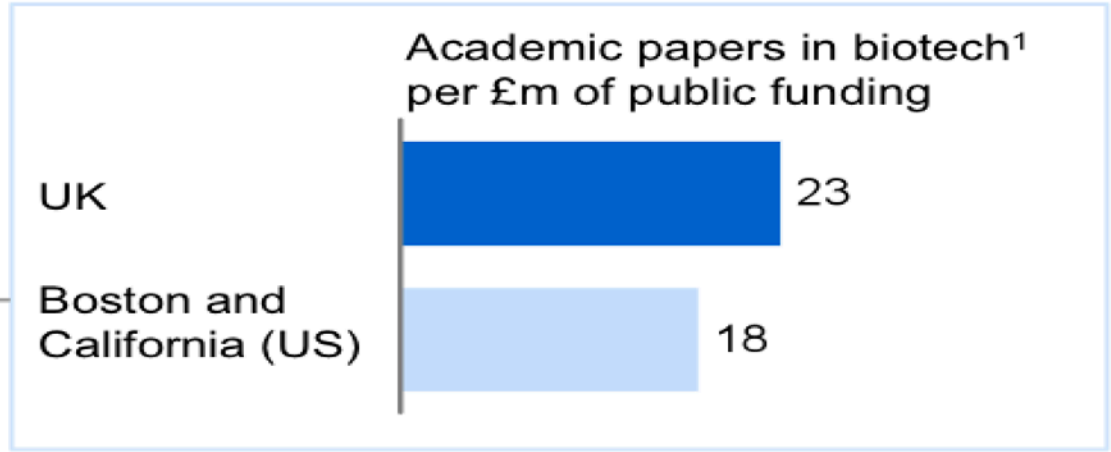
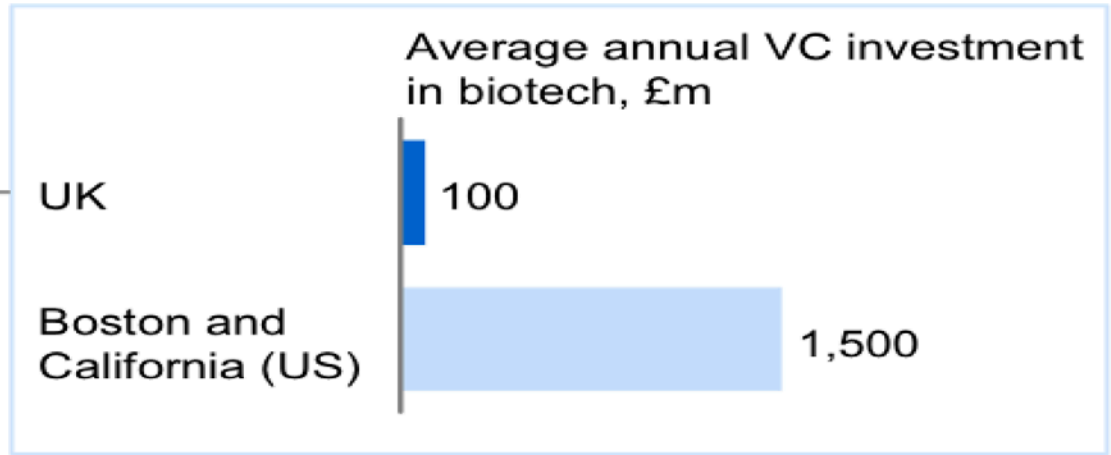
# 6. THE INCOMPLETE ECOSYSTEM OF THE UK IN BIOTECH

## Characteristics of successful ecosystems

1. World leading research
2. Access to adequate funding for growth and scale-up
3. Ability to integrate with the health delivery system
4. Availability of hybrid science + business talent to translate research into business
5. Global brand awareness of the UK as a life sciences hub




1 Proxy for precision medicine activity

SOURCE: Precision Medicine Taxonomy analysis (60+ sources in appendix), UK Bioindustry Association "A vision for the UK life sciences sector in 2025, Powel, Walter. "The Spacial Clustering of Science and Capital", Stanford University. "Singapore's Biopolis: A Success Story", www.a-star.edu.sg

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CATAPULT

Innovate UK
Technology Strategy Board

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# Precision Medicine Programme

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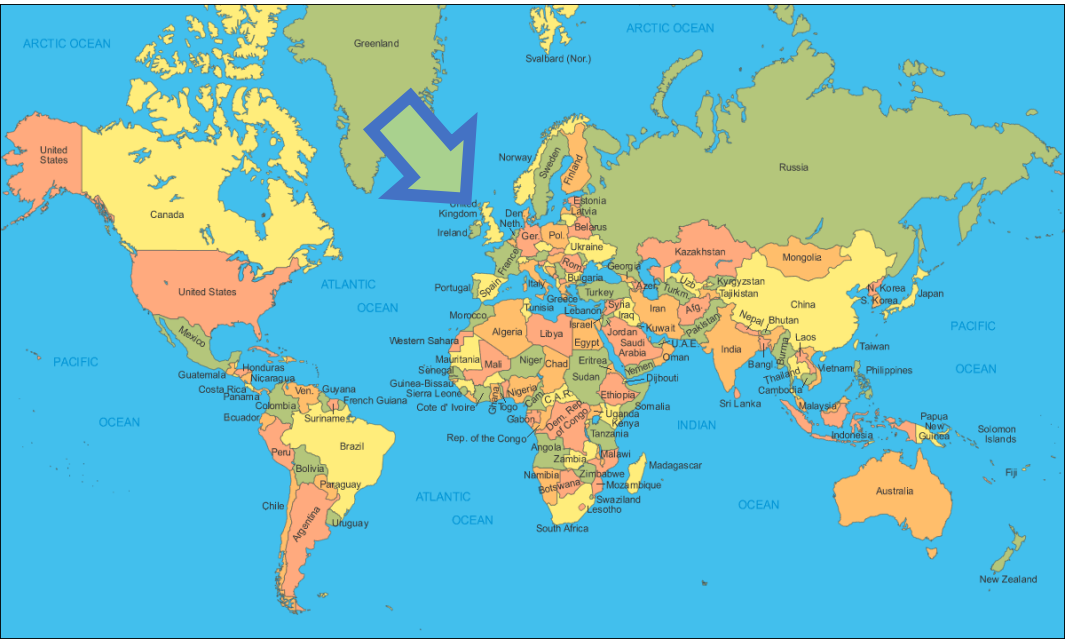


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4. THE CONUNDRUM OF DRUG DEVELOPMENT
5. THE RELATIVE RELEVANCE OF PERSONALISED MEDICINE
6. THE INCOMPLETE ECOSYSTEM OF THE UK IN BIOTECH

?

# Precision Medicine Programme

Manuel Salto-Tellez
Jackie James
David Gonzalez de Castro

Who are we?

The Northern Ireland Molecular Pathology Laboratory

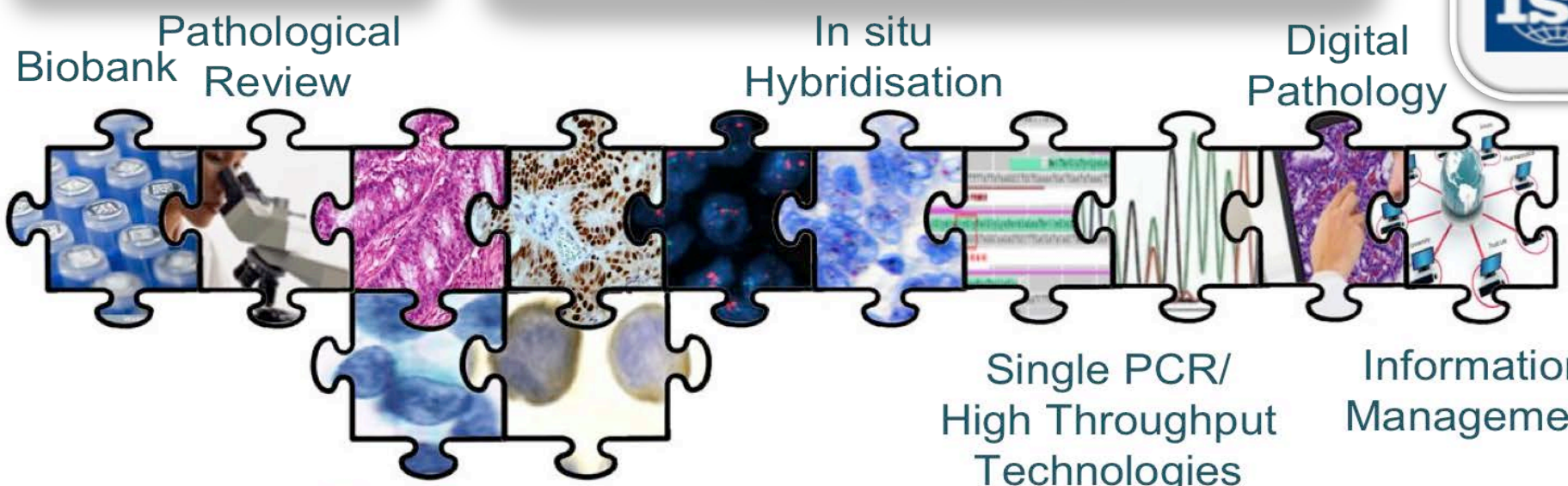
-launched 2012

CPA UKNEQAS

UKAS UNITED KINGDOM ACCREDITATION SERVICE

GCLP COMPLIANT

ISO International Organization for Standardization



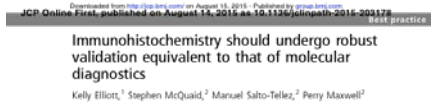

*Adapted from: Salto-Tellez, James & Hamilton. Molecular Oncology, 2014*



Review

Building a 'Repository of Science': The importance of integrating biobanks within molecular pathology programmes

Claire Lewis, Stephen McQuaid, Peter W. Hamilton, Manuel Salto-Tellez, Darragh McArt, Jacqueline A. James


JCP Online First, published on August 14, 2015 as 10.1136/jclinpath-2015-203178

Best practice

Immunohistochemistry should undergo robust validation equivalent to that of molecular diagnostics

Kelly Elliott, Stephen McQuaid, Manuel Salto-Tellez, Perry Maxwell


Journal of Pathology

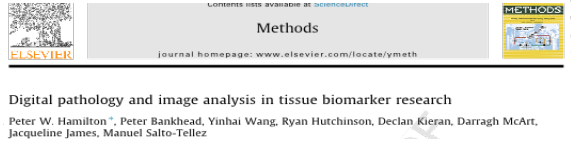
J Pathol 2014; 234: 5–10

Published online in Wiley Online Library (wileyonlinelibrary.com)

INVITED COMMENTARY

Next-generation sequencing: a change of paradigm in molecular diagnostic validation*

Manuel Salto-Tellez* and David Gonzalez de Castro


Methods

journal homepage: www.elsevier.com/locate/ymeth

Digital pathology and image analysis in tissue biomarker research

Peter W. Hamilton, Peter Bankhead, Yinhai Wang, Ryan Hutchinson, Declan Kieran, Darragh McArt, Jacqueline James, Manuel Salto-Tellez


ScienceDirect

Technical Note

PICan: An integromics framework for dynamic cancer biomarker discovery

Darragh G. McArt, Jaine K. Blayney, David P. Boyle, Gareth W. Irwin, Michael Moran, Ryan A. Hutchinson, Peter Bankhead, Declan Kieran, Yinhai Wang, Philip D. Dunne, Richard D. Kennedy, Paul B. Mullan, D. Paul Harkin, Mark A. Catherwood, Jacqueline A. James,

# Precision Medicine Programme

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Belfast Health and Social Care Trust

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Invest Northern Ireland

- Molecular Diagnostics
  MST / DGC / JJ
  Belfast Health and Social Care Trust
- Genomics Research
  DGC
  QUEEN'S UNIVERSITY BELFAST
- Digital Pathology & Artificial Intelligence
  MST / JJ
  CANCER RESEARCH UK
- PM Education & Training
  JJ
  QUEEN'S UNIVERSITY BELFAST
- PM Centre of Excellence
  MST / JJ / DGC
  Invest Northern Ireland
  Health and Social Care
  QUEEN'S UNIVERSITY BELFAST
- The Northern Ireland Biobank
  JJ
  NIBiobank

60 staff
£19.1M direct competitive funds
£35.0M including indirect funds
Molecular diagnostic service
± 150 peer reviewed papers
Significant traction and support with industry

# What is Molecular Pathology?

Molecular Pathology is the morphological and molecular interrogation of clinical samples, with all the technologies associated to these analyses, to better understand the nature of diseases – ***Translational Research***.

*Bench-to-Bedside*
*Nature Reviews Drug Discovery* ***7, 463-464 (June 2008)***

CLINICAL SAMPLES

↓

MORPHOLOGICAL ANALYSIS

↓

MOLECULAR INTERROGATION

↓

CLINICO-PATHOLOGICAL CORRELATIONS
(biostatistics / bioinformatics)

↓

RESULTS

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**Precision Medicine Centre of Excellence**

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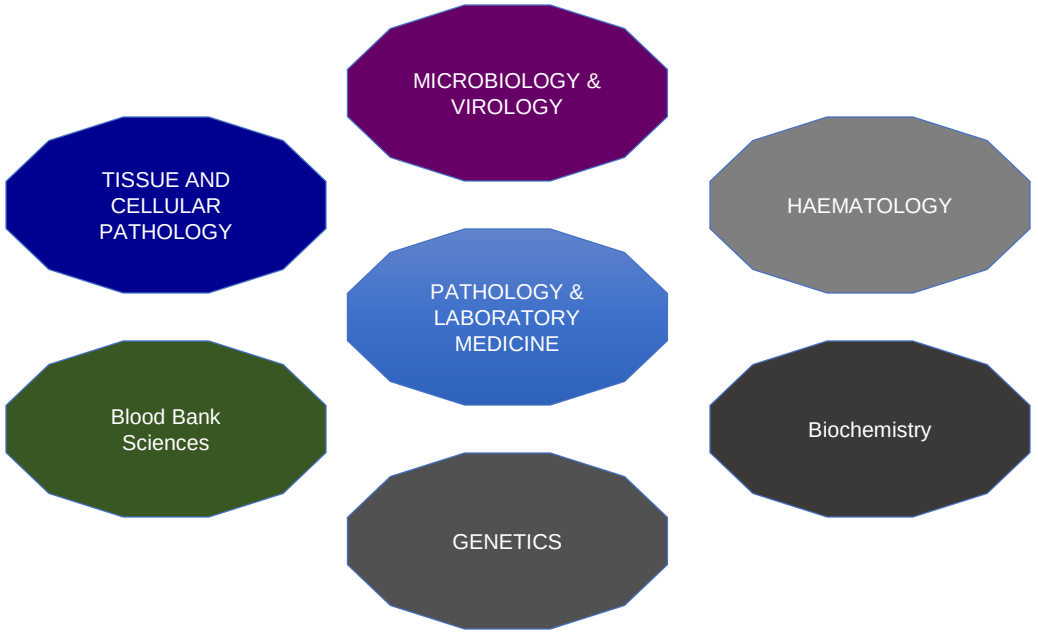
Molecular Pathology is the application of the knowledge of the genetic mechanisms of disease to **diagnosis**, **prognostication** and **treatment** of diseases – ***Molecular Diagnostics***

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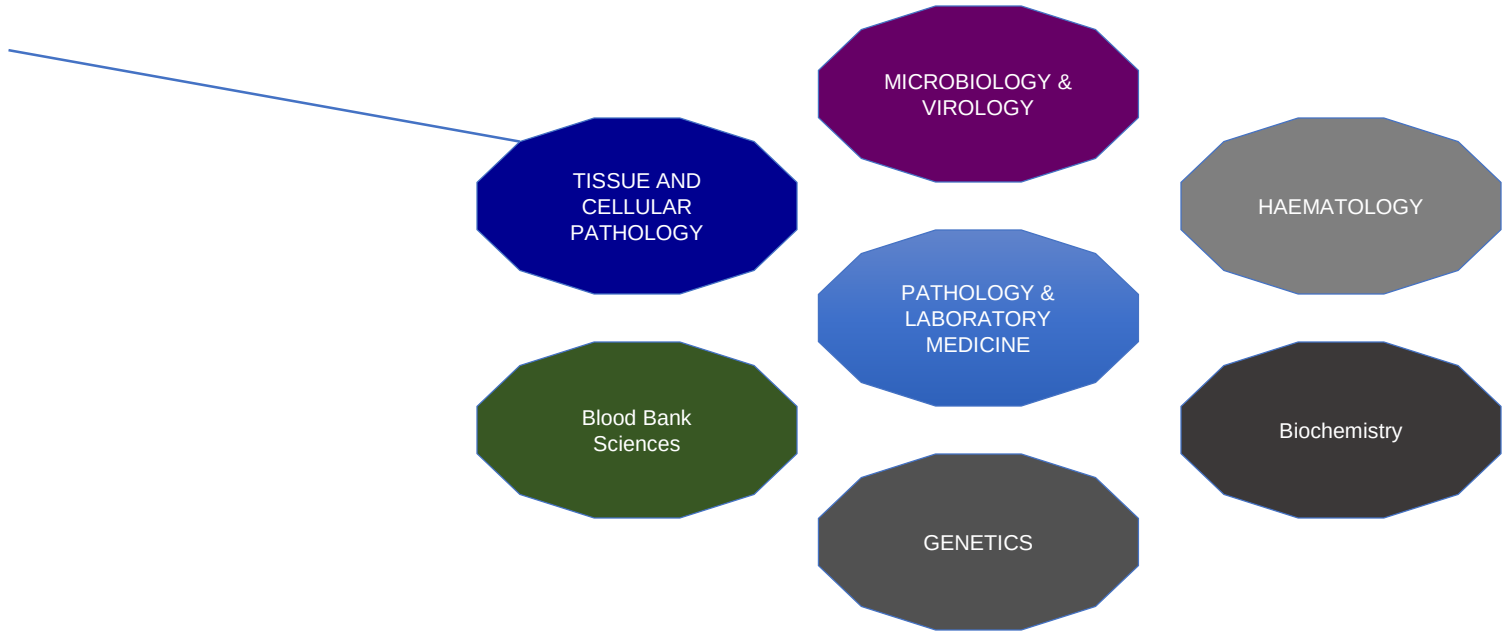
*Diagnostic Molecular Histopathology & Cytopathology*

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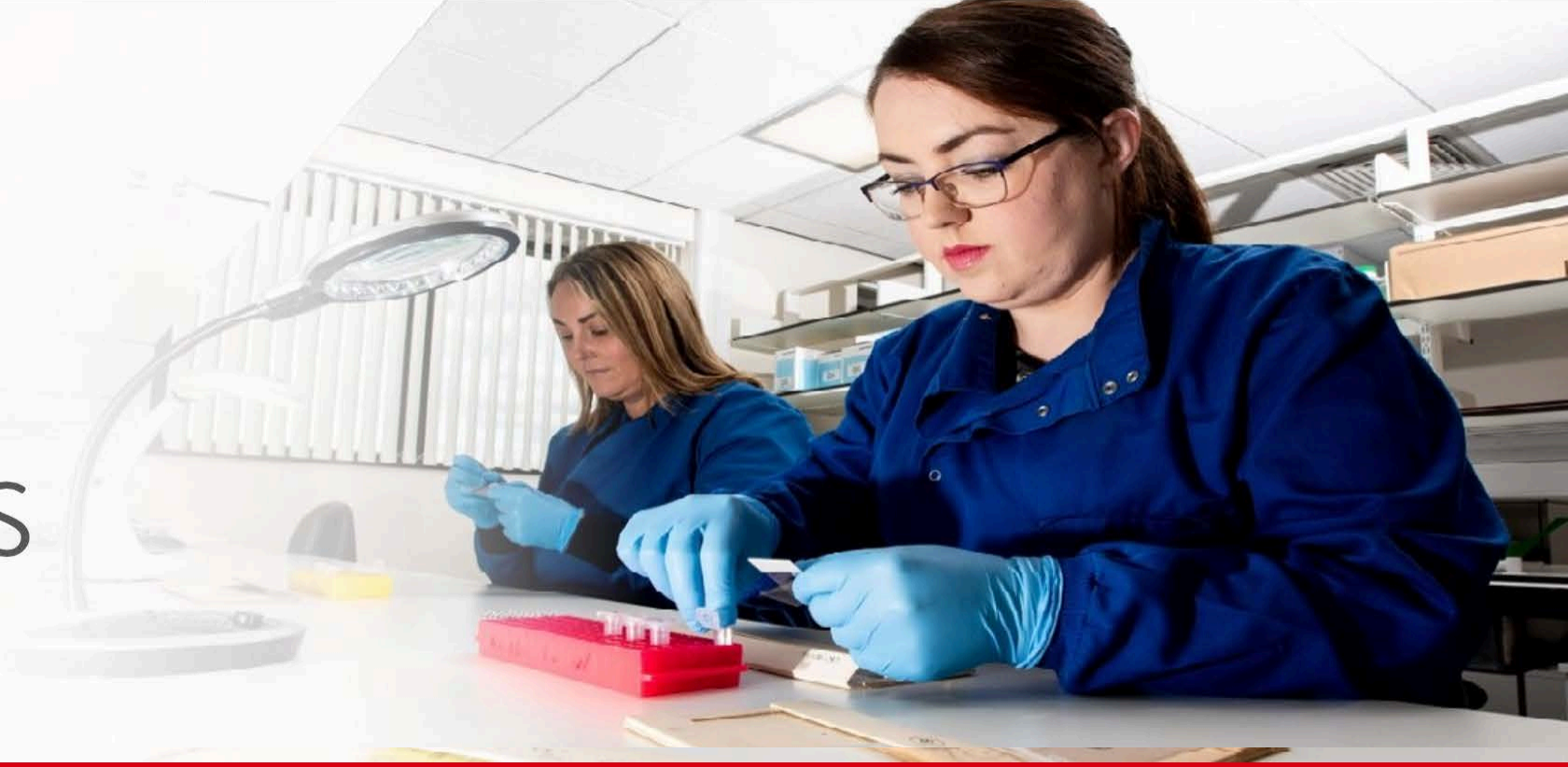
**Precision Medicine Centre of Excellence**

PRECISION MEDICINE CENTRE

# CLINICAL DIAGNOSTICS



www.qub.ac.uk/research-centres/PMC/

## MOLECULAR DIAGNOSTICS AT THE PRECISION MEDICINE CENTRE

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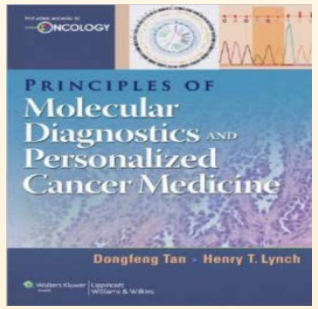
HSC Belfast Health and Social Care Trust

HSC Public Health Agency

# Selected target therapeutics in clinical oncology practice

| Targeted Therapeutics | Target | Tumor |
|---|---|---|
| *Antibodies* | | |
| Bevacizumab | VEGF | Breast Ca/CRC/NSCLC |
| Cetuximab | EGFR/KRAS | CRC and HN Ca |
| Panitumumab | EGFR | CRC |
| Rituximab | CD20 | B-cell lymphoma |
| Trastuzumab | Her-2 | Breast Ca/Gastric cancer |
| *Small molecule inhibitors* | | |
| Bortezomib | Proteasome | MM and MCL |
| Crizotinib | ALK | NSCLC |
| Erlotinib | EGFR | NSCLC/pancreatic cancer |
| Gefitinib | EGFR | NSCLC |
| Imatinib | c-kit/BCR-ABL | GIST/CML |
| Lapatinib | Her-2 and EGFR | Breast Ca |
| Sorafenib | VEGFR/PDGFR/RAF | HCC and RCC |
| Sunitinib | VEGFR/PDGFR/RET | GIST and RCC |
| Temsirolimus | mTOR | RCC |
| Vemurafenib | BRAF | Melanoma |
| Vorinostat/Bortezomib | HDAC | Cutaneous TCL |




*Salto-Tellez M. In: Tan & Lynch's Principles of Molecular Diagnostics and Personalized Cancer Therapy, Lippincott Williams & Wilkins, 2012.*

