Dublin 2019_Speaker Presentations

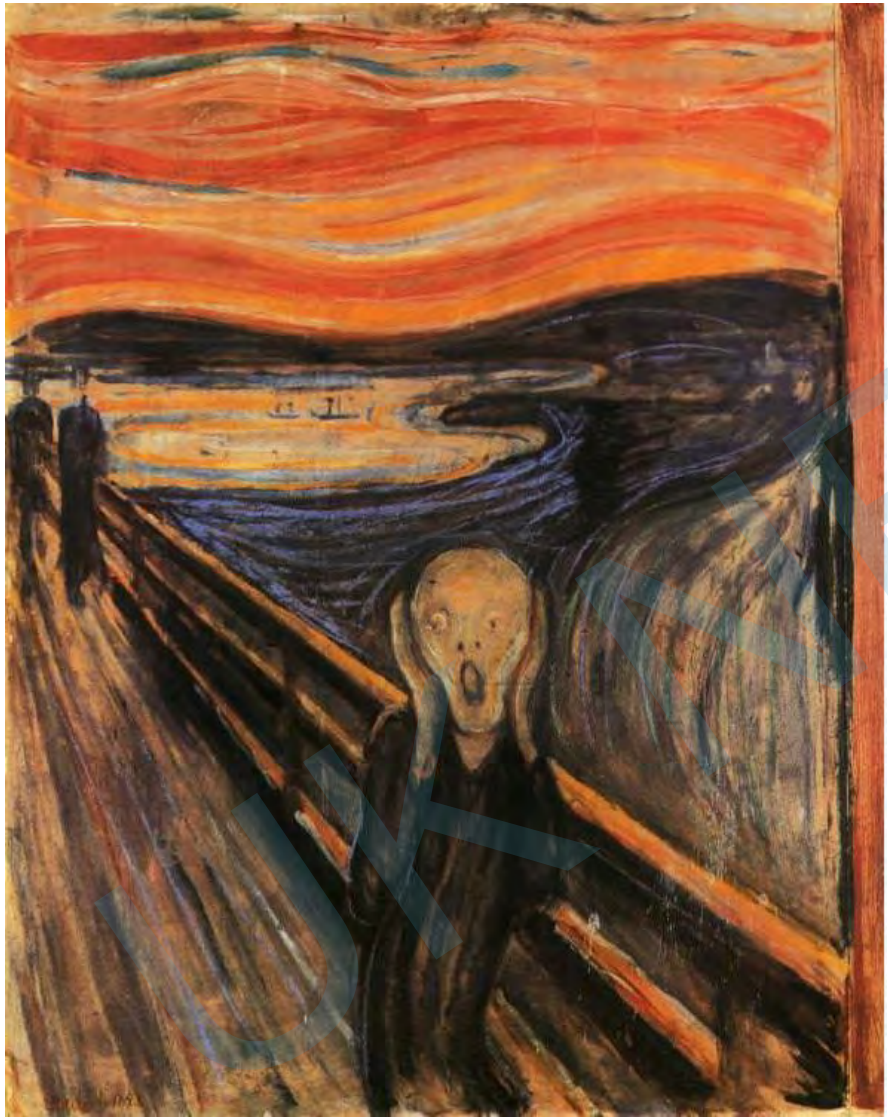
- 50 Years of Quality
- Digital Services Supporting Competency
- EQA for a Genomic Future
- External Quality Assessment and the Patient's Journey
- Keeping Control of Quality
- Melting the pre-analytical iceberg of errors
- You have got to be kidding me!

50 Years as World Leaders in EQA 1969–2019

UK NEQAS
International Quality Expertise

50 Years of Quality

Mr Liam Whitby
President
UK NEQAS
www.ukneqasli.org



The Scream, 1893 by Edvard Munch

- Small things form part of the large..... A drop of blood is a Universe.
  - *Edvard Munch. Worlds Within Us*

Abbreviations

- QC – Quality Control
- IQC – Internal Quality Control
- EQA – External Quality Assessment
- PT - Proficiency Testing
- UK NEQAS - UK National External Quality Assessment Service
- SOP – Standard Operating Procedure
- POCT- Point of Care Testing

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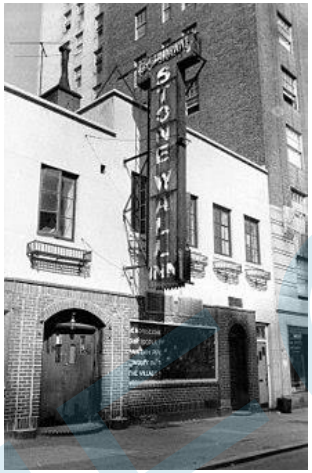
1969

First flight of a Boeing 747



Raid on the Stonewall Inn

Humans walk on the moon

Woodstock Festival

Loaf of bread – 9p

Pint of milk - 18p

Pint of beer – 20p

John Lennon quits Beatles

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1969
Haematology

Coulter Counter Model FN
Released 1968

Keeler 'Grey Wedge' Haemoscope
Circa 1966 - 1972

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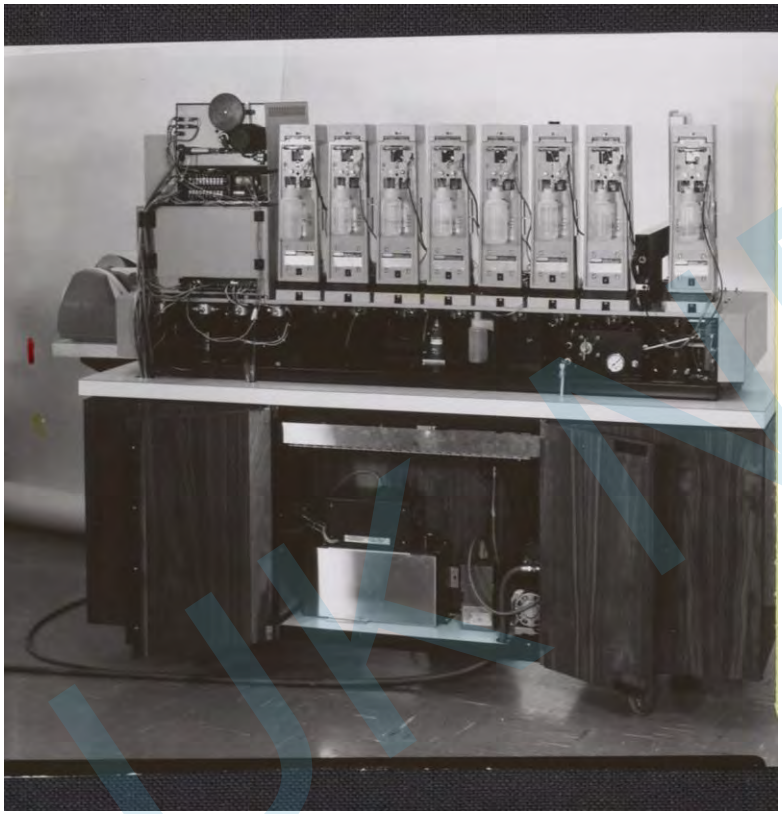
1969
Clinical Chemistry



Beckman DSA-560
Released 1968

Hycel Mark X
Released 1966

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UK NEQAS

- 1962: Dr Mitchell Lewis provided 50 leading laboratories with an identical blood sample
- Returned haemoglobins ranged from 120 to 170 g/L
- This highlighted the need for interlaboratory quality assessment
  - Internal quality controls were not enough

50 Years as World Leaders in EQA 1969–2019

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UK NEQAS

- Foundations of UK NEQAS laid in 1969 by
  - Professor Tom Whitehead in clinical chemistry
  - Dr. Mitchell Lewis in haematology
- £3000 per annum for 3 years for haematology
  - Equivalent to £48000/€55000 today
- £500 to fund the chemistry project for 2 years
  - Equivalent to £8000/€9200 today
- 'All issues will be resolved by then'
- 50 years later and we are still here

50 Years as World Leaders in EQA
1969–2019

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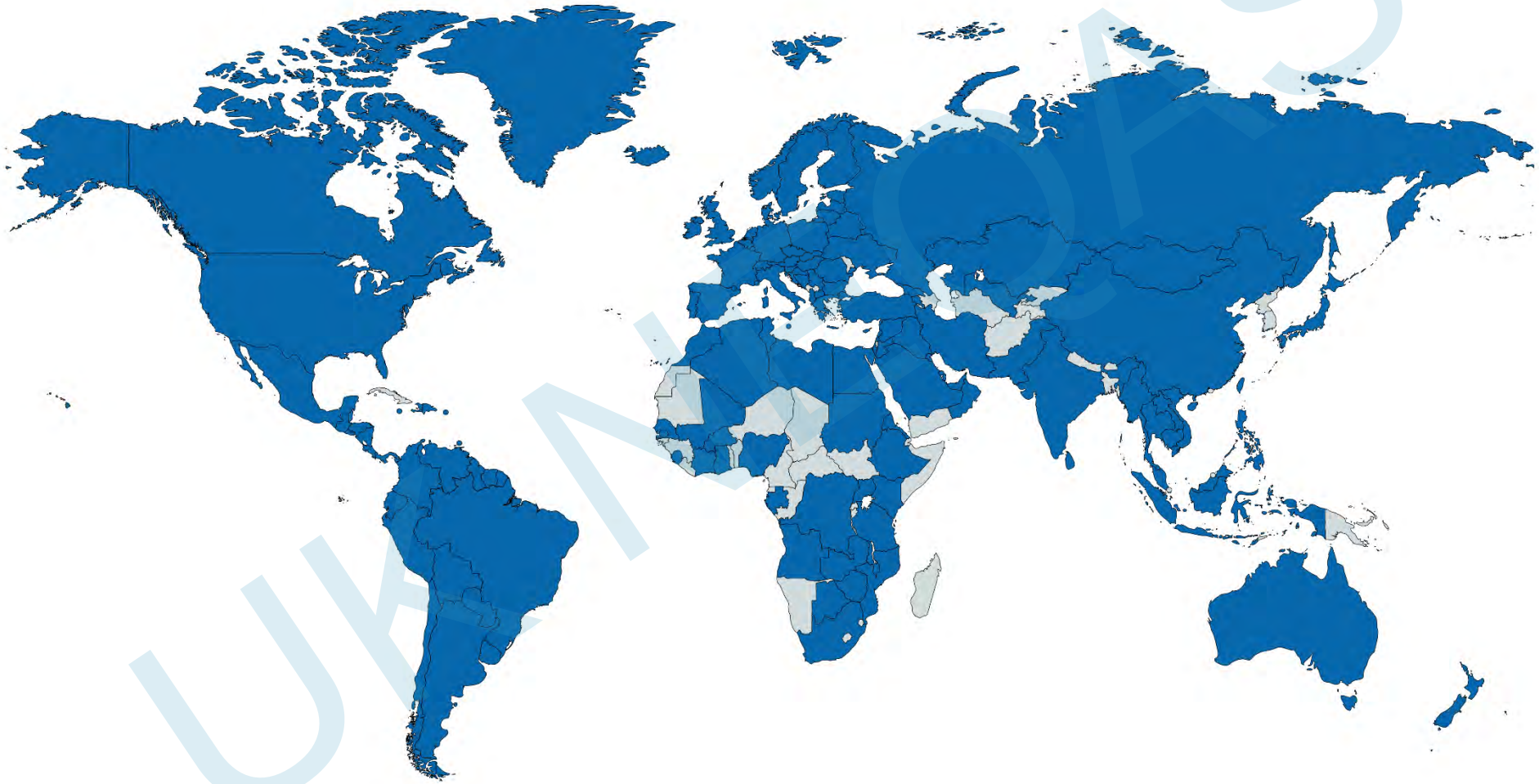

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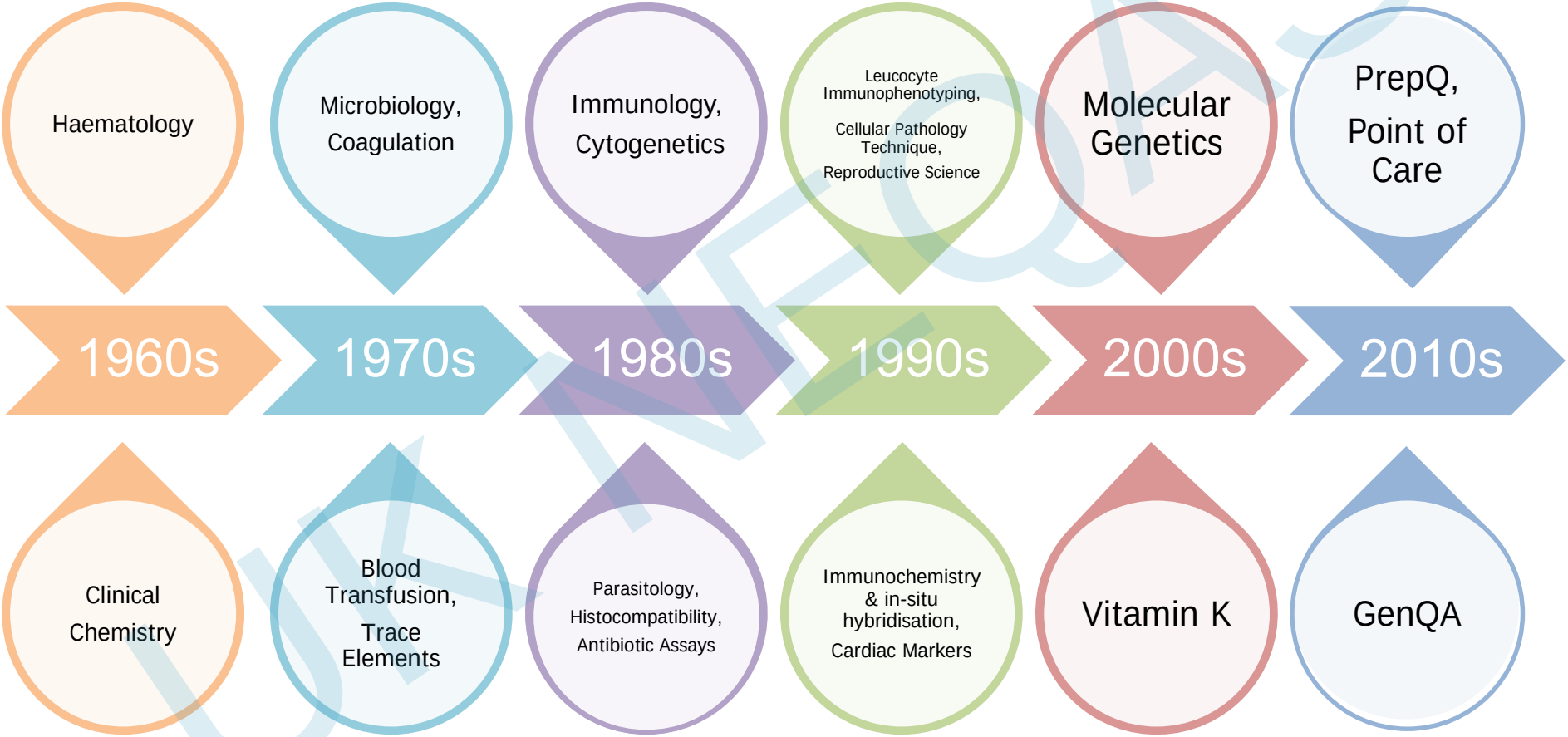

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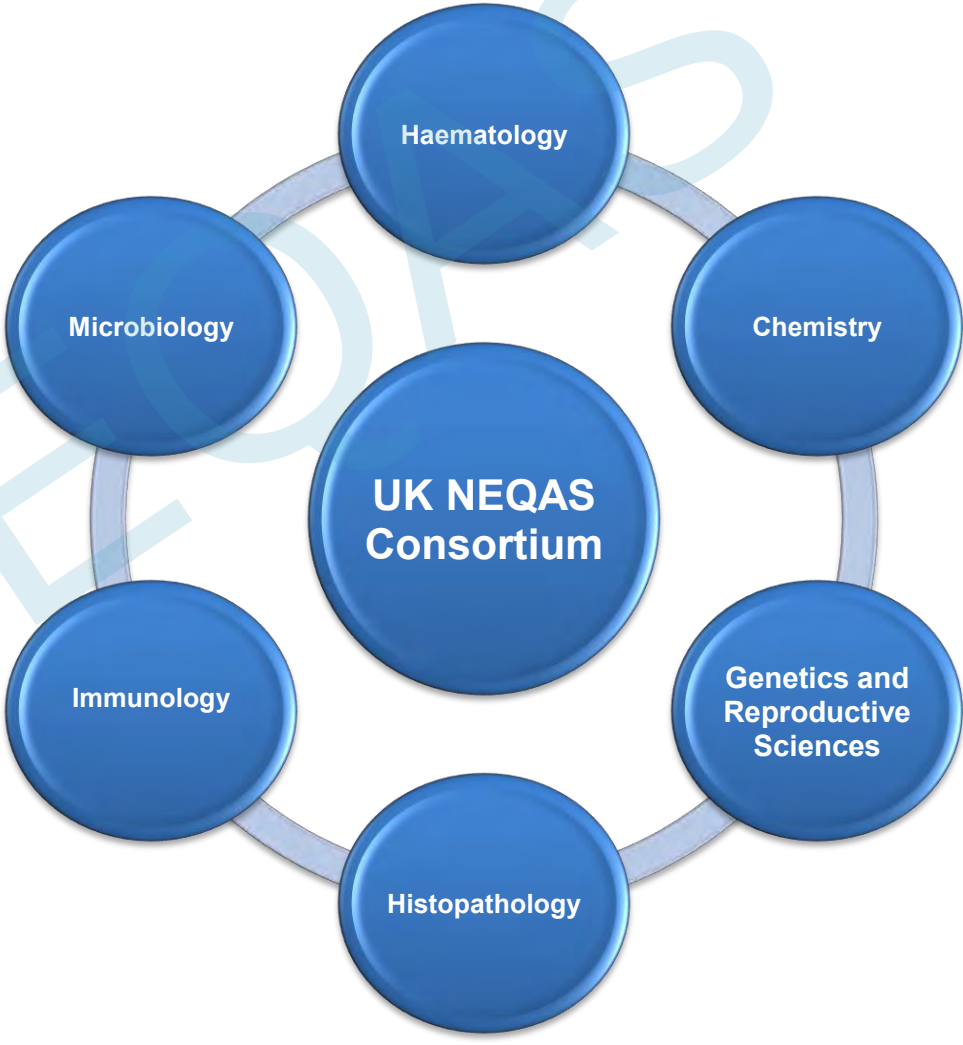

UK Charity number 1044013

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UK NEQAS: Objectives

- Our mission is the provision of External Quality Assessment (EQA) that is
  - Appropriate for the needs of participants
  - Responsive
  - High standard

To provide laboratories with:

- interlaboratory comparisons
- relative performance of kits and methods
- factors associated with good and poor performance

The primary role of UK NEQAS is educational

Support

- Experienced scientific staff available for advice and assistance
- Repeat samples of previous trials
- Regular scientific meetings
- Training courses
- 'Personalised' reports
- Laboratory visits

50 Years as World Leaders in EQA 1969–2019

UK NEQAS International Quality Expertise

Educational Activities Oct 2018 – Oct 2019

Posters 36

Presentations 137

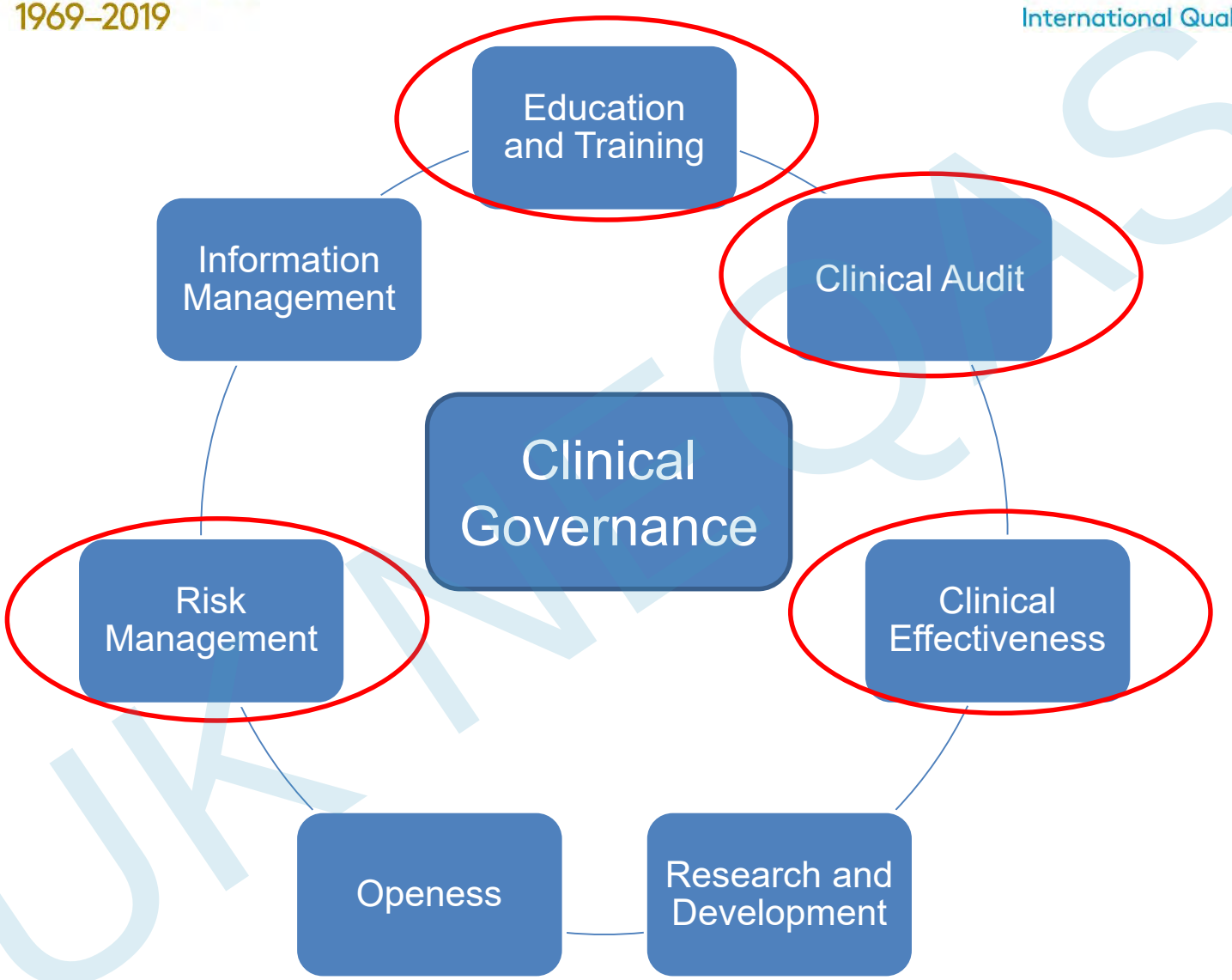
Publications 38

It's Not Just EQA

- Collaborate with UK and international organisations
  - WHO
  - Royal College of Pathologists
  - Genomics England
  - European Centre for Disease Prevention and Control
  - International Council for Standardisation in Haematology
  - Joint Committee for Traceability in Laboratory Medicine
- Collaborate with industry
- Involved in the production of UK and international guidelines

It's Not Just EQA- Clinical Governance

- The Department of Health defines clinical governance as:
  "A framework through which NHS organisations are accountable for continually improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish." (Department of Health 1998).



Clinical Governance and EQA

- Education and Training
  - Look around
  - Scientific meetings and laboratory master-classes
- Clinical Audit
  - 'Measurement of effectiveness of healthcare against agreed and proven standards'
  - EQA programmes are a form of clinical audit

Clinical Governance and EQA

- Clinical Effectiveness
  - Information on effectiveness of changes/interventions
- Risk Management
  - Helps in ensuring high quality work
  - A source of information on best practice

Future Challenges

- New tests
- Pathology network consolidation
- Point of Care Testing
- Pre and Post analytical variable monitoring

BBC

Sign in | News | Sport | Weather | iPlayer | Sounds | More | Search

Blood test

Filter | All | News | Sport | Programmes | Newsbeat | iWonder | About the BBC | More Filters

10 Sep 2019

New blood test trialled on 12,000 Scots catches lung cancer early

...A new **blood test** can detect if a person has lung cancer before symptoms ever... implications for the early detection of lung cancer by showing how a simple **blood test**... group. Lung cancer-specific deaths were also lower in the group whose **blood**...

News | Scotland

2 Aug 2019

Alzheimer's blood test 'one step closer'

... towards a reliable **blood test** for Alzheimer's to speed up dementia research... of the **blood test** improved to 94%. Senior study author Randall J Bateman, professor... of progress in dementia research. "But it's important to note this isn't a **blood test**...

News | Health

2 Apr 2019

NHS to offer mums-to-be new blood test for pre-eclampsia

...Pregnant women in England will be able to get a new type of **blood test** to check... PLGF (placental growth factor) **blood test**, which costs about £70, show it speeds up...