# Revolution in Oncology

New Drugs for Targeted Therapy



**Table 3. US FDA Approved Targeted Therapies and Indications.**

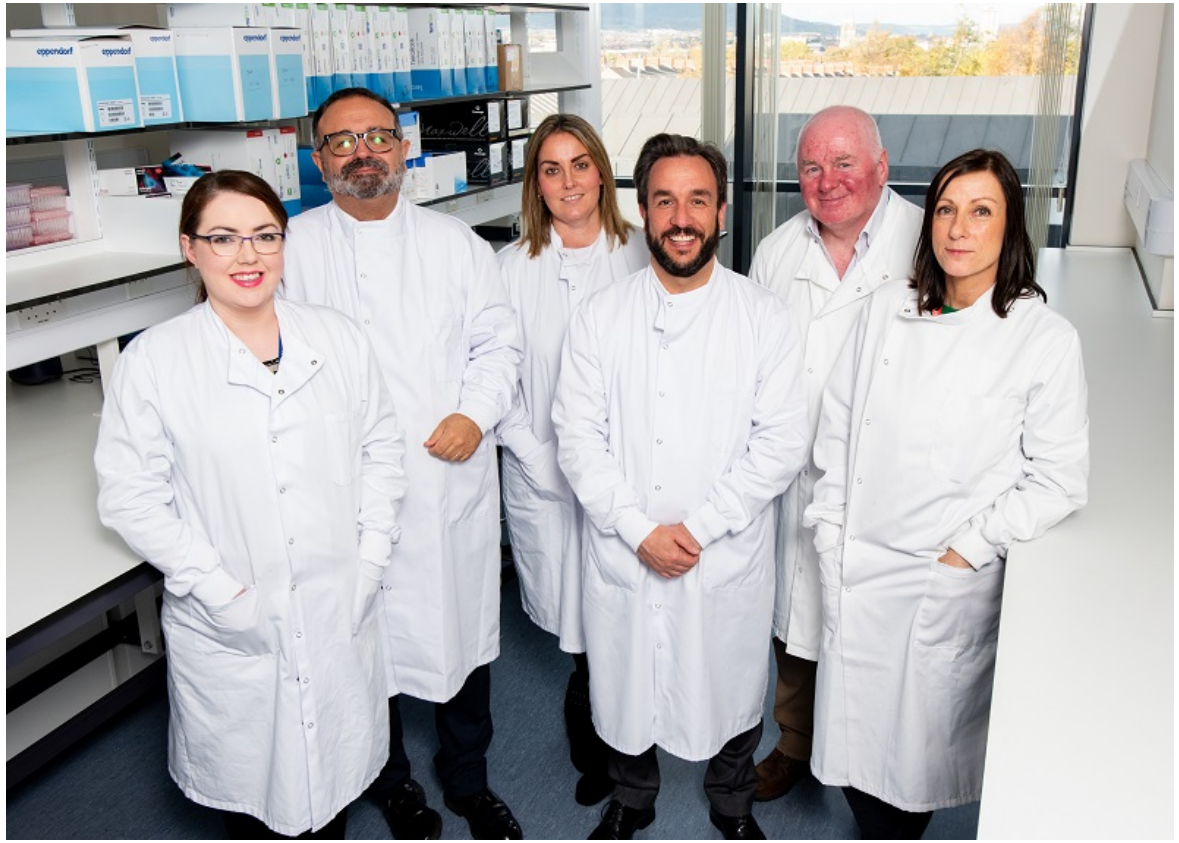
| Agent | Trade Name | Target(s) | FDA-approved Indication(s) | Company |
|---|---|---|---|---|
| | | | ***Monoclonal Antibodies*** | |
| Ado-trastuzumab emtansine (T-DM1)* | Kadcyla | HER2 | Breast cancer (HER2+)* | Genentech |
| Bevacizumab | Avastin | VEGF | CRC | Genentech |
| | | | GBM | |
| | | | NCLC | |
| | | | RCC | |
| Cetuximab* | Erbitux | EGFR | CRC (KRAS wild-type)* | Eli Lilly |
| | | | HNSCC | |
| Ipilimumab | Yervoy | CTLA-4 | Melanoma | Bristol-Myers Squibb |
| Obinutuzumab | Gazyva | CD-20 | CLL | Genentech |
| Panitumumab* | Vectibix | EGFR | CRC (KRAS wild-type)* | Amgen |
| Pertuzumab | Perjeta | HER2 | Breast Cancer (HER2+)* | Genentech |
| Trastuzumab* | Herceptin | HER2 | Breast cancer (HER2+)* | Genentech |
| | | | Gastric cancer (HER2+)* | |
| | | | ***Small Molecule Inhibitors*** | |
| Afatinib* | Gilotrif | EGFR, HER2 | NSCLC (with EGFR exon 19 deletions or L858R substitution)* | Boehringer Ingelheim |
| Axitinib | Inlyta | KIT, PDGFRβ, VEGFR1/2/3 | RCC | Pfizer |
| Bosutinib* | Bosulif | ABL | CML (Philadelphia chromosome positive)* | Pfizer |
| Cabozantinib | Cometriq | FLT3, KIT, MET, RET, VEGFR2 | Medullary thyroid cancer | Exelixis |
| Crizotinib* | Xalkori | ALK, MET | NSCLC (with ALK fusion)* | Pfizer |
| Dabrafenib* | Tafinlar | BRAF | Melanoma (with BRAF V600E mutation)* | GlaxoSmithKline |
| Dasatinib* | Sprycel | ABL | CML (Philadelphia chromosome positive)* | Bristol-Myers Squibb |
| | | | ALL (Philadelphia chromosome positive)* | |
| Denosumab | Xgeva | RANKL | Giant cell tumor of bone | Amgen |
| Erlotinib* | Tarceva | EGFR | NSCLC (with exon 19 deletions or L858R substitutions)* | Genentech & OSI |
| | | | Pancreatic cancer | |
| Everolimus* | Afinitor | mTOR | Pancreatic neuroendocrine tumor | Novartis |
| | | | RCC | |
| | | | Breast cancer (ER/PR+) in combination with exemestane* | |
| | | | Nonresectable subependymal giant cell astrocytoma associated with tuberous sclerosis | |
| Gefitinib | Iressa | EGFR | NSCLC with known prior benefit from gefitinib (limited approval) | AstraZeneca |
| Ibrutininb | Imbruvica | BTK | Mantle cell lymphoma | Pharmacyclics |
| Imatinib* | Gleevec | KIT, PDGFR, ABL | GI stromal tumor | Novartis |
| | | | Dermatofibrosarcoma protuberans | |
| | | | Multiple hematologic malignancies including Philadelphia chromosome-positive ALL and CML* | |
| Lapatinib* | Tykerb | HER2, EGFR | Breast cancer (HER2+)* | GlaxoSmithKline |
| Nilotinib* | Tasigna | ABL | CML (Philadelphia chromosome positive)* | Novartis |
| Pazopanib | Votrient | VEGFR, PDGFR, KIT | RCC | GlaxoSmithKline |
| | | | Soft tissue sarcoma | |
| Regorafenib | Stivarga | KIT, PDGFRβ, RAF, RET, VEGFR1/2/3 | CRC | Bayer |
| | | | Gastrointestinal stromal tumors | |
| Ruxolitinib | Jakafi | JAK1/2 | Myelofibrosis | Incyte |
| Sorafenib | Nexavar | VEGFR, PDGFR, KIT, RAF | Hepatocellular carcinoma | Bayer |
| | | | RCC | |
| Sunitinib | Sutent | VEGFR, PDGFR, KIT, RET | GIST | Pfizer |
| | | | Pancreatic neuroendocrine tumor | |
| | | | RCC | |
| Temsirolimus | Torisel | mTOR | RCC | Wyeth |
| Trametinib* | Mekinist | MEK | Melanoma (with BRAF V600E or V600K mutations)* | GlaxoSmithKline |
| Vandetanib | Caprelsa | EGFR, RET, VEGFR2 | Medullary thyroid cancer | AstraZeneca |
| Vemurafenib* | Zelboraf | BRAF | Melanoma (with BRAF V600 mutation)* | Roche |

*Note*: ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; GIST, gastrointestinal stromal tumor; ER, estrogen receptor; PR, progesterone receptor; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; GBM, glioblastoma; RCC, renal cell carcinoma; HNSCC, head and neck squamous cell carcinoma; CLL, chronic lymphoblastic leukemia; BTK, Bruton's tyrosine kinase. * Targeted therapy that is associated with a molecular-specific cancer subtype alteration. There are approximately 17 targeted therapies that are associated with 10 molecular-specific subtypes of cancer.

https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet

**What targeted therapies have been approved for specific types of cancer?The FDA has approved targeted therapies for the treatment of some patients with the following types of cancer (some targeted therapies have been approved to treat more than one type of cancer):**

**Adenocarcinoma of the stomach or gastroesophageal junction**Trastuzumab (Herceptin®), ramucirumab (Cyramza®)
Bladder cancer: Atezolizumab (Tecentriq™), nivolumab (Opdivo®), durvalumab (Imfinzi™), avelumab (Bavencio®), pembrolizumab (Keytruda®)
Brain cancer: Bevacizumab (Avastin®), everolimus (Afinitor®)
Breast cancer: Everolimus (Afinitor®), tamoxifen (Nolvadex), toremifene (Fareston®), Trastuzumab (Herceptin®), fulvestrant (Faslodex®), anastrozole (Arimidex®), exemestane (Aromasin®), lapatinib (Tykerb®), letrozole (Femara®), pertuzumab (Perjeta®), ado-trastuzumab emtansine (Kadcyla®), palbociclib (Ibrance®), ribociclib (Kisqali®), neratinib maleate (Nerlynx™), abemaciclib (Verzenio™), olaparib (Lynparza™)
Cervical cancer: Bevacizumab (Avastin®), pembrolizumab (Keytruda®)
Colorectal cancer: Cetuximab (Erbitux®), panitumumab (Vectibix®), bevacizumab (Avastin®), ziv-aflibercept (Zaltrap®), regorafenib (Stivarga®), ramucirumab (Cyramza®), nivolumab (Opdivo®), ipilimumab (Yervoy®)
Dermatofibrosarcoma protuberans: Imatinib mesylate (Gleevec®)
Endocrine/neuroendocrine tumors: Lanreotide acetate (Somatuline® Depot), avelumab (Bavencio®), lutetium Lu 177-dotatate (Lutathera®), iobenguane I 131 (Azedra®)
Head and neck cancer: Cetuximab (Erbitux®), pembrolizumab (Keytruda®), nivolumab (Opdivo®)
Gastrointestinal stromal tumor: Imatinib mesylate (Gleevec®), sunitinib (Sutent®), regorafenib (Stivarga®)
Giant cell tumor of the bone: Denosumab (Xgeva®)
Kidney cancer: Bevacizumab (Avastin®), sorafenib (Nexavar®), sunitinib (Sutent®), pazopanib (Votrient®), temsirolimus (Torisel®), everolimus (Afinitor®), axitinib (Inlyta®), nivolumab (Opdivo®), cabozantinib (Cabometyx™), lenvatinib mesylate (Lenvima®), ipilimumab (Yervoy®)
Leukemia: Tretinoin (Vesanoid®), imatinib mesylate (Gleevec®), dasatinib (Sprycel®), nilotinib (Tasigna®), bosutinib (Bosulif®), rituximab (Rituxan®), alemtuzumab (Campath®), ofatumumab (Arzerra®), obinutuzumab (Gazyva®), ibrutinib (Imbruvica®), idelalisib (Zydelig®), blinatumomab (Blincyto®), venetoclax (Venclexta™), ponatinib hydrochloride (Iclusig®), midostaurin (Rydapt®), enasidenib mesylate (Idhifa®), inotuzumab ozogamicin (Besponsa®), tisagenlecleucel (Kymriah®), gemtuzumab ozogamicin (Mylotarg™), rituximab and hyaluronidase human (Rituxan Hycela™), ivosidenib (Tibsovo®), duvelisib (Copiktra™)
Liver cancer: Sorafenib (Nexavar®), regorafenib (Stivarga®), nivolumab (Opdivo®), lenvatinib mesylate (Lenvima®)
Lung cancer: Bevacizumab (Avastin®), crizotinib (Xalkori®), erlotinib (Tarceva®), gefitinib (Iressa®), afatinib dimaleate (Gilotrif®), ceritinib (LDK378/Zykadia™), ramucirumab (Cyramza®), nivolumab (Opdivo®), pembrolizumab (Keytruda®), osimertinib (Tagrisso™), necitumumab (Portrazza™), alectinib (Alecensa®), atezolizumab (Tecentriq™), brigatinib (Alunbrig™), trametinib (Mekinist®), dabrafenib (Tafinlar®), durvalumab (Imfinzi™), dacomitinib (Vizimpro®)
Lymphoma: Ibritumomab tiuxetan (Zevalin®), denileukin diftitox (Ontak®), brentuximab vedotin (Adcetris®), rituximab (Rituxan®), vorinostat (Zolinza®), romidepsin (Istodax®), bexarotene (Targretin®), bortezomib (Velcade®), pralatrexate (Folotyn®), ibrutinib (Imbruvica®), siltuximab (Sylvant®), idelalisib (Zydelig®), belinostat (Beleodaq®), obinutuzumab (Gazyva®), nivolumab (Opdivo®), pembrolizumab (Keytruda®), rituximab and hyaluronidase human (Rituxan Hycela™), copanlisib hydrochloride (Aliqopa™), axicabtagene ciloleucel (Yescarta™), acalabrutinib (Calquence®), tisagenlecleucel (Kymriah®), venetoclax (Venclexta™), mogamulizumab-kpkc (Poteligeo®), duvelisib (Copiktra™)
Microsatellite instability-high or mismatch repair-deficient solid tumors: Pembrolizumab (Keytruda®)Multiple myeloma: Bortezomib (Velcade®), carfilzomib (Kyprolis®), panobinostat (Farydak®), daratumumab (Darzalex™), ixazomib citrate (Ninlaro®), elotuzumab (Empliciti™)
Myelodysplastic/myeloproliferative disorders: Imatinib mesylate (Gleevec®), ruxolitinib phosphate (Jakafi®)
Neuroblastoma: Dinutuximab (Unituxin™)Ovarian epithelial/fallopian tube/primary peritoneal cancers: Bevacizumab (Avastin®), olaparib (Lynparza™), rucaparib camsylate (Rubraca™), niraparib tosylate monohydrate (Zejula™)Pancreatic cancer: Erlotinib (Tarceva®), everolimus (Afinitor®), sunitinib (Sutent®)Prostate cancer: Cabazitaxel (Jevtana®), enzalutamide (Xtandi®), abiraterone acetate (Zytiga®), radium 223 dichloride (Xofigo®), apalutamide (Erleada™)Skin cancer: Vismodegib (Erivedge®), sonidegib (Odomzo®), ipilimumab (Yervoy®), vemurafenib (Zelboraf®), trametinib (Mekinist®), dabrafenib (Tafinlar®), pembrolizumab (Keytruda®), nivolumab (Opdivo®), cobimetinib (Cotellic™), alitretinoin (Panretin®), avelumab (Bavencio®), encorafenib (Braftovi™), binimetinib (Mektovi®), cemiplimab-rwlc (Libtayo®)
Soft tissue sarcoma: Pazopanib (Votrient®), olaratumab (Lartruvo™), alitretinoin (Panretin®)
Stomach cancer: Pembrolizumab (Keytruda®)Systemic mastocytosis: Imatinib mesylate (Gleevec®), midostaurin (Rydapt®)
Thyroid cancer: Cabozantinib (Cometriq®), vandetanib (Caprelsa®), sorafenib (Nexavar®), lenvatinib mesylate (Lenvima®), trametinib (Mekinist®), dabrafenib (Tafinlar®)



David Gonzalez de Castro
Jackie James
Manuel Salto-Tellez

Stephen McQuaid
Fiona McLeod
Patricia Higgins

Christine Quinn
New Band 8A

Perry Maxwell
Manisha Maurya

QUEEN'S UNIVERSITY BELFAST

More than 500m$^2$
350m$^2$ of which are the integrated laboratory

2,000 – 3,000 tests per year (across NI and RoI)

Tissue Molecular Diagnostics
N.A.-based tests – RAS, BRAF, EGFR, MSI, cfEGFR
Hybr. based tests – ALK, PDL-1, Her2 (Br Ca and Gas Ca)

This menu will be transformed by end of 2019 with the application of NGS

Analysis of clinical trials

Supports 100K Genomes, CRUK SMP2 through NIB

Committees: NEQAS, NICE, NIHR, RCPath

Numerous Advisory Boards with Industry

UKAS UNITED KINGDOM ACCREDITATION SERVICE
CPA
UK NEQAS
ISO International Organization for Standardization
GCLP COMPLIANT

# Lung Cancer Diagnostic Tests

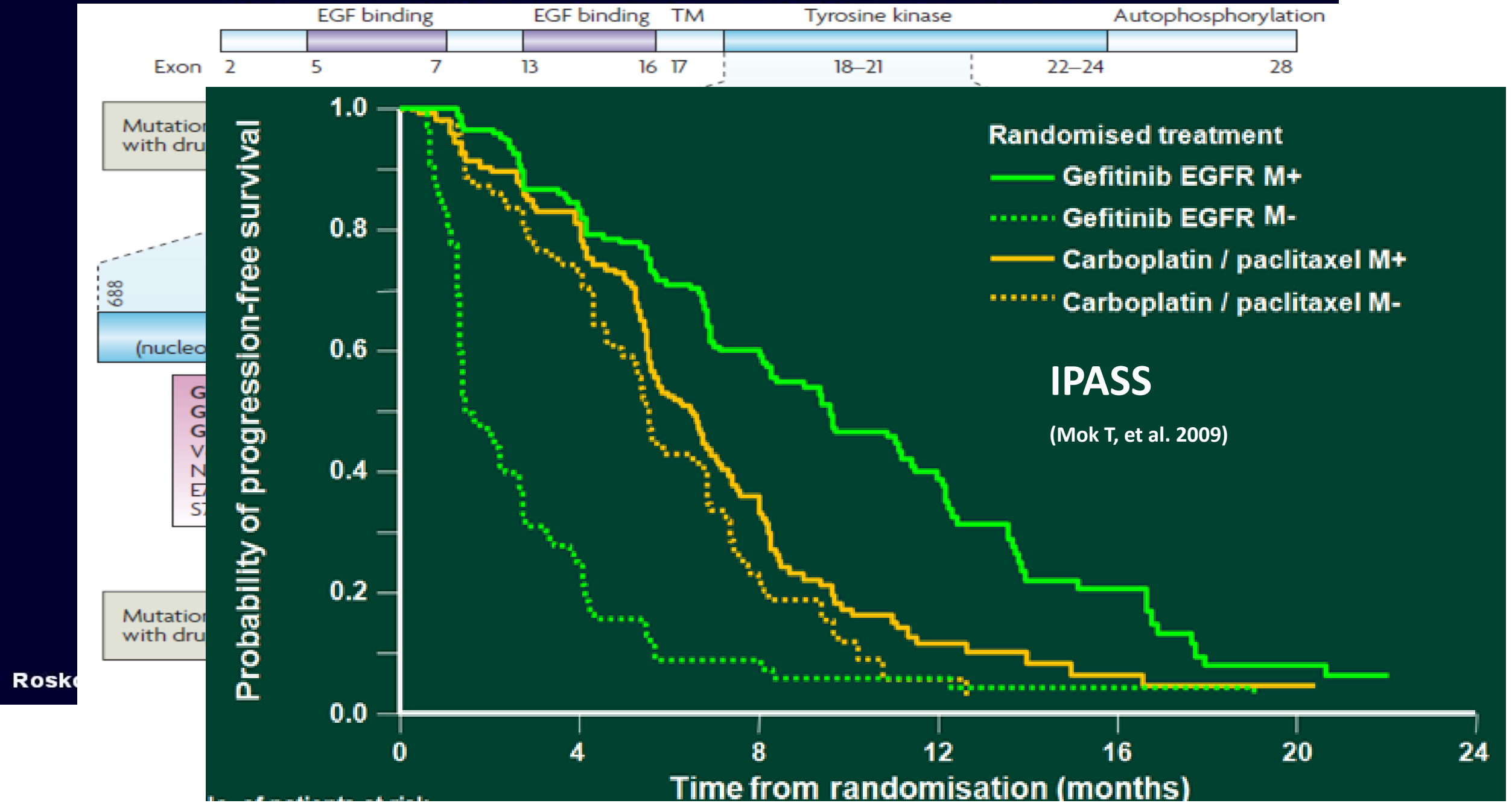
EGFR mutation analysis (tissues)

ALK overexpression

PD-L1 overexpression

EGFR mutation analysis (cfDNA)

ROS1 (under validation)


EGF binding
EGF binding
TM
Tyrosine kinase
Autophosphorylation
Exon
2
5
7
13
16
17
18–21
22–24
28
Mutation
with dru
688
(nucleo
Mutation
with dru
Probability of progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
4
8
12
16
20
24
Time from randomisation (months)
Randomised treatment
Gefitinib EGFR M+
Gefitinib EGFR M-
Carboplatin / paclitaxel M+
Carboplatin / paclitaxel M-
IPASS
(Mok T, et al. 2009)

# EGFR

**MAY 2012 TO DECEMBER 2018**

2459 EGFR TISSUE-BASED TESTS

13.19% OF MUTANT CASES

6.10% INADEQUATES

2.15% INVALIDS

8.25% ATTRITION RATE

UK NEQAS
Molecular Genetics

***UK-MolGen for EGFR (COBAS) in NSCLC***

***Participation since 2012***

***All satisfactory***

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# EGFR cfDNA

Clinical Utility:

- Molecular testing for EGFR mutation where a tissue or cytology sample is not available
- Monitoring of EGFR mutation status during therapy
- Identification of acquired TKI resistance EGFR mutations e.g. Thr790Met

Methodology:

- Whole blood – plasma separation
- DNA extraction (COBAS, Roche)
- EGFR mutation QPCR (COBAS, Roche)

Reporting:

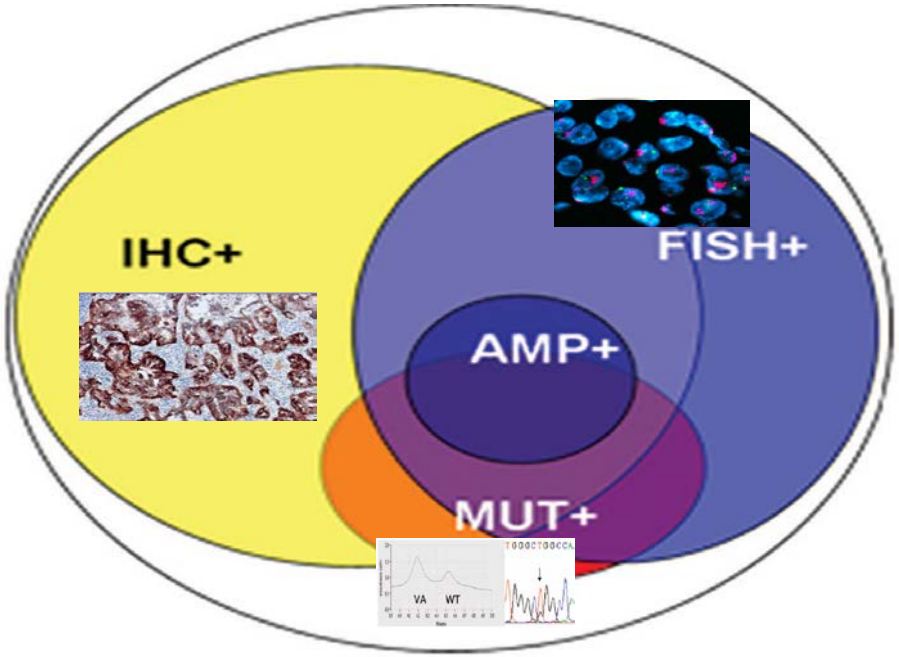
- Context of Clinical utility (see above)

## EGFR cfDNA

**JAN 2018 TO DECEMBER 2018**

85 EGFR cfDNA TESTS

17.65% OF MUTANT CASES



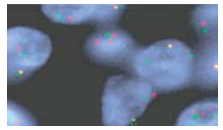
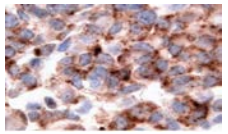
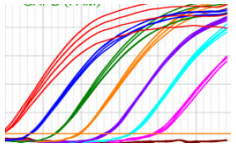

EGFR - Pinter et al. J Mol Diagn, 2008

Cell PRESS

Cancer Cell
Minireview

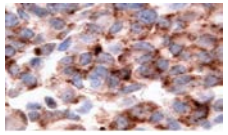
## ALK Inhibition for Non-Small Cell Lung Cancer: From Discovery to Therapy in Record Time

David E. Gerber[1,4,*] and John D. Minna[1,2,3,4,*]
[1]Department of Internal Medicine -Division of Hematology-Oncology
[2]Department of Pharmacology
[3]Hamon Center for Therapeutic Oncology Research
[4]Simmons Cancer Center,
University of Texas Southwestern Medical Center, Dallas, Texas 75390
*Correspondence: david.gerber@utsouthwestern.edu (D.E.G.), john.minna@utsouthwestern.edu (J.D.M.)
DOI 10.1016/j.ccr.2010.11.033

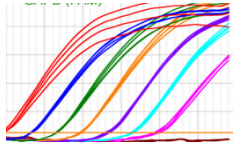




## *Europe??*

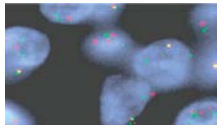
Screening



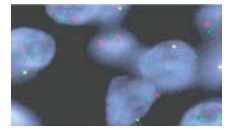
*or*



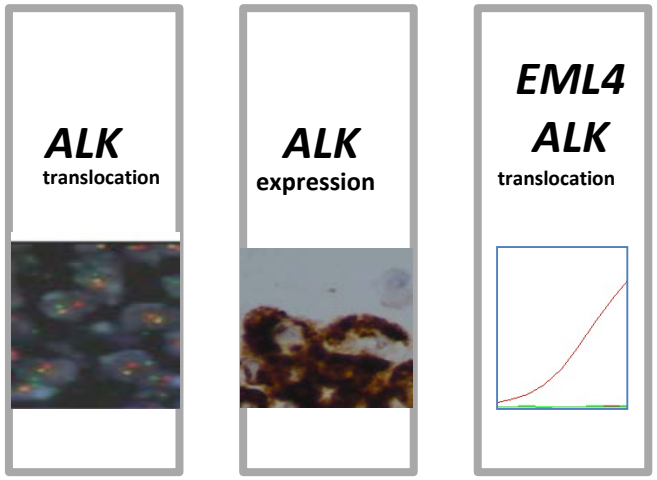
Confirmation



## *U.S.A.*



September 1, 2011 — The US FDA granted approval to Crizotinib for adbvanced-stage NSCLC. A companion diagnostic test – Vysis ALK Break apart probe, was approved concurrently




| TEST TYPE | POTENTIAL SHORTFALL |
|---|---|
| FISH | PROLONGED FIXATION IN RESECTION SAMPLES |
| IHC | MIXED ADENOSQUAMOUS TYPES MAY BE EQUIVOCAL |
| Q-PCR | SMALL BIOPSY/CYTOLOGY SAMPLES LIMIT TEST |

**Table 2.** Summary of the issues encountered in routine diagnostics and which need to be taken into account when making the best possible use of several technology platforms.

**Prospective diagnostic validation of *EML4-ALK* gene fusions or surrogates in NSCLC in the routine diagnostic setting: the effect of several testing methodologies and sample types.**

*Perry Maxwell[1] PhD, FRCPath, Claire McGready[1] BSc, Stephen McQuaid[1] PhD, Graeme O'Hara[2] FRCPath, Neil Anderson[2] MD, FRCPath, Jacqueline James[1] PhD, FRCPath, Tony O'Grady[3] PhD, Elaine Kay[3] MD, FRCPath, Manuel Salto-Tellez[1] MD, FRCPath

# ALK IHC

**MAY 2013 TO DECEMBER 2018**

1651 ALK IHC TESTS
(103 ALK FISH tested – 6.23%)

1.88% POSITIVE CASES

UK NEQAS
International Quality Expertise

Immunocytochemistry
& In-Situ Hybridisation

(since 2014)

| | |
|---|---|
| ALK: UK-NEQAS | 11 excellent<br>3 Acceptable |
| ALK-In-house | 10 excellent<br>1 acceptable<br>3 borderline*** |

***staining satisfactory but low volume of tumour in the negative control example.

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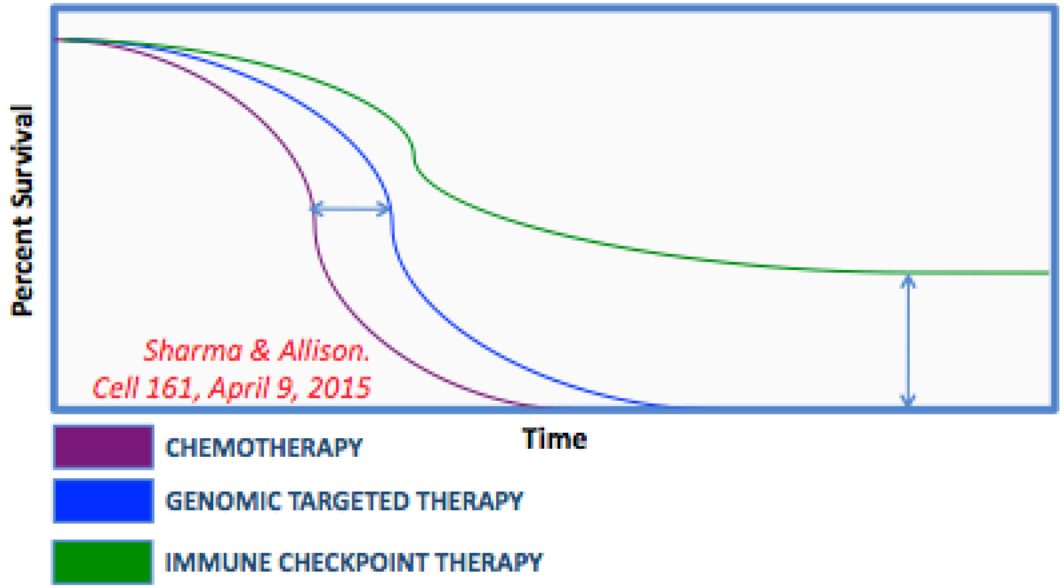
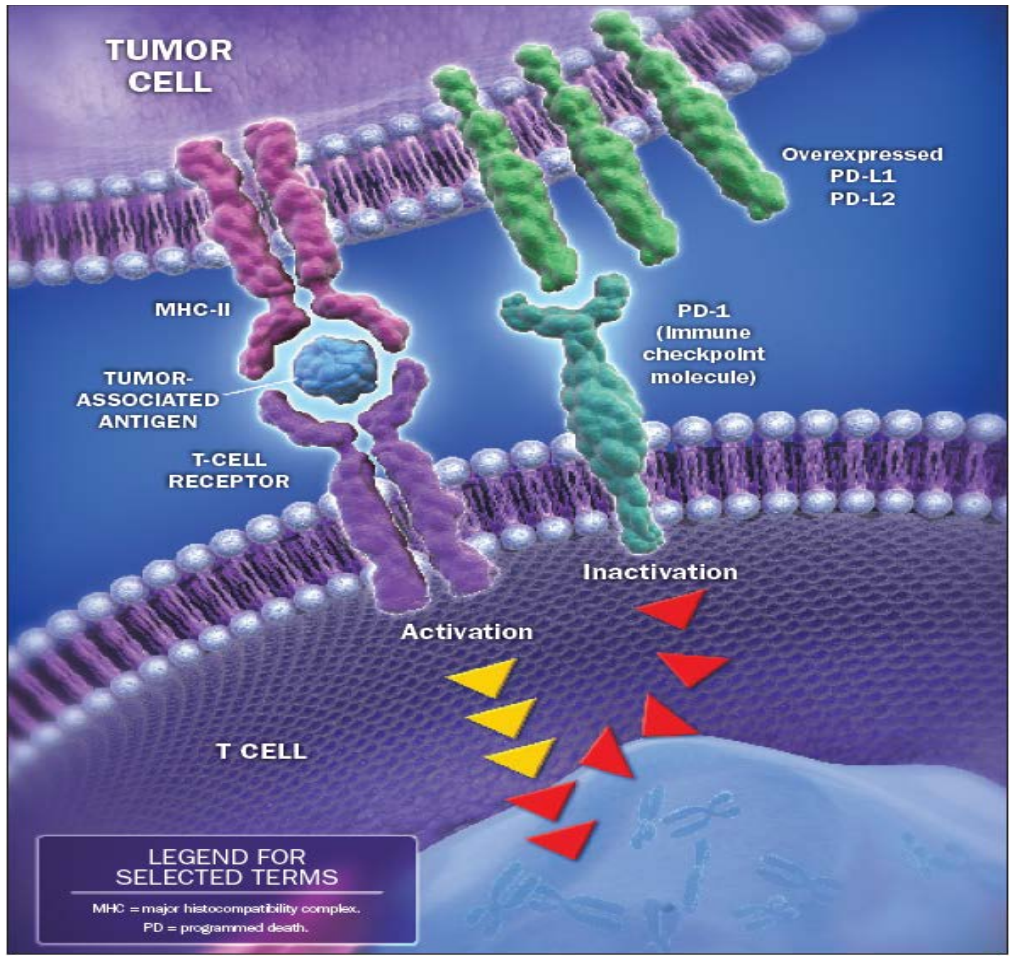
# Role of the PD-1 Pathway in Cancer

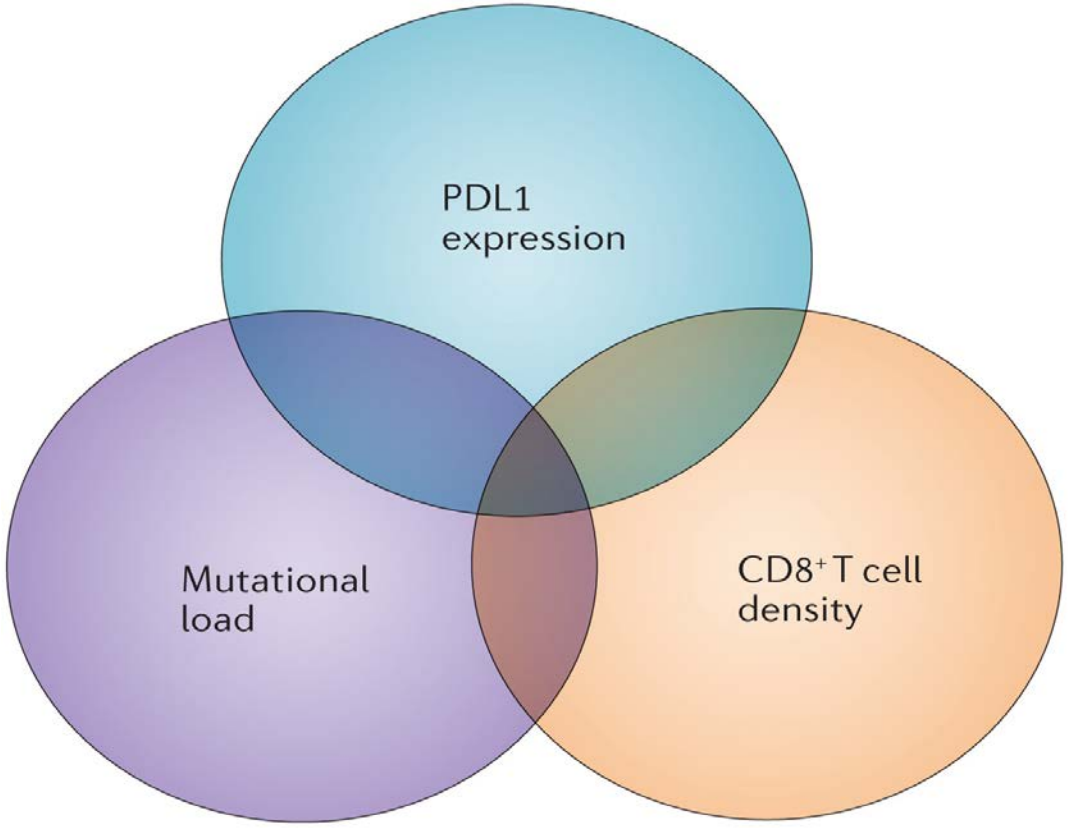
- Programmed death 1 (PD-1) pathway is an immune checkpoint pathway that is expressed on the surface of activated T cells
- One of its ligands, PD-L1, is highly expressed on the surface of tumor cells
- Binding of PD-1 with PD-L1 inhibits T cell activation, allowing immunosuppression and neoplastic growth




**Pardoll DM.**
**The blockade of immune checkpoints in cancer immunotherapy.**
**Nat Rev Cancer. 2012;12:252–264.**

# Role of the PD-1 Pathway in Cancer – The Broader Picture

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ORIGINAL ARTICLE

# Critical Appraisal of Programmed Death Ligand 1 Reflex Diagnostic Testing: Current Standards and Future Opportunities

Matthew P. Humphries, PhD,[a] Stephen McQuaid, PhD,[a,b,c] Stephanie G. Craig, PhD,[a] Victoria Bingham, MSc,[a] Perry Maxwell, PhD,[a,b] Manisha Maurya, PhD,[a] Fiona McLean, BSc,[a,b] James Sampson, MBChB,[a] Patricia Higgins, BSc,[a,b] Christine Greene, BSc,[a,b,c] Jacqueline James, PhD,[a,b,c] Manuel Salto-Tellez, MBChB[a,b,*]

[a]*Molecular Pathology Programme, Centre for Cancer Research and Cell Biology, Queen's University, Belfast, Ireland, United Kingdom*
[b]*Cellular Pathology, Belfast Health and Social Care Trust, Belfast City Hospital, Belfast, Ireland, United Kingdom*
[c]*Northern Ireland Biobank, Centre for Cancer Research and Cell Biology, Queen's University, Belfast, Ireland, United Kingdom*

Received 24 May 2018; revised 27 July 2018; accepted 28 September 2018
Available online - 5 October 2018

QUEEN'S UNIVERSITY BELFAST

ELSEVIER

Journal of Thoracic Oncology
Volume 14, Issue 1, January 2019, Pages 45-53

A

| Manual Assessment \ Digital Assessment | <1% | 1-49% | >50% |
|---|---|---|---|
| <1% | 4 | 2 | 0 |
| 1-49% | 0 | 16 | 1 |
| >50% | 0 | 3 | 5 |

B

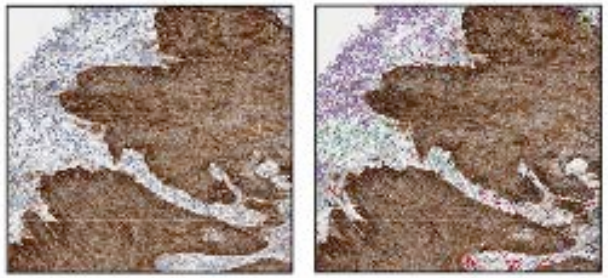
| Manual Assessment \ Digital Assessment | <1% | 1-49% | >50% |
|---|---|---|---|
| <1% | 10 | 5 | 0 |
| 1-49% | 1 | 6 | 0 |
| >50% | 0 | 0 | 9 |

# QuPath

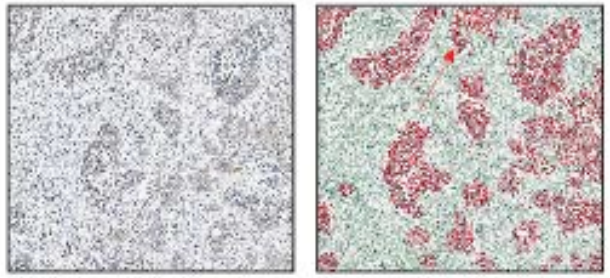
27% discrepancies

Most of these discrepancies were around the <1% - 3% threshold, Some around the 45%-55% threshold.

C



D




QUEEN'S UNIVERSITY BELFAST

ELSEVIER

Journal of Thoracic Oncology
Volume 14, Issue 1, January 2019, Pages 45-53

I publish my annual report on health in England as part of my statutory role. In this edition of my report, I take a detailed look at genomics, exploring how we currently utilise genomics in our health and care system and how its potential may be developed.

Leading figures from the field of genomics have contributed specialist chapters. I include topics such as the care and treatment of cancer, diagnosing rare diseases, the use of genomics in screening and 'personalised' prevention, precision medicine – the targeting of drugs to do the most good and least harm. I wanted also to consider genomics within the context of society and include a chapter considering the ethical and societal discourse around genomics. Using the evidence I make recommendations, aimed at those able to bring about change, to guide how our potential can be realised to both improve patients' outcomes and maintain the UK's leadership role in genomics.

Annual Report of the Chief Medical Officer 2016

Generation Genome

Genomics is not tomorrow. Its here today. I believe genomic services should be available to more patients, whilst being a cost-effective service in the NHS. This is exciting science with the potential for fantastic improvements in prevention, health protection and patient outcomes. Now we need to welcome the genomic era and deliver the genomic dream!

Prof Dame Sally C Davies



## Genomic Medical Centres

***Genetic samples (blood, tissues)***

***Genetic information (raw, semi-processed)***

## Genetic Hubs

**All molecular testing in a single building**

**Using Common Molecular Technology**

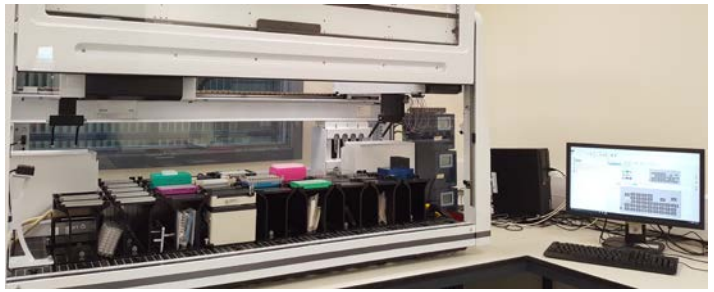
In line with Royal College of Pathologists recommendations, characterised by **high throughput** to justify investment & provide economies of scale

2012

QUEEN'S UNIVERSITY BELFAST

**Precision Medicine Centre of Excellence**

## BioMek i7 Liquid Handler

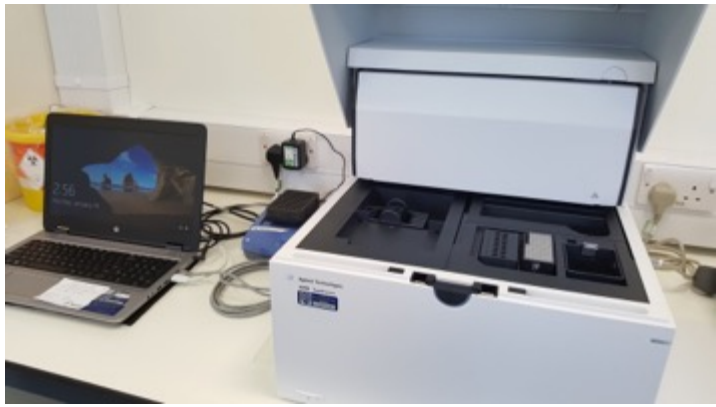


## NextSeq 550

## Digital Doplet PCR

## Illumina NovaSeq 6000


## QC – Agilent Tapestation



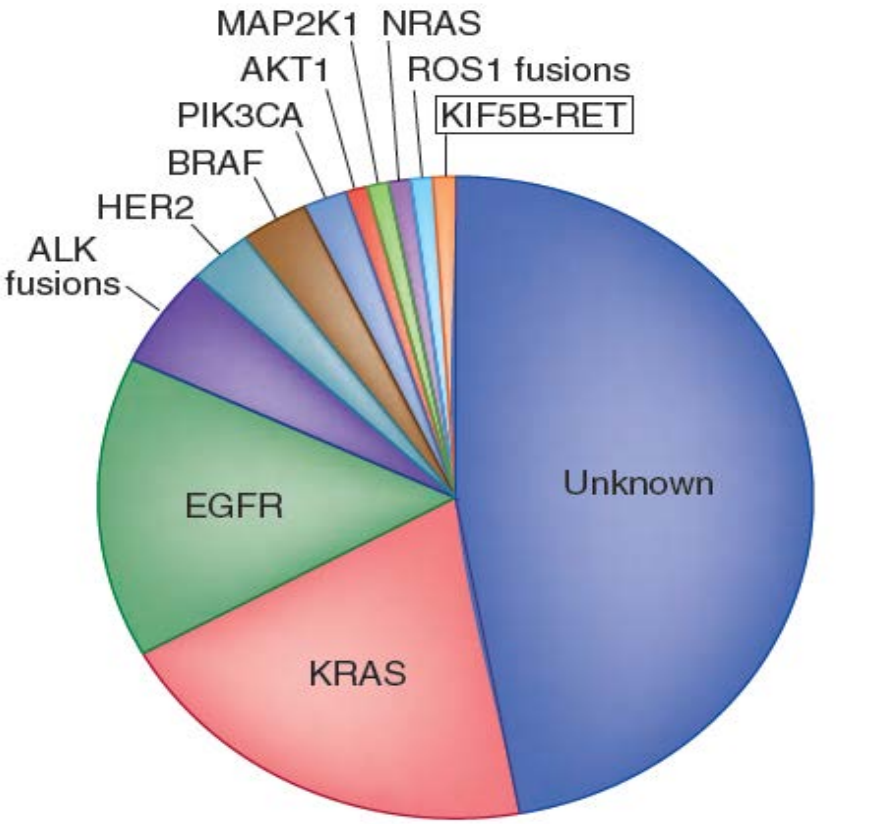
QUEEN'S UNIVERSITY BELFAST

Precision Medicine Centre of Excellence

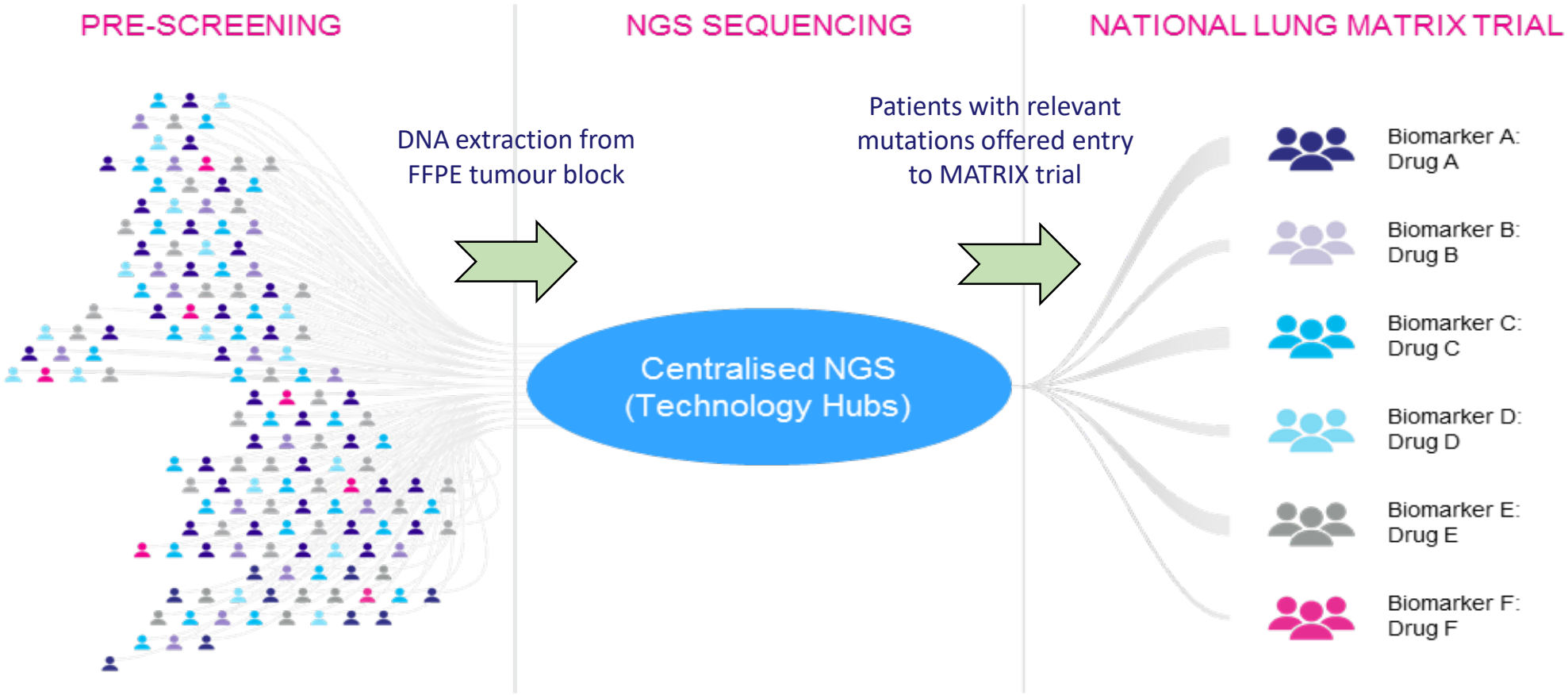
| | | | | |
|---|---|---|---|---|
| MSI | CHEK1 | H3F3C | PIK3CA | VHL |
| TMB | CHEK2 | HIST1H3B | PMS2 | ZFY |
| AKT1 | CTNNB1 | HIST1H3C | POLE | |
| ALK | DDR2 | HRAS | PPP2R2A | |
| APC | DPYD | IDH1 | PTEN | |
| AR | EGFR | IDH2 | RAD50 | |
| ATM | ERBB2 | JAK2 | RAD51 | |
| BAP1 | ETV6 | KIT | RAD51B | |
| BARD1 | FANCC | KRAS | RAD51C | |
| BRAF | FANCL | MET | RAD51D | |
| BRCA1 | FBXW7 | MLH1 | RAD54L | |
| BRCA2 | FGFR1 | MSH2 | RB1 | |
| CDK12 | FGFR2 | MSH6 | RET | |
| CDK4 | FGFR3 | MYC | ROS1 | |
| CDK6 | GATA3 | MYCN | SRY | |
| CDKN1A | GNA11 | NRAS | STAT3 | |
| CDKN1B | GNAQ | NTRK1 | STK11 | |
| CDKN2A | GNAS | NTRK3 | TMPRSS2 | |
| CDKN2B | H3F3A | PALB2 | TP53 | |
| CDKN2C | H3F3B | PDGFRA | UGT1A1 | |

**Chipping away at the lung cancer genome**

William Pao & Katherine E Hutchinson



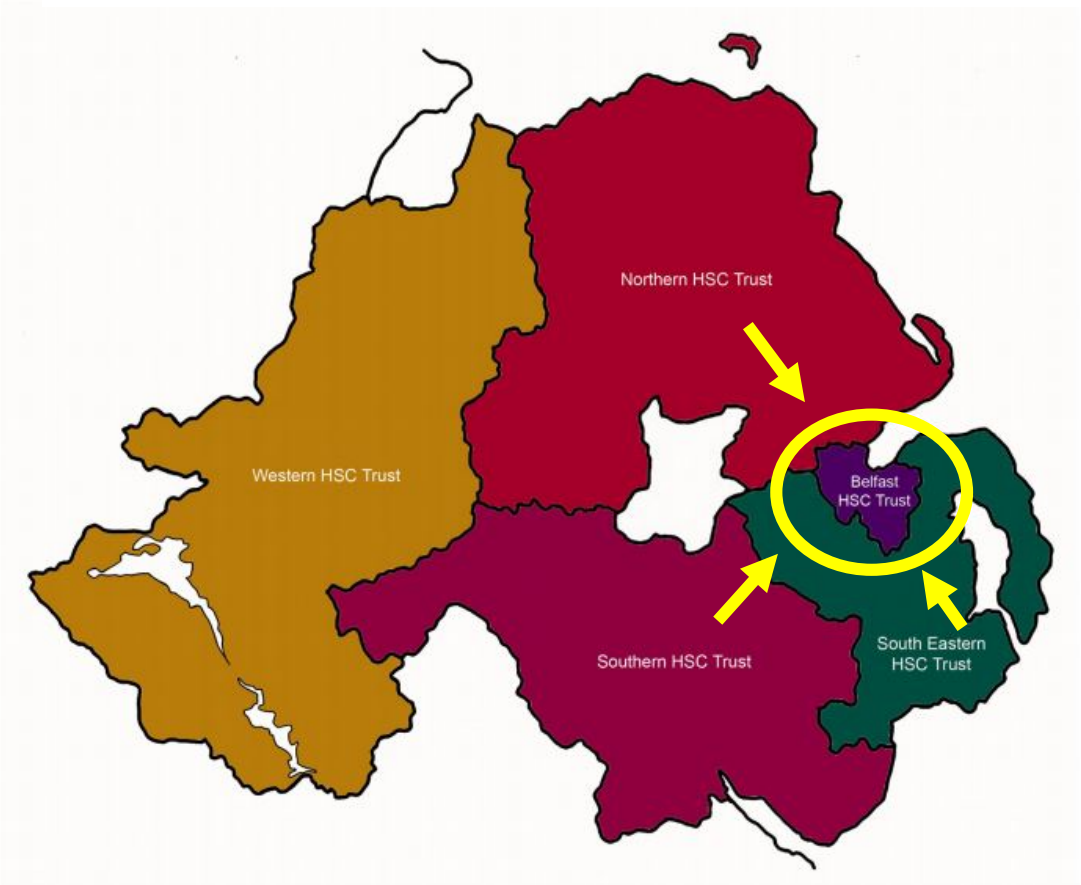
# SMP2 Study




**The National Lung Matrix Trial is the largest precision medicine trial in NSCLC globally, testing a range of therapies tailored specifically to target key biomarkers**

# SMP2 Northern Ireland

- ‘Hub and spoke’ model in NI co-ordinated by NI Biobank
- Patients currently consented for SMP2 at 4 participating Trusts:
  - Belfast HSCT
  - South Eastern HSCT
  - Southern HSCT
  - Northern HSCT
- All DNA is extracted by NI Biobank staff at the Northern Ireland Molecular Pathology Laboratory prior to dispatch to the CRUK technology hub



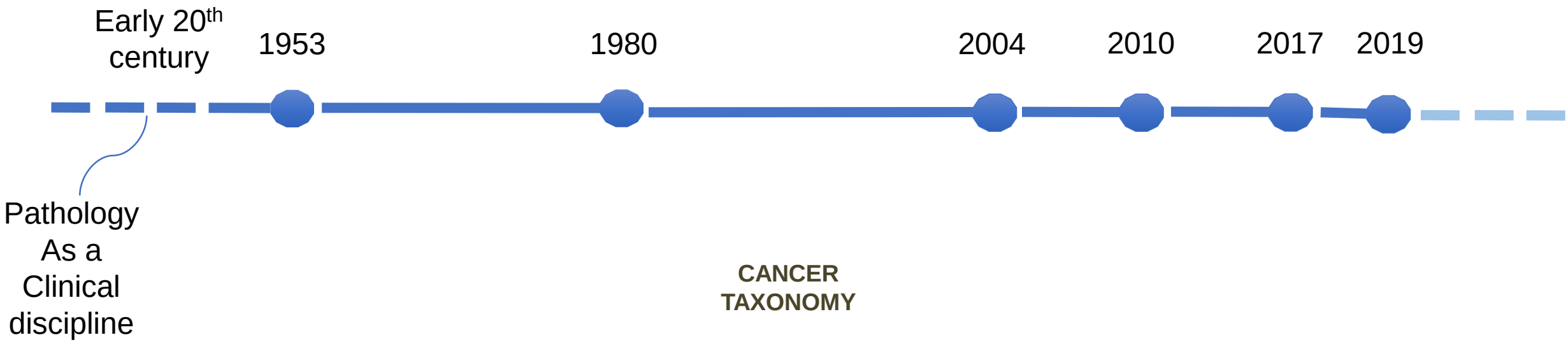
# SMP2 Achievements

- 110 patients consented since 2016
- 69 samples sent for NGS
- 2018 most successful year to date, NI 137% over target for number of samples sent for NGS
- 2018 data for NI also revealed:
  - 100% of patients who passed DNA QC (Programme Average 84%)
  - 97% of patients with NGS result (Programme Average 77%)

# The Promise and Reality of Precision Medicine in Northern Ireland

1. GLOBAL CHALLENGES TO MODERN MEDICINE
2. THE MOLECULAR PATHOLOGY PROGRAMME IN NORTHERN IRELAND
3. THE THIRD REVOLUTION IN PATHOLOGY
4. THE FUTURE