News | Health

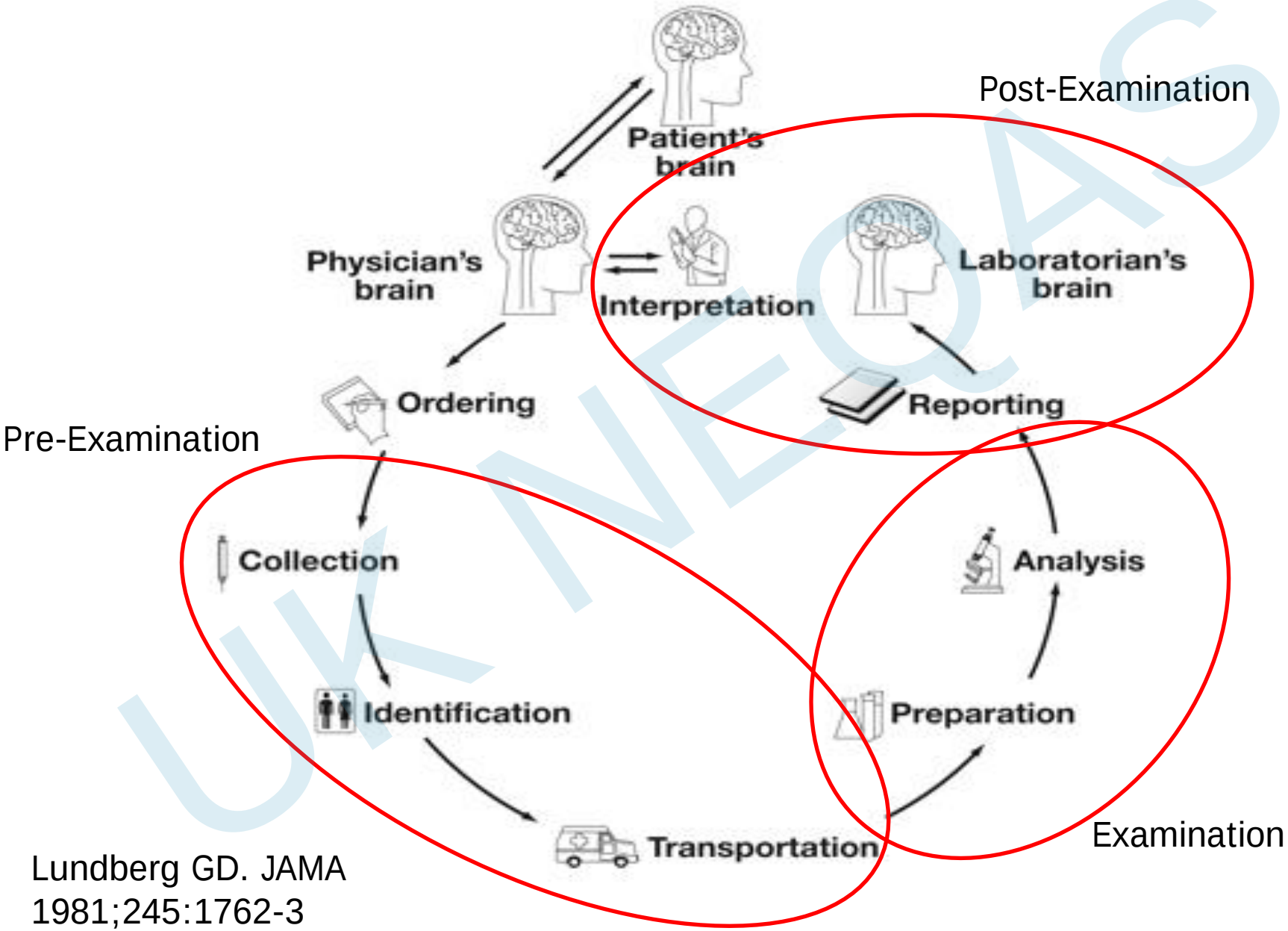
Pathology Networks

- New modes of EQA
  - Ensure consistency within networks
    - Different statistical models may be required
    - Different statistics to ensure programme viability
  - Referral models to replicate patient pathway
  - Challenging samples for central testing hubs
  - Reporting performance issues
    - To laboratory
    - To central hub
    - To National oversight bodies

Point of Care Testing

- Challenges (for EQA and laboratories)
  - Who is doing the testing
  - What are they using
  - How are results reported
    - How are results integrated into records
  - Will they undertake EQA?
  - Reporting performance issues
    - To tester
    - To co-ordinator

Pre and Post Analytical Variables



Lundberg GD. JAMA 1981;245:1762-3

Pre and Post Analytical EQA PREPQ

- Web based EQA programme
  - Benefit of UK NEQAS membership for UK/ROI laboratories

Categories for Reporting Failures or Rejections	
Patient identification	Sample identification
Sample collection	Sample volume
Storage and transport	Turnaround time
Corrected reports	Critical result reporting
Sample suitability	Blood culture (microbiology)

- For information email prepq@ukneqas.org.uk

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Conclusion

- Challenging times ahead
  - But it is also exciting
  - Tremendous opportunities for laboratories and UK NEQAS to produce new styles of EQA
  - Keen to work with laboratories
    - Want to hear your views
- We need to work in unison to provide maximum benefit for patients

Conclusion

EQA:

- Gives confidence in results generated by laboratories
- allows peer laboratory comparison
- drives standardisation
- facilitates production of guidelines
- promotes education

However participation DOES NOT guarantee the right patient result

Back to Top

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Digital Services Supporting Competency

Jon Sims
UK NEQAS Haematology

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What's in a name?

Digital services?

Definition:

Digital – in contrast to **Analogue**

1.1 Relating to, using, or storing data or information in the form of digital signals - *'digital TV', a 'digital recording'*

1.2 Involving or relating to the use of computer technology

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What's in a name?

Digital services?

Digital microscopy
Digital morphology

Digital pathology
Virtual pathology

Virtual EQA
Online EQA

Telepathology
Whole Slide Imaging (WSI)

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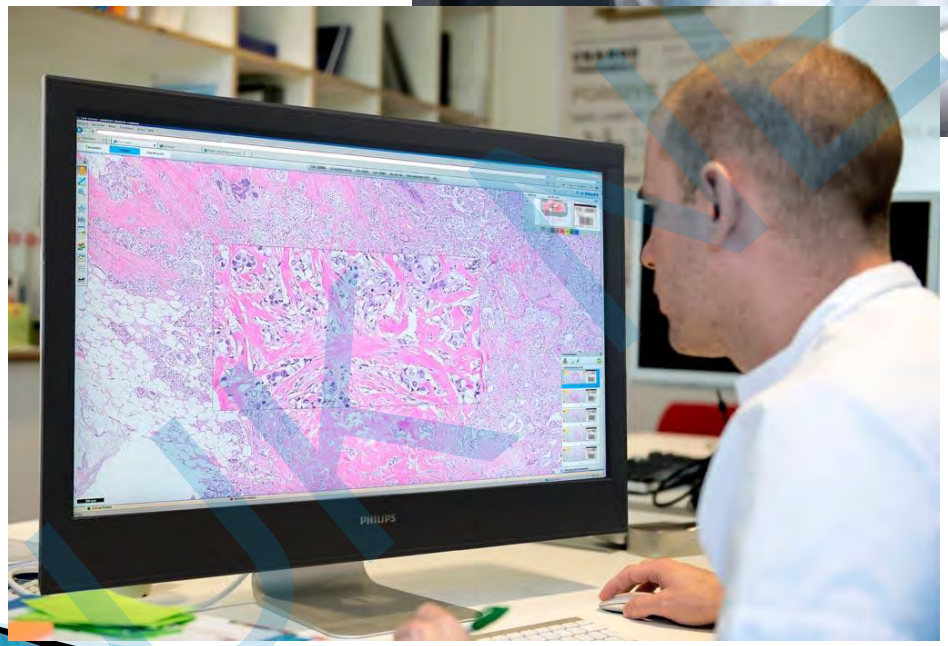

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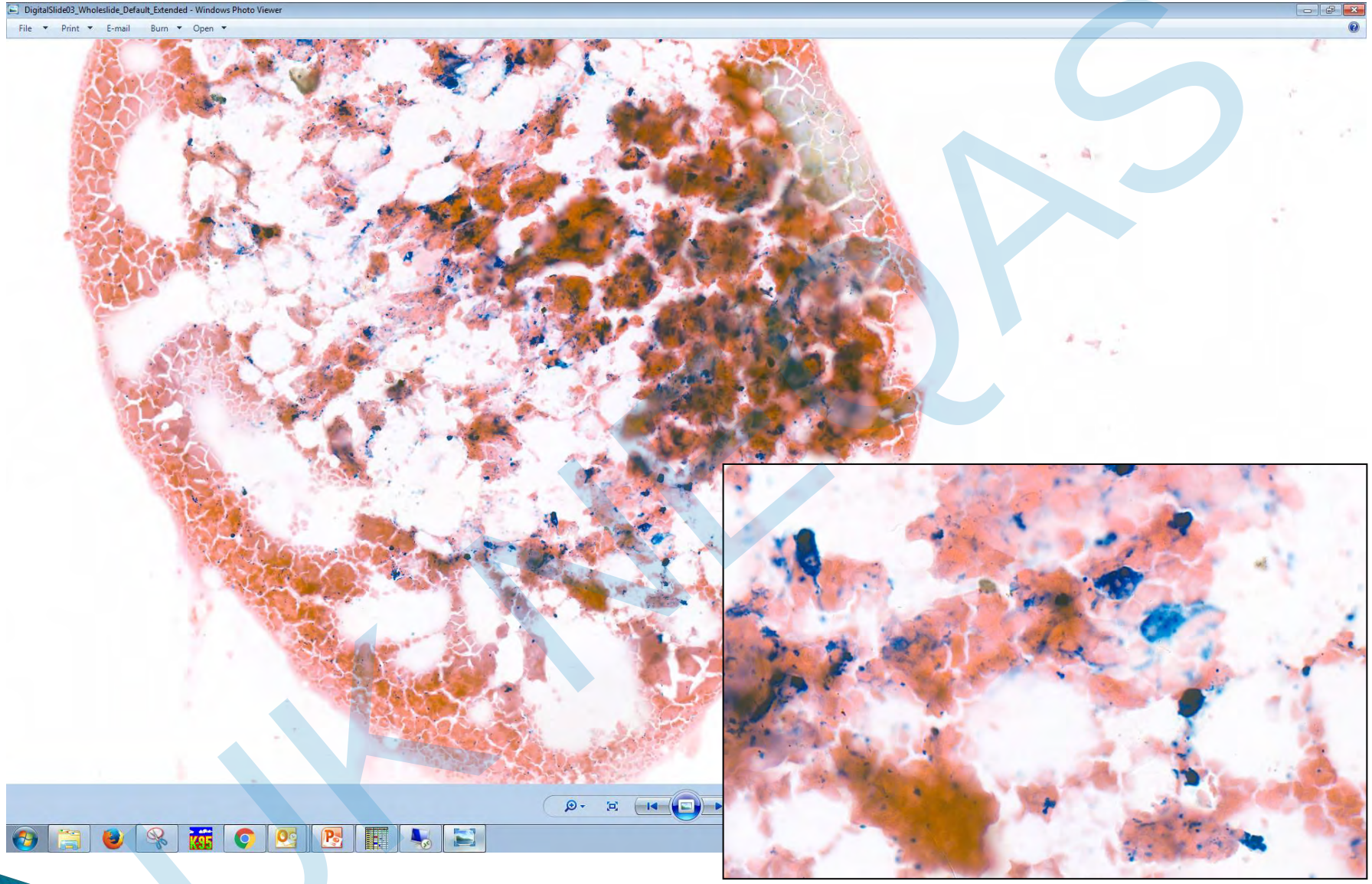
3DHISTECH Pannoramic DESK II Slide scanner - Sysmex



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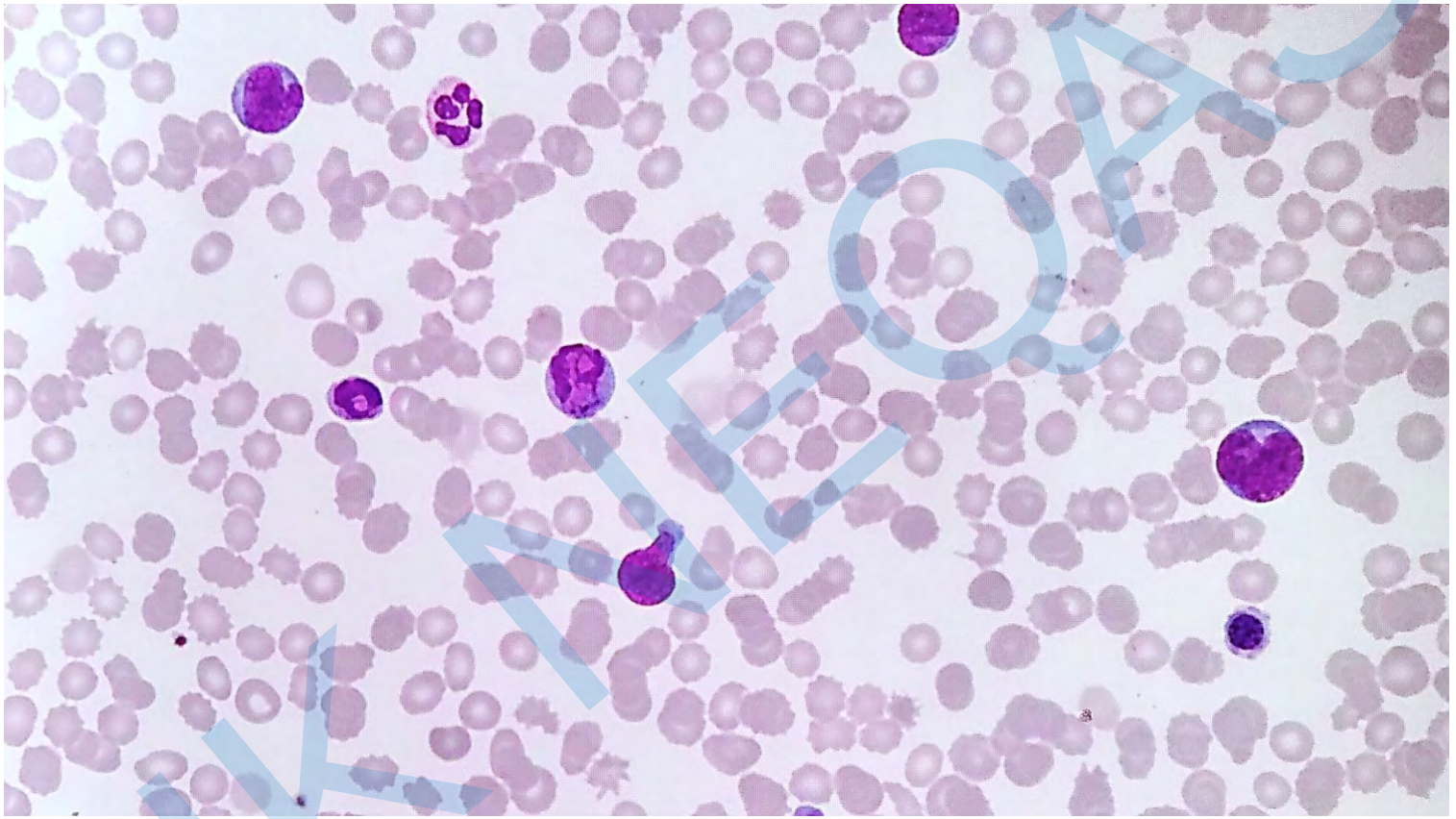

Digital services – the provision of systems employing the acquisition, management, sharing and interpretation of information - including images and data - in a digital environment

Digital services supporting competency

3.5 **competence**:
Demonstrated ability to apply knowledge and skills
ISO 15189:2012

Competency: is defined as the application of knowledge, skills and behaviours used in performing specific job tasks. Accurate laboratory test results depend on staff being competent in performing a range of procedures that occur throughout the entire examination process.
(Laboratory quality management system: Handbook – World Health Organization 2011)

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Digital services supporting competency

5.1.6 Competence assessment:
Following appropriate training, the laboratory shall assess the competence of each person to perform assigned managerial or technical tasks according to established criteria.
ISO 15189:2012

Competency assessment: is defined as any system for measuring and documenting personnel competency. The goal of competency assessment is to identify problems with employee performance and to correct these issues before they affect patient care.
(Laboratory quality management system: Handbook – World Health Organization 2011)

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Digital services supporting competency

UKAS & Competency Assessment :
"It is the laboratory's responsibility to define the criteria that it uses to determine the competence of its staff"

(Technical Bulletin – UKAS Position Paper: Assessment of a Medical Laboratory's approach to the assurance of clinical staff competence and use of EQA
28 November 2017)

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The role of UK NEQAS ?

UK National
External
Quality
Assessment
Service

No mention of Competency …..??

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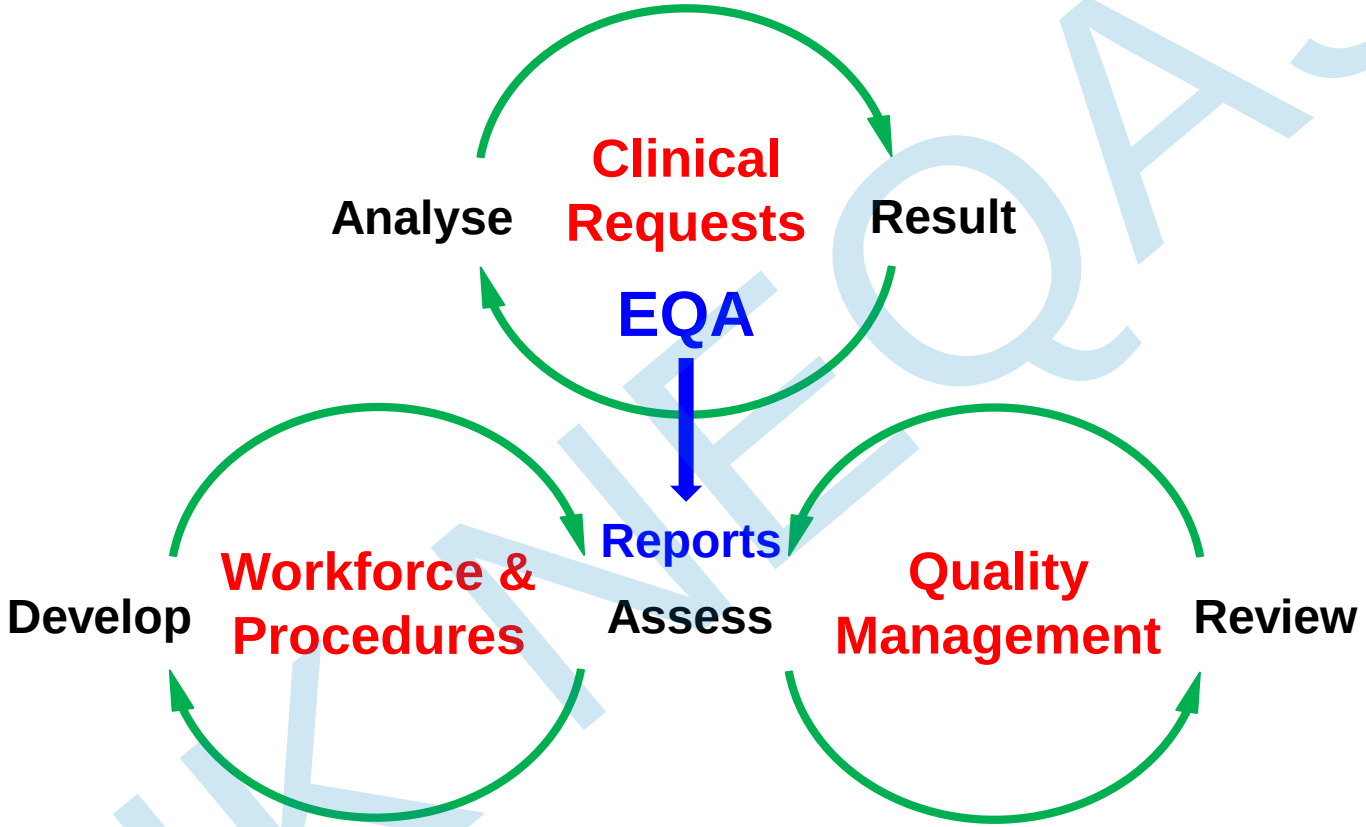
The role of UK NEQAS



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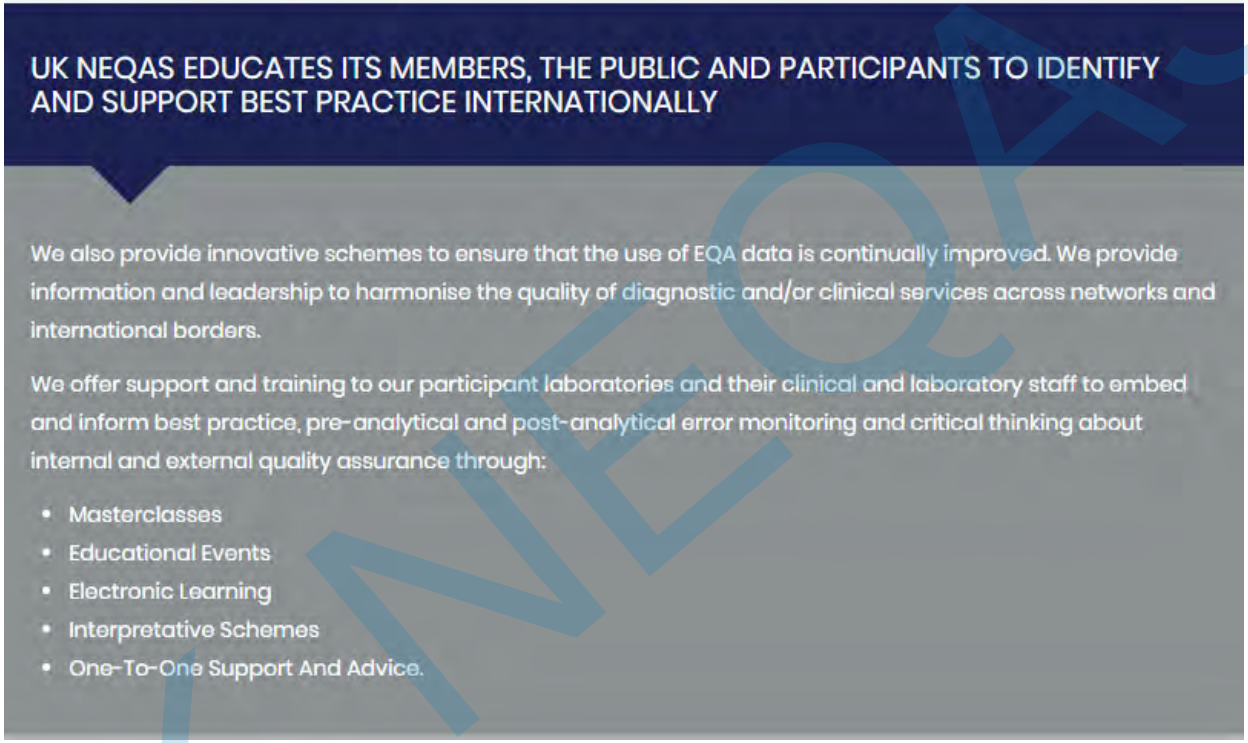
Digital services supporting competency



EQA is by its nature – a training and educational exercise….

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UK NEQAS

150+ schemes

operating from

20+ centres based in major hospitals, research institutions and universities throughout the UK.