QUEEN'S UNIVERSITY BELFAST

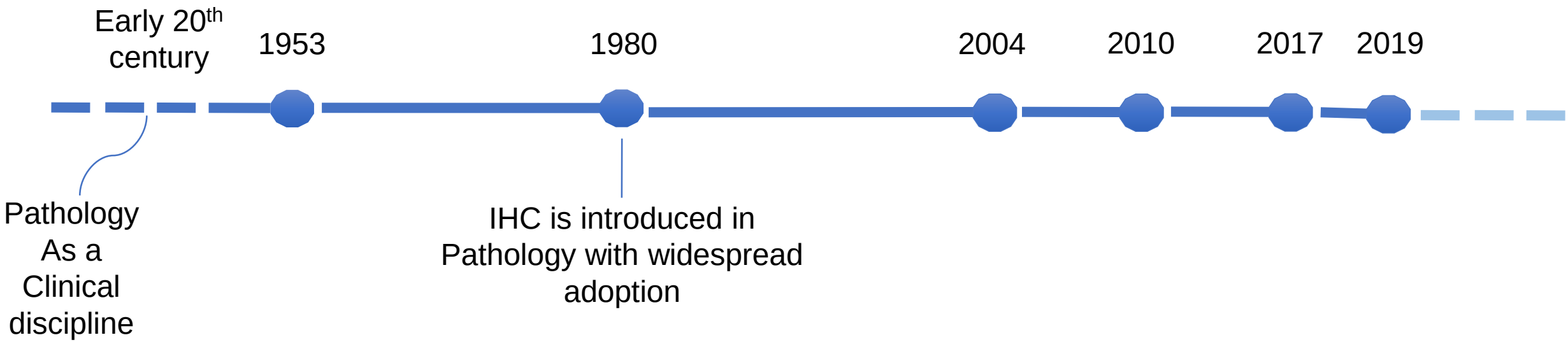



QUEEN'S UNIVERSITY BELFAST

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

# 15 The Antibody Revolution: How 'Immuno' Changed Pathology

*Elizabeth Soilleux and Kevin C. Gatter*

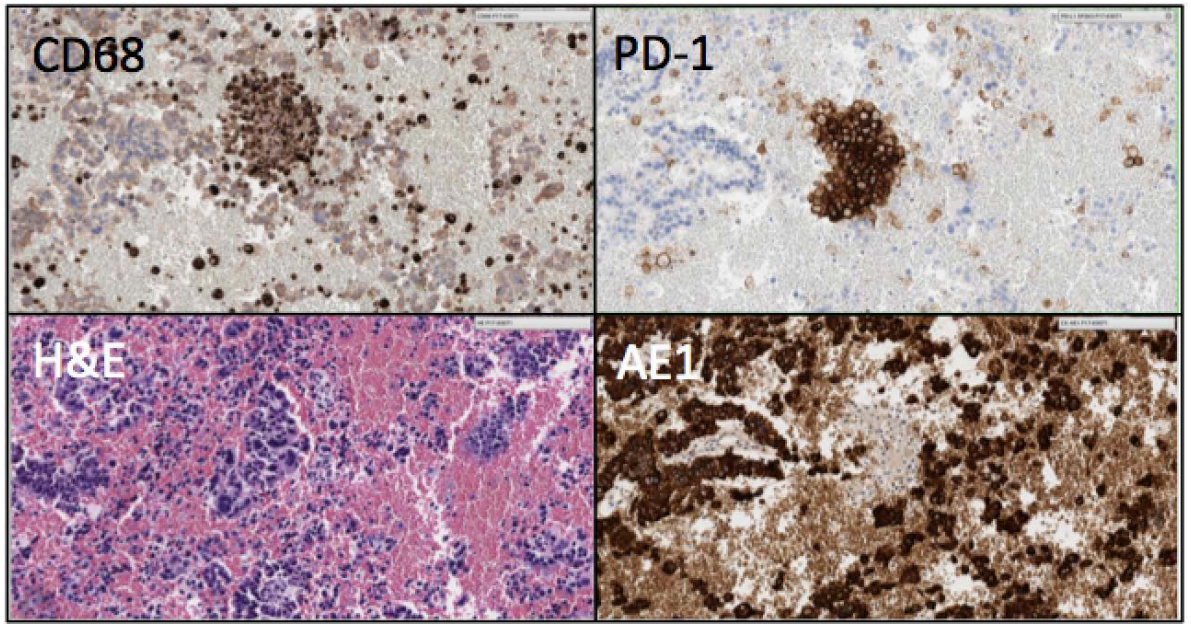



**FIRST REVOLUTION IN PATHOLOGY**

QUEEN'S UNIVERSITY BELFAST

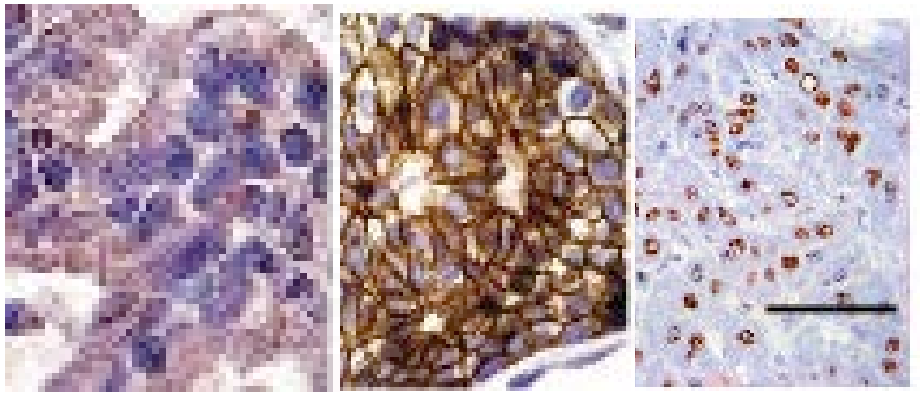
*Salto-Tellez, Maxwell and Hamilton. Artificial Intelligence - The Third Revolution in Pathology Histopathology. 2019 Feb;74(3):372-376*

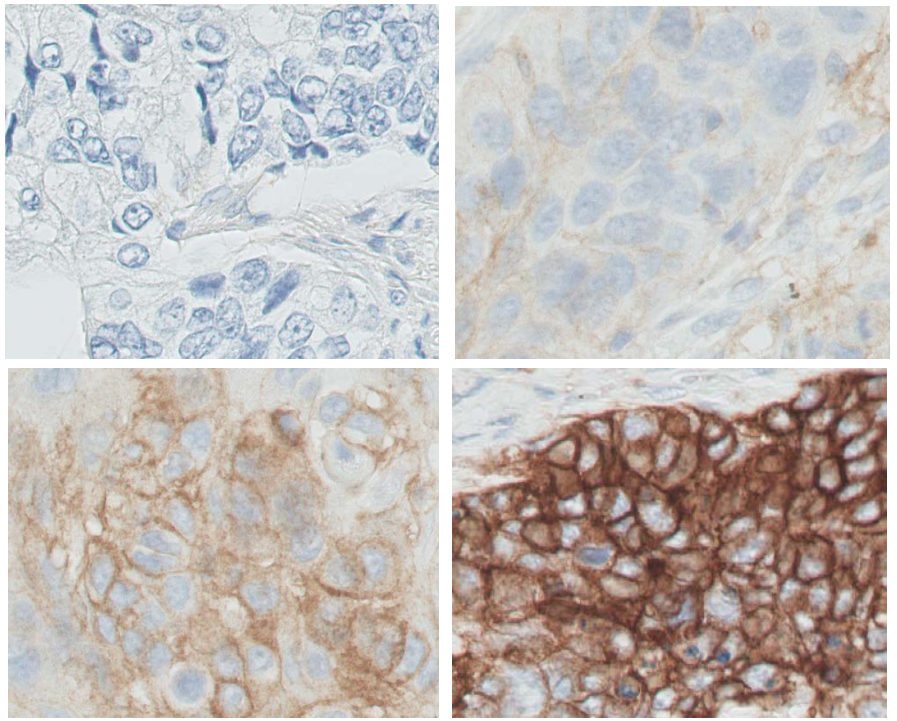
# IHC




Tissue Specificity
(lineage specific)

Subcellular localization

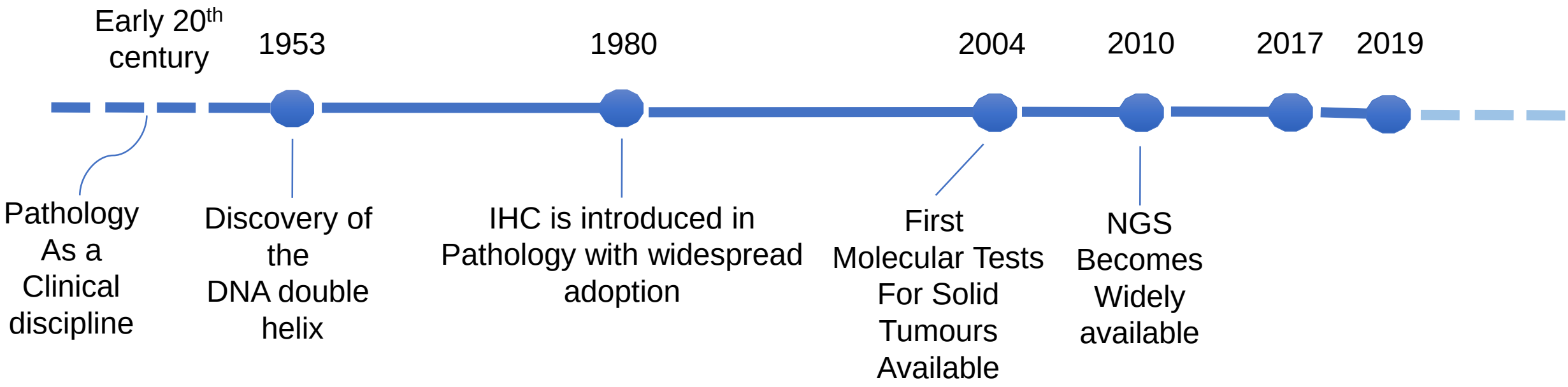




Intensity

QUEEN'S UNIVERSITY BELFAST | PMC PRECISION MEDICINE CENTRE OF EXCELLENCE

# THE GENOMIC REVOLUTION / PERSONALISED MEDICINE




**FIRST REVOLUTION IN PATHOLOGY**

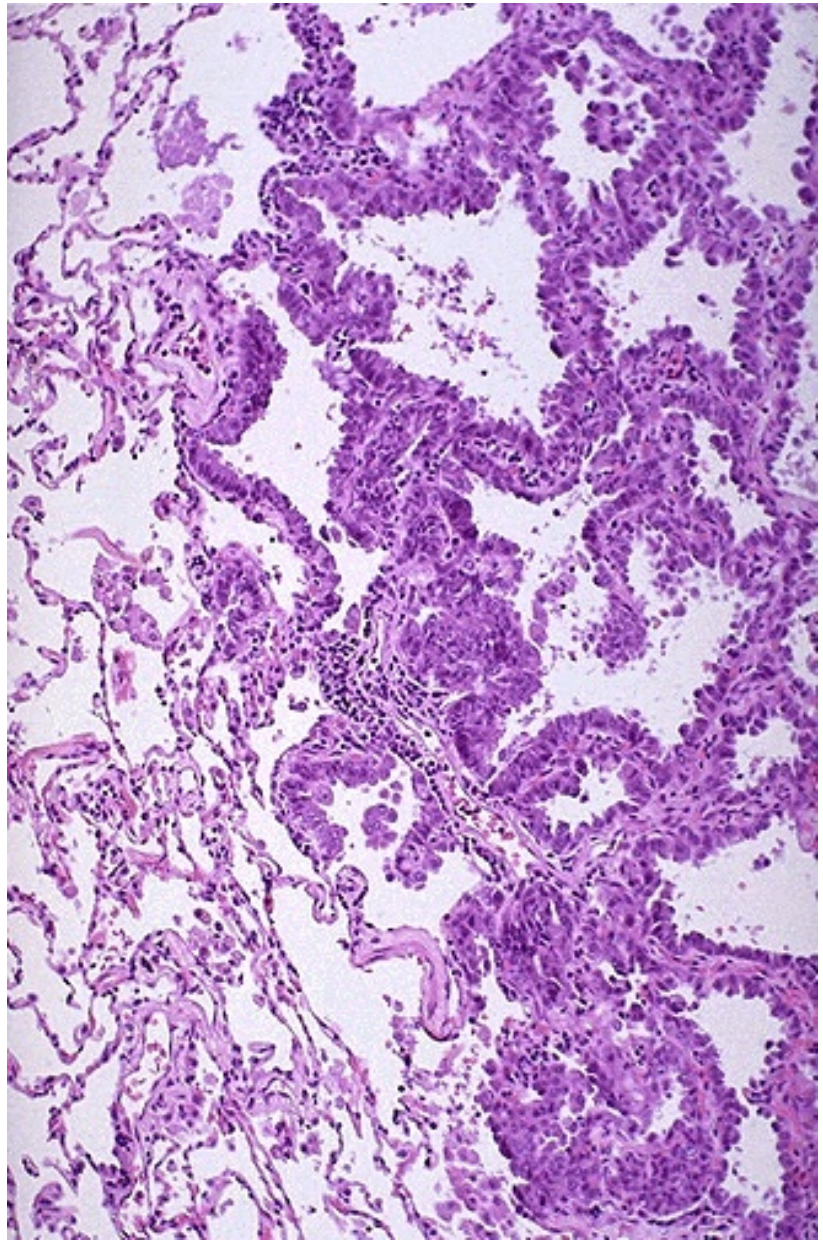
**SECOND REVOLUTION IN PATHOLOGY**

QUEEN'S UNIVERSITY BELFAST

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

**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 adernocarcinoma



QUEEN'S UNIVERSITY BELFAST

## WHO classification of lung adenocarcinoma

1.3.3. Adenocarcinoma
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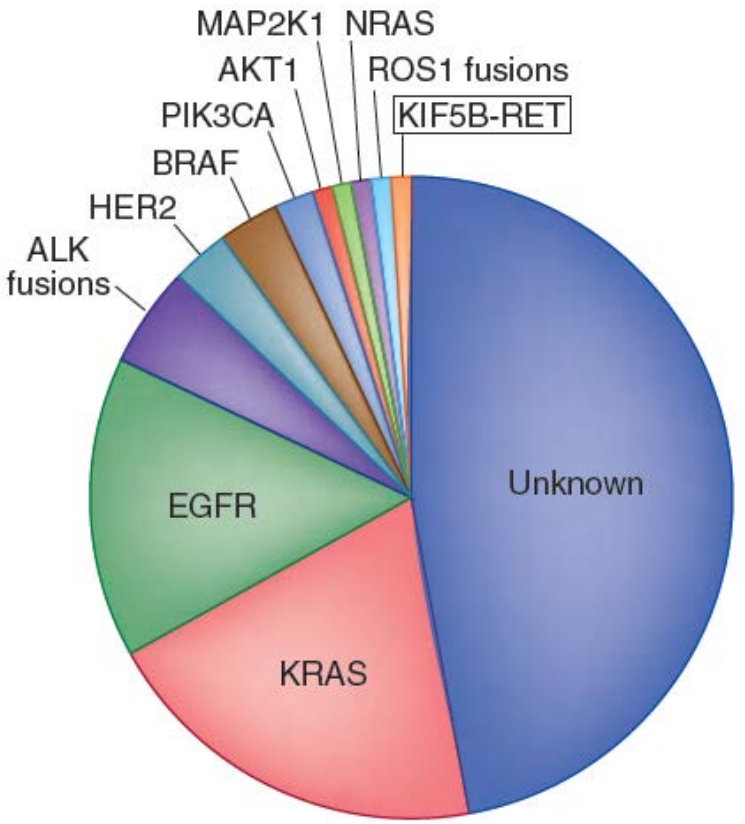



**Chipping away at the lung cancer genome**

William Pao & Katherine E Hutchinson

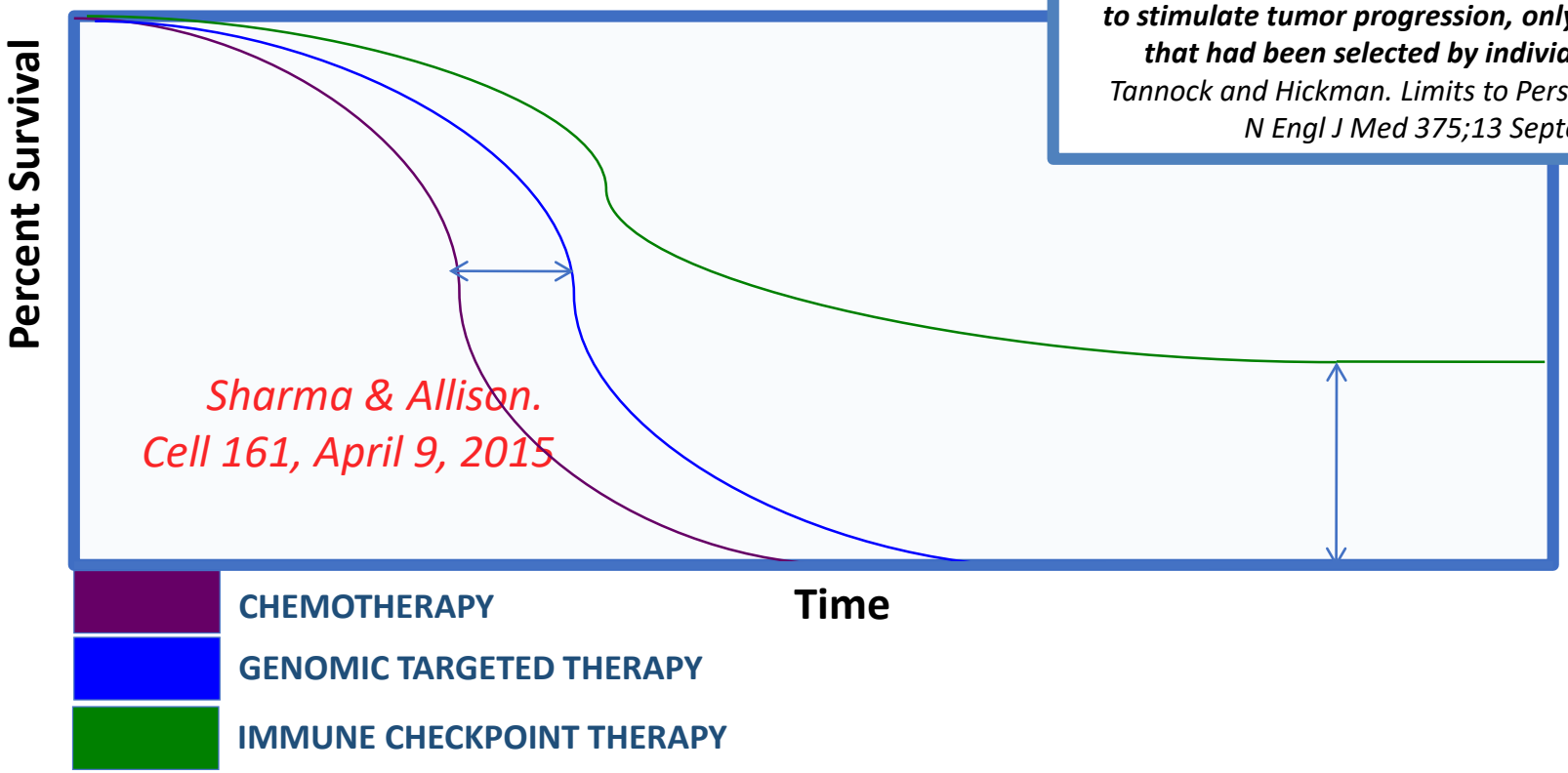
Pao W & Hutchinson KE.
Nat Med 2012;18:349–51.

QUEEN'S UNIVERSITY BELFAST

# 5. THE RELATIVE RELEVANCE OF PERSONALISED MEDICINE

***"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."***

*Tannock and Hickman. Limits to Personalized Cancer Medicine. N Engl J Med 375;13 September 29, 2016*

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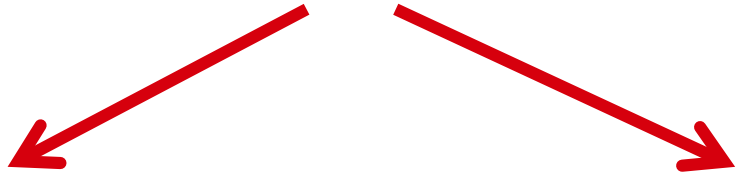
# WE NEED DIAGNOSIS, PROGNOSIS & PREDICTION

## BEYOND GENOMICS



NEW BIOMARKERS ALTOGETHER

NEW WAYS OF SCORING EXISTING BIOMARKERS

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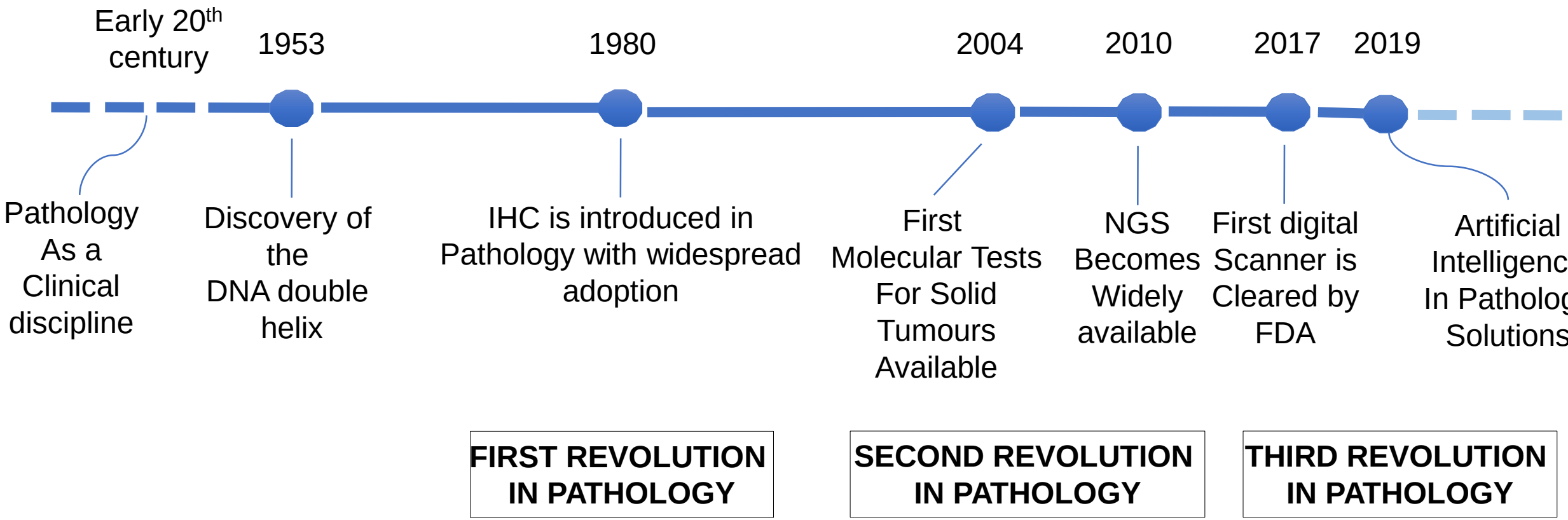
# DIGITAL PATHOLOGY / ARTIFICIAL INTELLIGENCE



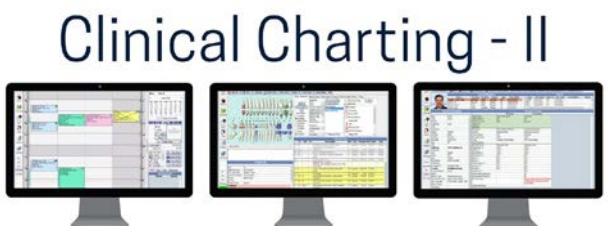

QUEEN'S UNIVERSITY BELFAST

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

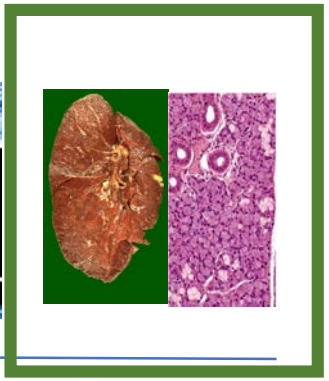
# THE PROMISE OF ARTIFICIAL INTELLIGENCE IN HEALTHCARE DELIVERY

**POPULATION “BIG DATA”**

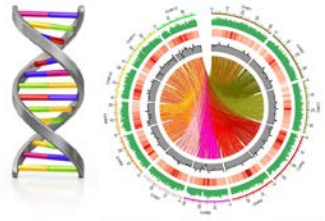
**WEB HISTORY**




**CLINICAL RECORDS**



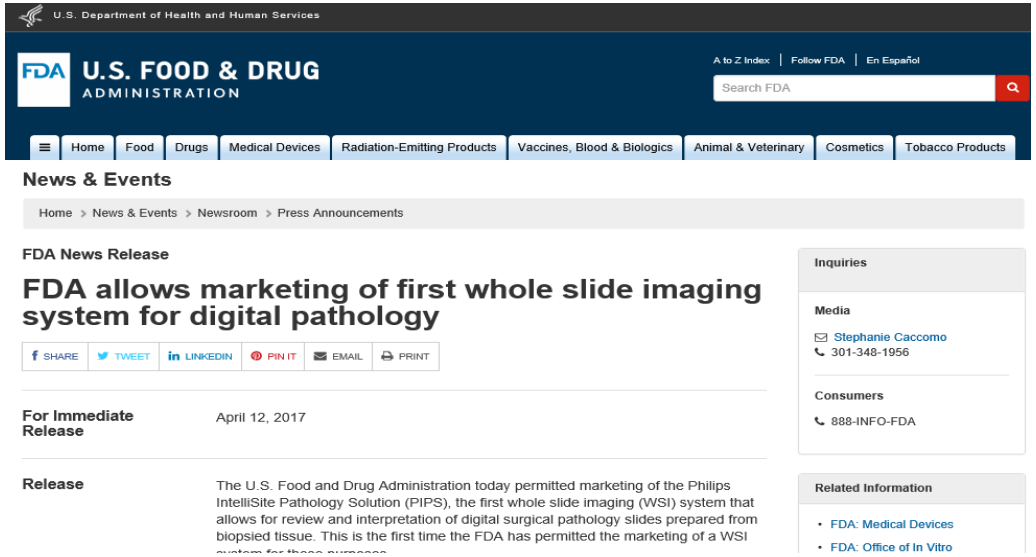
**CLINICAL IMAGING**



**GENOMICS “INTEGROMICS”**


PREVENTION & PREDISPOSITION
DIAGNOSTIC INTERPRETATION
DIAGNOSTIC AND THERAPEUTIC DECISION PATHWAYS
EFFECT OF THE INDIVIDUAL CASE IN THE “GLOBAL HEALTH”

# *CONDITION SINE QUA NON* TO APPLY DIGITAL PATHOLOGY TO DIAGNOSTICS: DIGITALIZATION OF DIAGNOSTIC SERVICES



U.S. Department of Health and Human Services

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FDA News Release

**FDA allows marketing of first whole slide imaging system for digital pathology**

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

**For Immediate Release** April 12, 2017

**Release** The U.S. Food and Drug Administration today permitted marketing of the Philips IntelliSite Pathology Solution (PIPS), the first whole slide imaging (WSI) system that allows for review and interpretation of digital surgical pathology slides prepared from biopsied tissue. This is the first time the FDA has permitted the marketing of a WSI

**Inquiries**

**Media**

Stephanie Caccomo
301-348-1956

**Consumers**

888-INFO-FDA

**Related Information**

- FDA: Medical Devices
- FDA: Office of In Vitro

Leica Biosystems Receives FDA 510(k) Clearance to Market a Digital Pathology System for Primary Diagnosis

Leica BIOSYSTEMS

NEWS PROVIDED BY
Leica Biosystems →
May 29, 2019, 05:00 ET

SHARE THIS ARTICLE

VISTA, Calif., May 29, 2019 /PRNewswire/ -- Leica Biosystems, the global leader in pathology workflow solutions, announced that it has received clearance from the U.S. Food and Drug Administration (FDA) to market its Aperio AT2 DX System for clinical diagnosis in the U.S.