Each scheme is supported by a panel of expert pathologists

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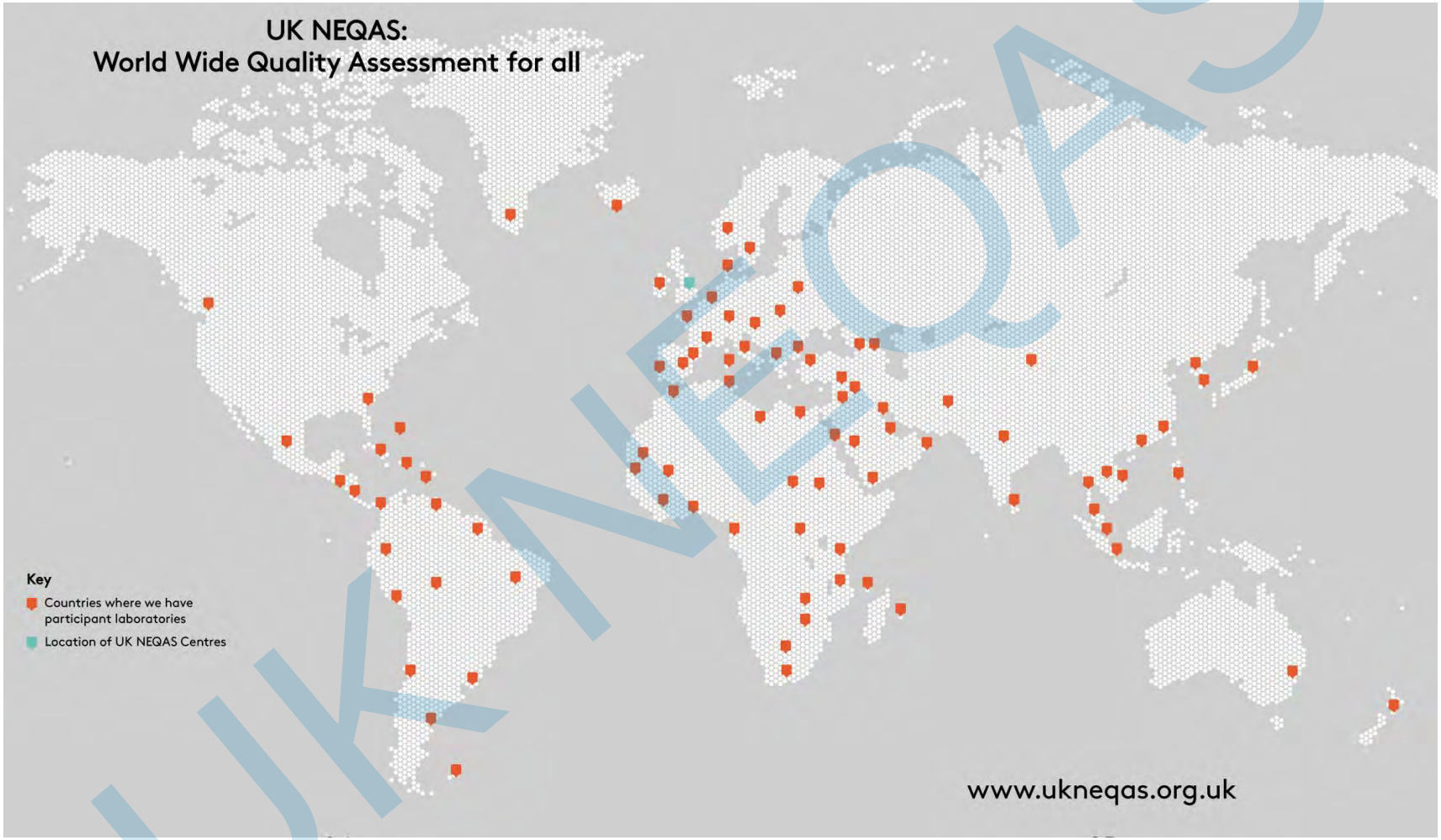
International participant base



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UK NEQAS Haematology – EQATE CPD online survey April 2019

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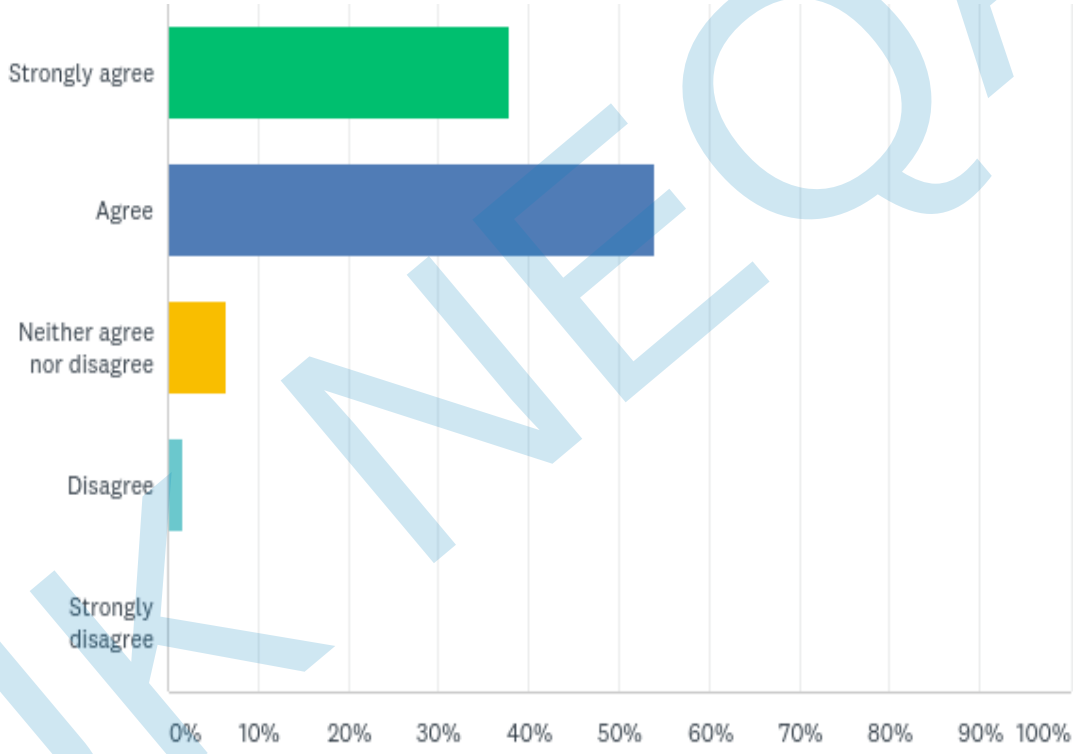
Q14: If a module for Interpretive Cases was included in the EQATE platform, which would cover general haematology and could be used for example for CPD or to inform competency, would you find this useful in your work?



314 Responses

UK NEQAS centres

Antibiotic Assay	Peptide Hormones	Leucocyte Immunophenotyping
Blood Coagulation	Genomics	Microbiology
Blood Transfusion Laboratory Practice	Haematology	Neuropathology
Breast Screening Pathology	Head & Neck Histopathology	Parasitology
Cardiac Markers	Histocompatability & Immunogenetics	Reproductive Science
Cellular Pathology Technique	Immunocytochemistry & In Situ Hybridisation	Trace Elements
Clinical Chemistry	Immunology, Immunocytochemistry & Allergy	Vitamin K

Digital services supporting competency

- Competency
  - BTLP TACT
  - Cellular Pathology Technique
  - Genomics GTACT
- CPD
- Educational material

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Blood Transfusion Laboratory Practice

TACT – Training and Competency Tool

- 5 years
- 132 laboratories
- 1746 registered users
- Random access cases
- Monitored by laboratory supervisors
- *Modules planned for TPs, Porters, MLAs and APs*

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Blood Transfusion Laboratory Practice

Virtual laboratory

UK NEQAS

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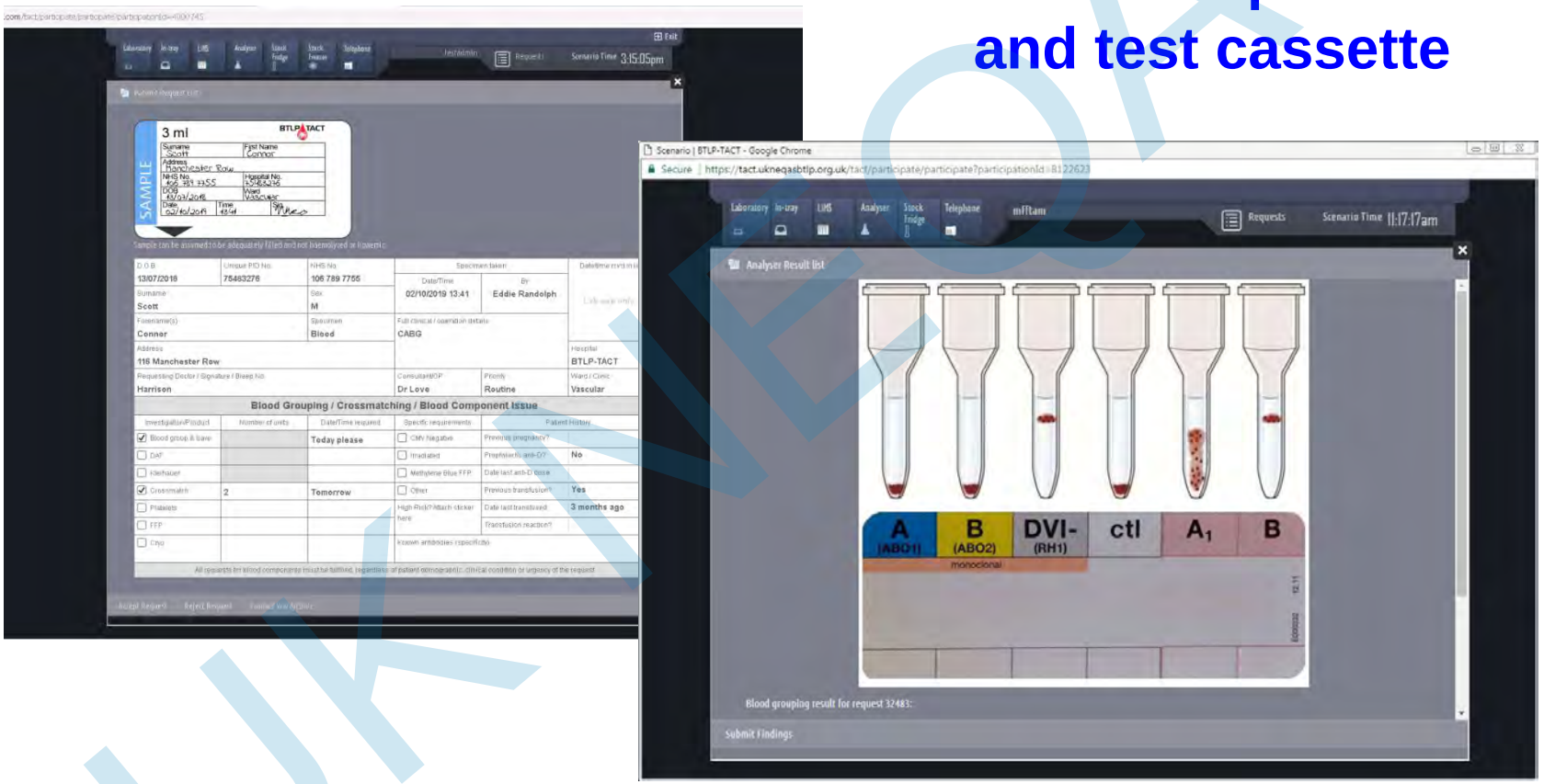
Blood Transfusion Laboratory Practice

Virtual request form and test cassette



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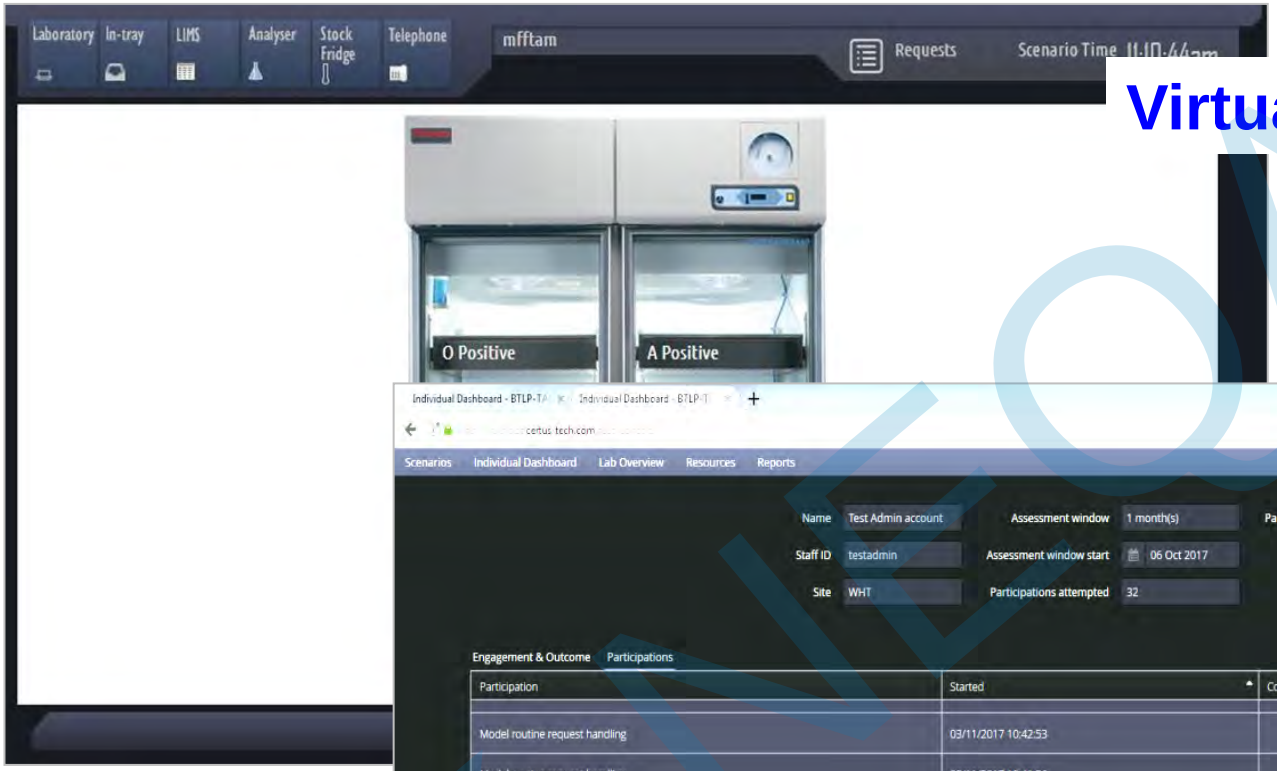
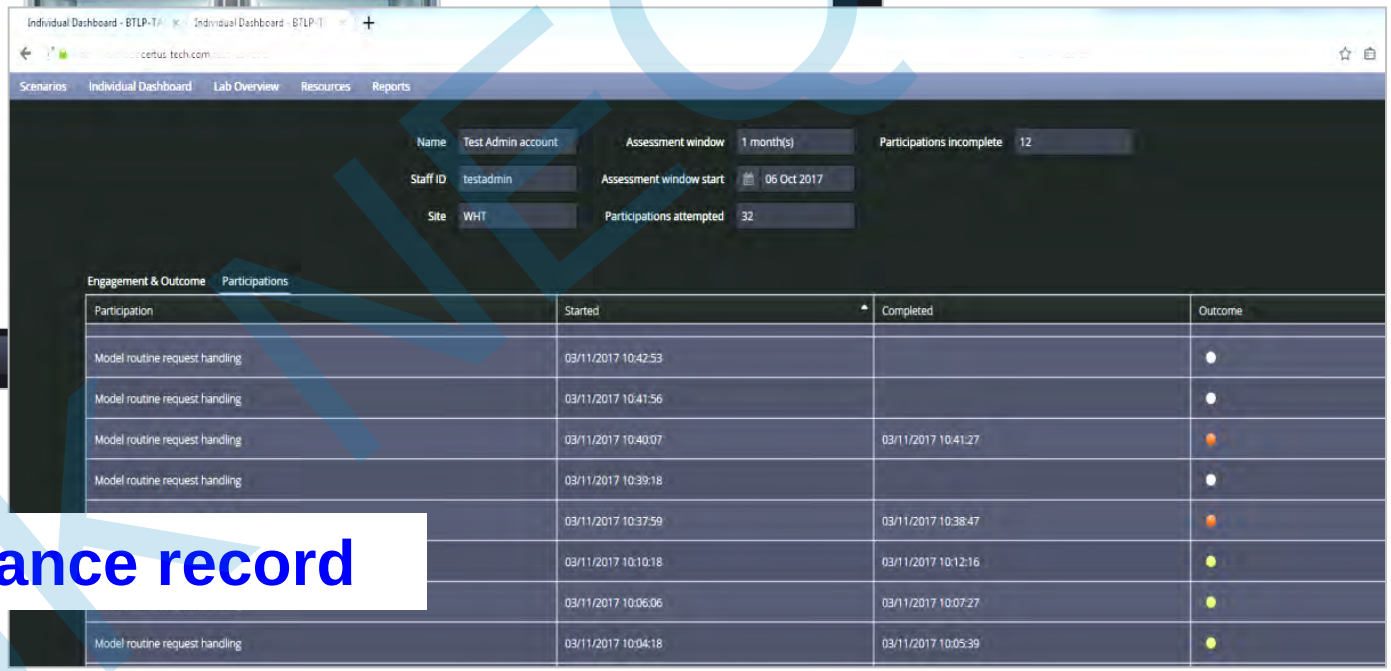
Blood Transfusion Laboratory Practice



Virtual blood bank



Performance record

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Genomics

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GTACT

GenQA GENOMICS QUALITY ASSESSMENT

Genomics Training, Assessment and Competence Tool

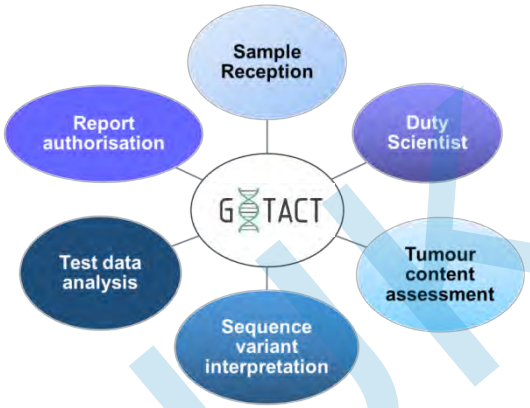
GenQA website access

Task scenarios randomly generated

Automated assessment

Complete at your own pace

Training/Performance review



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- Individuals can be users or line managers (or both)
- Line managers are able to manage user accounts

Continuously available modules

- Sample Reception
- Variant Analysis (SNV Classification)
- Report Authorisation
- Data Analysis (Sequencing) – limited

Fixed modules (available for a fixed time period)

- BRCA Variant Classification (2017, 2018)
- SNV Classification trial (2018)

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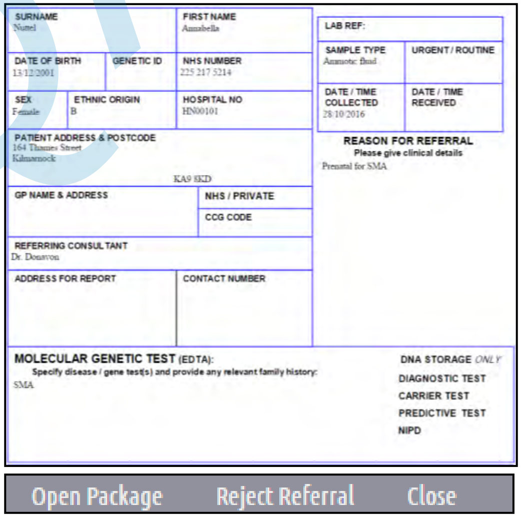
Sample Reception Module

The aim of this module is to assess an individual’s competency to determining whether a sample received in the laboratory is suitable for receipt and testing.

- Click on sample in-tray
- Number of samples will be displayed, each with a unique ID and patient’s name
- Select each sample and review the details on the referral card
- Decide whether to open the package or reject the sample (requires a reason).
- If package is opened then the sample is logged onto the LIMS system.
- Need to check the details on the sample and referral match
- Transcribe the referral information
- Repeated for each sample in the in-tray



SURNAME Nuttel
FIRST NAME Annabella
DATE OF BIRTH 13/12/2001
GENETIC ID
NHS NUMBER 225 217 5214
SEX Female
ETHNIC ORIGIN B
HOSPITAL NO HN00101
PATIENT ADDRESS & POSTCODE 164 Thames Street Kilmarnock KA9 8KD
GP NAME & ADDRESS
NHS / PRIVATE
CCG CODE
REFERRING CONSULTANT Dr. Donavon
ADDRESS FOR REPORT
CONTACT NUMBER
LAB REF:
SAMPLE TYPE Amniotic fluid
URGENT / ROUTINE
DATE / TIME COLLECTED 28/10/2016
DATE / TIME RECEIVED

REASON FOR REFERRAL
Please give clinical details
Prenatal for SMA

MOLECULAR GENETIC TEST (EDTA):
Specify disease / gene test(s) and provide any relevant family history:
SMA

DNA STORAGE *ONLY*
DIAGNOSTIC TEST
CARRIER TEST
PREDICTIVE TEST
NIPD

SAMPLE
3 ml
Surname Brogel
First Name Derrick
Address
NHS No. 154 059 4645
Hospital No.
DOB 13/12/2001
Ward
Date 01/11/2016
Time 02:53
Sig.

Report Authorisation Module

The aim of this module is to assess an individual's competency to determine whether a laboratory report is suitable for authorisation.

Two scenarios are currently available for Report Authorisation:

- **Breast and Ovarian Cancer (BRCA)**
- **Fragile X Syndrome.**

Up to five reports will be selected for each scenario.

- Select either FraX or BRCA module
- Presented with up to 5 patients awaiting report authorisation
- View the patient report
- Check all the details and determine whether the report can be authorised
- Either authorise a report or reject the report (providing reason)
- Complete all patients

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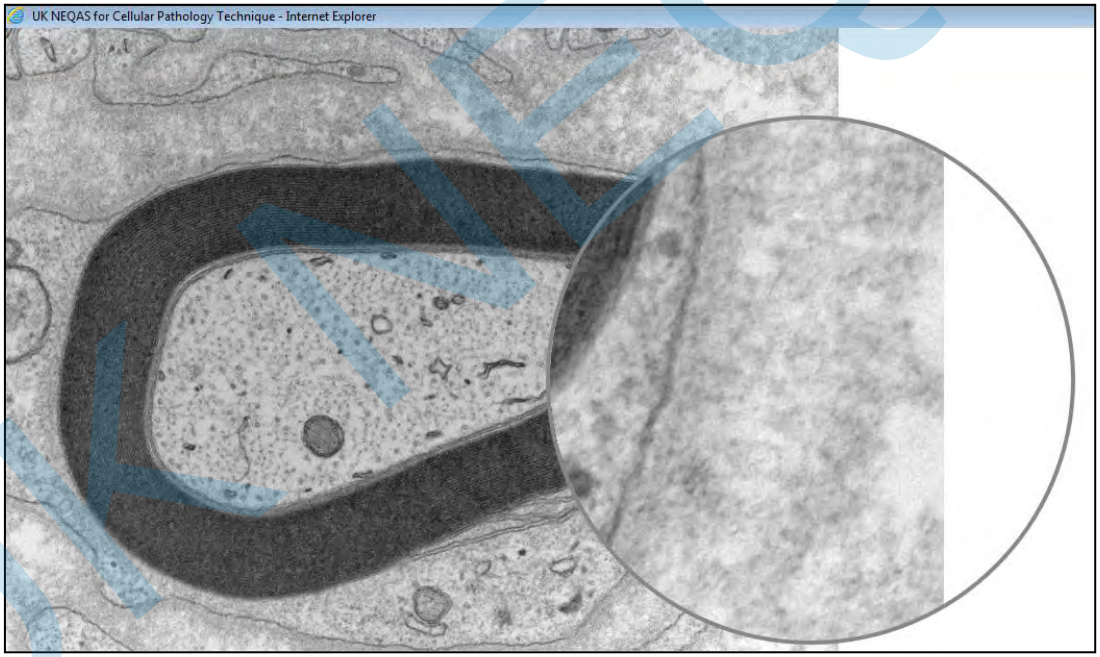
Cellular Pathology Technique

Current Provision

- **Transmission electron microscopy (TEM)** scheme allows participants to submit digital images on line. These can then be viewed for assessment using software which mimics viewing a slide down a microscope.



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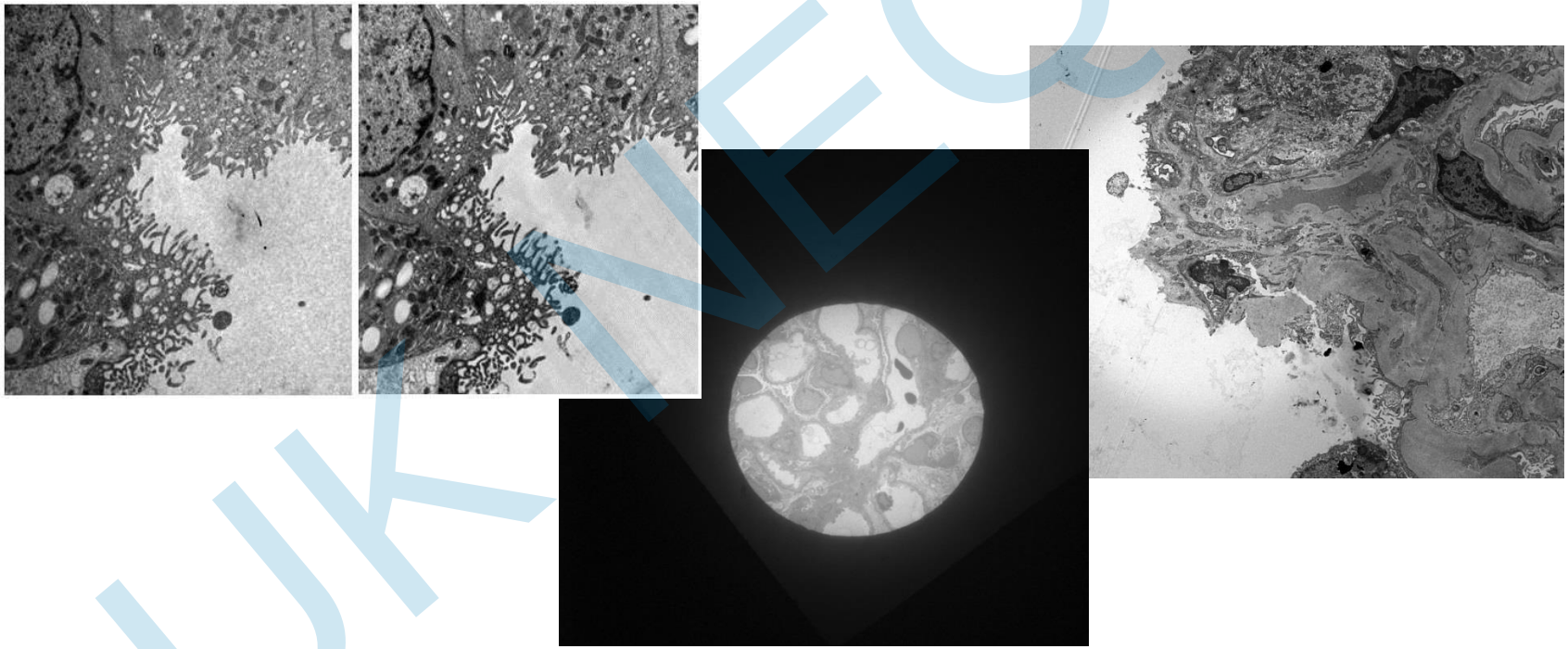
Cellular Pathology Technique

Current Provision

- **Transmission electron microscopy (TEM)** also includes a knowledge and competency exercise using digital images



Digital services supporting competency

- Competency programs
- CPD programs
  - Genomics Tissue-I
  - Genomics Clinical Genetics EQA
  - Haematology EQATE
  - Leucocyte Immunophenotyping
- Educational material

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Genomics

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Histopathology assessment - Educational EQA

Molecular testing of solid tumour requires accurate selection of tumour regions for macrodissection to ensure:

- **sample quality**
- **sufficiency of tumour DNA and**
- **precision of the test result.**

The annotation of tumour and estimation of neoplastic nuclei can be highly variable and standardisation is necessary to promote high-quality molecular pathology testing.

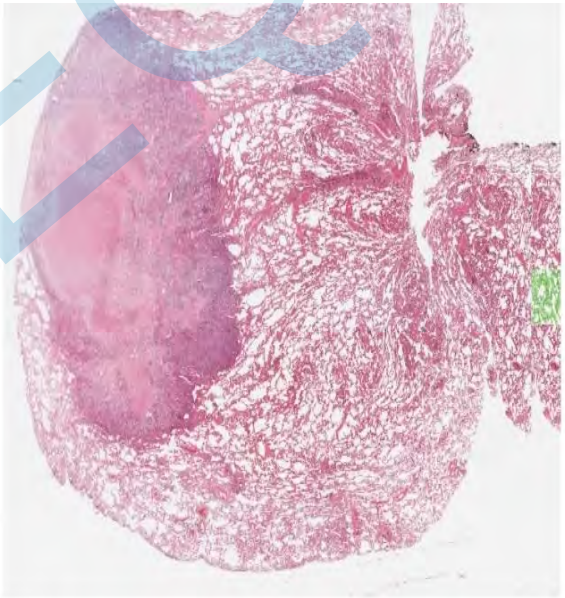
A range of tissue types are included: **breast, colorectal/gastrointestinal tract, central nervous system, gynaecological tract, lung, melanoma** and **urology.**

Regions of tumour for macrodissection for molecular testing, are outlined by the participants using the online module. Estimation of the cellularity and percentage of neoplastic nuclei across the slide and within the annotated region are requested.

Lung cancer – EQA case

CASE HISTORY

This patient presented with a nodule in her right lower lobe of lung and subsequently had a wedge resection of the right lower lobe which was diagnosed as adenocarcinoma. There are now signs on her CT of further disease in the left lobe and the original resection specimen has been submitted for molecular studies.



Participants are asked to estimate the % of tumour nuclei and the cellularity content across the whole slide:

Tissue-I

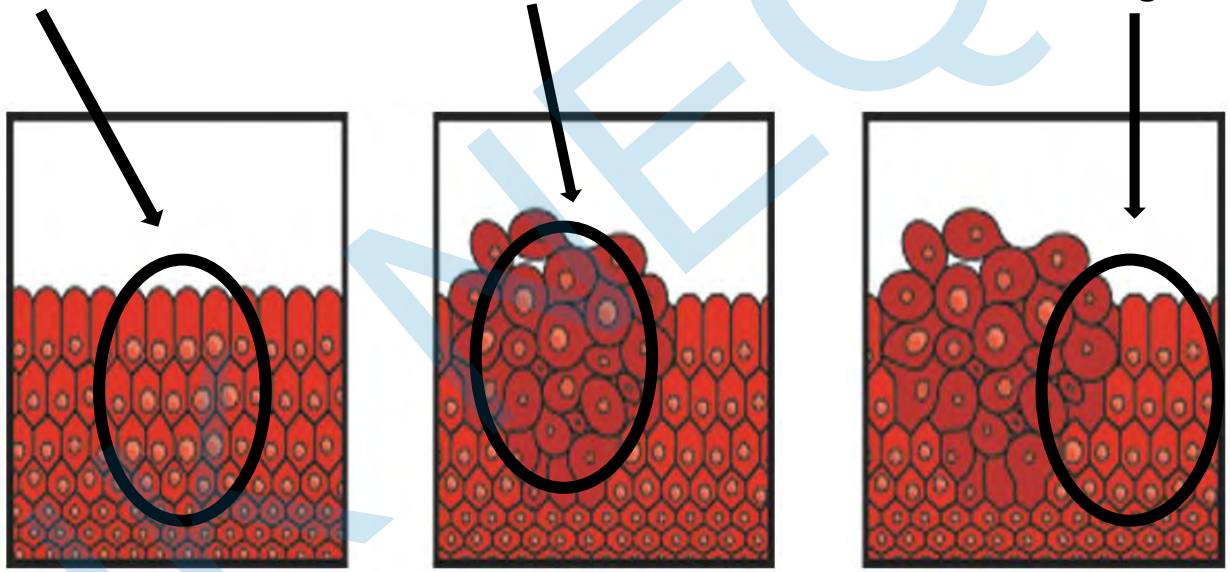
GenQA GENOMICS QUALITY ASSESSMENT

Tumour selection

100% normal tissue
= no tumour result

~ 99% tumour
= good sequencing of the tumour

90% normal and 10% tumour
= difficult to detect low level tumour sequences against normal background



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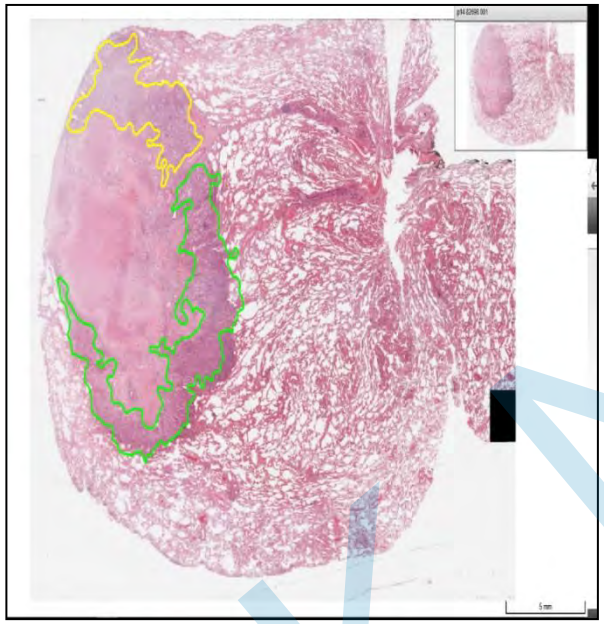
Tissue-I

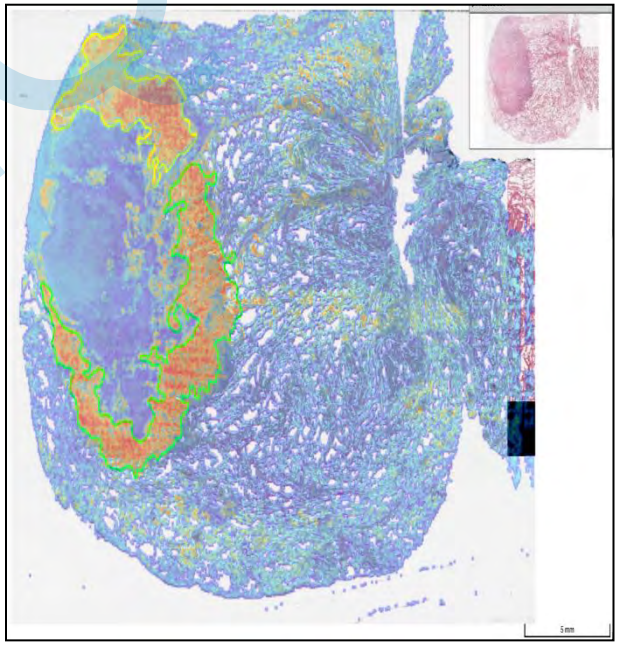
GenQA GENOMICS QUALITY ASSESSMENT

Regions for Macro Dissection Boundary



Lung cancer – EQA case

TissueMark - automated identification of tumour tissue



Tumour % Nuclei across whole sample – 11%

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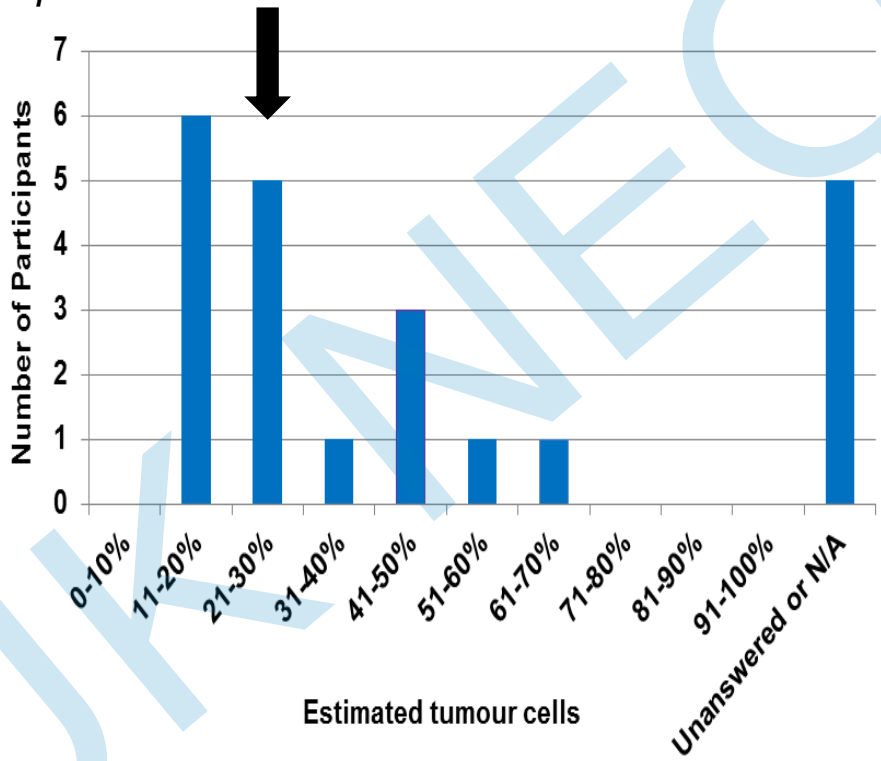
International Quality Expertise

Summary of tumour nuclei estimations across the whole slide

Lung cancer – EQA case

'Expert' and TissueMark value



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Genomics

GenQA GENOMICS QUALITY ASSESSMENT

Clinical Genetics Educational EQA - CEQAS

Clinical information provided sequentially to represent real patient case scenarios:

- Referral letter from general practitioner/clinician
- Images of patients, family history, test results, and clinical information given sequentially with questions online
- Submit answers to questions at each stage online
- Submit answers to stage 1 before can see stage 2 clinical details
- Can review previous stage but not change submission
- Feedback of assessors on expected vs submitted answers
- Recommendations within the individual centre report and summary EQA report

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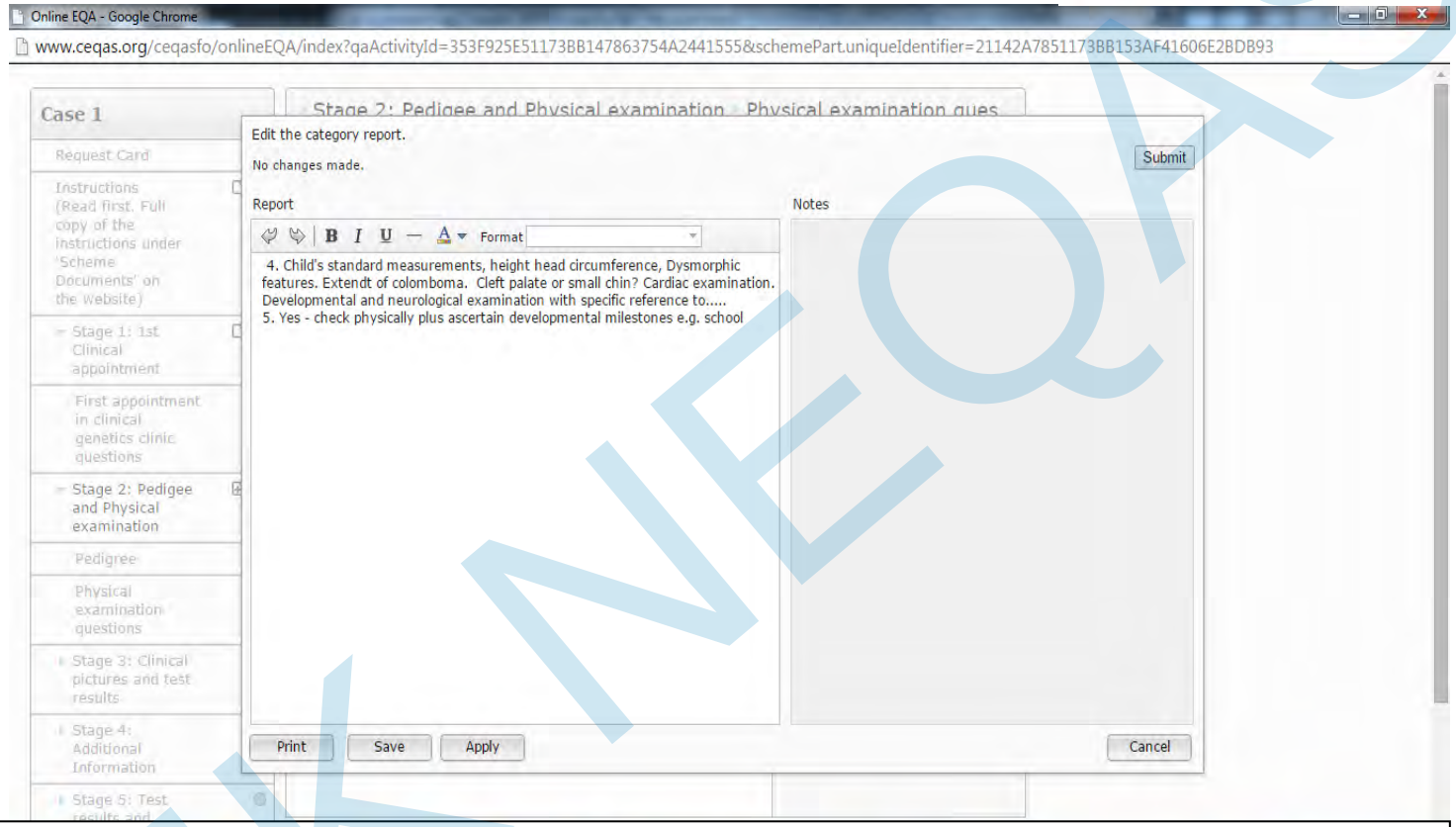
Genomics



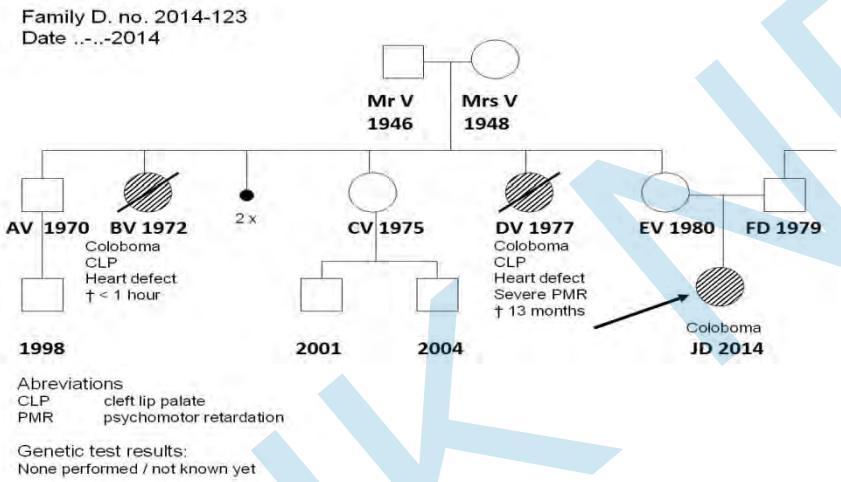
Sequential submission and access:

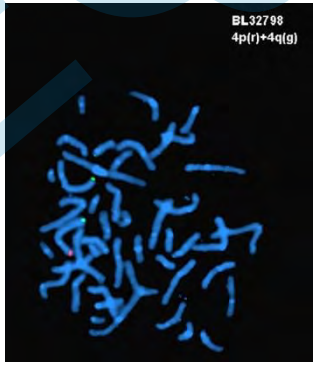
Submit answer to stage 1 before the clinical details in stage 2 can be viewed

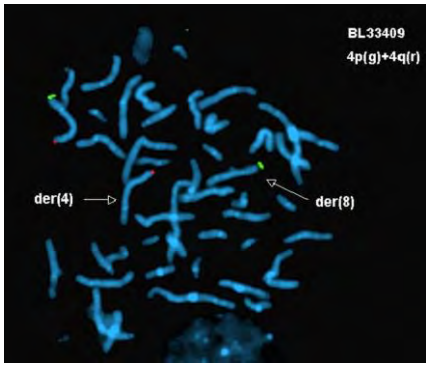
Genomics

GenQA GENOMICS QUALITY ASSESSMENT

Stage 1: Clinical appointment.
Stage 2: Pedigree and physical examination
Stage 3- 4: Clinical pictures and test results
Stage 5: Test results and genetic counselling
Stage 6: Recurrence risk and patient report







FISH test results

Array result: arr 4p16.3p16.1(69,511-10,044,976)x1,8p23.3p23.1(172,852-6,930,975)x3 hg19

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GenQA GENOMICS QUALITY ASSESSMENT

EQA case scenarios 2014 - 2017

Monogenic
Cystic Fibrosis
Deafness (GJB2)
MUYTH
Polycystic kidney

Oncogenetic
Lynch syndrome
FH of breast cancer (not Lynch)
NF1
von Hippel-Lindau syndrome

Dysmorphology
Wolf-Hirschhorn syndrome
Fragile X
CHARGE syndrome
Turner syndrome

Cardiovascular
Marfan syndrome
DMD patient/heart disorder
Congenital cardiomyopathy
TSC2/PKD1 contiguous gene synd.

All case scenarios based on a real patient referral

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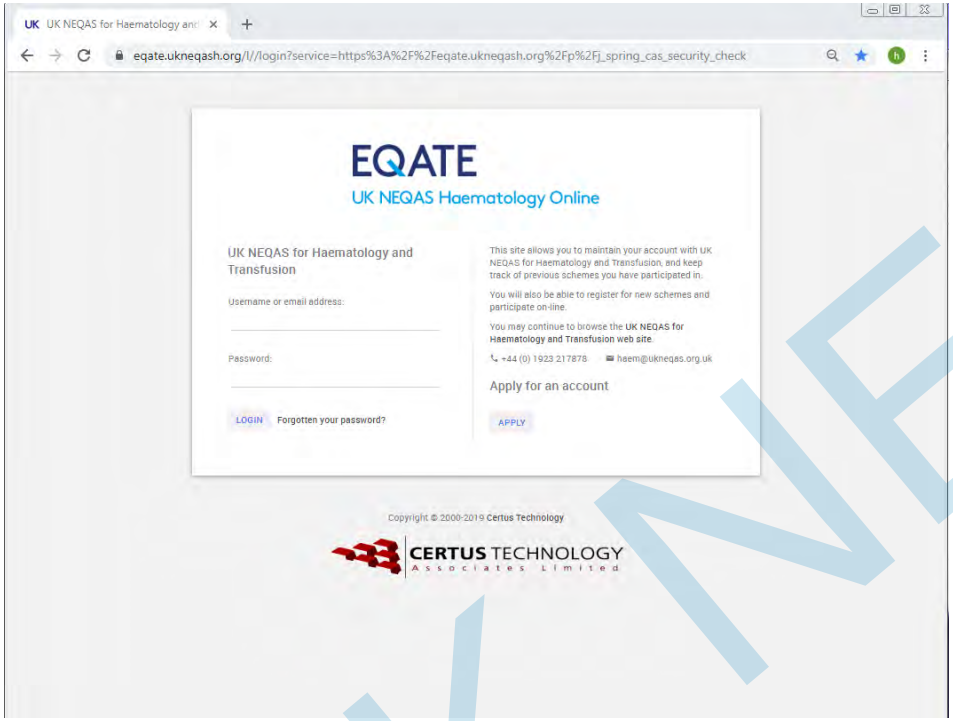
Haematology

UK NEQAS
International Quality Expertise

EQATE

EQA, Training and Education

UK NEQAS Haematology Online



Digital Morphology
Launched in 2008 - 55 cases

Re-launched in 2018
First case December 2018
6 cases completed to date

- > 3200 users
- 292 laboratories
- 16 countries

https://eqate.ukneqash.org

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International Quality Expertise

Haematology

DM 2019-20 1904DM

16/07/2019 00:00
11/08/2019 23:59

Case is open

1904DM

QUESTIONNAIRE

Outline Description

A 65-year old man feeling unwell, presents to the emergency department. Haemoglobin and platelets are normal, but white cell count is raised. For help with the case we have prepared some additional pages in the morphology section see Click to try our web pages - Follow the link as appropriate

User Observations

Erythrocytes

Leucocytes

Platelets

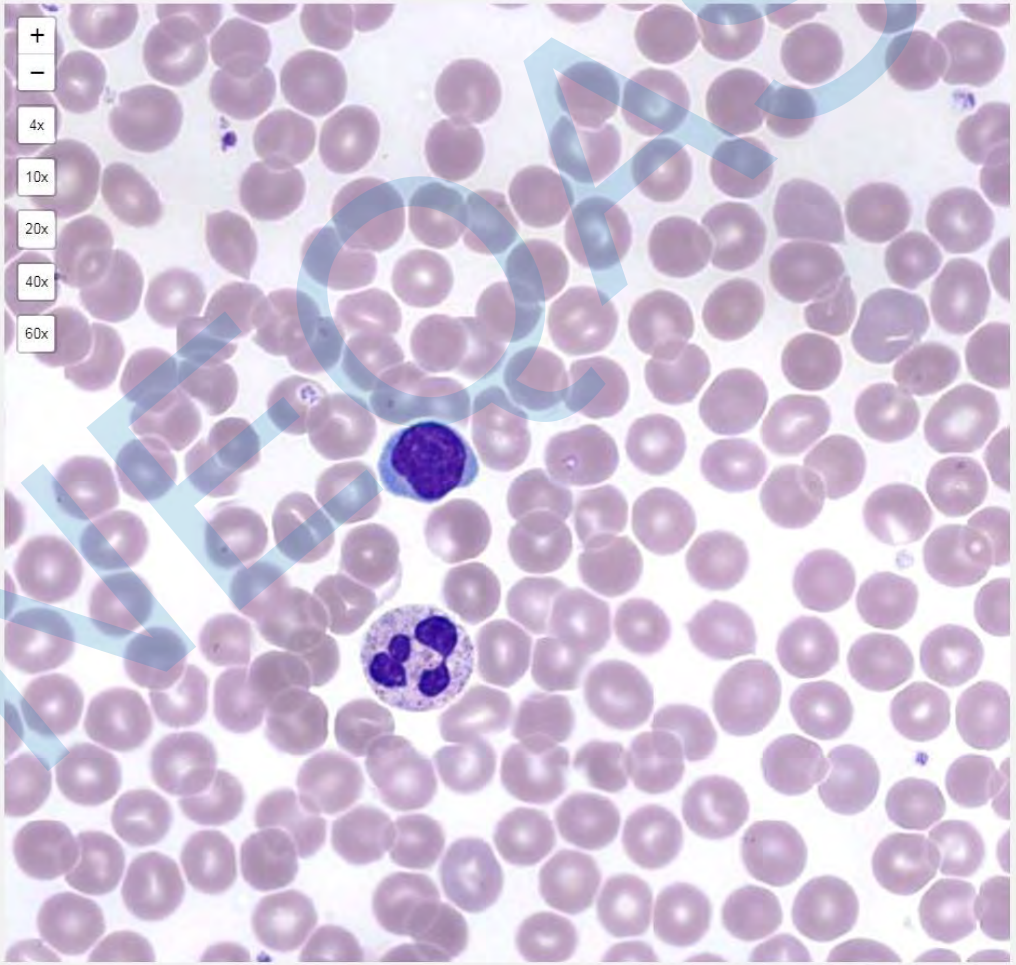
Various

Observations in order of priority:

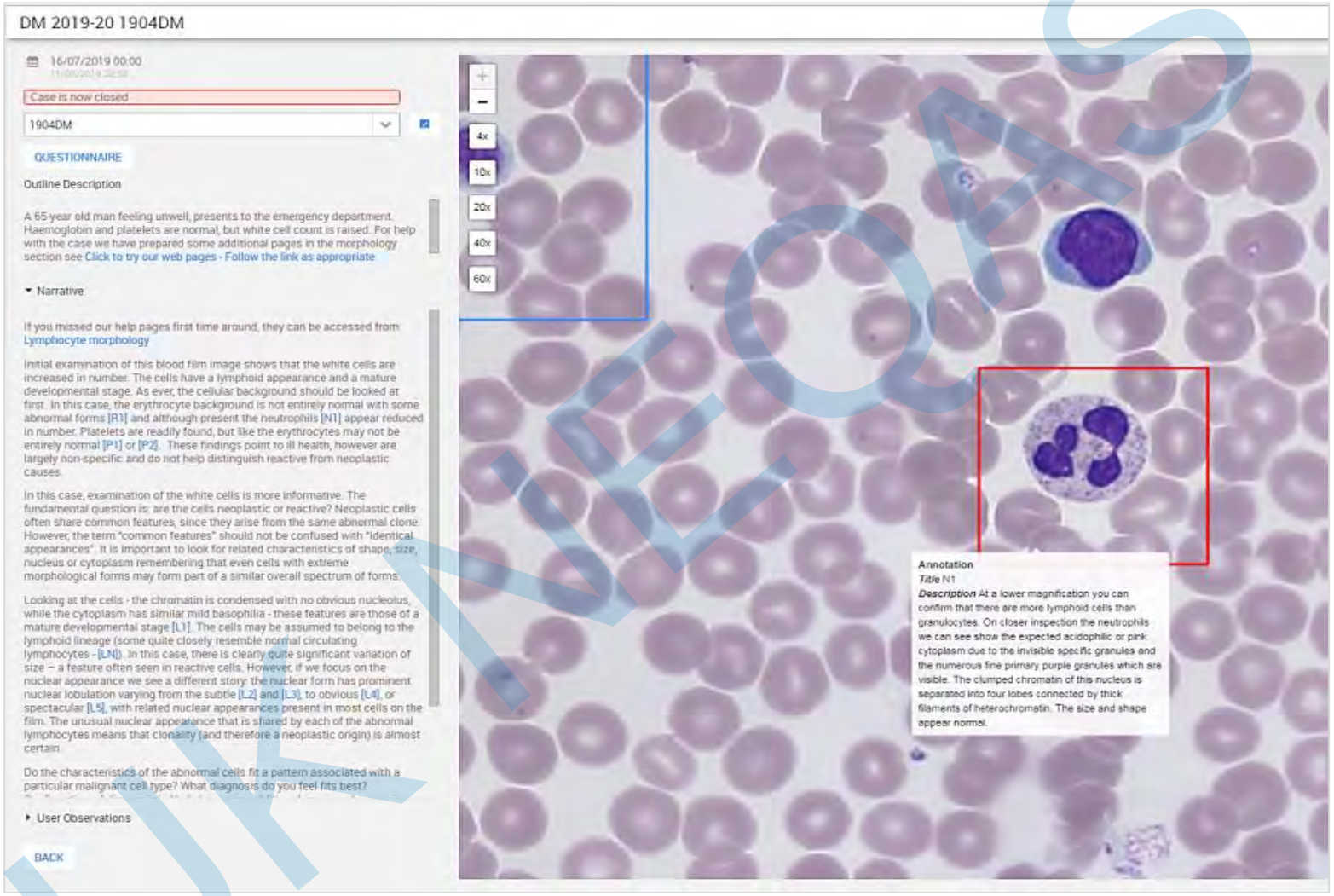
Apoptotic cells

Thrombocytosis

SUBMIT BACK



Haematology



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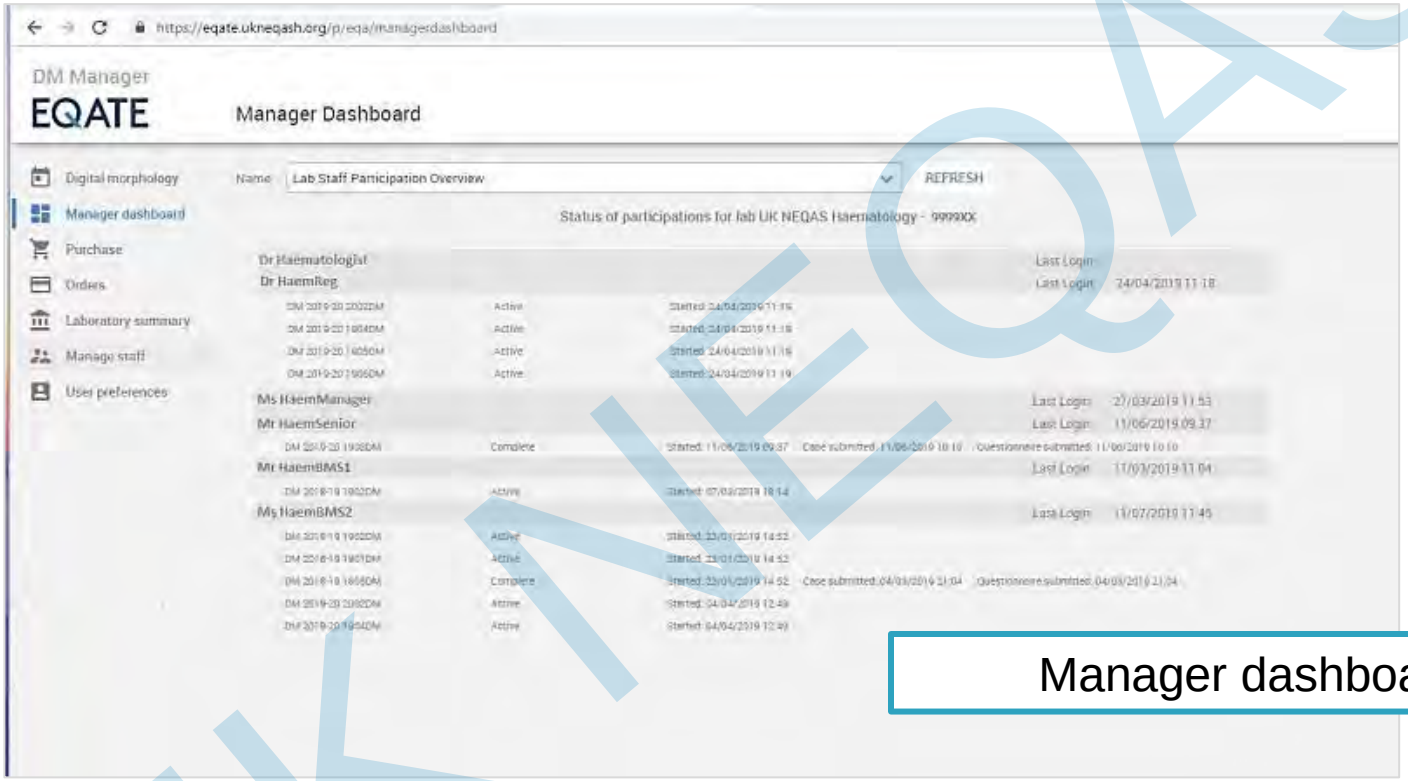
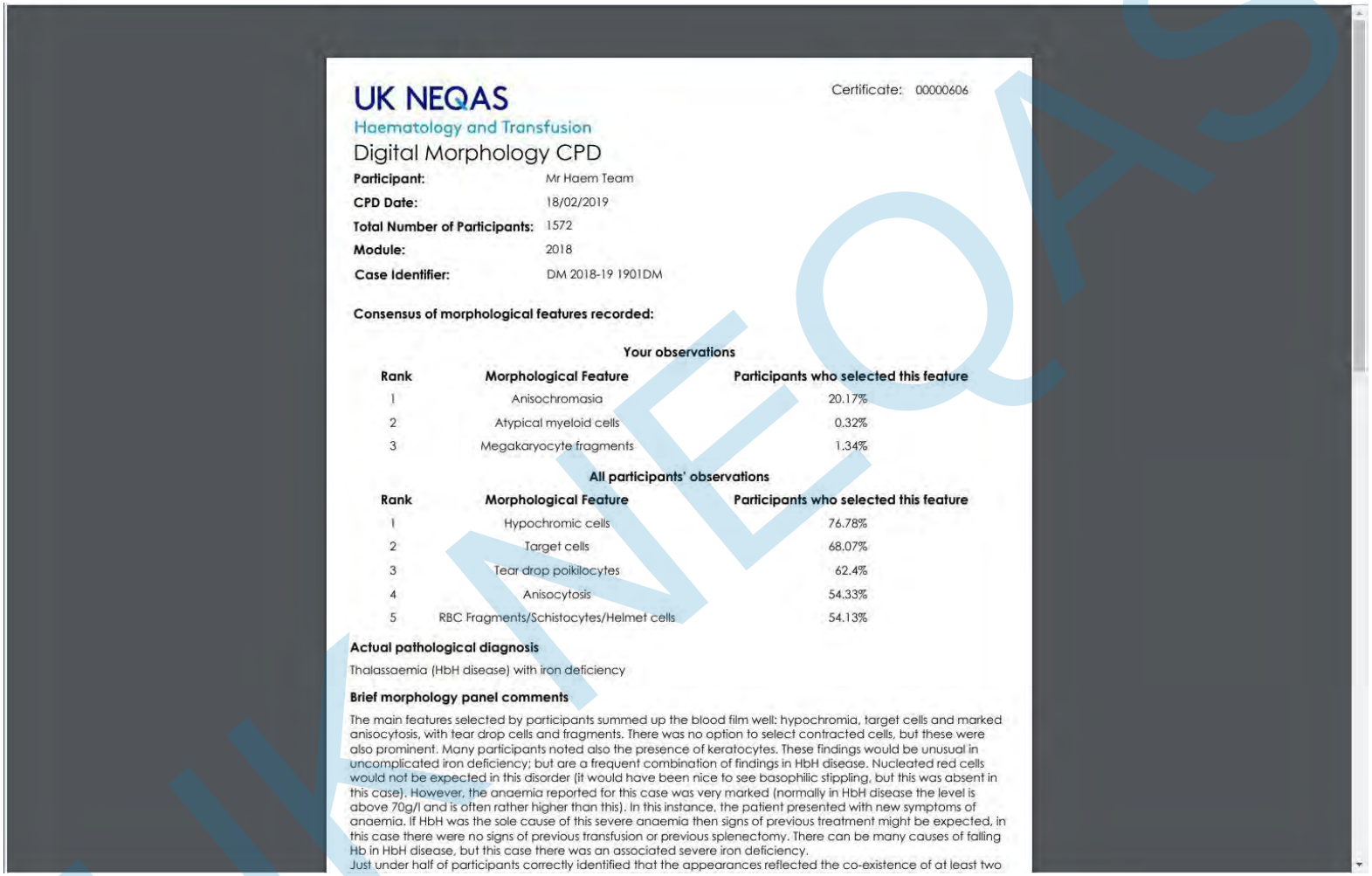
Haematology



Manager dashboard

Haematology



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Haematology and Transfusion

Digital Morphology CPD

Certificate: 00000606

Participant: Mr Haem Team

CPD Date: 18/02/2019

Total Number of Participants: 1572

Module: 2018

Case Identifier: DM 2018-19 1901DM

Consensus of morphological features recorded:

Your observations

Rank	Morphological Feature	Participants who selected this feature
1	Anisochromasia	20.17%
2	Atypical myeloid cells	0.32%
3	Megakaryocyte fragments	1.34%

All participants' observations

Rank	Morphological Feature	Participants who selected this feature
1	Hypochromic cells	76.78%
2	Target cells	68.07%
3	Tear drop poikilocytes	62.4%
4	Anisocytosis	54.33%
5	RBC Fragments/Schistocytes/Helmet cells	54.13%

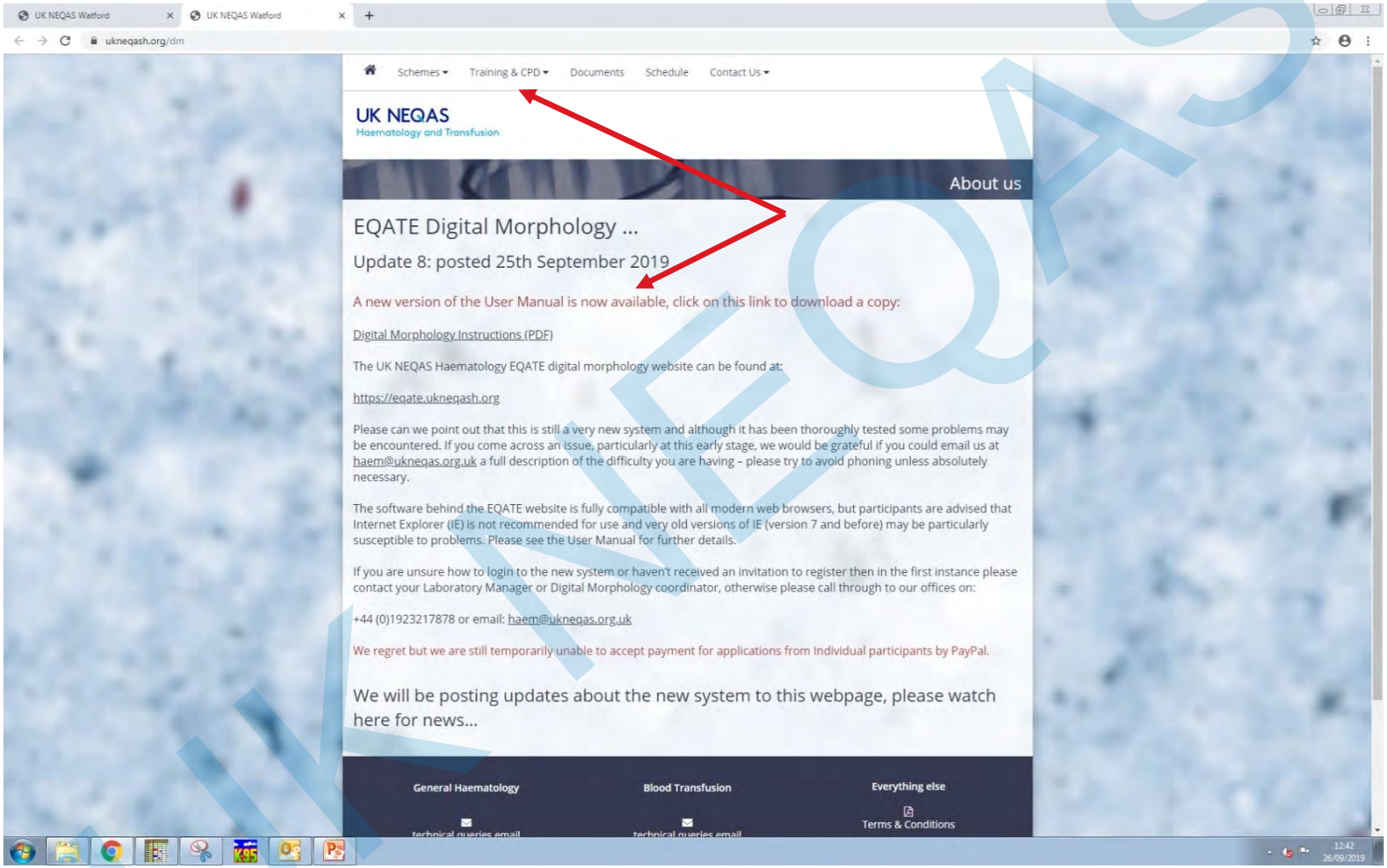
Actual pathological diagnosis

Thalassaemia (HbH disease) with iron deficiency

Brief morphology panel comments

The main features selected by participants summed up the blood film well: hypochromia, target cells and marked anisocytosis, with tear drop cells and fragments. There was no option to select contracted cells, but these were also prominent. Many participants noted also the presence of keratocytes. These findings would be unusual in uncomplicated iron deficiency; but are a frequent combination of findings in HbH disease. Nucleated red cells would not be expected in this disorder (it would have been nice to see basophilic stippling, but this was absent in this case). However, the anaemia reported for this case was very marked (normally in HbH disease the level is above 70g/l and is often rather higher than this). In this instance, the patient presented with new symptoms of anaemia. If HbH was the sole cause of this severe anaemia then signs of previous treatment might be expected, in this case there were no signs of previous transfusion or previous splenectomy. There can be many causes of falling Hb in HbH disease, but this case there was an associated severe iron deficiency.
Just under half of participants correctly identified that the appearances reflected the co-existence of at least two

Haematology



UK NEQAS

International Quality Expertise

Leucocyte Immunophenotyping

Leukaemia Diagnostic Interpretation

- Totally web-based and examines a wide variety of cases

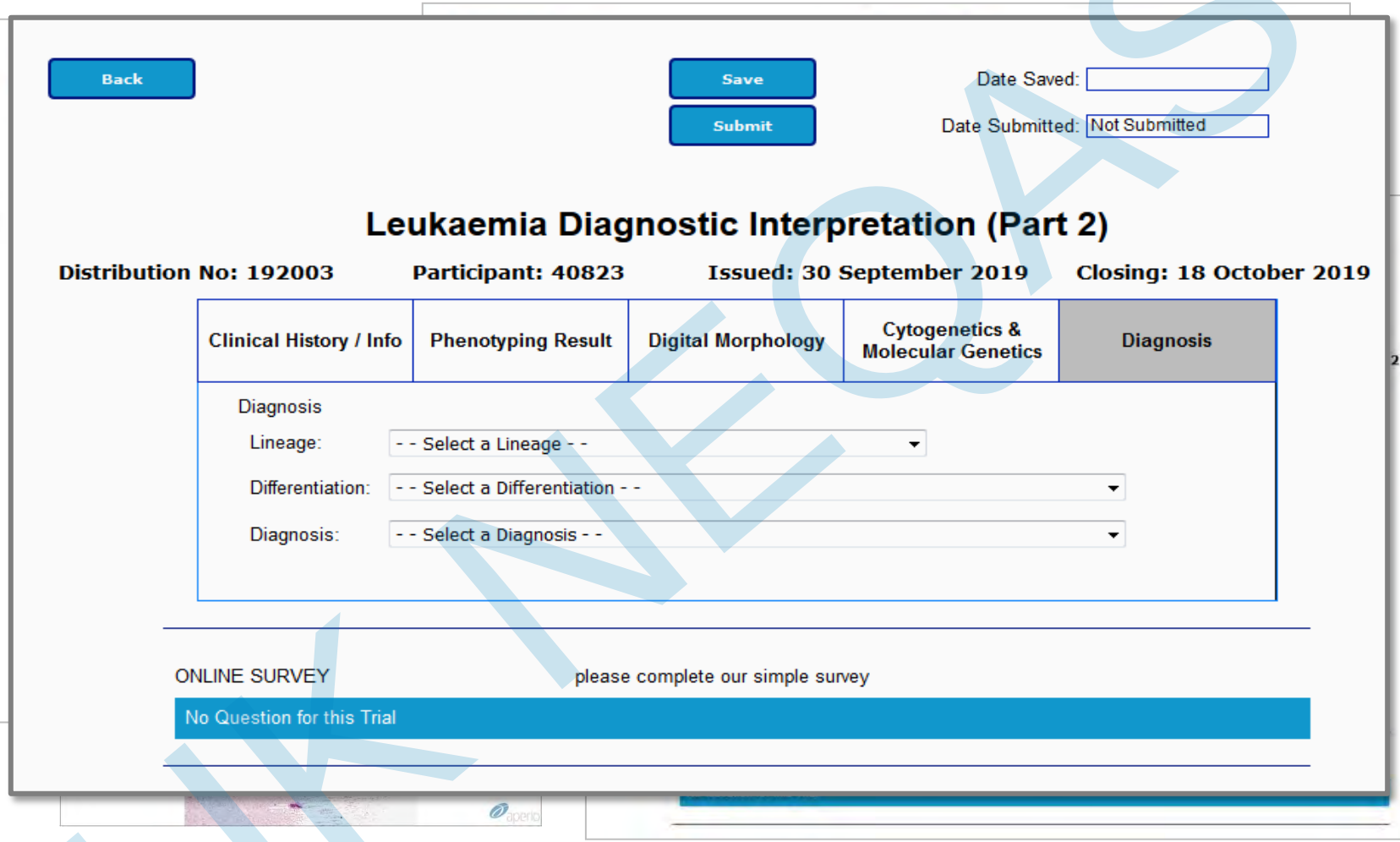
Each trial consists of:

- Consensus phenotype
- Detailed case history
- Digital blood/marrow smears for morphological analysis
- Cytogenetics and Molecular Genetics data

Participants are expected to use the information to arrive at a diagnosis.

The final report is designed to be educational and is for individual scientists or medical staff for the purposes of CPD

Leucocyte Immunophenotyping



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International Quality Expertise

Immunology, Immunochemistry & Allergy (IIA)

iEQA - Interpretative External Quality Assessment

- Multi-disciplinary, self-directed, reflective learning resource, focused on QA, current lab practice and clinical cases
- Web-based, login anywhere, anytime
- Aimed at all staff grades
- Cases always open (>1 attempt per case)
- CPD opportunity (certificate awarded if spend ≥10 minutes and case completed)
- Lab manager functionality

UK NEQAS
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Immunology, Immunochemistry & Allergy (IIA)

Cases available:

Case Category	Number of Cases
Allergy	29
Autoimmunity & Rheumatology	49
Clinical	161
Haematinics	1
Immunochemistry	40
Immunodeficiency	12
Laboratory	159
Quality Assurance/Quality Control	154
Tumour Markers & Oncology	13
IGRA	114

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Immunology, Immunochemistry & Allergy (IIA)

All cases start with either request card or email:

iEQA Interpretative External Quality Assessment

Case 197: Wrong pattern, does it matter?

Actions: Seek Further Information | Request Card | RCA/Report | Finish and send report

Diagnostic Tests: Biochemistry | Cytopathology | Genetics | Haematology | Histopathology | Immunology | Microbiology | Nuclear Medicine | Radiology | Virology

Request Card

Send

To... sally.albright@nhs.net

Cc...

Subject FW: MedQ results- Urgent

Dear Sally,

Please could you look at the results for the patient below.

Results have come to the MED Q. I seem to remember seeing something similar on a recent EQA return.

IMMUNOLOGY — Oldhouses Hospital, Middlesfield

SURNAME Smith	FORENAME Paul	HOSPITAL NUMBER AB1234	AGE (YEARS) 58	SEX Male
PATIENT ADDRESS 123 Cherry Tree Avenue, Middlesfield		SURGERY ADDRESS Main Street Surgery, Middlesfield		
CONSULTANT or GP Dr. Woodward		HOSPITAL/WARD/OPD		
INVESTIGATIONS REQUIRED: FBC, CRP, ESR, ANCA		CLINICAL DETAILS: ?Vasculitis		
SPECIMEN TYPE Serum	DATE 28/11/18	TIME 09:30	REQUESTED BY	
LABORATORY NUMBER				

Kind regards,

Harry Burns

Clinical Scientist

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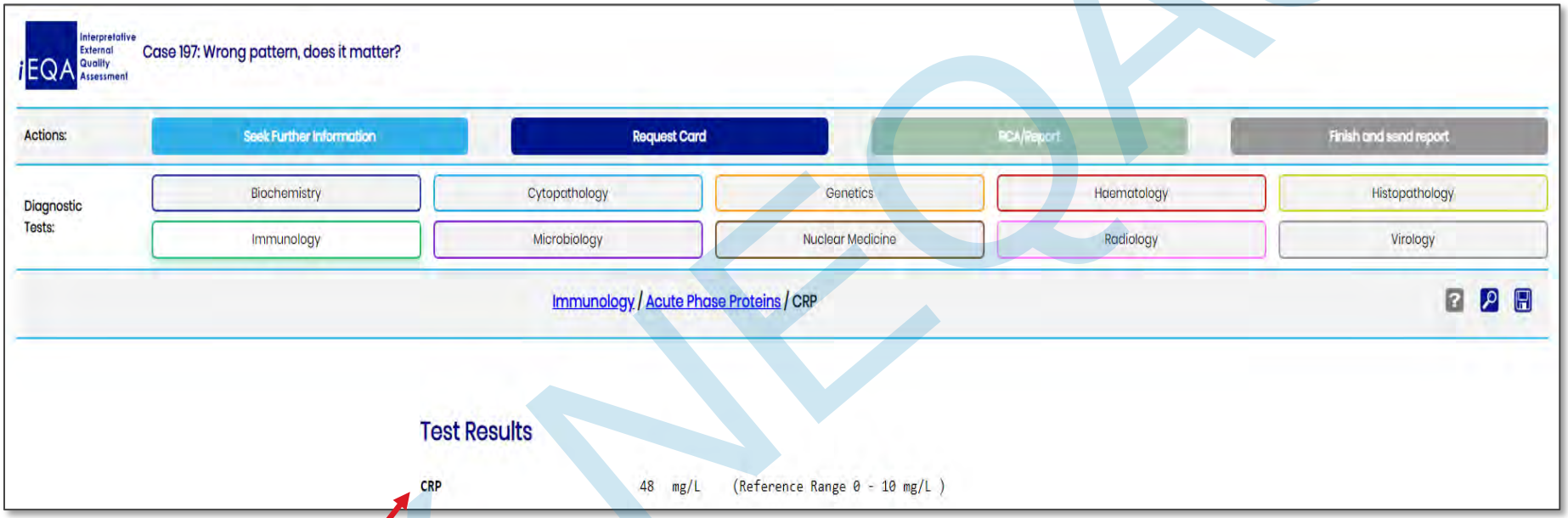
Immunology, Immunochemistry & Allergy (IIA)

Cases also contain data:



Immunology, Immunochemistry & Allergy (IIA)

And images:

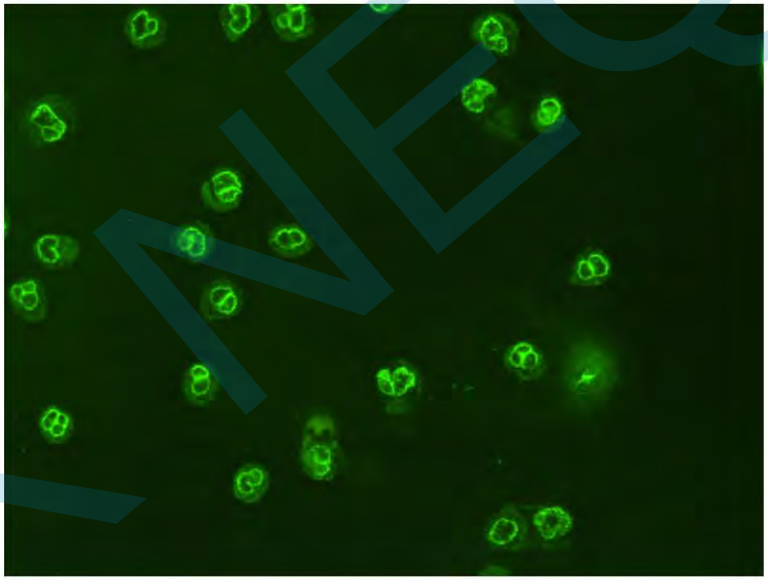
iEQA Interpretative External Quality Assessment

Case 197: Wrong pattern, does it matter?