QUEEN'S UNIVERSITY BELFAST

Review

Future-proofing pathology: the case for clinical adoption of digital pathology

Bethany Jill Williams,[1] David Bottoms,[2] Darren Treanor[3]

Thematic management

Future-proofing pathology part 2: building a business case for digital pathology

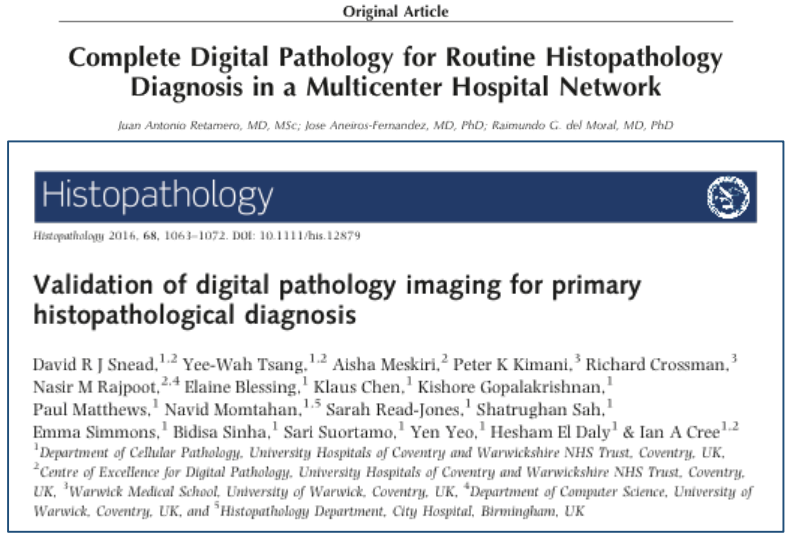
Bethany Jill Williams,[1,2] David Bottoms,[3] David Clark,[4] Darren Treanor[1,2]

Original article

Maintaining quality diagnosis with digital pathology: a practical guide to ISO 15189 accreditation

Bethany Jill Williams,[1,2] Chloe Knowles,[1] Darren Treanor[1,2]

J Clin Pathol: first publis J Clin Pathol: first published J Clin Pathol: first published



Original Article

Complete Digital Pathology for Routine Histopathology Diagnosis in a Multicenter Hospital Network

Juan Antonio Retamero, MD, MSc; Jose Aneiros-Fernandez, MD, PhD; Raimundo G. del Moral, MD, PhD

Histopathology

Histopathology 2016, 68, 1063–1072. DOI: 10.1111/his.12879

**Validation of digital pathology imaging for primary histopathological diagnosis**

David R J Snead,[1,2] Yee-Wah Tsang,[1,2] Aisha Meskiri,[2] Peter K Kimani,[3] Richard Crossman,[3] Nasir M Rajpoot,[2,4] Elaine Blessing,[1] Klaus Chen,[1] Kishore Gopalakrishnan,[1] Paul Matthews,[1] Navid Momtahan,[1,5] Sarah Read-Jones,[1] Shatrughan Sah,[1] Emma Simmons,[1] Bidisa Sinha,[1] Sari Suortamo,[1] Yen Yeo,[1] Hesham El Daly[1] & Ian A Cree[1,2]

[1]Department of Cellular Pathology, University Hospitals of Coventry and Warwickshire NHS Trust, Coventry, UK, [2]Centre of Excellence for Digital Pathology, University Hospitals of Coventry and Warwickshire NHS Trust, Coventry, UK, [3]Warwick Medical School, University of Warwick, Coventry, UK, [4]Department of Computer Science, University of Warwick, Coventry, UK, and [5]Histopathology Department, City Hospital, Birmingham, UK

"The 14 Steps of Routine Tissue Diagnostics". In Salto-Tellez, Maxwell & Hamilton; *Histopathology, 2019 Feb;74(3):372-376*

SAMPLE

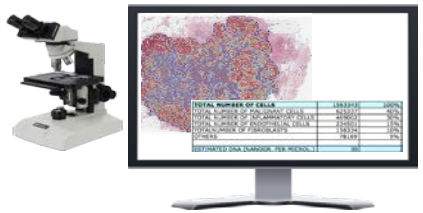
SAMPLE PREPARATION

AUTOMATED H+E

IMAGING SCANNING

MORPHOLOGICAL OR DIGITAL EVALUATION

AUT NA EXTR



MANUAL OR DIGITAL ANNOTATION

AUTOM. FISH

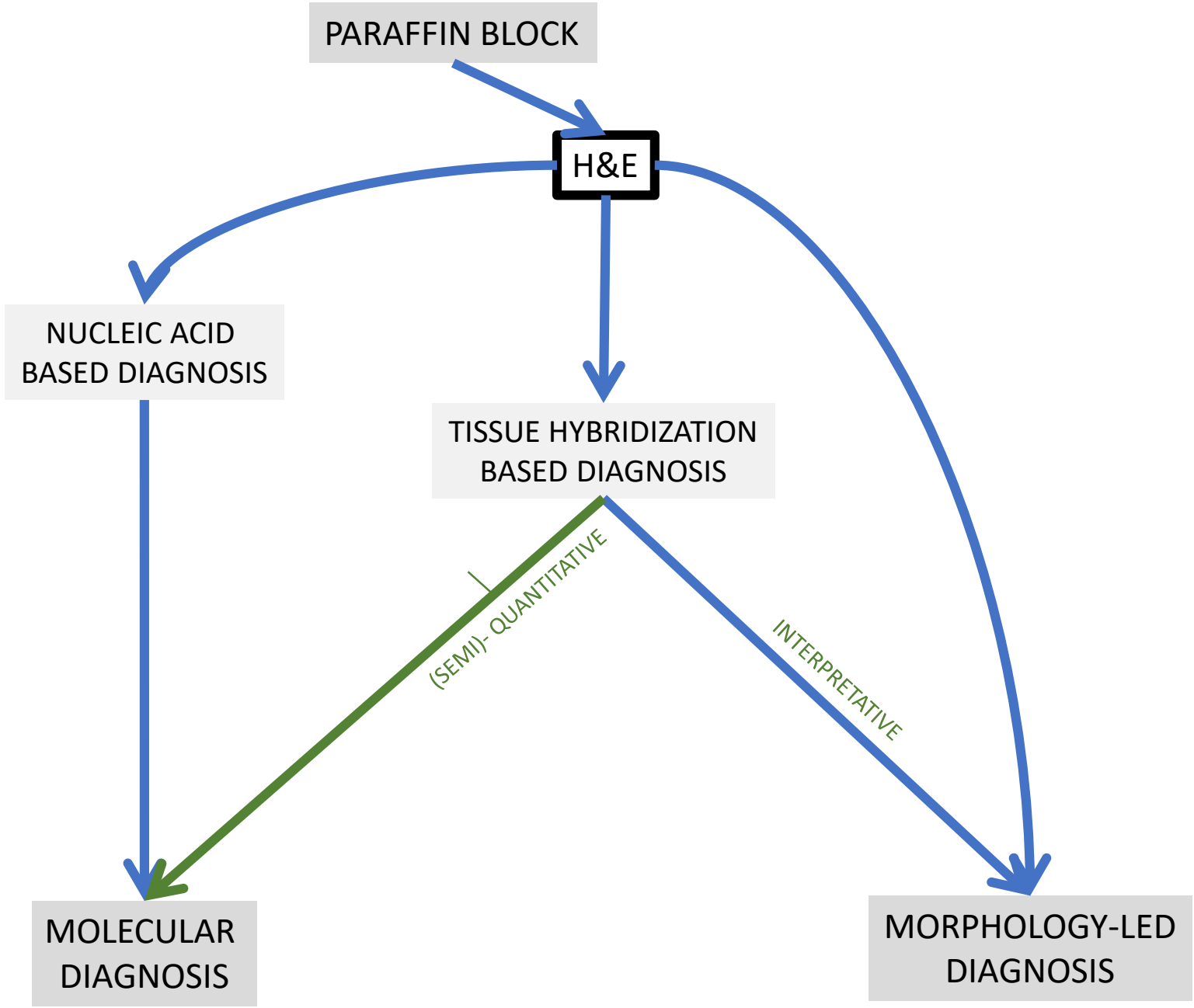
AUTOMATED IHC

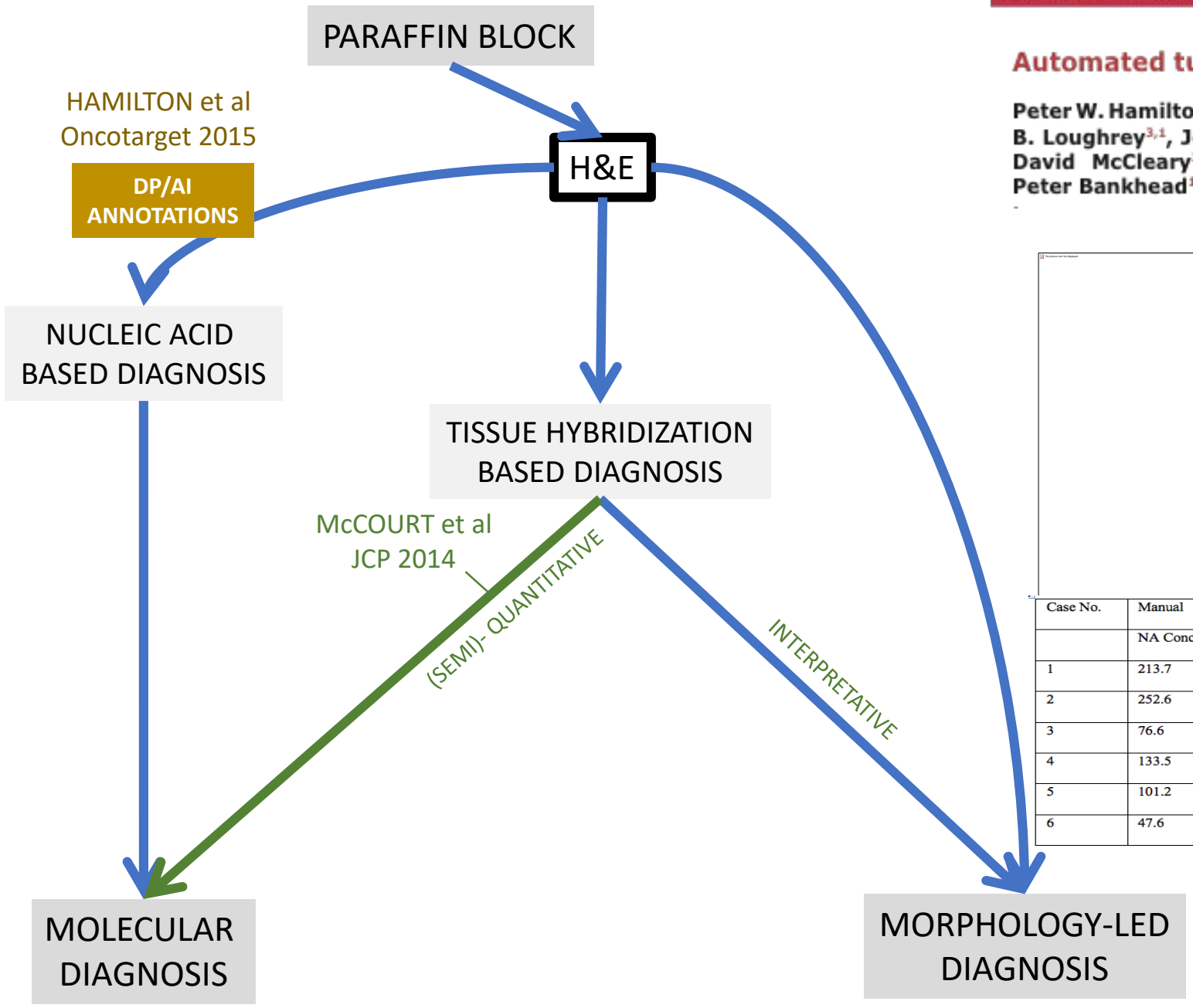
LOW THROUGHPUT TESTING

HIGH THROUGHPUT TESTING

MANUAL OR DIGITAL SCORING


CLINICAL DIAGNOSIS


PARAFFIN BLOCK
H&E
NUCLEIC ACID BASED DIAGNOSIS
TISSUE HYBRIDIZATION BASED DIAGNOSIS
(SEMI)- QUANTITATIVE
INTERPRETATIVE
MOLECULAR DIAGNOSIS
MORPHOLOGY-LED DIAGNOSIS




www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2015

## Automated tumor analysis for molecular profiling in lung cancer

Peter W. Hamilton[1,4,*] Yinhai Wang[1,4,*], Clinton Boyd[2], Jacqueline A. James[1], Maurice B. Loughrey[3,1], Joseph P. Hougton[3], David P. Boyle[1], Paul Kelly[3], Perry Maxwell[1], David McCleary[3], James Diamond[3], Darragh G. McArt[1], Jonathon Tunstall[3], Peter Bankhead[1], Manuel Salto-Tellez[1,3]

| Case No. | Manual | | | Automated | | |
|---|---|---|---|---|---|---|
| | NA Conc'n | 260/280 | Mutation Result | NA Conc'n | 260/280 | Mutation Result |
| 1 | 213.7 | 1.8 | MUTATION EXON 21 L858R | 253.2 | 1.88 | MUTATION EXON 21 L858R |
| 2 | 252.6 | 1.85 | MUTATION NOT DETECTED | 207.8 | 1.87 | MUTATION NOT DETECTED |
| 3 | 76.6 | 1.84 | MUTATION NOT DETECTED | 129.2 | 1.83 | MUTATION NOT DETECTED |
| 4 | 133.5 | 1.88 | MUTATION EXON 21 L858R | 187.2 | 1.87 | MUTATION EXON 21 L858R |
| 5 | 101.2 | 1.83 | MUTATION NOT DETECTED | 179.6 | 1.88 | MUTATION NOT DETECTED |
| 6 | 47.6 | 1.85 | MUTATION EXON 19 DELETION | 72.3 | 1.86 | MUTATION EXON 19 DELETION |

PARAFFIN BLOCK

HAMILTON et al
Oncotarget 2015

DP/AI ANNOTATIONS

H&E

NUCLEIC ACID BASED DIAGNOSIS

TISSUE HYBRIDIZATION BASED DIAGNOSIS

McCOURT et al
JCP 2014

(SEMI)- QUANTITATIVE

INTERPRETATIVE

DP/AI QUANTITATION

HUMPHRIES et al
J Thorac Oncol 2019

MOLECULAR DIAGNOSIS

MORPHOLOGY-LED DIAGNOSIS

ORIGINAL ARTICLE

Journal of Thoracic Oncology
Volume 14, Issue 1, January 2019, Pages 45-53

# Critical Appraisal of Programmed Death Ligand 1 Reflex Diagnostic Testing: Current Standards and Future Opportunities

Matthew P. Humphries, PhD,[a] Stephen McQuaid, PhD,[a,b,c] Stephanie G. Craig, PhD,[a] Victoria Bingham, MSc,[a] Perry Maxwell, PhD,[a,b] Manisha Maurya, PhD,[a] Fiona McLean, BSc,[a,b] James Sampson, MBChB,[a] Patricia Higgins, BSc,[a,b] Christine Greene, BSc,[a,b,c] Jacqueline James, PhD,[a,b,c] Manuel Salto-Tellez, MBChB[a,b,*]

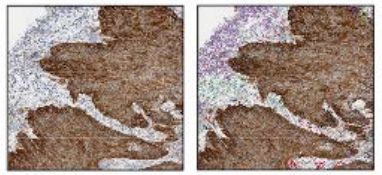
A

| Manual Assessment \ Digital Assessment | <1% | 1-49% | >50% |
|---|---|---|---|
| <1% | 4 | 2 | 0 |
| 1-49% | 0 | 16 | 1 |
| >50% | 0 | 3 | 5 |

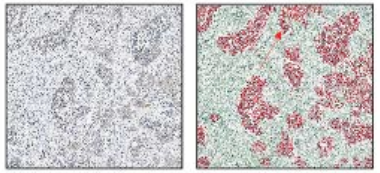
B

| Manual Assessment \ Digital Assessment | <1% | 1-49% | >50% |
|---|---|---|---|
| <1% | 10 | 5 | 0 |
| 1-49% | 1 | 6 | 0 |
| >50% | 0 | 0 | 9 |

C



D



QuPath

# Digital Pathology in Drug Development, Biomarker discovery and Stratified Medicine

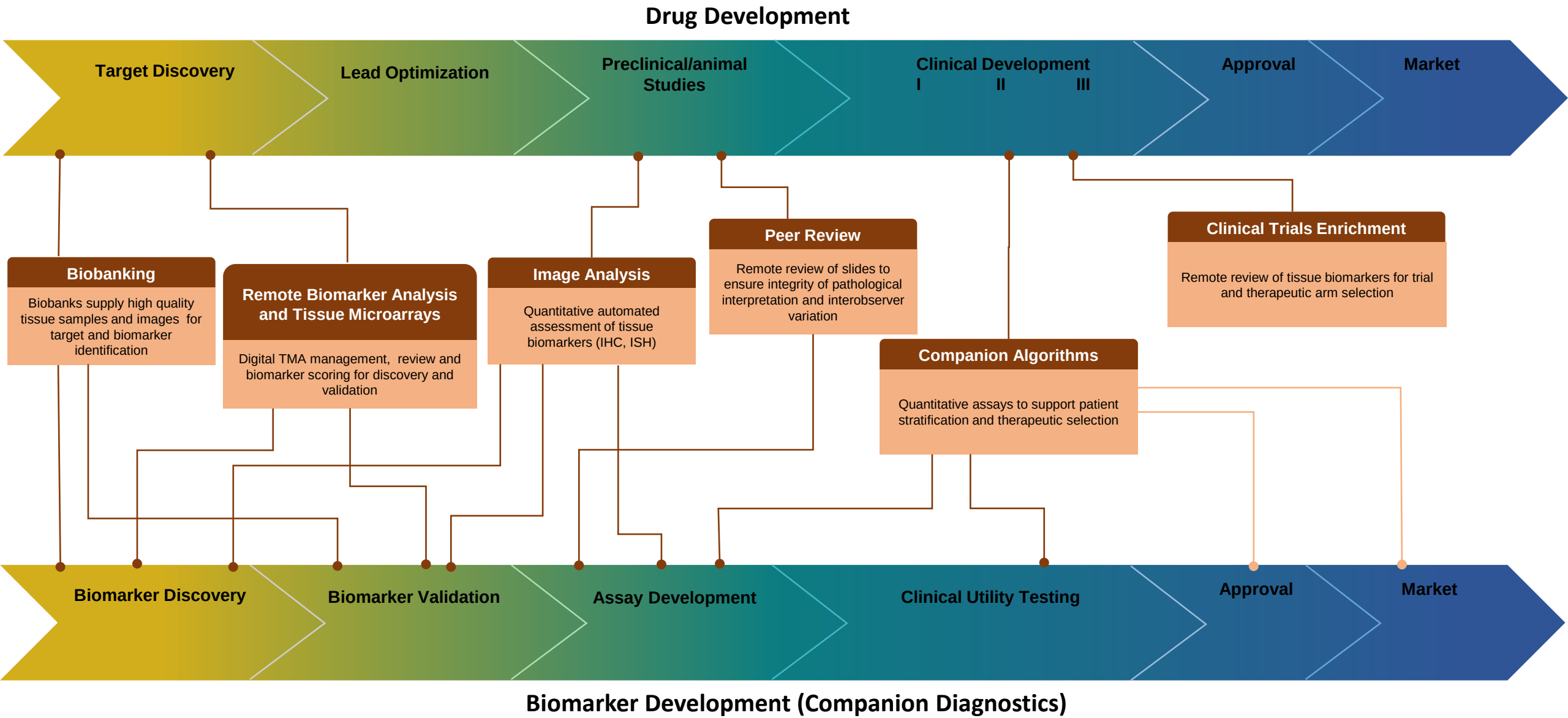

## AI-TOOLS AN *BONA FIDE* COMPANION DIAGNOSTICS

**Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices. July 14, 2011**

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


*Hamilton PW, et al, (**Salto-Tellez** M). Methods. 2014 Nov;70(1):59-73.*

# Digital Pathology in Drug Development, Biomarker discovery and Stratified Medicine




*Hamilton PW, et al, (**Salto-Tellez** M). Methods. 2014 Nov;70(1):59-73.*

PARAFFIN BLOCK

HAMILTON et al
Oncotarget 2015

DP/AI ANNOTATIONS

H&E

NUCLEIC ACID BASED DIAGNOSIS

TISSUE HYBRIDIZATION BASED DIAGNOSIS

BEJNORDI et al
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DP/AI INTERPRETATION

McCOURT et al
JCP 2014

(SEMI)- QUANTITATIVE

INTERPRETATIVE

DP/AI QUANTITATION

HUMPHRIES et al
J Thorac Oncol 2019

MOLECULAR DIAGNOSIS

MORPHOLOGY-LED DIAGNOSIS

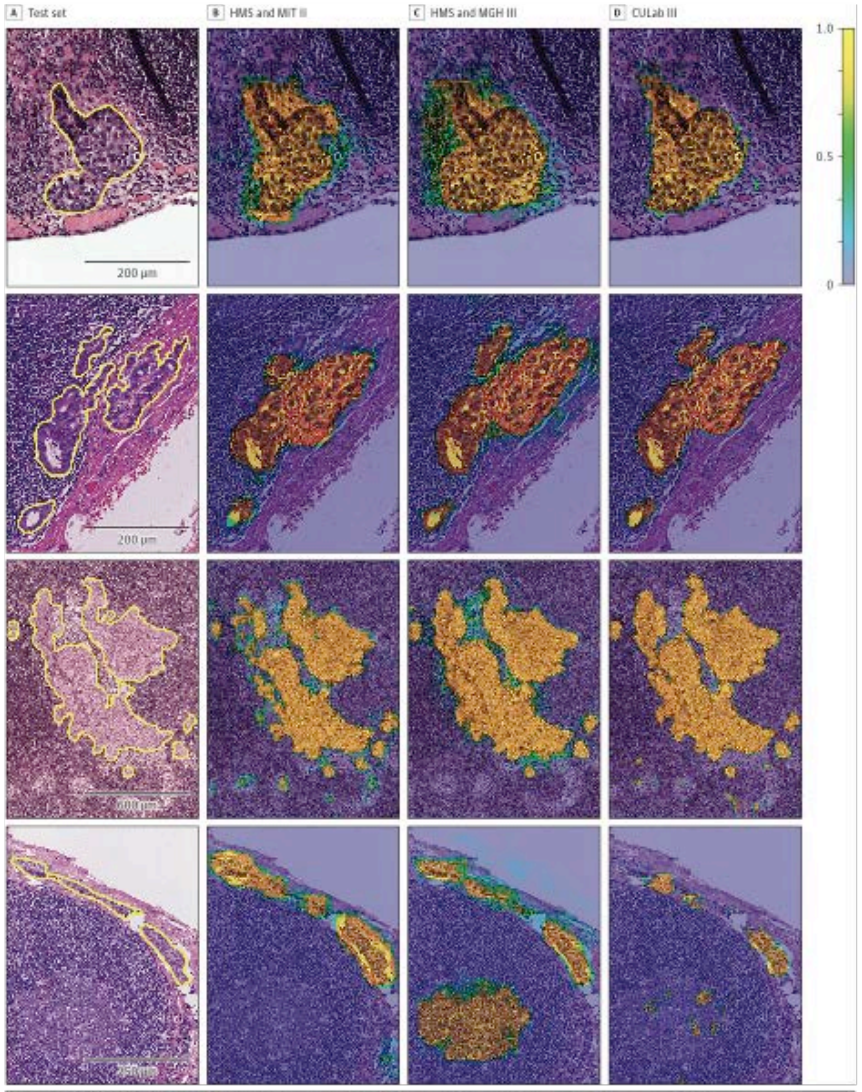
Research

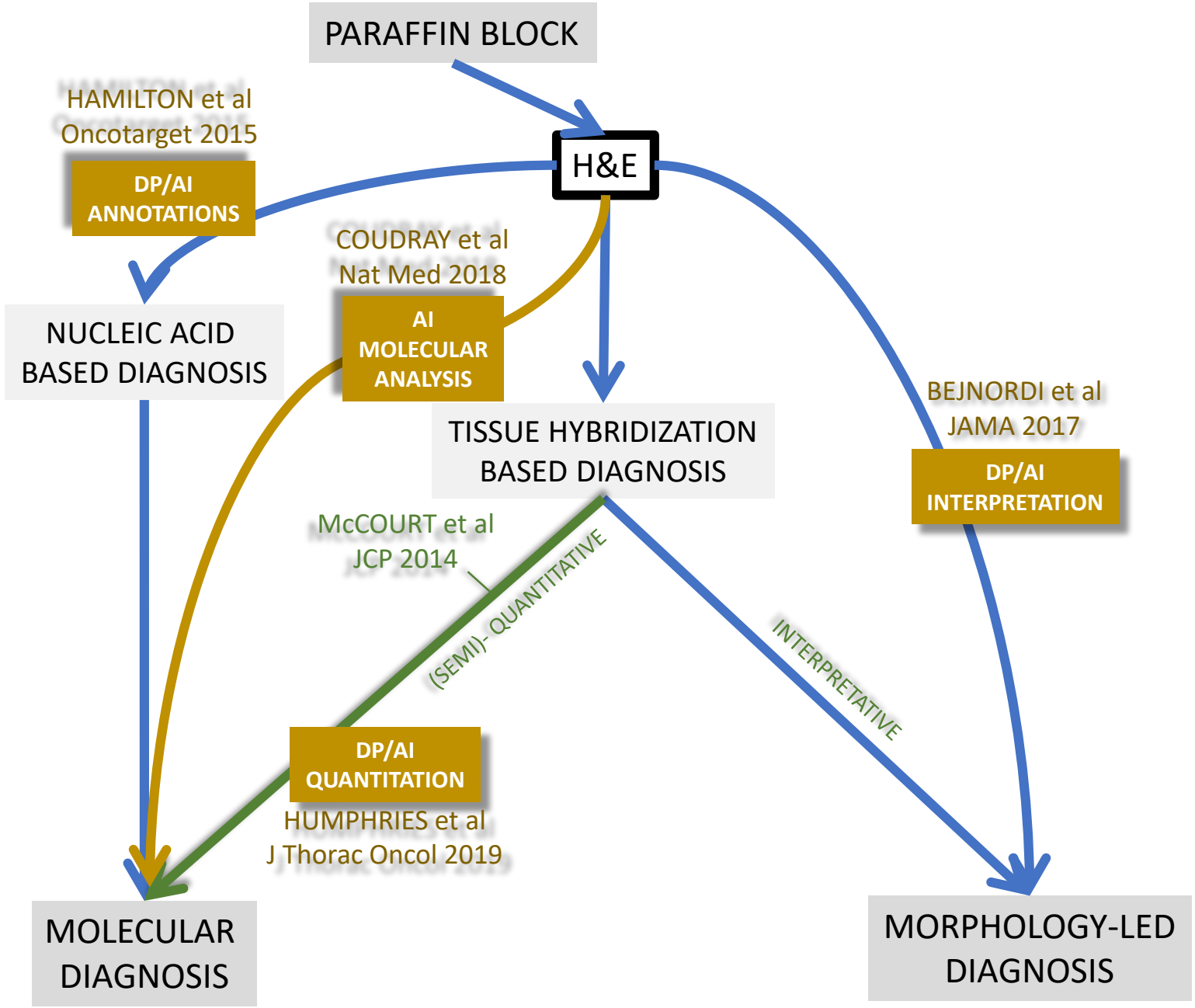
JAMA | Original Investigation

# Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women With Breast Cancer

Babak Ehteshami Bejnordi, MS; Mitko Veta, PhD; Paul Johannes van Diest, MD, PhD; Bram van Ginneken, PhD; Nico Karssemeijer, PhD; Geert Litjens, PhD; Jeroen A. W. M. van der Laak, PhD; and the CAMELYON16 Consortium