Actions: Seek Further Information | Request Card | RCA/Report | Finish and send report

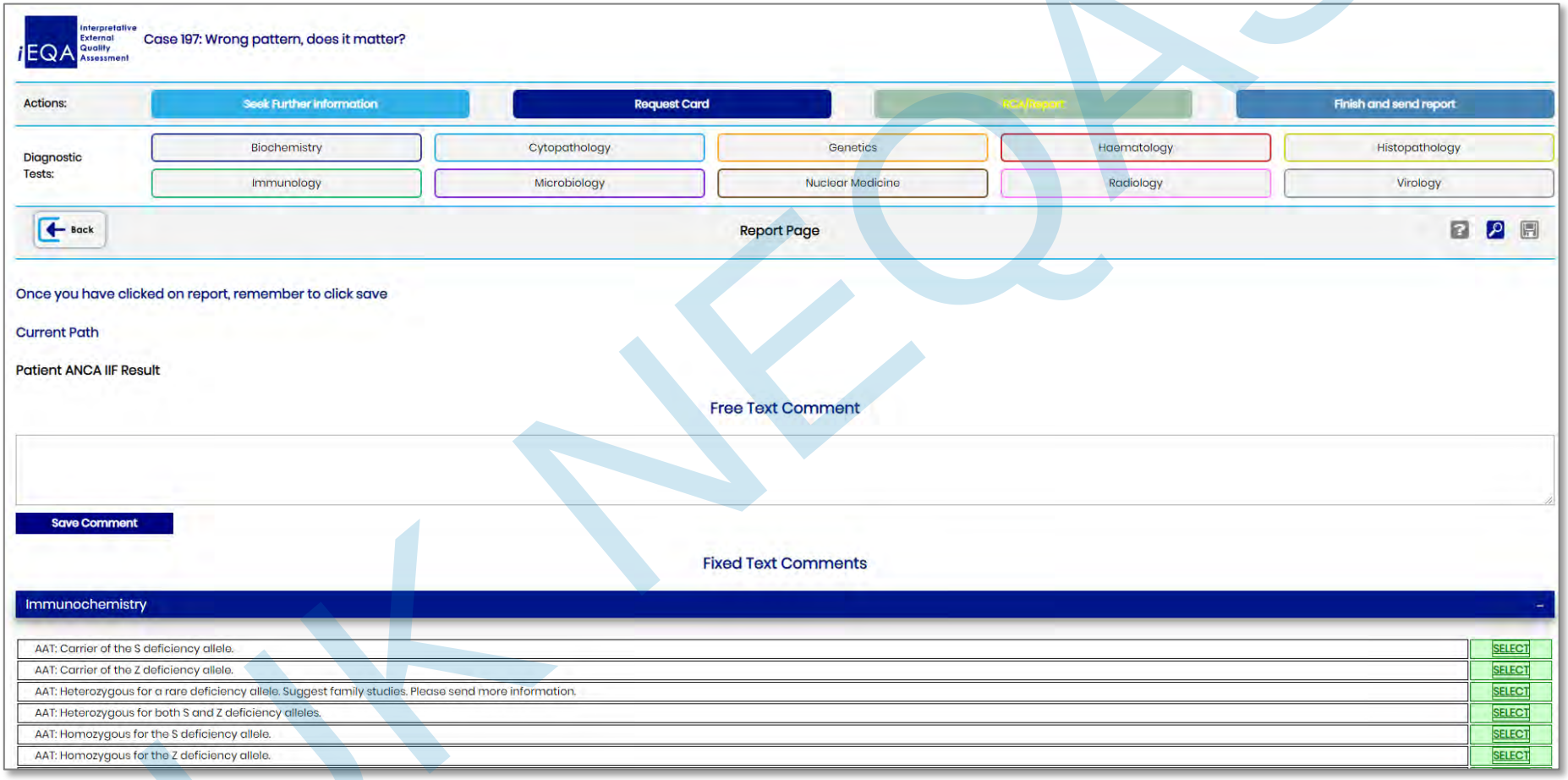
Diagnostic Tests: Biochemistry | Cytopathology | Genetics | Haematology | Histopathology | Immunology | Microbiology | Nuclear Medicine | Radiology | Virology

Immunology / Antibody Assays (Autoimmunity and Other) / Autoantibodies / Anti-neutrophil cytoplasmic Antibodies (ANCA) / Patient ANCA IIF Result



Immunology, Immunochemistry & Allergy (IIA)

Report can be free and/or fixed text comments:



Immunology, Immunochemistry & Allergy (IIA)

Answer is released on case completion:

Finish Assessment of Case 197: Wrong pattern, does it matter?

Selected Comments

Immunochemistry

Tumour Markers

Autoimmunity

General Comments

Answer

Suggested Answer

This lab got the "wrong" pattern, but they were not alone. Why would that be? A quick check for all the likely causes of error (sample ID, IQC, method, ongoing EQA issues) are negative and the result matches the clinical scenario, so the question is really that of a risk assessment – is it important to the patient's management, or is it a known issue of no critical significance, or does it mean that we should re-assess the appropriateness of our practice to assure ourselves that we are consistent with acceptable practice?

The symptoms, and the patient request form, point towards a diagnosis of vasculitis. Well done if you considered farmer's lung and infection in the differential, although some of the clinical details makes these less likely. Depending on which enzymes are involved, MPO or PR3, a classical C-ANCA or P-ANCA pattern would be expected. Although the immunofluorescence pattern observed (P-ANCA) does not reflect the expected pattern (C-ANCA) for GPA the EIA results do (PR3 pos/MPO neg). This is a case of granulomatosis with polyangiitis (GPA) (previously known as Wegener's Granulomatosis).

It is important to make the diagnosis from the full clinical picture as this sets the pre-test probability, then use the available laboratory test results to increase or decrease the probability and/or influence management. For example, abnormal renal function or poor blood gases might suggest serious involvement of vital organs that would require urgent treatment and the need to communicate the results urgently to the clinical team.

Immunofluorescence patterns are mostly used to screen samples for the presence of a positive staining that would lead to reflex specific immunoassay for specificities that are strongly predictive of disease when used in the correct clinical context. In this case EIA for MPO which is usually (but not exclusively) associated with Microscopic Polyangiitis, and PR3 which is usually (but not exclusively) associated with GPA. Remember that both can occur in other conditions, including infections and anti-GBM disease (Goodpasture's) which can present in a similar way.

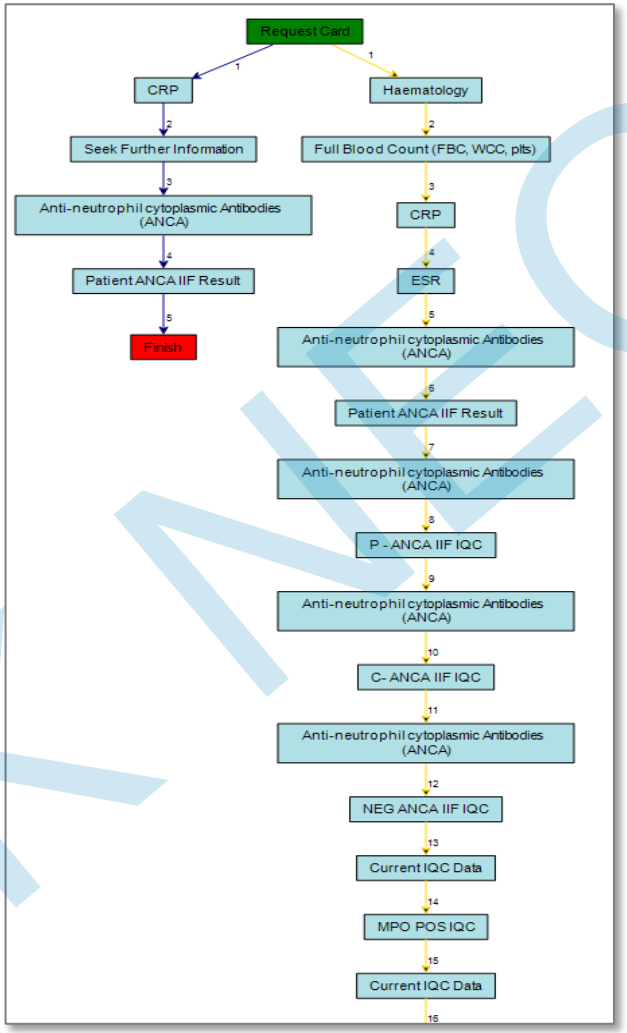
The clinical treatment of severe vasculitis of these types is sufficiently similar to make a strong IIF pattern clinically helpful and highly diagnostic, and the pattern is often of secondary importance. The key clinical risk is in failing to identify anti-GBM disease, where treatment may be modified specifically for that condition. Thus the GBM is almost always mandatory where there is lung and/or kidney involvement in a case of suspected vasculitis. EIA assays dominate in GBM disease . The place of immunofluorescence screening for ANCA is currently a topic of debate, with many favoring appropriately validated EIA as first line tests.

Obtaining discrepant IIF patterns for ANCA and EIA MPO/PR3 results is of little clinical risk to the patient in a laboratory that understands the occasional discrepant pattern and reports appropriately.

The Revised 2017 International Consensus on the testing of ANCAs promotes the use of enzyme immunoassay without the need for IIF confirmation/screening when ANCA testing is for the diagnosis of vasculitis.

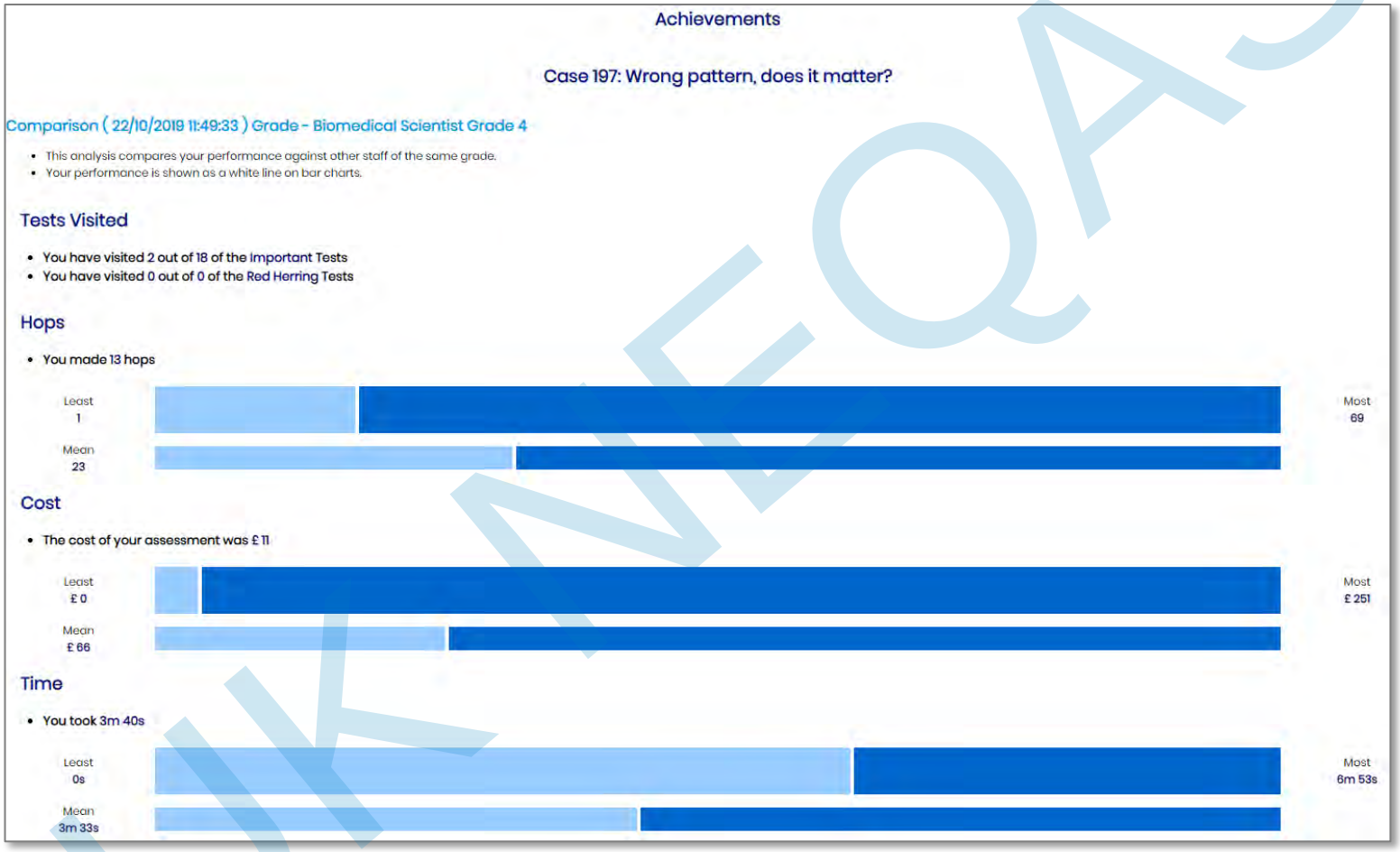
Immunology, Immunochemistry & Allergy (IIA)

Route compared against the 'expert path':



Immunology, Immunochemistry & Allergy (IIA)

Performance in the case compared against others:

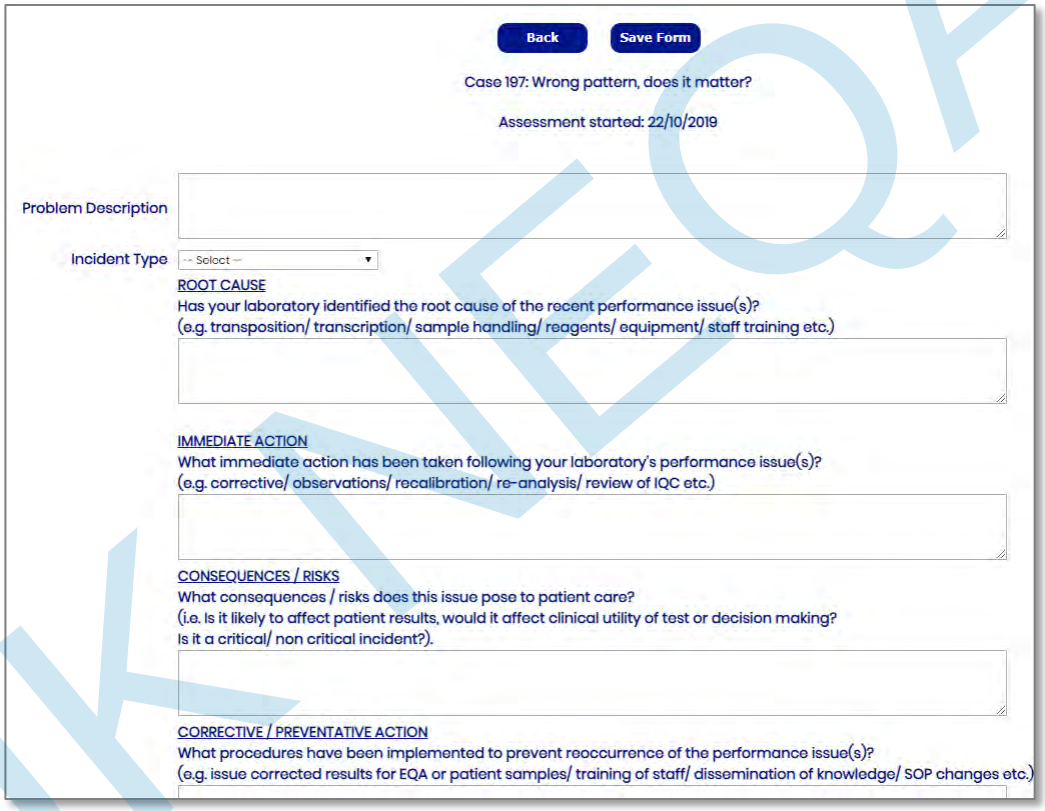


Immunology, Immunochemistry & Allergy (IIA)

Managers can allocate licences and cases and view performance:

Immunology, Immunochemistry & Allergy (IIA)

RCA form structured to provide guidance:



Digital services supporting competency

- Competency programs
- CPD programs
- Educational material
  - Cellular Pathology Technique
  - Haematology
  - Leucocyte Immunophenotyping
  - Parasitology

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Cellular Pathology Technique

- Extensive image libraries available on the web

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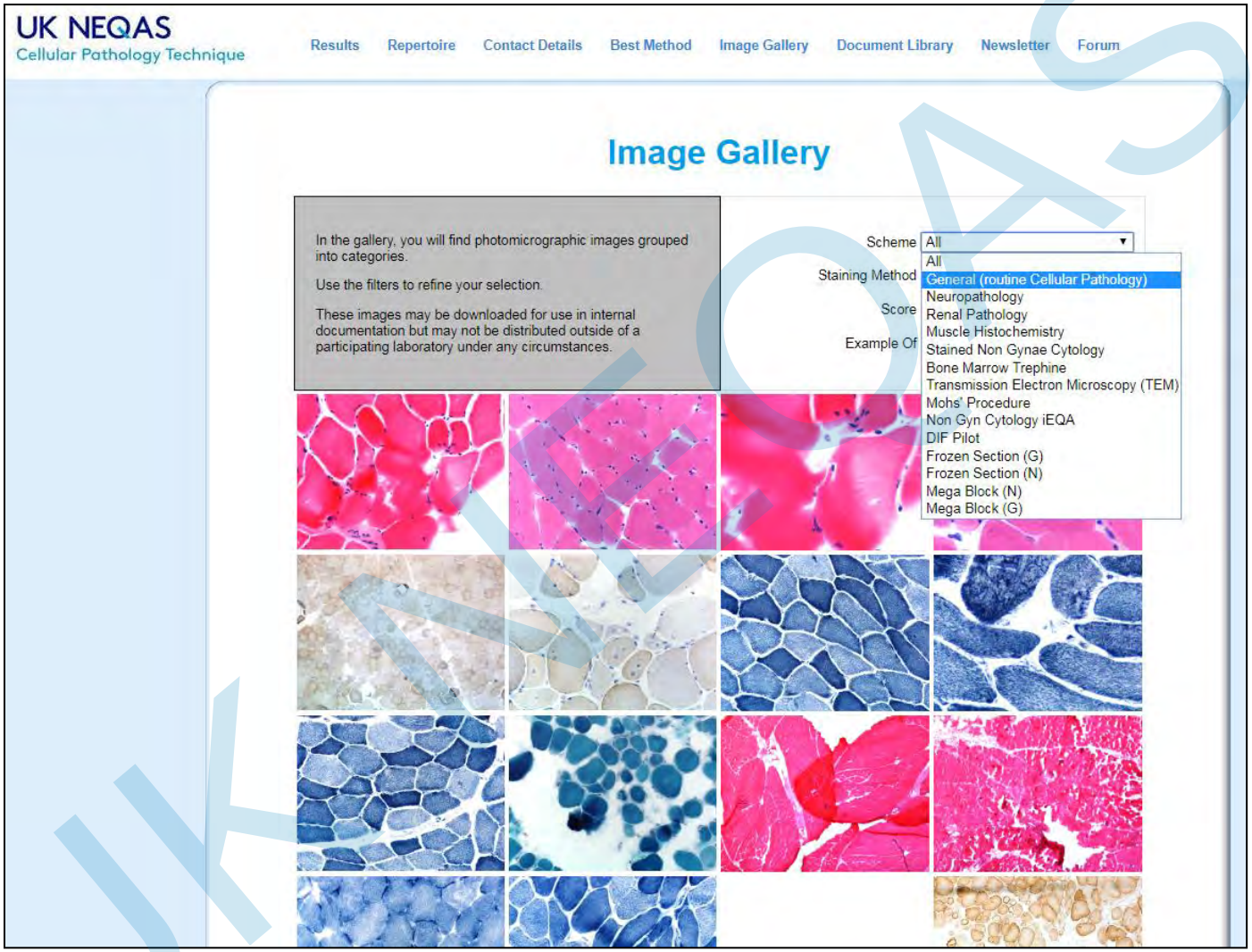
Cellular Pathology Technique



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Haematology

UK NEQAS
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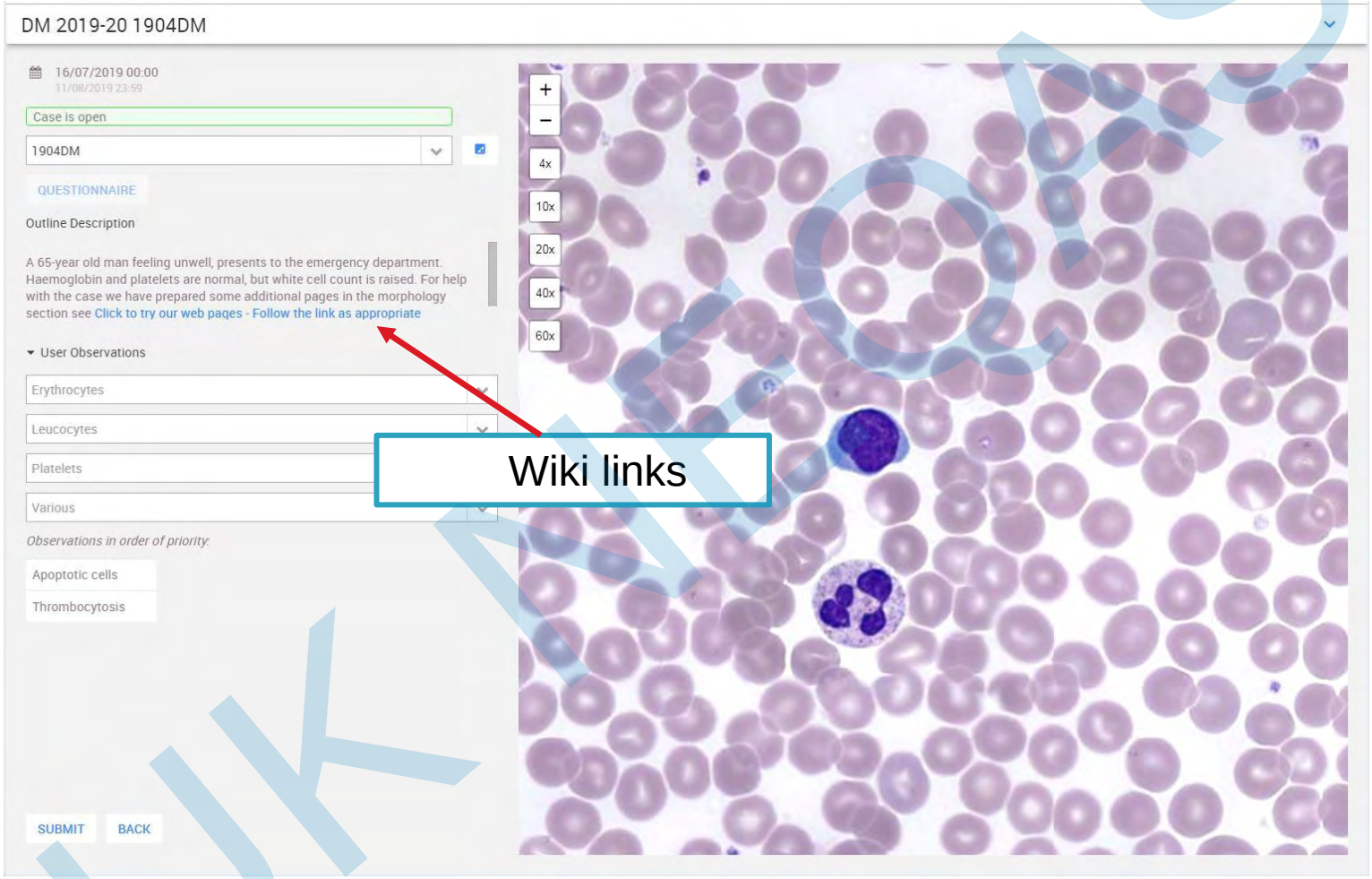
Haematology



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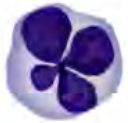
Haematology

www.haemtologyetc.co.uk Return to Home Search www.haemtologye Search

Mature T and NK cell disorders

Actions

From www.haemtologyetc.co.uk



Adult T cell Leukaemia Lymphoma (ATLL)

The abnormal cells generally have a range of size and appearances. The most characteristic feature is probably the nuclear shape that may appear as a convoluted or folded form, or may be spread out with a "clover leaf" appearance (generally only a minority of cells have clover leaf nuclei).