Figure 2. Probability Maps Generated by the Top 3 Algorithms From the CAMELYON16 Competition






nature medicine ARTICLES
https://doi.org/10.1038/s41591-018-0177-5

## Classification and mutation prediction from non–small cell lung cancer histopathology images using deep learning

Nicolas Coudray[1,2,9], Paolo Santiago Ocampo[3,9], Theodore Sakellaropoulos[4], Navneet Narula[3], Matija Snuderl[3], David Fenyö[5,6], Andre L. Moreira[3,7], Narges Razavian[8*] and Aristotelis Tsirigos[1,3*]

BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-019-0462-y
nature medicine

## Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer

Jakob Nikolas Kather[1,2,3,4,5*], Alexander T. Pearson[4], Niels Halama[2,5,6], Dirk Jäger[2,3,5], Jeremias Krause[1], Sven H. Loosen[1], Alexander Marx[7], Peter Boor[8], Frank Tacke[9], Ulf Peter Neumann[10], Heike I. Grabsch[11,12], Takaki Yoshikawa[13,14], Hermann Brenner[2,15,16], Jenny Chang-Claude[17,18], Michael Hoffmeister[15], Christian Trautwein[1] and Tom Luedde[1*]

JAMA Network Open

Original Investigation | Oncology

## Artificial Intelligence Algorithms to Assess Hormonal Status From Tissue Microarrays in Patients With Breast Cancer

Gil Shamai, MSc; Yoav Binenbaum, MD, PhD; Ron Slossberg, MSc; Irit Duek, MD; Ziv Gil, MD, PhD; Ron Kimmel, DSc

# 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.***

QUEEN'S UNIVERSITY BELFAST

Genomics england

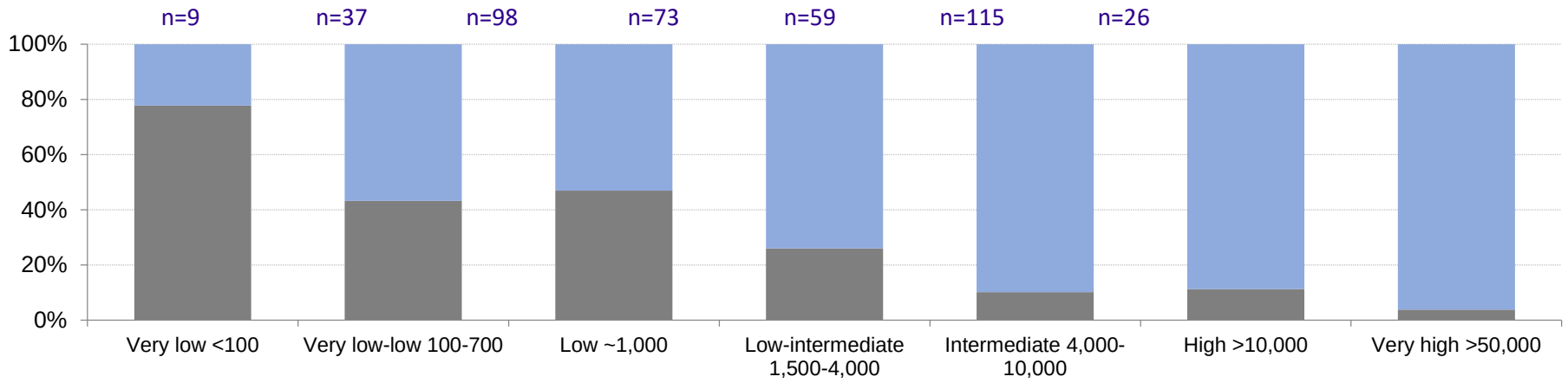
CANCER RESEARCH UK SMP2

## NGS Failure Rates

**Quantity of DNA**

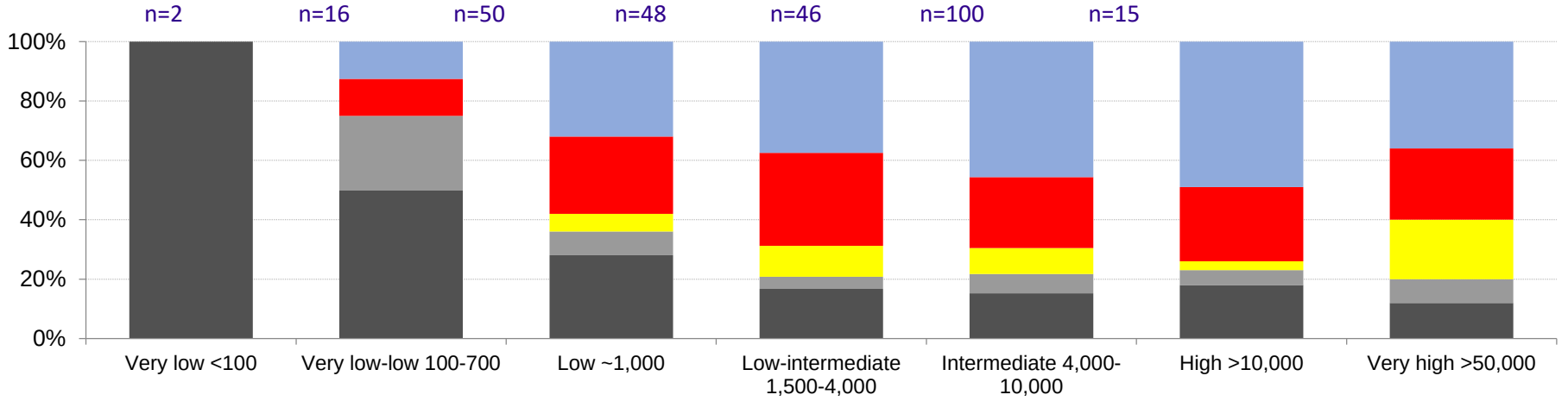
**Quality of DNA**

QC fail result at varying sample cellularity




Sample size: 417

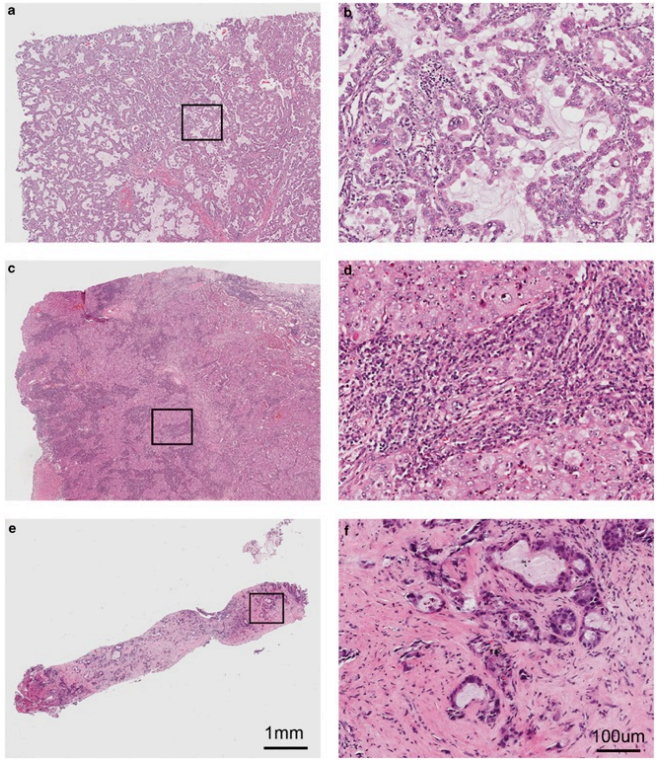
Number of genes failed at varying sample cellularity (samples run on NGS)

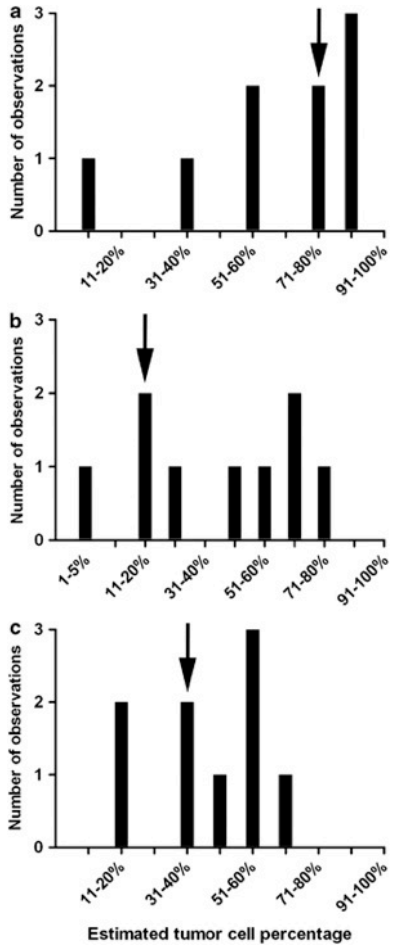


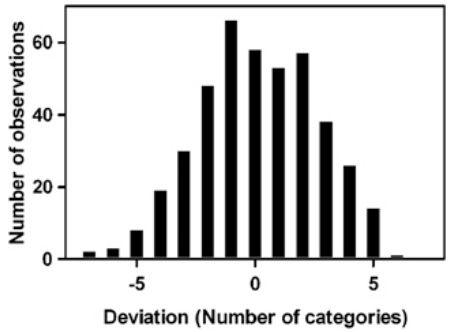

Sample size: 287

*From: Prof. David Gonzalez de Castro*

# Lung Cancer: Variation in % Tumor Cell Evaluation

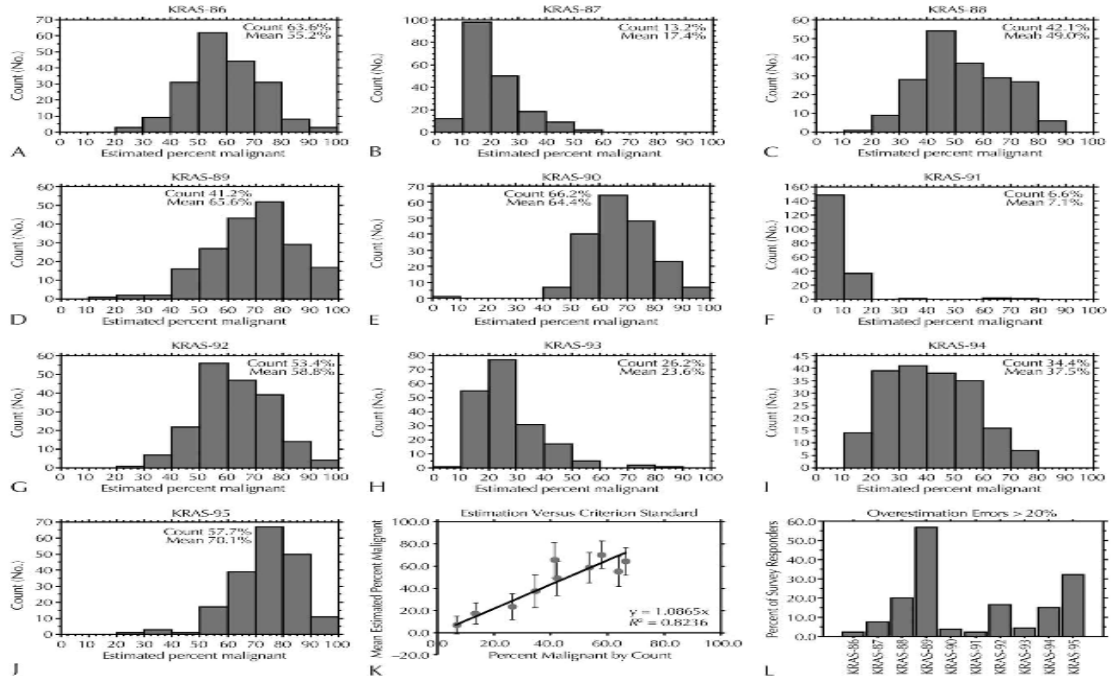



*Viray, et al. Arch Pathol Lab Med. 2013;137:1545–154*

# 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)*

| Case No. | Manual | | | Automated | | |
|---|---|---|---|---|---|---|
| | NA Conc'n | 260/280 | Mutation Result | NA Conc'n | 260/280 | Mutation Result |
| 1 | 213.7 | 1.8 | MUTATION EXON 21 L858R | 253.2 | 1.88 | MUTATION EXON 21 L858R |
| 2 | 252.6 | 1.85 | MUTATION NOT DETECTED | 207.8 | 1.87 | MUTATION NOT DETECTED |
| 3 | 76.6 | 1.84 | MUTATION NOT DETECTED | 129.2 | 1.83 | MUTATION NOT DETECTED |
| 4 | 133.5 | 1.88 | MUTATION EXON 21 L858R | 187.2 | 1.87 | MUTATION EXON 21 L858R |
| 5 | 101.2 | 1.83 | MUTATION NOT DETECTED | 179.6 | 1.88 | MUTATION NOT DETECTED |
| 6 | 47.6 | 1.85 | MUTATION EXON 19 DELETION | 72.3 | 1.86 | MUTATION EXON 19 DELETION |

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2015

# Automated tumor analysis for molecular profiling in lung cancer

**Peter W. Hamilton[1,4,*] Yinhai Wang[1,4,*], Clinton Boyd[2], Jacqueline A. James[1], Maurice B. Loughrey[3,1], Joseph P. Hougton[3], David P. Boyle[1], Paul Kelly[3], Perry Maxwell[1], David McCleary[3], James Diamond[3], Darragh G. McArt[1], Jonathon Tunstall[3], Peter Bankhead[1], Manuel Salto-Tellez[1,3]**

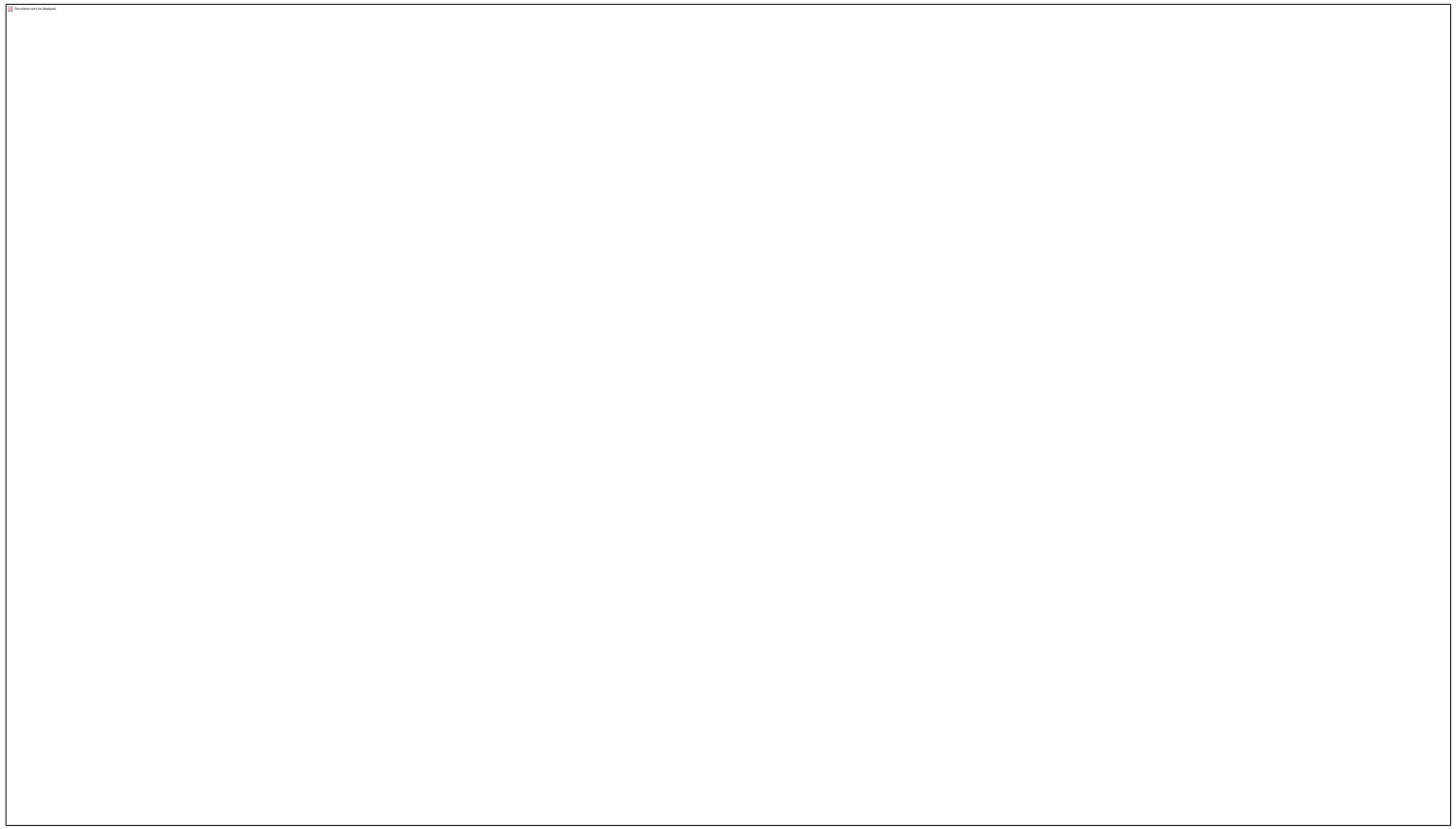
[1]Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, UK

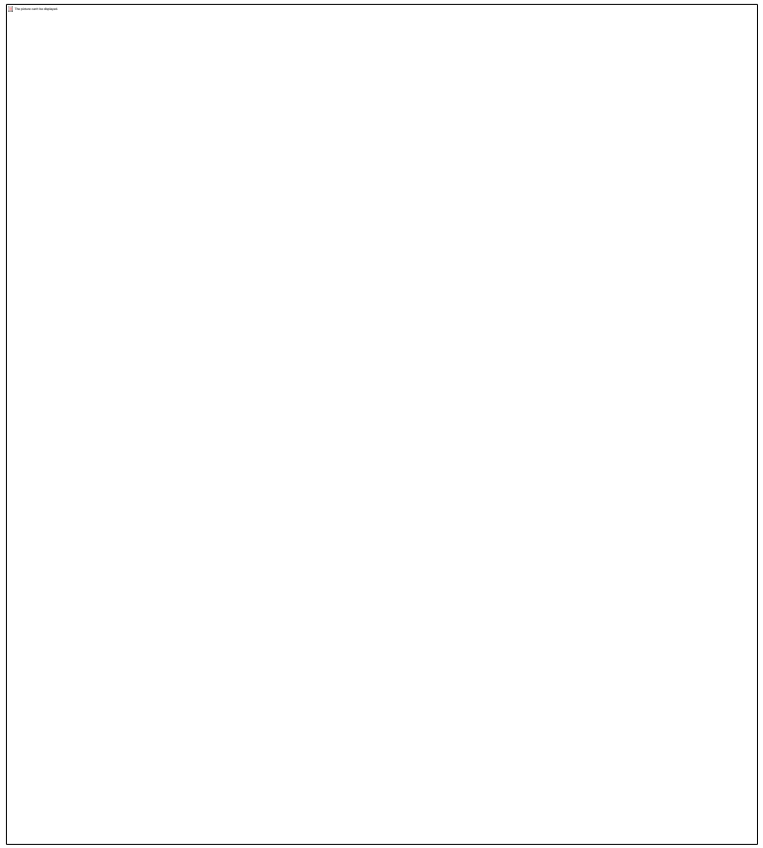
[2]Department of Cellular and Molecular Pathology, Antrim Area Hospital, Antrim, UK

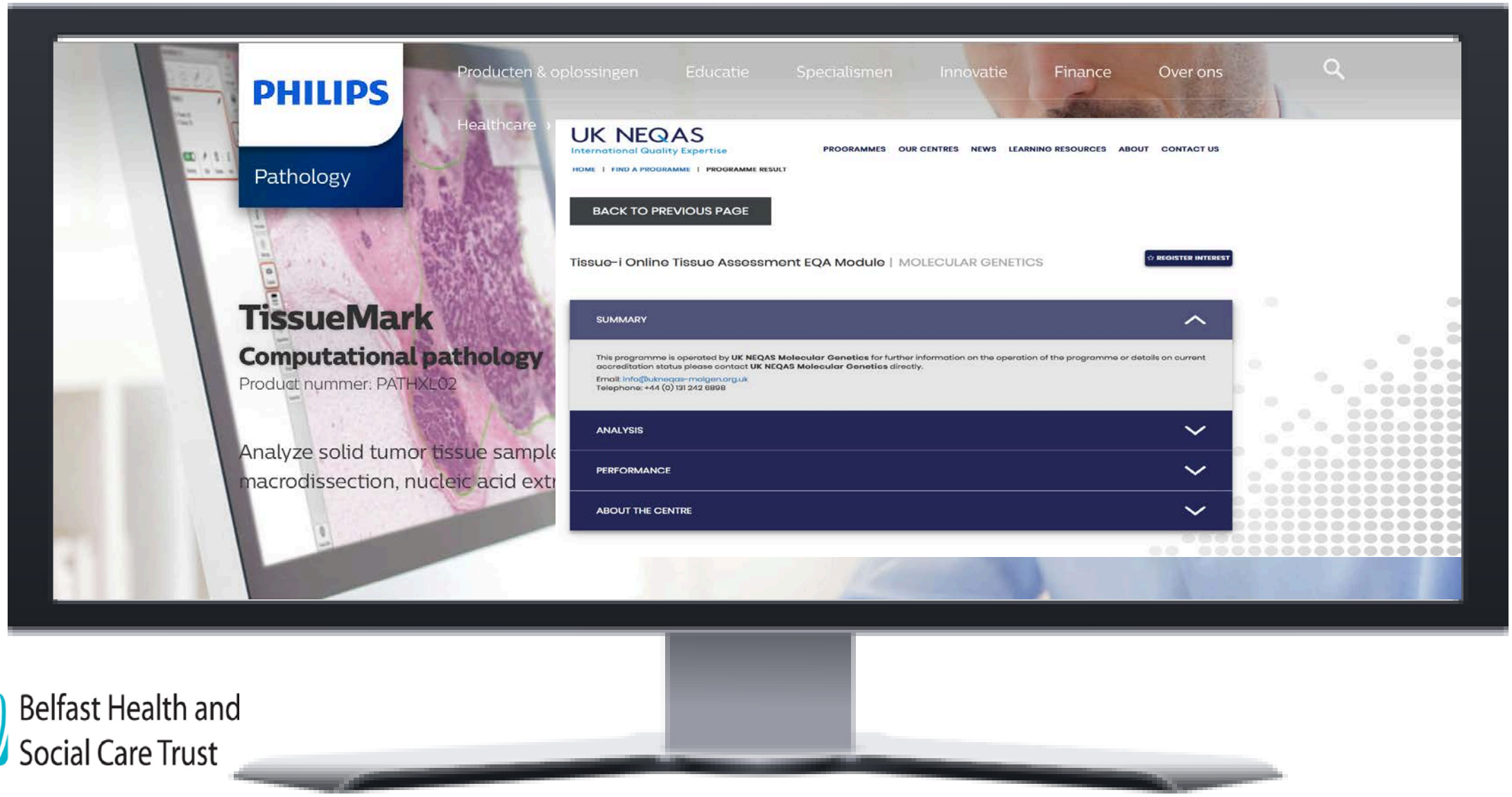
[3]Institute of Pathology, Royal Victoria Hospital, Belfast, N. Ireland