Click for detailed description

Sézary cells

In this instance the very complex nuclei have a folded shape - the "cerebriform" appearance that is said to resemble the surface of the brain. This appearance may require careful scrutiny to detect. Size, shape and nuclear chromatin can be quite variable even within a single blood film.

Click for detailed description

http://haematologyetc.co.uk

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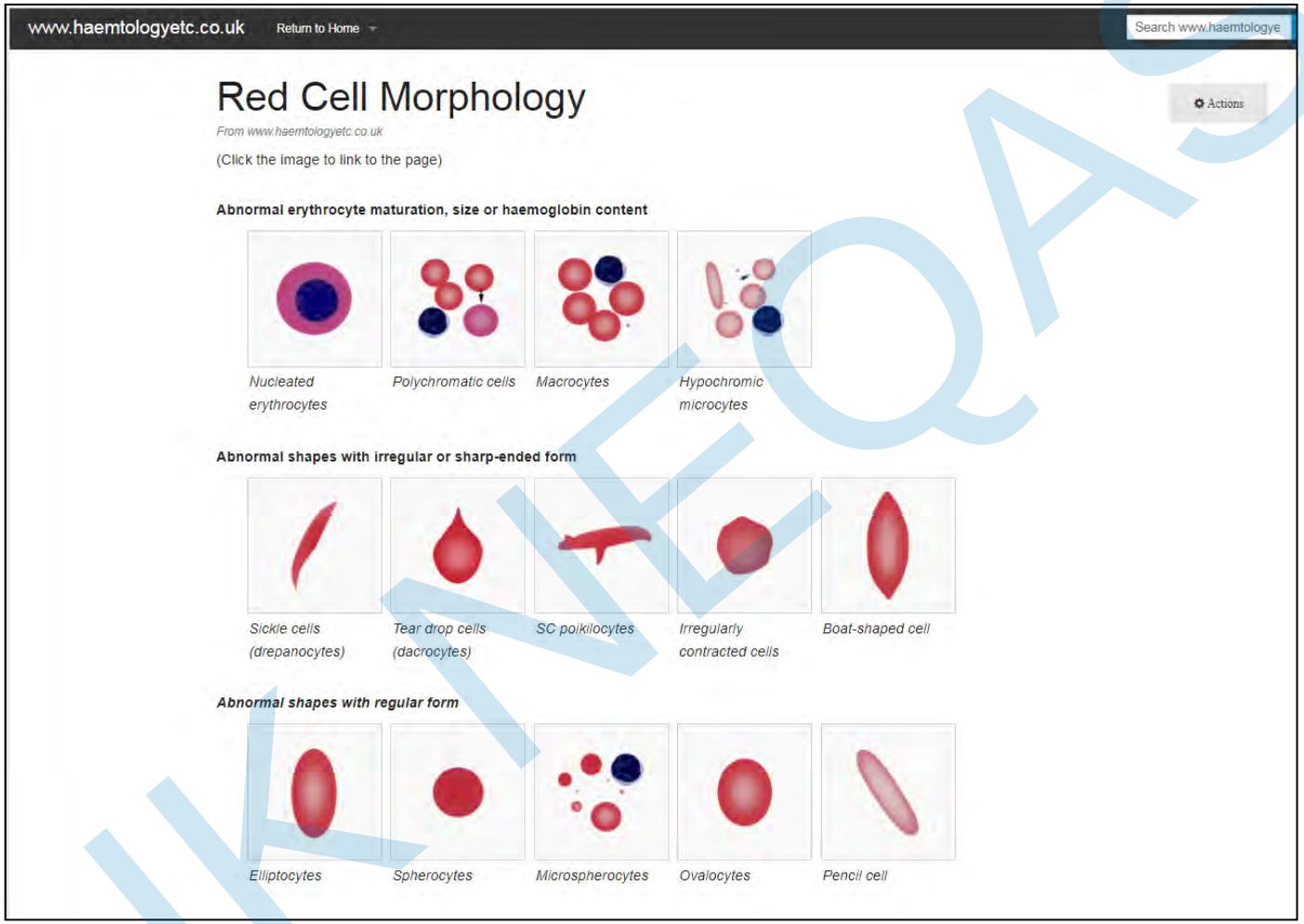
International Quality Expertise

Haematology



http://haematologyetc.co.uk

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Leucocyte Immunophenotyping

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Leucocyte Immunophenotyping

http://www.uknegasli.co.uk/news-events/educational-videos-user-guides/

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Parasitology

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Parasitology

http://www.ukneqasmicro.org.uk/parasitology/index.php/ct-menu-item-2

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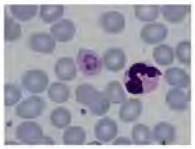
Parasitology

Notes on the stained film.

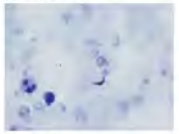
a. Examine the tail end of the slide where the red cells are separated into a one-cell-layer thick.
b. An alkaline buffer pH 7.2 is vital for clear differentiation of nuclear and cytoplasmic material and to visualise inclusions such as Schuffner's/James's dots in the red cells. **Acidic buffer is unsuitable.**
c. The red cells are fixed in the thin film so the morphology of the parasitised cells and the parasites can be seen.
d. On a well stained film the chromatin stains red/purple and the cytoplasm blue. Leucocytes have purple nuclei, the red stippling , if present should be clearly visible.



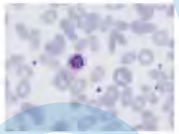
Trophozoite of *Plasmodium ovale*

The gametocyte stage.

The gametocyte stage is sexual in that the parasites become either male or female in preparation for the next stage, which takes place in the stomach of the female Anopheline mosquito.
Gametocytes may be either rounded or banana/crescent in shape, depending on the species.
The way in which the parasite takes up the stain is usually an indication of which sex the gametocytes are. Male gametocytes appear to stain more of a "pink" colour than do the female gametocytes.



Gametocyte



Schizont

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Parasitology

PHE National Parasitology Reference Laboratory, Hospital for Tropical Diseases, 3rd Floor Mortimer Market, Centre, Capper Street, London WC1E 6JB, TEL: +44 (0) 207 383 0482, FAX +44 (0) 207 388 8980

Examination of Thin Blood Films for malaria

1. **Rapid Field's stain for thin films**

This is a modification of the original Field's stain to enable rapid staining of fixed thin films. This method is suitable for malaria parasites, Babesia sp., Borrelia sp. and Leishmania sp.

Method.

a. Air dry the film
b. Fix in methanol for 1 minute.
c. Flood the slide with 1 ml of **Field's stain B, diluted 1 in 4 with distilled water.**
d. **Immediately,** add an equal volume of **undiluted** Field's stain A, mix well and allow to stain for 1 minute.
e. Rinse well in tap water and drain dry.

Uses.

This is a useful method for rapid presumptive species identification of malaria parasites. It shows adequate staining of all stages including stippling (mainly Maurer's clefts). However , staining with Giemsa is always the method of choice for definitive species differentiation.

2. **Giemsa stain for thin films.**

Method.

a. Air dry thin films
b. Fix in methanol for 1 minute
c. Wash in tap water and flood the slide with Giemsa diluted **1 in 10** with buffered distilled water **pH 7.2.** The diluted stain **must be freshly prepared each time.**
d. Stain for 25 - 30 minutes.
e. Run tap water on to the slide to float off the stain and to prevent deposition of precipitate on to the film. Drain dry vertically.
f. Examine the film using the x100 objective.

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Introduction to Malaria species

There are 5 species of malaria which affect man

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*
- *Plasmodium knowlesi*

Stages of the malaria parasite seen in the blood

The trophozoite stage.

This stage is the most commonly seen; it is often referred to as the ring stage, although it sometimes takes the form of an incomplete ring.
Because the trophozoite form is a growing stage, the parasite within the red cell may vary in size from small to quite large. Pigment appears as the parasites grows. Malaria pigment - haemozoin, is a metabolic by-product of the parasite. It does not stain, but has a colour of its own, which may range from pale yellow to dark brown or black.

The schizont stage.

At the schizont stage the parasite starts to divide. This is referred to as schizogony and takes place in the liver and in the peripheral blood.
The parasite reproduces by simple division. There are several obvious phases in this stage, ranging from parasites with two chromatin pieces to parasites with a number of chromatin dots and definite cytoplasm - merozoites.

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Digital services supporting competency

- Don’t forget the EQA surveys…

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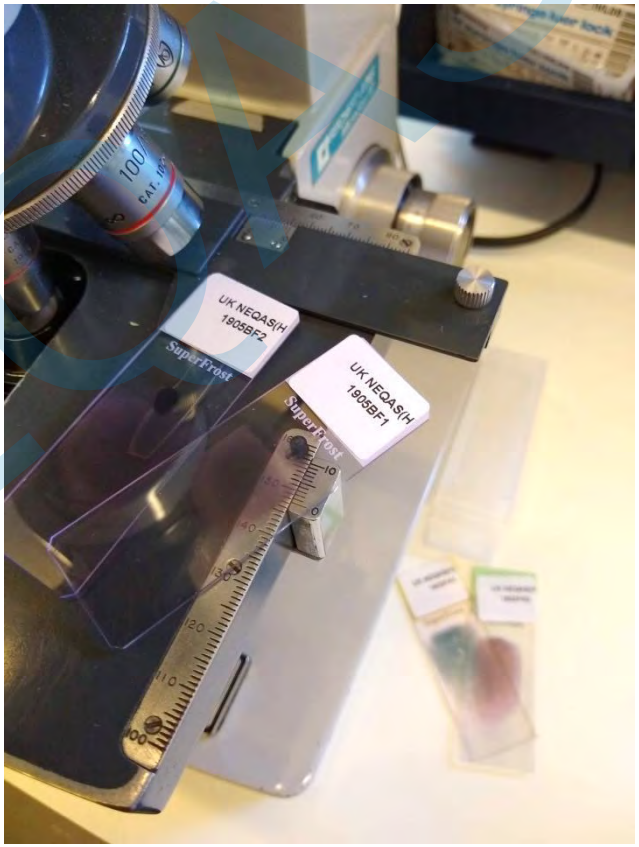
Haematology - Blood Film Morphology

- Established in 1978
- 16 glass slide cases annually
- 550 participating laboratories in the UK and abroad
- Participants select five most significant morphological features



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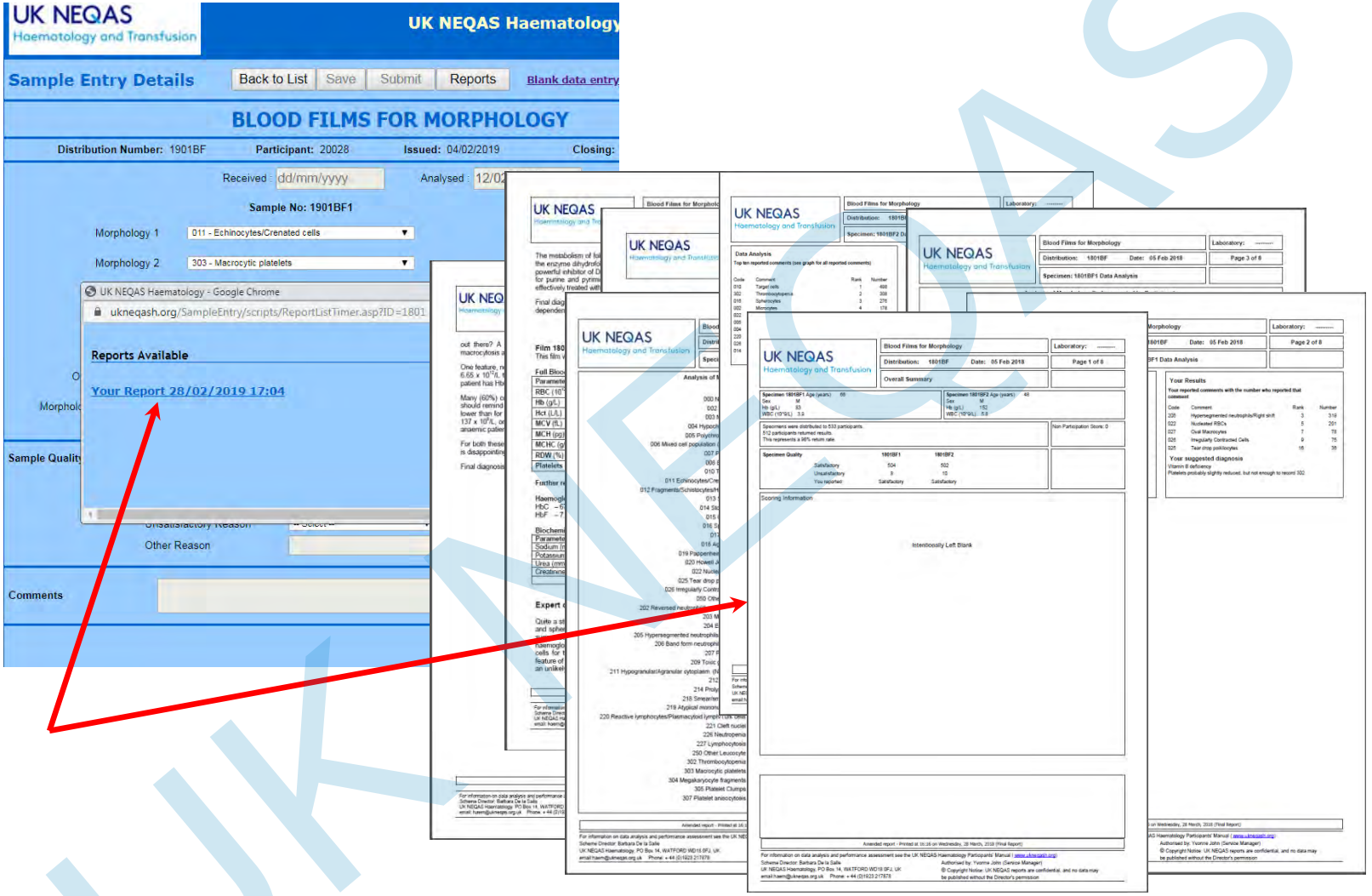
Haematology



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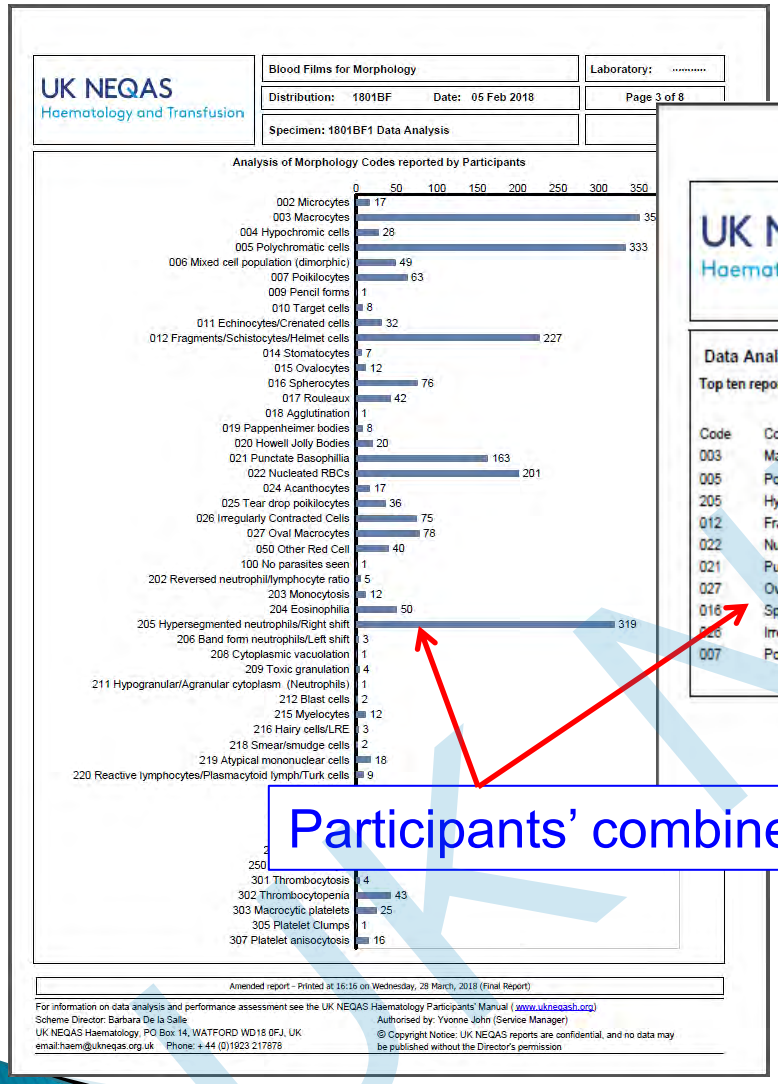
Haematology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Haematology and Transfusion

Blood Films for Morphology | Laboratory: .....
Distribution: 1801BF Date: 05 Feb 2018 | Page 3 of 8
Specimen: 1801BF1 Data Analysis

Analysis of Morphology Codes reported by Participants

002 Microcytes	17
003 Macrocytes	35
004 Hypochromic cells	28
005 Polychromatic cells	333
006 Mixed cell population (dimorphic)	49
007 Poikilocytes	63
009 Pencil forms	1
010 Target cells	8
011 Echinocytes/Crenated cells	32
012 Fragments/Schistocytes/Helmet cells	227
014 Stomatocytes	7
015 Ovalocytes	12
016 Spherocytes	76
017 Rouleaux	42
018 Agglutination	1
019 Pappenheimer bodies	8
020 Howell Jolly Bodies	20
021 Punctate Basophillia	163
022 Nucleated RBCs	201
024 Acanthocytes	17
025 Tear drop poikilocytes	36
026 Irregularly Contracted Cells	75
027 Oval Macrocytes	78
050 Other Red Cell	40
100 No parasites seen	1
202 Reversed neutrophil/lymphocyte ratio	5
203 Monocytosis	12
204 Eosinophilia	50
205 Hypersegmented neutrophils/Right shift	319
206 Band form neutrophils/Left shift	3
208 Cytoplasmic vacuolation	1
209 Toxic granulation	4
211 Hypogranular/Agranular cytoplasm (Neutrophils)	1
212 Blast cells	2
215 Myelocytes	12
216 Hairy cells/LRE	3
218 Smear/smudge cells	2
219 Atypical mononuclear cells	18
220 Reactive lymphocytes/Plasmacytoid lymph/Turk cells	9
301 Thrombocytosis	4
302 Thrombocytopenia	43
303 Macrocytic platelets	25
305 Platelet Clumps	1
307 Platelet anisocytosis	16

Amended report - Printed at 16:16 on Wednesday, 28 March, 2018 (Final Report)

For information on data analysis and performance assessment see the UK NEQAS Haematology Participants' Manual (www.ukneqash.org)
Scheme Director: Barbara De la Salle
Authorised by: Yvonne John (Service Manager)
UK NEQAS Haematology, PO Box 14, WATFORD WD18 0FJ, UK
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UK NEQAS
Haematology and Transfusion

Blood Films for Morphology | Laboratory: .....
Distribution: 1801BF Date: 05 Feb 2018 | Page 2 of 8
Specimen: 1801BF1 Data Analysis

Data Analysis

Top ten reported comments (see graph for all reported comments)

Code	Comment	Rank	Number
003	Macrocytes	1	351
005	Polychromatic cells	2	333
205	Hypersegmented neutrophils/Right shift	3	319
012	Fragments/Schistocytes/Helmet cells	4	227
022	Nucleated RBCs	5	201
021	Punctate Basophillia	6	163
027	Oval Macrocytes	7	78
016	Spherocytes	8	76
026	Irregularly Contracted Cells	9	75
007	Poikilocytes	10	63

Your Results

Your reported comments with the number who reported that comment

Code	Comment	Rank	Number
205	Hypersegmented neutrophils/Right shift	3	319
022	Nucleated RBCs	5	201
027	Oval Macrocytes	7	78
026	Irregularly Contracted Cells	9	75
025	Tear drop poikilocytes	16	36

Your suggested diagnosis

Vitamin [illegible] deficiency
Platelets probably slightly reduced, but not enough to record 302

Participants' combined results

Individual laboratory's results

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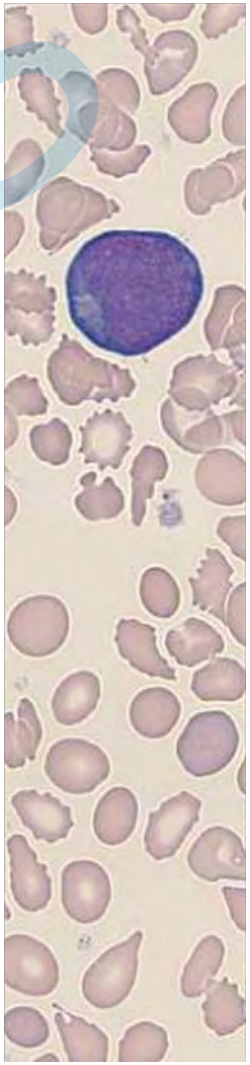
A Morphology EQA scoring system

- The returns are ‘scored’ whereby the individual’s top five comments are compared with the national consensus
- If a participant’s ‘feature’ is found in the top ten of the national returns, then a point is awarded for that feature
- If the morphological syndrome is identical to, or closely related to the actual patient condition when revealed by the ‘expert’ summariser, an additional point is awarded, or if more than one syndrome is present, two or more points may be awarded



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Haematology

NEQAS BF07 November 2016			Lab	005	011	012	013	014	015	016	017	018
1607BF1												
1	212	Blasts			■	■		■		■	■	
2	203	Monocytosis	■		■	■		■	■		■	
3	204	Eosinophilia		■			■		■			
4	022	Nucleated RBCs										
5	301	Thrombocytosis										
6	215	Myelocytes										
7	303	Macrocytic Plat										
8	206	Band form/L shi										
9	211	Hypogranular/a										
10	225	Neutrophilia										
		Diagnosis										
		CMM										

Films		Lab					Blood Films			
	Ref	005	011	012	013	014	015	016	017	018
1601BF	15		14	10	12	12	8	8	12	8
1602BF	14	10	13	7	13	13	8	5	9	10
1603BF	12	11	12	11	12	12	12	5	12	0
1604BF	12	0	11	11	11	8	3	0	5	10
1605BF	12	10	13	12	13	8	11	6	9	10
1606BF	12	6	9	10	7	11	8	8	10	0
1607BF	12	8	12	11	11	8	7	7	10	0
Total	89	45	84	72	79	72	57	39	67	38
% Score		60.8	94.4	80.9	88.8	80.9	64.0	50.6	75.3	71.7

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Digital services supporting competency

- The future…

2020 Fixed modules:

- BRCA Variant Run 4
- SNV Trial Run 2
- HaemOnc Trial Run 1
- CNV Trial Run 1

Expanding scope:

- Sample reception: increase sample types and referrals
- Variant Analysis: increase number of variants
- Data analysis: increase data types e.g. FraX, arrays, karyotyping
- Report Authorisation: add other disorders e.g CF

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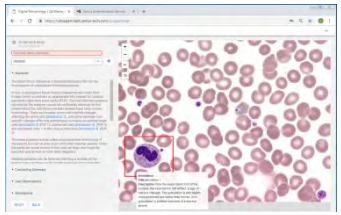
EQATE Haematology

Morphology module:



EQA module:

Electronic EQA cases
'Dry'cases

Interpretive EQA module:

Case studies
Individual assessment

Competency assessment

Education module:

Galleries
Self-assessment tools

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GenQA GENOMICS QUALITY ASSESSMENT

EQA for a Genomic Future

Becky Treacy
Deputy Director, GenQA, Edinburgh, UK

UK NEQAS Molecular Genetics

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CEQAS Cytogenomic External Quality Assessment Service

GenQA GENOMICS QUALITY ASSESSMENT

Collaboration between CEQAS and UK NEQAS Molecular Genetics

Member of UK NEQAS consortium

Genomics	vs	Genetics
• The study of an organism's complete set of genetic information.		• The study of heredity
• The genome includes both genes (coding) and non-coding DNA.		• The study of the function and composition of single genes.
• 'Genome': the complete genetic information of an organism.		• 'Gene': specific sequence of DNA that codes for a functional molecule.