[4]PathXL Ltd, Northern Ireland Science Park, Belfast, UK

[*]These authors have contributed equally to this work








HSC Belfast Health and Social Care Trust

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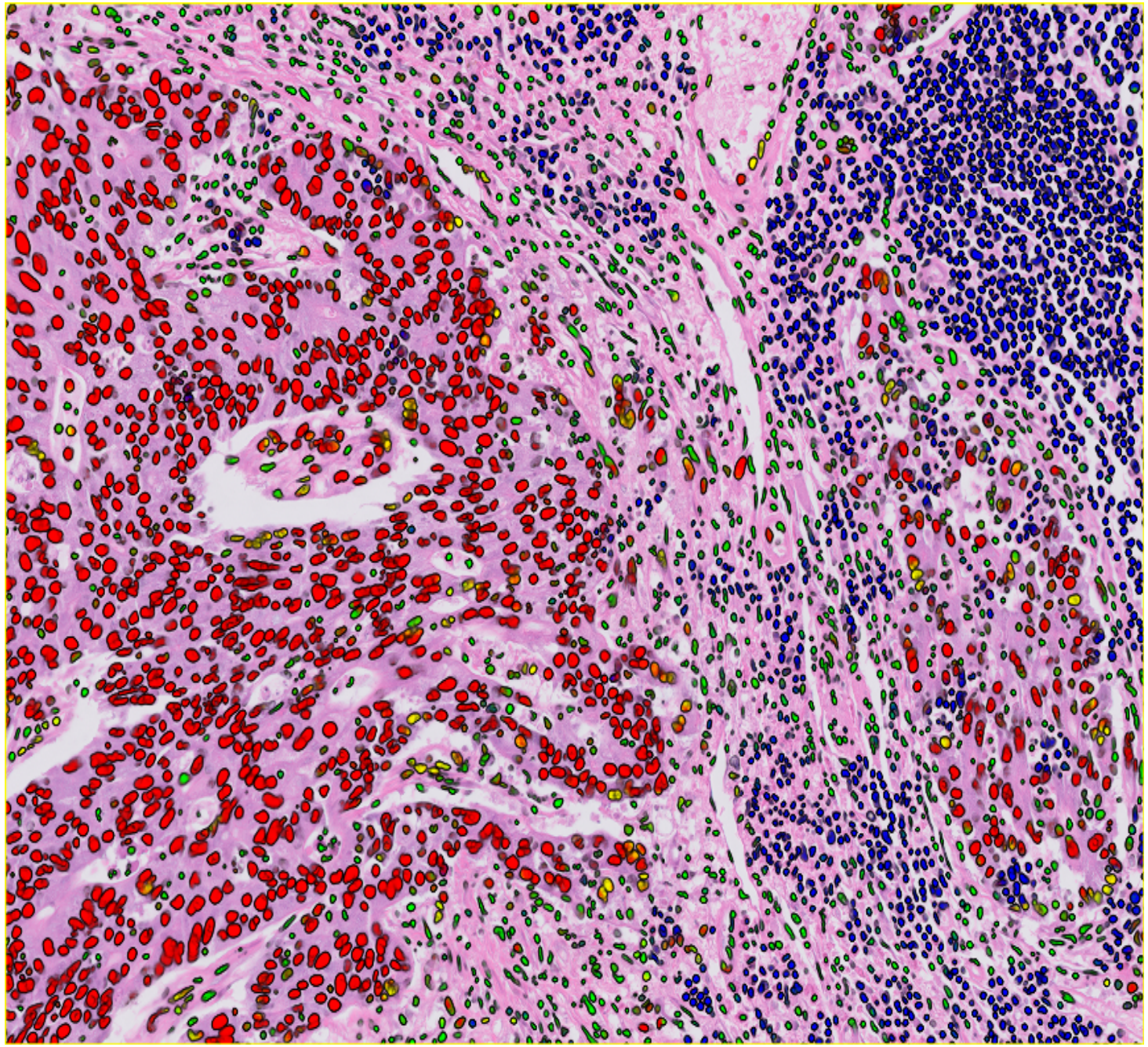
# Deep Learning for Cellular Identification



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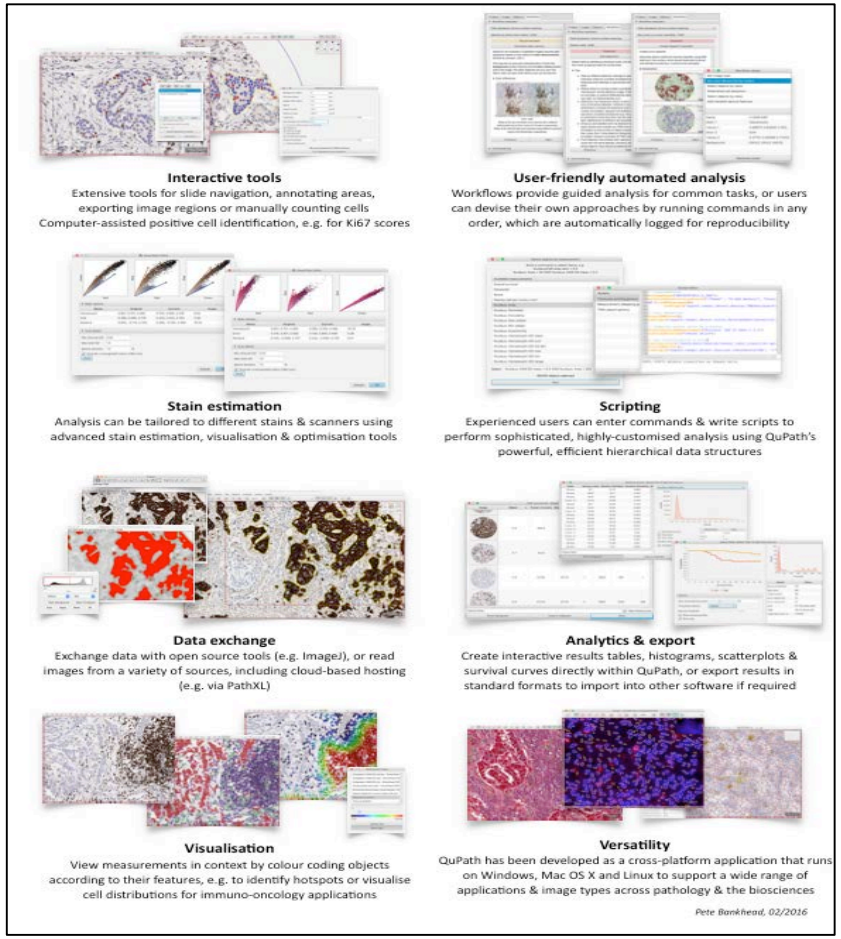
SCIENTIFIC REPORTS

OPEN

# QuPath: Open source software for digital pathology image analysis

Peter Bankhead[1], Maurice B. Loughrey[1,2], José A. Fernández[1], Yvonne Dombrowski[1], Darragh G. McArt[1], Philip D. Dunne[1], Stephen McQuaid[1,2], Ronan T. Gray[4], Liam J. Murray[4], Helen G. Coleman[4], Jacqueline A. James[1,2], Manuel Salto-Tellez[1,2] & Peter W. Hamilton[1]

Received: 20 July 2017


**KEY RELEVANCE**

> 50,000 downloads, used by both academia and industry

> 200 citations in peer-reviewed journals in less than 18 months

QuPath is a true global phenomenon: most widely used tool for biomarker quantitation in tissues

LETTER

doi:10.1038/nature25492

## TGFβ drives immune evasion in genetically reconstituted colon cancer metastasis

Daniele V. F. Tauriello[1,2], Sergio Palomo-Ponce[1,2], Diana Stork[1], Antonio Berenguer-Llergo[1], Jordi Badia-Ramentol[1], Mar Iglesias[2,3,4,5], Marta Sevillano[1,2], Sales Ibiza[1], Adrià Cañellas[1], Xavier Hernando-Momblona[1,2], Daniel Byrom[1], Joan A. Matarin[1], Alexandre Calon[†], Elisa I. Rivas[†], Angel R. Nebreda[1,6], Antoni Riera[1,2], Camille Stephan-Otto Attolini[1] & Eduard Batlle[1,2,6]

### Immunohistochemical quantifications

Scanned CD3, CD4, CD8, FoxP3, T-bet and pSMAD3 immunohistochemistry stainings were analysed in QuPath (v.0.1.2) using the positive cell detection feature with empirical parameters. Several ROIs (tumours) were taken per section. In cases in which multiple sections per mouse or liver were considered, care was taken to avoid quantifying the same tumour more than once. Data were processed and visualized with R and RStudio[33] (v.3.4.2 and v.1.1.383, respectively) and the ggplot2[34] package (v.2.2.1) (see Statistics and reproducibility).

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

| Characteristic | NI Biobank remit n=740 (%) | Not retrieved N=79 (%) | NI Biobank retrieved n=661 (%) | P-value* |
|---|---|---|---|---|
| Year of diagnosis | | | | |
| 2004 | 121 (16.4) | 19 (24.1) | 102 (15.4) | |
| 2005 | 155 (21.0) | 25 (31.7) | 130 (19.7) | |
| 2006 | 136 (18.4) | 10 (12.7) | 126 (19.1) | |
| 2007 | 154 (20.8) | 13 (16.5) | 141 (21.3) | |
| 2008 | 174 (23.5) | 12 (15.2) | 162 (24.5) | 0.01 |
| Sex | | | | |
| Male | 398 (53.8) | 40 (50.6) | 358 (54.2) | |
| Female | 342 (46.2) | 39 (49.4) | 303 (45.8) | 0.55 |
| Age at diagnosis, years | | | | |
| Mean ±SD | 70.3±11.5 | 67.1±11.8 | 70.6±11.4 | 0.01 |
| <50 | 47 (6.4) | 9 (11.4) | 38 (5.8) | |
| 50-<60 | 75 (10.1) | 11 (13.9) | 64 (9.7) | |
| 60-<70 | 205 (27.7) | 25 (31.7) | 180 (27.2) | |
| 70-<80 | 262 (35.4) | 23 (29.1) | 239 (36.2) | |
| ≥80 | 151 (20.4) | 11 (13.9) | 140 (21.2) | 0.08 |
| Stage | | | | |
| II | 426 (57.6) | 32 (40.5) | 394 (59.6) | |
| III | 314 (42.4) | 47 (59.5) | 268 (40.4) | 0.01 |
| Tumour grade | | | | |
| Well-moderate | 631 (85.3) | 64 (81.0) | 567 (85.8) | |
| Poor | 105 (14.2) | 15 (19.0) | 90 (13.6) | |
| Unknown | 4 (0.5) | 0 (0.0) | 4 (0.6) | 0.35 |
| Family history of CRC | | | | |
| No | 371 (50.1) | 41 (51.9) | 330 (49.9) | |
| Yes | 105 (14.2) | 19 (24.05) | 86 (13.0) | |
| Unknown | 264 (35.7) | 19 (24.05) | 245 (37.1) | 0.009 |
| Adjuvant chemotherapy use | | | | |
| No | 512 (69.2) | 37 (46.8) | 475 (71.9) | |
| Yes | 228 (30.8) | 42 (53.2) | 186 (28.1) | <0.001 |
| ECOG performance status | | | | |
| 0-1 | 378 (51.1) | 40 (50.6) | 338 (51.1) | |
| 2 | 47 (6.4) | 5 (6.3) | 42 (6.4) | |
| 3-4 | 33 (4.5) | 3 (3.8) | 30 (4.5) | |
| Unknown | 282 (38.1) | 31 (39.2) | 251 (38.0) | 0.99 |
| Deaths by 31st Dec 2013 | | | | |
| No | 401 (54.2) | 47 (59.5) | | |
| Yes, all-cause | 339 (45.8) | 32 (40.5) | | |
| Yes, colorectal-cancer specific | 237 (32.0) | 25 (34.7) | | |

*Chi-squared or t-tests comparing patients with Biobank remit v. patients with non-retrieved sam
**Area-based measure of socio-economic status usual address at time of colon cancer diagnosis.

# EPI 700 COLORECTAL CANCER COHORT

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).

| Risk factor | Alive n=354 | All Deaths n=308 | Hazard ratio (95% CI) | CRC Deaths n=212 (%) | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| Sex | | | | | |
| Male | 194 | 164 | 1.00 | 116 | 1.00 |
| Female | 160 | 143 | 0.98 (0.78-1.23) | 96 | 0.93 (0.71-1.23) |
| Age at diagnosis, years | | | | | |
| <50 | 26 | 12 | 1.00 | 11 | 1.00 |
| 50-<60 | 43 | 21 | 0.72 (0.35-1.48) | 17 | 0.64 (0.29-1.37) |
| 60-<70 | 119 | 61 | 0.79 (0.42-1.50) | 52 | 0.77 (0.39-1.51) |
| 70-<80 | 123 | 116 | 0.95 (0.51-1.76) | 71 | 0.64 (0.32-1.24) |
| ≥80 | 43 | 97 | 1.62 (0.85-3.08) | 61 | 1.15 (0.57-2.32) |
| Stage | | | | | |
| II | 229 | 165 | 1.00 | 94 | 1.00 |
| III | 125 | 142 | 2.02 (1.55-2.63) | 118 | 2.74 (1.99-3.78) |
| Tumour grade | | | | | |
| Well-moderately differentiated | 307 | 260 | 1.00 | 178 | 1.00 |
| Poorly differentiated | 44 | 46 | 1.44 (1.02-2.04 | 34 | 1.58 (1.06-2.36) |
| Unknown | 3 | 1 | / | 0 | / |
| Adjuvant chemotherapy receipt | | | | | |
| No | 228 | 247 | 1.00 | 157 | 1.00 |
| Yes | 126 | 60 | 0.47 (0.33-0.67) | 55 | 0.53 (0.35-0.79) |
| Family history of colorectal cancer | | | | | |
| No | 195 | 135 | 1.00 | 94 | 1.00 |
| Yes | 52 | 34 | 1.08 (0.73-1.60) | 27 | 1.15 (0.73-1.79) |
| Unknown | 107 | 138 | 1.43 (1.11-1.83) | 91 | 1.48 (1.09-2.01) |
| ECOG performance status | | | | | |
| 0-1 | 196 | 142 | 1.00 | 99 | 1.00 |
| 2 | 15 | 27 | 1.43 (0.93-2.20) | 19 | 1.47 (0.88-2.46) |
| 3-4 | 11 | 19 | 1.63 (0.98-2.70) | 16 | 2.02 (1.15-3.56) |
| Unknown | 132 | 119 | 1.11 (0.86-1.43) | 78 | 1.00 (0.73-1.36) |

All results mutually adjusted – we recommend all models are adjusted for (control 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.

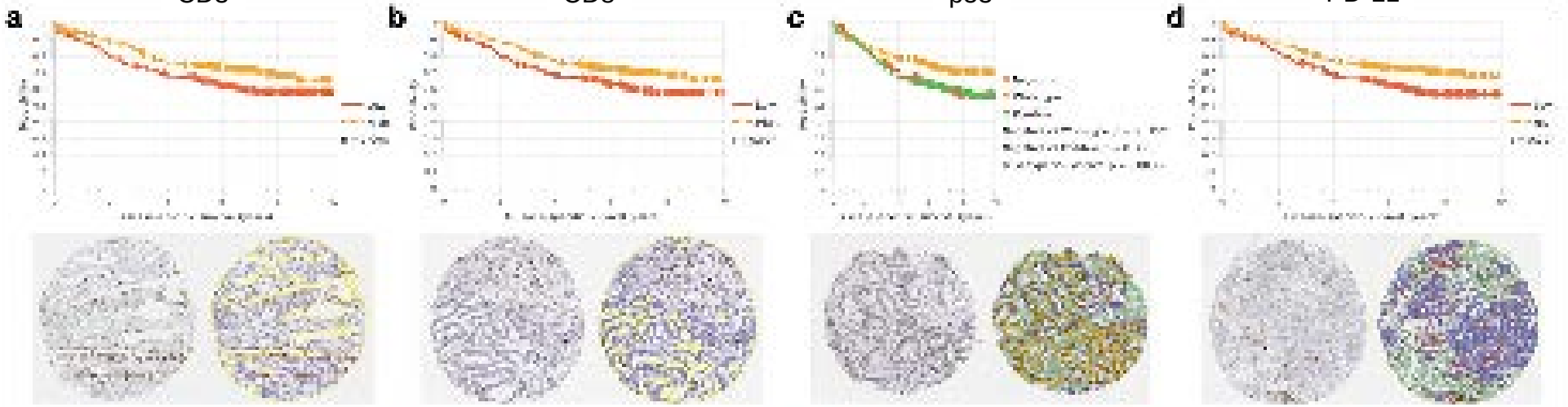
*Gray RT, et al (Salto-Tellez M). Br J Cancer. 2017;116(12):1652-1659.*

CD3

CD8

p53

PD-L1

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QuPath: Open source software for digital pathology image analysis

Received: 20 July 2017

Peter Bankhead[1], Maurice B. Loughrey[1,2], José A. Fernández[2], Yvonne Dombrowski[1], Darragh G. McArt[1], Philip D. Dunne[1], Stephen McQuaid[1,2], Ronan T. Gray[1], Liam J. Murray[3], Helen G. Coleman[3], Jacqueline A. James[1,2], Manuel Salto-Tellez[1,2] & Peter W. Hamilton[1]

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## QuPath

Quantitative Pathology & Bioimage Analysis

**Latest stable release (v0.1.2)**

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***QuPath* is an open, powerful, flexible, extensible software platform for whole slide image analysis.**

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- Milestones 3
- Milestones 4

**Please cite the QuPath paper if you use it in your work!**

Bankhead, P. et al. **QuPath: Open source software for digital pathology image analysis**. *Scientific Reports* (2017). https://doi.org/10.1038/s41598-017-17204-5

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**[HTML] QuPath: Open source software for digital pathology image analysis**

P Bankhead, MB Loughrey, JA Fernández… - Scientific reports, 2017 - nature.com

**QuPath** is new bioimage analysis software designed to meet the growing need for a user-friendly, extensible, open-source solution for digital pathology and whole slide image analysis. In addition to offering a comprehensive panel of tumor identification and high …

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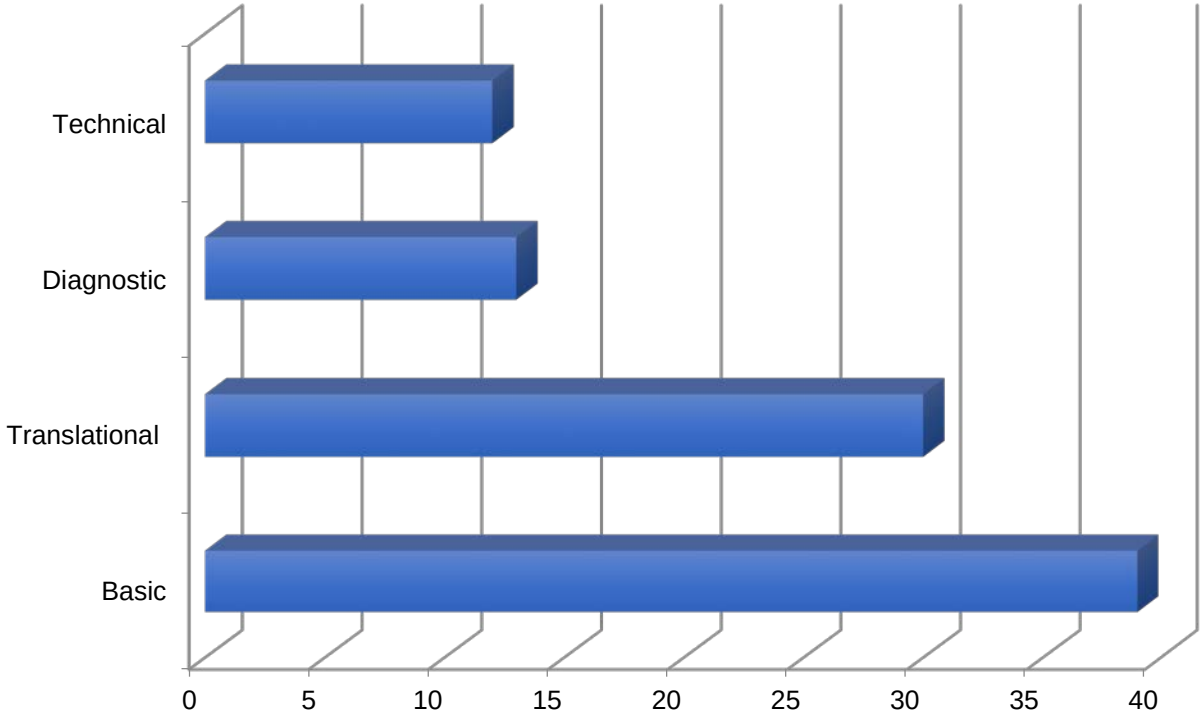
**QuPath: Open source software for digital pathology image analysis**

By: Bankhead, Peter; Loughrey, Maurice B.; Fernandez, Jose A.; et al.

SCIENTIFIC REPORTS Volume: 7 Article Number: 16878 Published: DEC 4 2017

| | | | | | | |
|---|---|---|---|---|---|---|
| 0 | 0 | 22 | 72 | 0 | 94 | 31.33 |

| | |
|---|---|
| Technical | 12 |
| Diagnostic | 13 |
| Translational | 30 |
| Basic | 39 |
| **TOTAL** | **94** |

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## QuPath: Open source software for digital pathology image analysis

By: Bankhead, P (Bankhead, Peter)[1]; Loughrey, MB (Loughrey, Maurice B.)[1,2]; Fernandez, JA (Fernandez, Jose A.)[1]; Dombrowski, Y (Dombrowski, Yvonne)[3]; Mcart, DG (Mcart, Darragh G.)[1]; Dunne, PD (Dunne, Philip D.)[1]; McQuaid, S (McQuaid, Stephen)[1,2]; Gray, RT (Gray, Ronan T.)[4]; Murray, LJ (Murray, Liam J.)[4]; Coleman, HG (Coleman, Helen G.)[4] ...More

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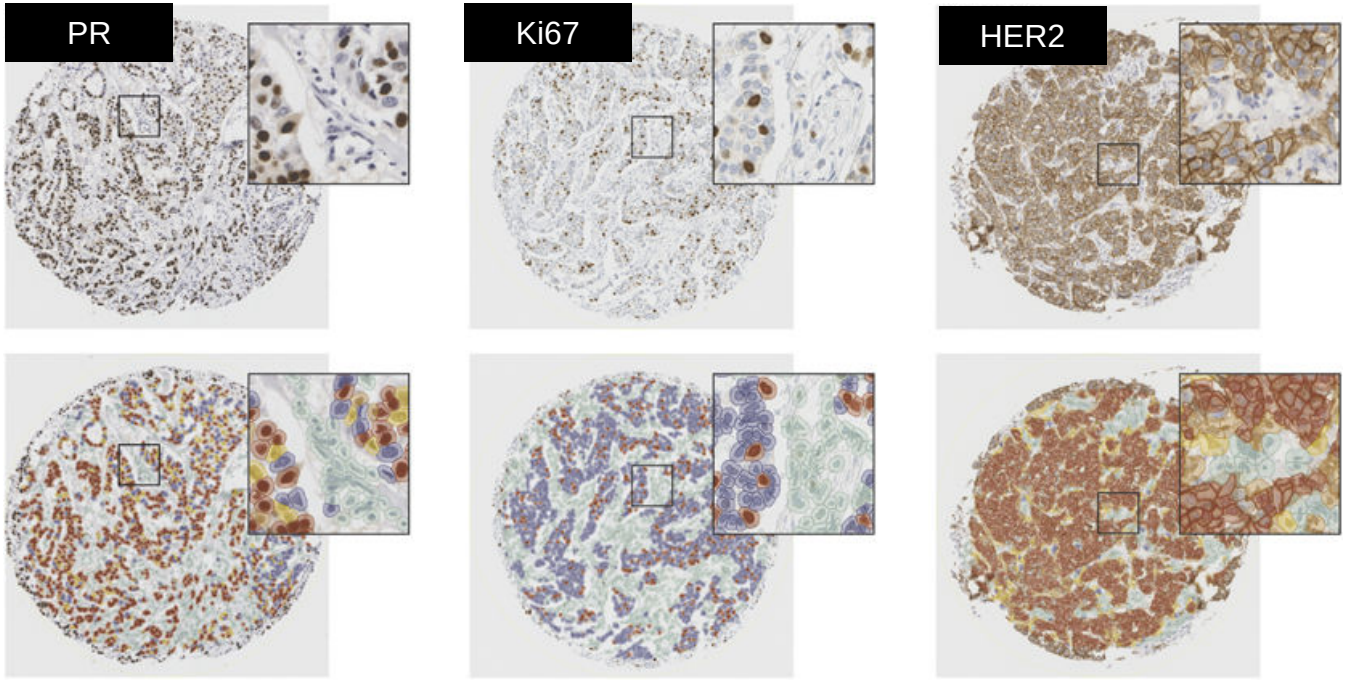


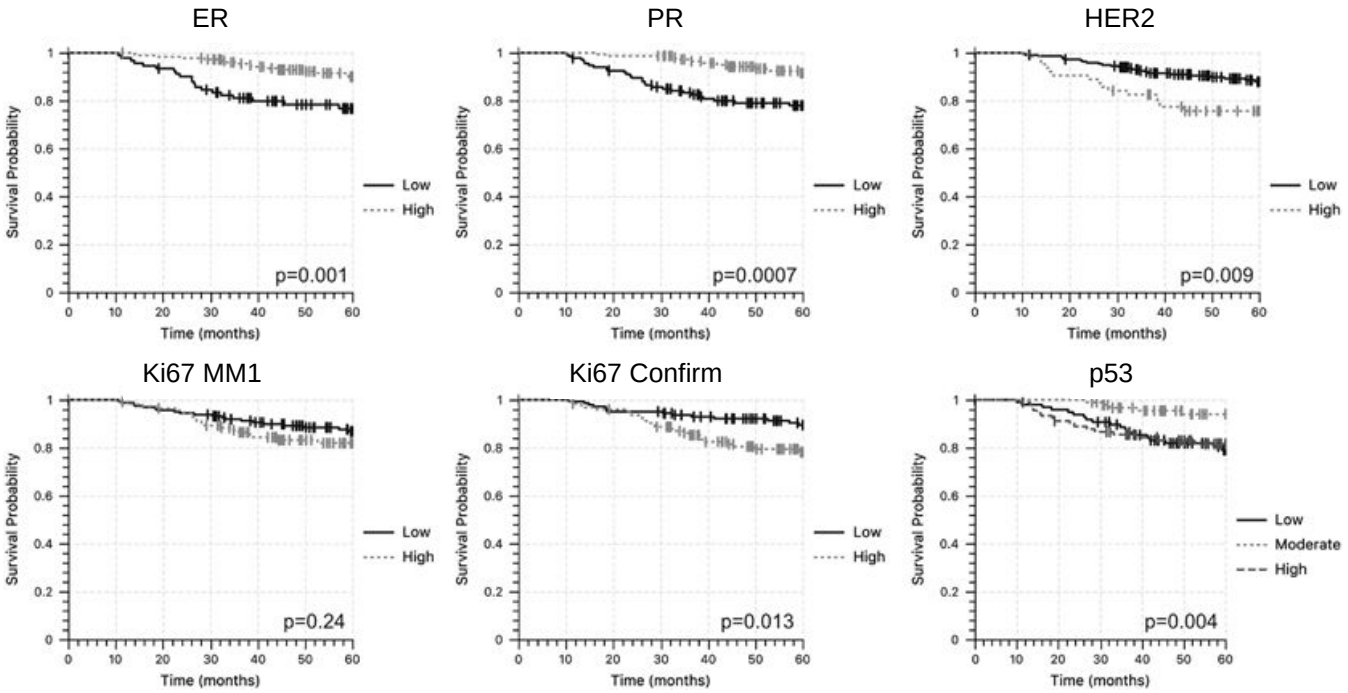


Laboratory Investigation (2017), 1–12
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PATHOBIOLOGY IN FOCUS

# Integrated tumor identification and automated scoring minimizes pathologist involvement and provides new insights to key biomarkers in breast cancer

Peter Bankhead[1], José A Fernández[1], Darragh G McArt[1], David P Boyle[1], Gerald Li[1], Maurice B Loughrey[1,2], Gareth W Irwin[3], D Paul Harkin[3], Jacqueline A James[1,2], Stephen McQuaid[1,2], Manuel Salto-Tellez[1,2] and Peter W Hamilton[1]

# A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: a systematic review and meta-analysis

*Xiaoxuan Liu*, Livia Faes*, Aditya U Kale, Siegfried K Wagner, Dun Jack Fu, Alice Bruynseels, Thushika Mahendiran, Gabriella Moraes, Mohith Shamdas, Christoph Kern, Joseph R Ledsam, Martin K Schmid, Konstantinos Balaskas, Eric J Topol, Lucas M Bachmann, Pearse A Keane, Alastair K Denniston*

*Lancet Digital Health* 2019

Published Online
September 24, 2019
https://doi.org/10.1016/
S2589-7500(19)30123-2

Diagnostic performance of deep learning models to be equivalent to that of health-care professionals.

However:
Few studies presented externally validated results or made comparisons using the same sample.
Poor reporting is prevalent in deep learning studies, which limits reliable interpretation of the reported diagnostic accuracy.

**New reporting standards that address specific challenges of deep learning could improve future studies, enabling greater confidence in the results of future evaluations of this promising technology.**

Laboratory Investigation (2019) 99:107–117
https://doi.org/10.1038/s41374-018-0123-7

ARTICLE

# Ki67 reproducibility using digital image analysis: an inter-platform and inter-operator study

Balazs Acs[1] · Vasiliki Pelekanou[1,2] · Yalai Bai[1] · Sandra Martinez-Morilla[1] · Maria Toki[1] · Samuel C. Y. Leung[3] · Torsten O. Nielsen[3] · David L. Rimm[1]

149 breast cancers, TMA format

The Mib-1 antibody (Dako) was used to detect Ki67 (dilution 1:100).

- HALO (IndicaLab),
- QuantCenter (3DHistech)
- QuPath (open source software)

*" Our results showed outstanding reproducibility both within and between-DIA platforms, including one freely available DIA platform (QuPath)."*

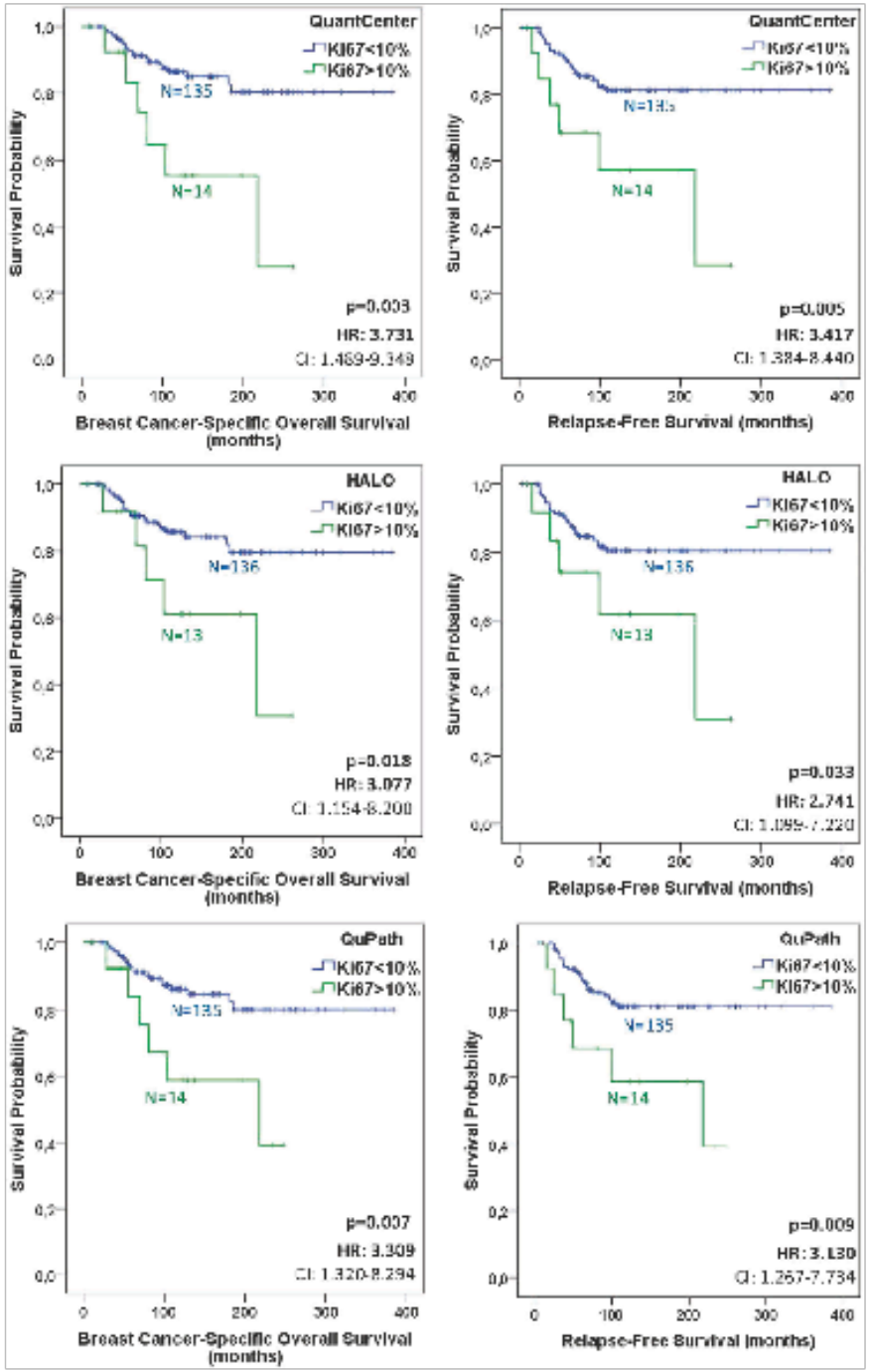


Fig. 6 Kaplan–Meier plots of automated Ki67 scores from the investigated digital image analysis platforms. *P* values are from Log-rank test

Journal of Thoracic Oncology

IASLC

Log in at IASL

Article in Press

# Critical appraisal of PD-L1 reflex diagnostic testing: current standards and future opportunities

Matthew P. Humphries, Stephen McQuaid, Stephanie Craig, Victoria Bingham, Perry Maxwell, Manisha Maurya, Fiona McLean, James Sampson, Patricia Higgins, Christine Greene, Jacqueline James, Manuel Salto-Tellez

DOI: https://doi.org/10.1016/j.jtho.2018.09.025

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**A**

| Manual Assessment \ Digital Assessment | <1% | 1-49% | >50% |
|---|---|---|---|
| <1% | 4 | 2 | 0 |
| 1-49% | 0 | 16 | 1 |
| >50% | 0 | 3 | 5 |

**B**

| Manual Assessment \ Digital Assessment | <1% | 1-49% | >50% |
|---|---|---|---|
| <1% | 10 | 5 | 0 |
| 1-49% | 1 | 6 | 0 |
| >50% | 0 | 0 | 9 |

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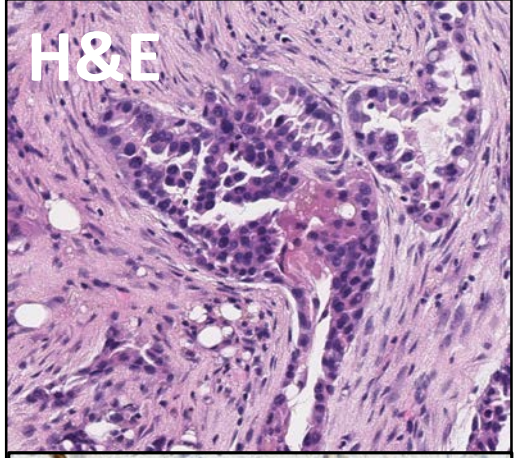


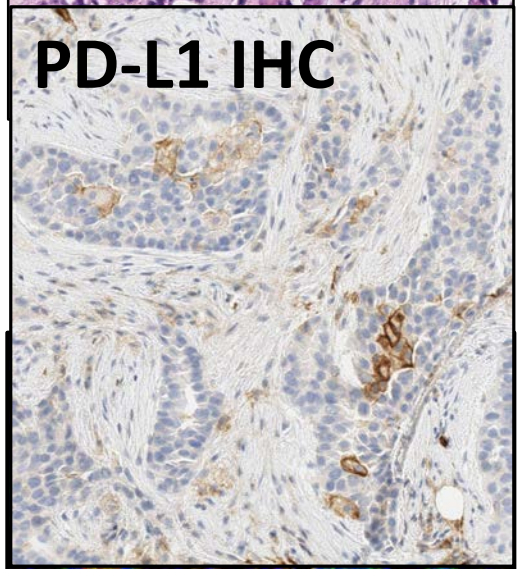


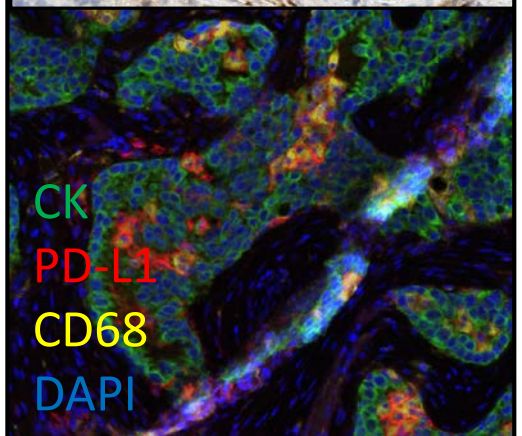

# The Promise and Reality of Precision Medicine in Northern Ireland

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MOLECULAR ONCOLOGY 8 (2014) 1163–1168

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Review

# Molecular pathology – The value of an integrative approach

Manuel Salto-Tellez[a,b,*], Jacqueline A. James[a,b], Peter W. Hamilton[a]

[a]Northern Ireland Molecular Pathology Laboratory, Centre for Cancer Research and Cell Biology, Queen's University, Belfast, Northern Ireland, UK

[b]Tissue Pathology, Belfast Health and Social Care Trust, Belfast, Northern Ireland, UK

*Salto-Tellez, James & Hamilton.*
*Molecular Oncology, 2014 Oct;8(7):1163-8*

Drug Discovery Today • Volume 00, Number 00 • November 2015 REVIEWS

ELSEVIER

# Integrated molecular pathology: the Belfast model

Manuel Salto-Tellez[1] and Richard D. Kennedy[1,2]

Reviews • POST SCREEN

*Salto-Tellez & Kennedy.*
*Drug Discovery Today, 2015, in press.*

QUEEN'S UNIVERSITY BELFAST

**Precision Medicine Centre of Excellence**

# Precision Medicine Programme

Manuel Salto-Tellez
Jackie James
David Gonzalez de Castro

Belfast Health and Social Care Trust

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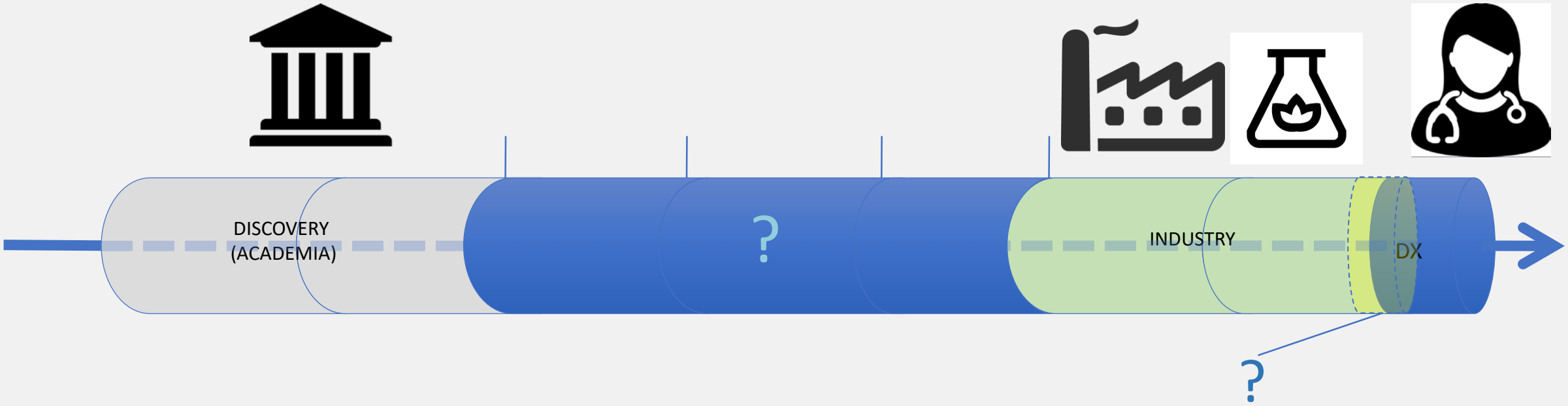
Invest Northern Ireland

- Molecular Diagnostics
  MST / DGC / JJ
  Belfast Health and Social Care Trust
- Genomics Research
  DGC
  QUEEN'S UNIVERSITY BELFAST
- Digital Pathology & Artificial Intelligence
  MST / JJ
  CANCER RESEARCH UK
- PM Education & Training
  JJ
  QUEEN'S UNIVERSITY BELFAST
- PM Centre of Excellence
  MST / JJ / DGC
  Invest Northern Ireland
  Health and Social Care
  QUEEN'S UNIVERSITY BELFAST
- The Northern Ireland Biobank
  JJ
  NIBiobank

60 staff
£19.1M direct competitive funds
£35.0M including indirect funds
Molecular diagnostic service
± 150 peer reviewed papers
Significant traction and support with industry

# PMC - FROM DISCOVERY TO ADOPTION

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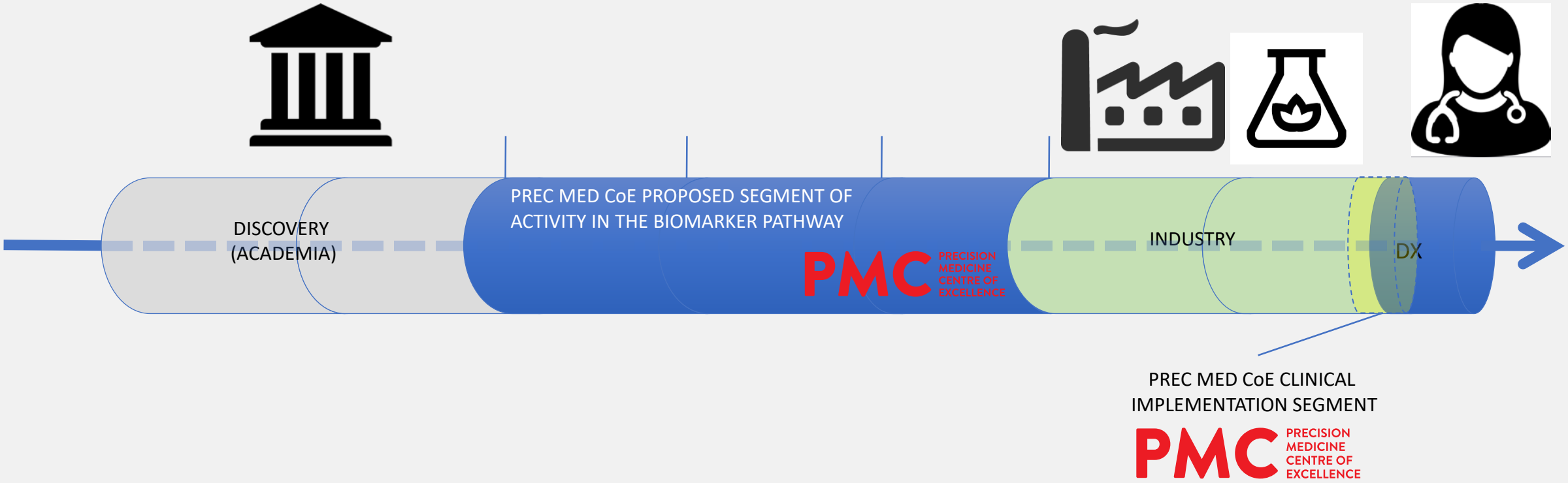
Precision Medicine
Centre of Excellence

# PMC - FROM DISCOVERY TO ADOPTION

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**Precision Medicine Centre of Excellence**

BERYL GRAHAM
BUSINESS & PROJECT MANAGER

CATHAL McNALLY
QUALITY & TRAINING MANAGER

MANUEL SALTO-TELLEZ JACKIE JAMES
DAVID GONZALEZ DE CASTRO DARRAGH McART

LIZ HODGES
HEAD OF LABORATORY OPERATIONS

CHANG KIM
LEAD BIOINFORMATICIAN

SHAMBHAVI SRIVASTAVA
BIOINFORMATICIAN

**Bioinformatics**

QUEEN'S UNIVERSITY BELFAST

PERRY MAXWELL
CLINICAL LEAD

MATT HUMPHRIES
SCIENTIFIC LEAD

**Tissue Hybridization & Digital Pathology**

LOUISE HAREWOOD
SCIENTIFIC LEAD

MANISHA MAURYA
CLINICAL LEAD

**Genomics**

Joanne McCrossan
Eda Tarnai-Nagy
Cheryl Bennett
Leanne McIlreavey
Kirsty Trewellard
Jana Gazdova

# GENOMICS

## MAIN ASSAYS OFFERED

- DNA extraction, purification and QC
- Whole Genome Sequencing
- Shallow whole genome sequencing
- Exome Sequencing
- Hybrid capture panels (multiple panels available)
- Droplet digital PCR

**Sample types:**

- Whole blood
- Plasma/serum
- FFPE material
- Fresh frozen tissue
- DNA

## KEY EQUIPMENT

**BioMek i7 Liquid Handler**

- Automated Sample Prep
- Can perform multiple sample prep methods
- Highly reproducible results
- Limited interaction required
- Can be run 24 hours a day
- Hundreds of samples can be prepared per run

**Agilent 4200 TapeStation**

- Allows QC of 96 samples per run
- Provides quantification and sizing information
- Easy load and limited set up required

**Droplet Digital PCR, QX200 with AutoDG**

- Allows extremely sensitive detection of varia
- Up to 96 samples per run
- Limited hands on time required
- Automated droplet generation yields highly reproducible results

**NovaSeq 6000**

- NovaSeq provides high throughput sequenci
- Highly flexible sequencing outputs, from 65 6000 Gb of data per run
- At full capacity, each NovaSeq run can seque whole human genomes or 500 human exom
- Can perform multiple runs per week
- 50x more output than the NextSeq 500
- Vastly reduces per sample sequencing costs
- NextSeq 500 also available for smaller seque
- MiSeq available for QC runs of sequencing li

**For details of Genomics services contact:**
Dr Louise Harewood at l.harewood@qub.ac.uk or Dr Manisha Maurya at m.maurya@qub.ac.uk

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# SERVICES AND EQUIPMENT



# BIOINFORMATICS

## KEY SERVICES OFFERED

**Supporting the Genomics and Tissue Hybridisation and Digital Pathology groups, the Bioinformatics team provide two main services:**

- Custom-tailored genomic data analysis beyond the predefined analysis offered by the data-generating platforms at the Precision Medicine Centre
- Computational infrastructure on Microsoft Azure Cloud including data management and genomic data analysis tools for the clinical genomic diagnostics and research.

**For details of Bioinformatics services contact:**
Dr Chang Kim at c.kim@qub.ac.uk or Dr Shambhavi Srivastava at s.srivastava@qub.ac.uk



# TISSUE HYBRIDISATION AND DIGITAL PATHOLOGY

## MAIN ASSAYS OFFERED

- Single and multiplexing biomarker Immunohistochemistry, fluorescence and chromogenic (DDISH)
- In situ hybridisation, fluorescence and chromogenic (RNAScope)
- Antibody technical validation
- Microtomy, Haematoxylin and Eosin staining service
- Digital and glass Pathology review/annotation for TMA bespoke design, mapping and construction
- Full spectrum digital analysis capability; choice of image analysis programs and algorithms

**Sample types:**

- Formalin Fixed Paraffin Embedded (FFPE) blocks and sections

## KEY EQUIPMENT AND SOFTWARE

**Roche/Ventana Ultra**

- Fully automated Immunohistochemistry and In situ Hybridisation platform

**Bond Rx**

- Fully automated Immunohistochemistry and In situ Hybridisation platform

**3D Histech Grandmaster**

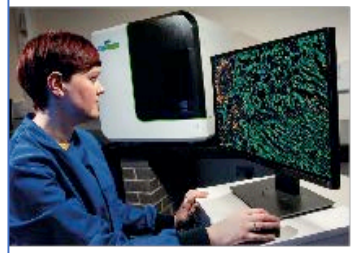
- Allows Core size options: 0.06 mm, 1 mm, 1.5 mm and 2 mm with up to 558 cores per TMA, depending on core size

**Aperio AT2 Scanning**

- Up 400 slide loading capacity for scanning of glass microscope slides x20 and x40

**Polaris, Multichannel Fluorescence**

- Continuous scan loading capacity
- Scans at x10-x40 brightfield and fluorescence
- Up to nine, unmixed colour capture



**Analysis**

- Project oriented image analysis with a choice of programs and algorithms available
- QuPath
- Definiens
- Visiopharm
- Halo (RUO)

**For details of Tissue Hybridisation and Digital Pathology services contact:**
Matt Humphries at m.humphries@qub.ac.uk or Dr Perry Maxwell at p.maxwell@qub.ac.uk

# PARALLEL DIAGNOSTIC PATHWAYS

H&E - ISH – IHC - digitalization

MDT

DNA Extraction – LT PCR – Library Prep/NGS

# INTEGRATED DIAGNOSTIC PATHWAYS

H&E - ISH – IHC - digitalization

DNA Extraction – LT PCR – Library Prep/NGS

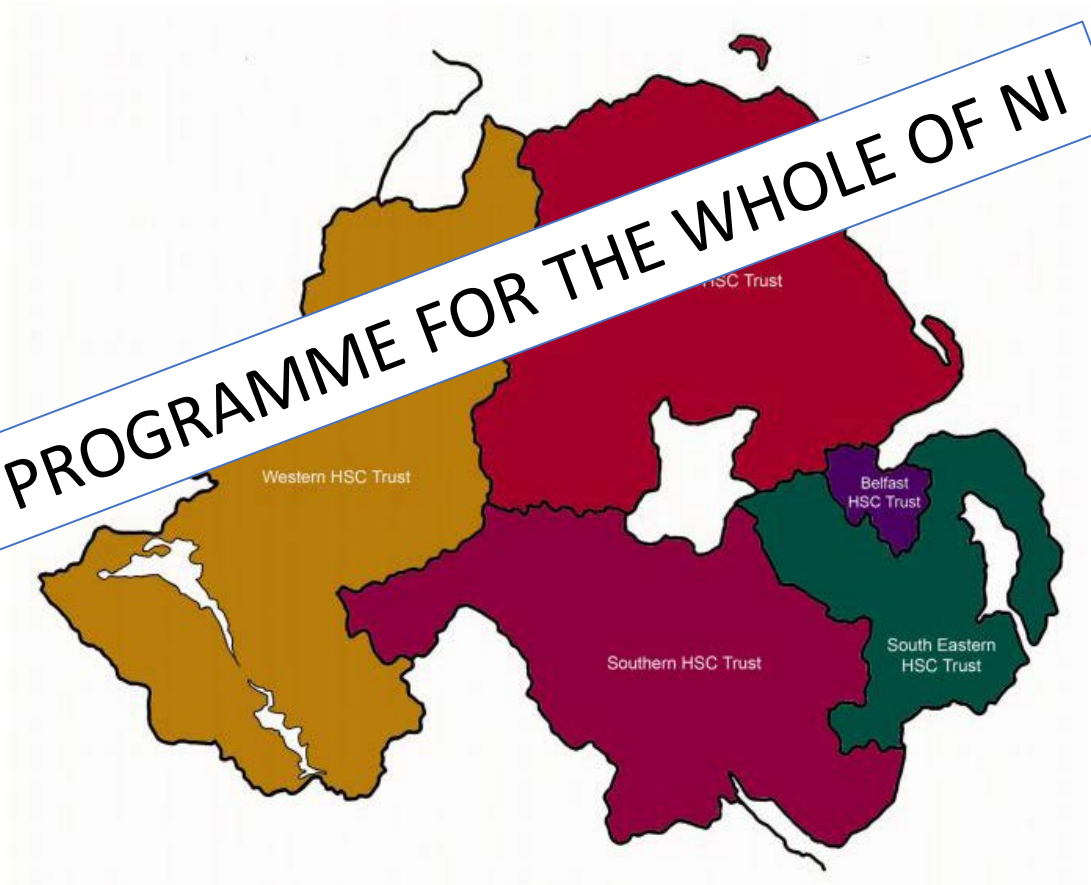
Clinical Opinion

MDT

- 5 Trusts
- 4 Pathology Departments
- 2 Cancer Centres
- 2 Universities

- Catching p[illegible]on = 1.9M

SINGLE PERSONALISED MEDICINE PROGRAMME FOR THE WHOLE OF NI

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EST 1845
PMC
PRECISION MEDICINE CENTRE OF EXCELLENCE
QUB CR-UK Accelerator Teams - QuPATH
Jackie James
Stephanie Craig
Matt Humphries
Svenja Mende
Vicky Bingham
Stephen McQuaid
Peter Hamilton
Jackie James
Pete Bankhead
Jose A Fernandez
Vicky Bingham
Stephen McQuaid
Colorectal Cancer
S Craig
M Humphries
M Alderdice
V Bingham
M Loughrey
H Coleman
G Murray
A Blake
E Domingo
J Robineau
L Brown
D Fisher
S Richman
M Seymour
P Quirke
P Bankhead
S McQuaid
M Lawler
DG McArt,
TS Maughan
JA James
PDL-1
Matt Humphries
Stephen McQuaid
Stephanie Craig
Victoria Bingham
Perry Maxwell
Manisha Maurya
Fiona McLean
James Sampson
Patricia Higgins
Christine Greene
Jacqueline James
Esophageal Cancer
MP Humphries
R Kacprzyk
N Fisher
SG Craig
V Bingham
S McQuaid
GI Murray
R Turkington
J James
TissueMark
Hamilton PW
Wang Y
Boyd C
Jackie James
Loughrey MB
Hougton J
Boyle DP
Kelly P
Maxwell P
McCleary D
Diamond J
McArt DG
Tunstall J
Bankhead P
Breast Cancer
David Boyle
D. Paul Harkin
Gareth Irwin
Health Sciences
S:CORT
Stratification in COloRecTal cancer
Graeme Murray
Tim Maugham
UNIVERSITY OF OXFORD
UNIVERSITY OF ABERDEEN
HSC Belfast Health and Social Care Trust
HSC Public Health Agency
Laughing Matters
NHS National Institute for Health Research
Tom Simms Memorial Fund
CANCER RESEARCH UK
Invest Northern Ireland
Innovate UK