2019

Delivery of 94 EQAs, including:

- EQAs with multiple distributions
- 12 pilot EQAs

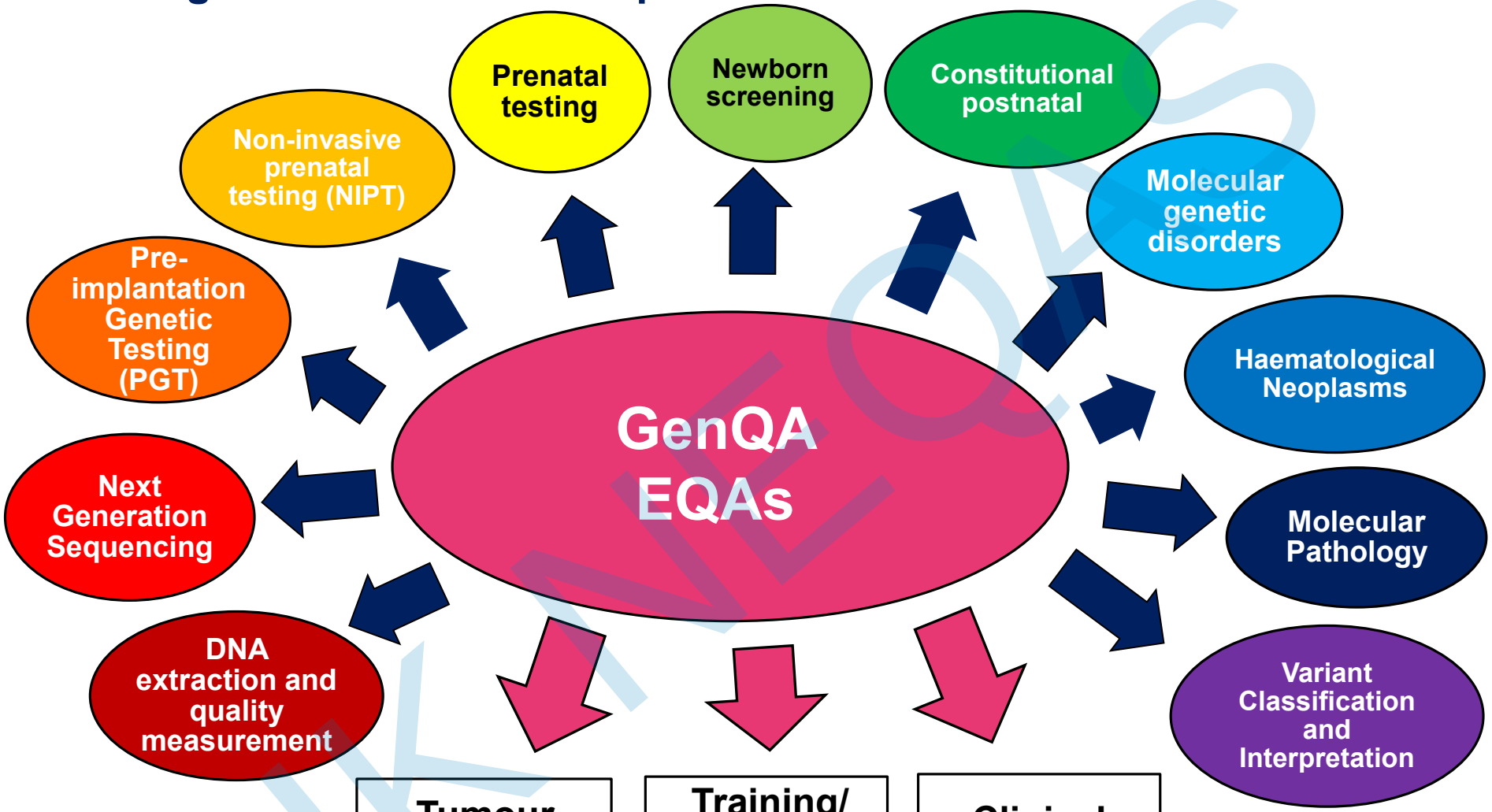
79 Countries

2020

98 EQAs planned so far, including:

- EQAs with multiple distributions
- 17 new EQAs

Delivering 98 EQAs across 14 specialities



Genomic testing and EQAs encompass patient lifespan

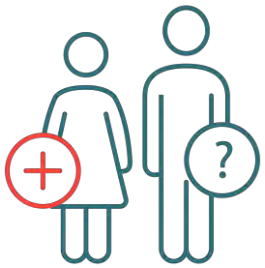
Pre-conception testing:	Carrier/Presymptomatic testing e.g. CF/HD
Pregnancy testing:	Preimplantation genetic testing (PGT) Non-invasive prenatal testing (NIPT) Direct fetal testing (CVS/Amniocentesis)
Newborn screening:	Molecular testing for CF (raised IRT)
Postnatal testing:	Neonatal/childhood/adult-onset disorders Pharmacogenomics (drug reactions)
Acquired (somatic) testing:	Molecular pathology (solid tumours) Haematological malignancies (liquid tumours)

Genomics different to other pathology specialties: less sample volume BUT most patients will have a **single DNA test** in their lifetime. I**mplications for all family members**.

Pre-conception testing

Carrier or presymptomatic testing for unaffected individuals

Carrier testing: Test an individual / couple to determine their risk of having a child with a genetic disorder.



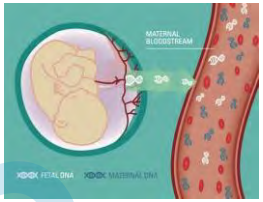
e.g. cystic fibrosis – 1 in 25 people (without a family history) in the UK are likely to be a carrier of CF

1 in 2500 births in UK have cystic fibrosis

Presymptomatic testing: Test an individual with a family history of an autosomal dominant disorder e.g. HD (at 50% risk of going on to develop HD)

Future: Direct To Consumer (DTC) testing: more individuals finding out carrier status….but no clinical interpretation or subsequent support!

Pregnancy testing:



Testing the fetus by non-invasive or invasive methods

Preimplantation genetic testing (PGT): testing an embryo created by IVF to determine its risk of inheriting a specific genetic disorder (e.g. HD) and only implant embryos that are normal at the HD locus.

Non-invasive prenatal testing (NIPT): testing the fetal DNA within the maternal plasma e.g. for aneuploidies e.g. Trisomy 21 (screening) or for a specific genetic disorder (diagnosis). Low risk to fetus as non-invasive.

Direct prenatal fetal testing (CVS/Amniocentesis): testing a fetus for a known familial genetic disorder or potential disorder due to ultrasound findings e.g. echogenic bowel and CF.
Testing for the presence of maternal cell contamination which can mask the 'true' result.

Future: Prenatal Exome testing for abnormal ultrasound findings – launching in NHS England in January 2020.

Newborn bloodspot screening:

Heel-prick test at 5 days of life

- Babies are routinely testing for **9 rare genetic disorders**
- Testing is performed using biochemical assays.
- For some disorders a **second level molecular test** may be indicated e.g. raised IRT (immuno-reactive trypsinogen) for CF

New NBS test for SCID: Proposed by Public Health England.

- molecular assay to detect TREC (T-cell receptor excision circles) levels.
- Collaboration with UKNSLN and CDC.

UK Newborn Screening Laboratories Network

Public Health England

CDC
Centers for Disease Control and Prevention

Future:

- Introduction of **panel tests for newborn screening.**
- To include disorders where early detection/intervention can make a difference to the clinical outcome/progression.

Postnatal testing:

Neonatal/childhood/adult-onset disorders and pharmacogenomics

- Traditional genetic testing for molecular and cytogenetic disorders.
- Blurred boundaries due to genome–wide testing strategies rather than specific/targeted testing for changes in the genome e.g. WES, NGS/arrays.
- Multi-gene disorders - tested sequentially > performed simultaneously.
- Broader referrals with clinical indication, rather than specific target genes.

- **Pharmacogenomics** - drug toxicity assays are now be used to determine a patient's reaction to a specific drug for cancer treatment.

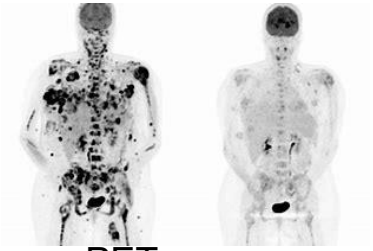
- **Future: Polygenic risk scores** quantify cumulative effects of several genes, (individually have a very small effect on susceptibility).
- Predict likelihood of displaying any trait with a genetic component.

Acquired (somatic) testing:

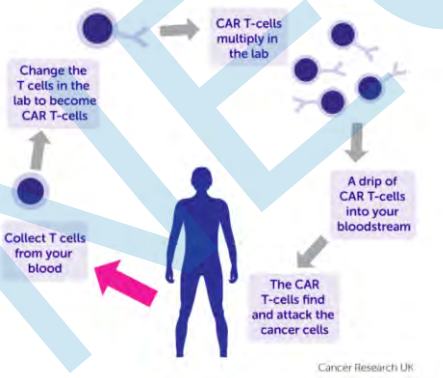
Molecular pathology and haematological malignancies

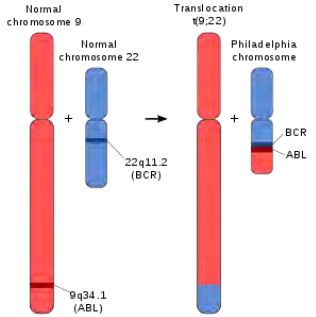
- Testing for somatic variants associated with malignancy in:
  solid (molecular pathology) and **liquid tumours** (haem. malignancies)

- Direct treatment pathways e.g. ***BRAF* mutation** testing for **melanoma**.
- Mutation indicates a potential positive response to *BRAF* inhibitors.



PET scan





- **ALLtogether trial** - B-cell **Acute Lymphoblastic Leukaemia** patients and suitability for CAR-T (chimeric antigen receptor T-cell) therapy.
- If patients are **Philadelphia +ve**, i.e. have the t(9;22)(q34;q11) rearrangement, then they are NOT suitable for the CAR-T therapy trial.

Challenges for EQAs in the field of Genomics:

- Genomic testing is incorporated across **laboratory medicine**
- Can directly **affect patient treatment** and clinical management
- **Fast changing technology** e.g. panels, WES/trios and NIPT
- **Interpretation** of results at two levels
  - are the genetic variants disease causing or not?
  - are the genes linked to clinical case?

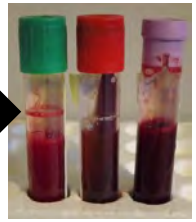
How does GenQA meet the challenges?

- Providing **end to end testing** as all elements rely on the full pathway
  - **Laboratory processes:** sample processing through to reporting
  - **Counselling and clinical interpretation** process
- **Training and competency for individuals** (scientists, technologists, clinicians, counsellors, pathologists)
- **Reflecting the changes** in how genetic community are testing patients, confirming, interpreting and reporting of results (fit for purpose).

End to End testing (genomic sample/patient journey)

Pre-test consultation/ Referral | Sample | Analysis | Interpretation | Reporting | MDT | Consultation

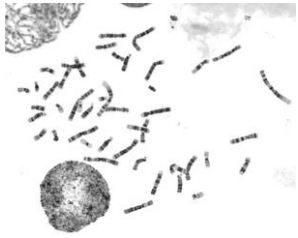
Pre-test referral



Sample handling (blood, DNA, FFPE etc)

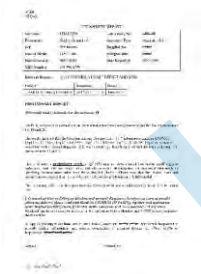
DNA extraction DNA quality

DNA quantity



Analysis – online images/ genotyping accuracy / technical

Interpretation



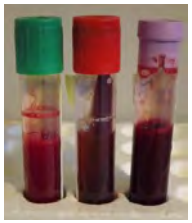
Reporting

Consultation

End to End testing

Pre-test consultation/ Referral | **Sample** | Analysis | Interpretation | Reporting | MDT | Consultation

Pre-test referral



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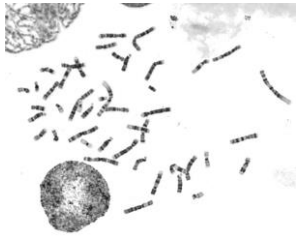

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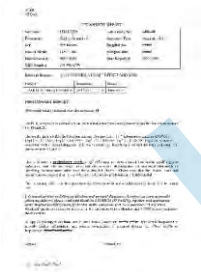


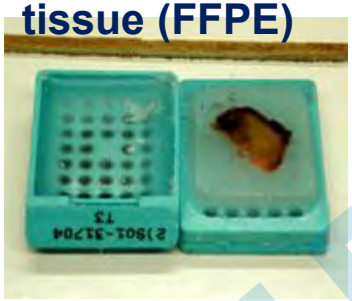
Consultation

EQA for DNA extraction from different sample types

Assess quality and quantity of DNA extracted

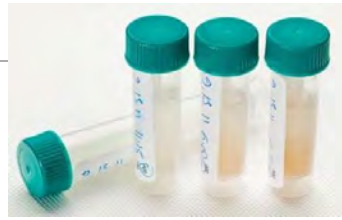
Fresh/frozen tissue (FF)

Formalin-fixed paraffin-embedded tissue (FFPE)



Blood

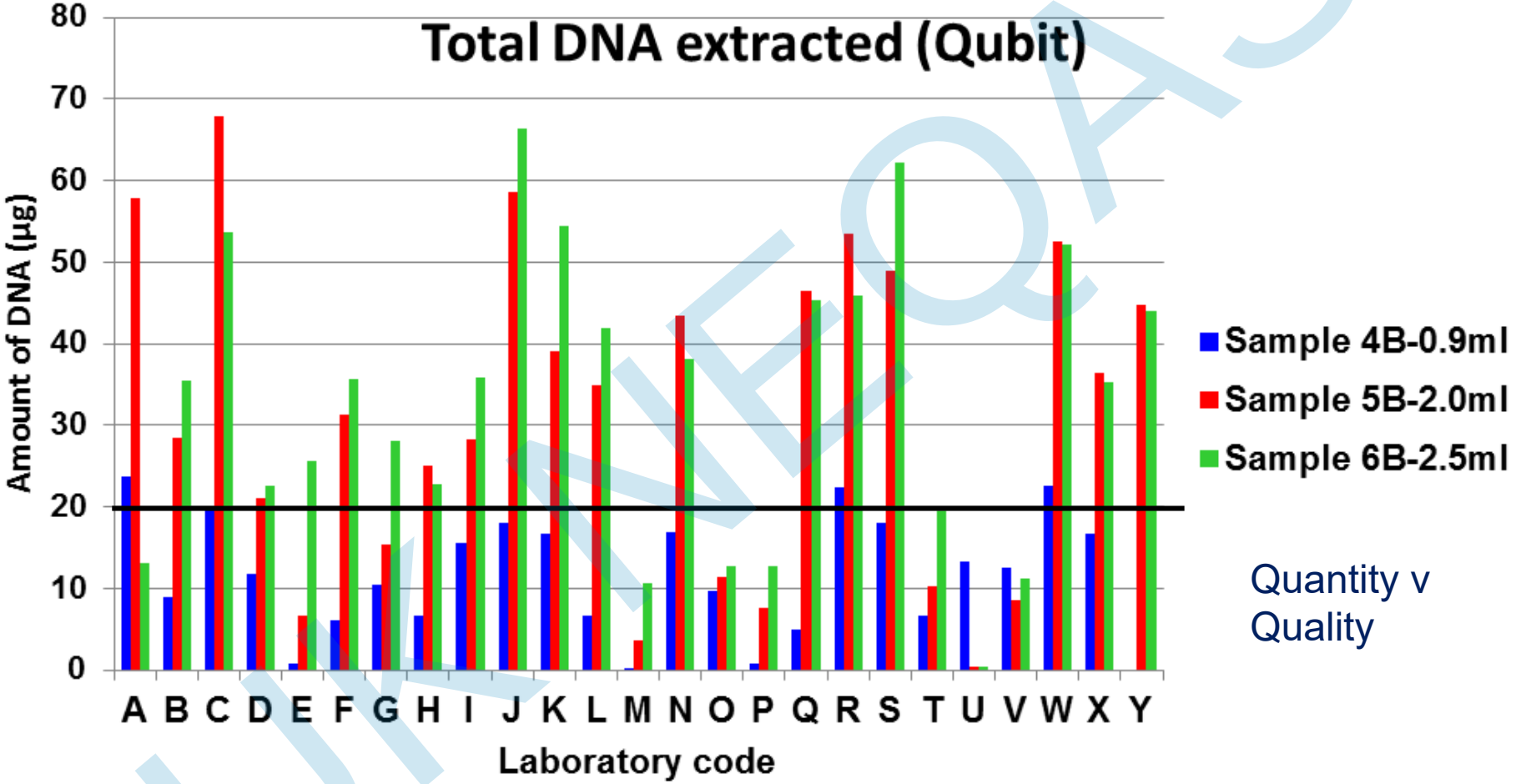
Saliva



Extract DNA from sample provided and return to GenQA for assessment.

EQA for DNA extraction from blood

Variable amount of DNA extracted from same samples

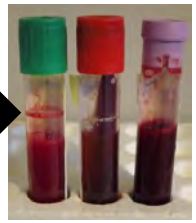


Quantity v Quality

End to End testing

Pre-test consultation/ Referral | **Sample** | Analysis | Interpretation | Reporting | MDT | Consultation

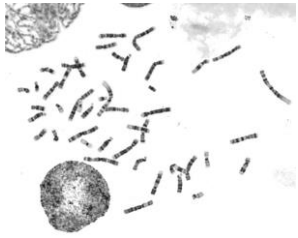
Pre-test referral



Sample handling (blood, DNA, FFPE etc)

DNA extraction DNA quality

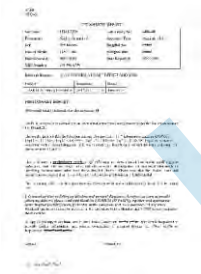
DNA quantity



Analysis – online images/ genotyping accuracy / technical

Interpretation

Reporting

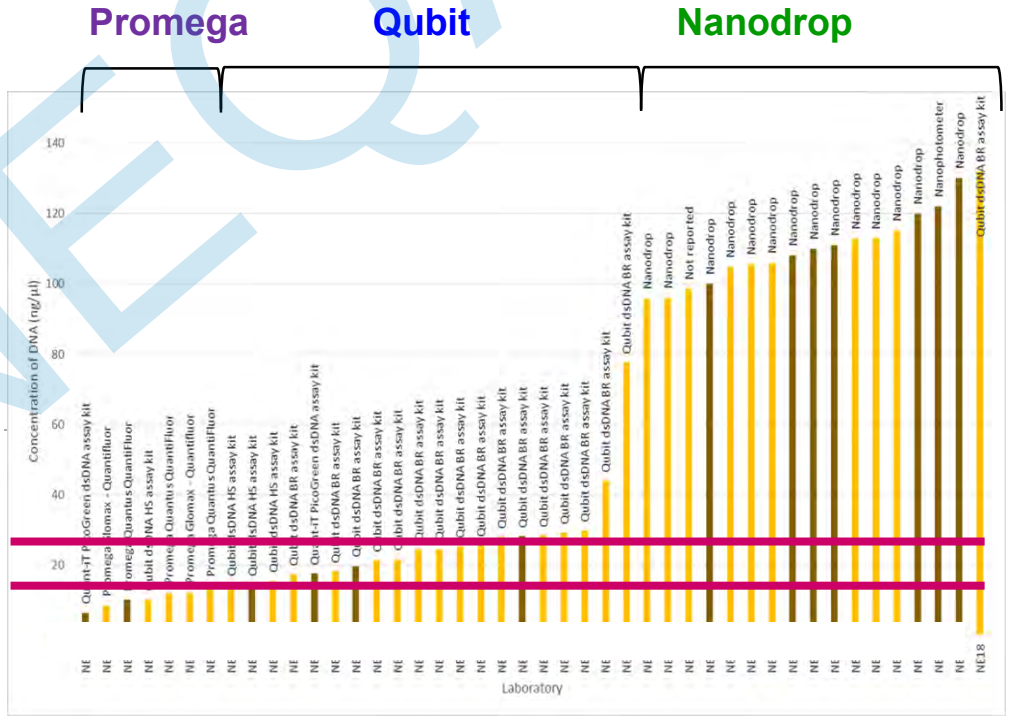


Consultation

EQA for DNA quantity measurement

Variable concentration measurements of same samples

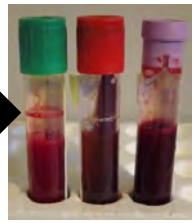
- Six EQA DNA samples (extracted from different tissue types)
- Laboratories measure the DNA concentration using their usual method.
- Concentration influenced by method used.
- Particularly important for techniques such as NGS



End to End testing

Pre-test consultation/ Referral | Sample | **Analysis** | Interpretation | Reporting | MDT | Consultation

Pre-test referral



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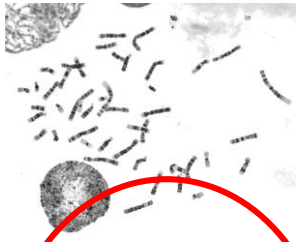

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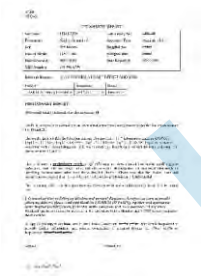
Interpretation



Reporting

Consultation

Technical EQA for Next Generation Sequencing (NGS)

EMQN
The European Molecular Genetics Quality Network

- Available to **all laboratories** as not linked to disease or testing approach, clinical and research
- Two parallel EQAs provided: **Germline and Somatic testing**
- **Platform agnostic**
- **Testing agnostic:**

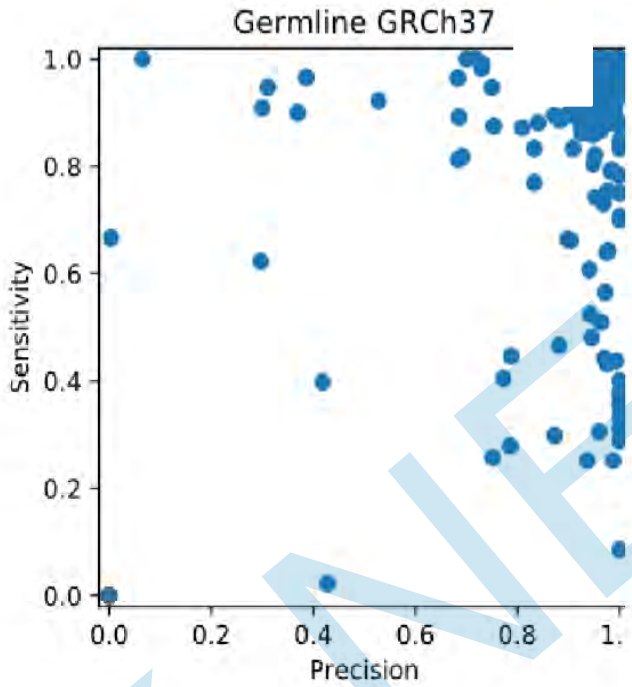
  Single gene, panels, CES, WES and WGS
- 3 submissions of NGS data for assessment

  (VCF, BED, FASTQ, BAM)
- 2018 EQA:

  260 participants from 30 countries

NGS EQA 2018: Sensitivity and Precision

Examples of data collected



Sensitivity - Proportion of actual positives that are correctly identified as such

Laboratories not detecting positives

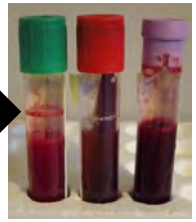
Precision - Proportion of actual positives among all reported positives

Laboratories reporting false positives

End to End testing

Pre-test consultation/ Referral | Sample | Analysis | **Interpretation** | Reporting | MDT | Consultation

Pre-test referral



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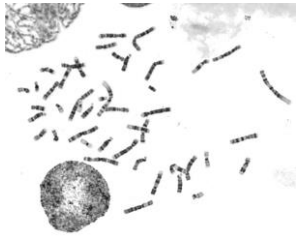
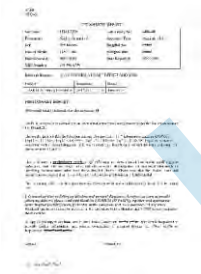
DNA extraction DNA quality

DNA quantity



Analysis – online images/ genotyping accuracy /technical

Interpretation



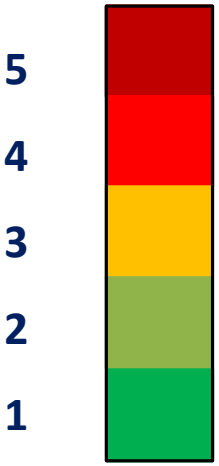
Reporting

Consultation

Interpretation EQAs

Traditional disease based EQAs and very rare disorders/genes

"Genomic testing is (relatively) straightforward"



5 Pathogenic

4 Likely pathogenic

3 Uncertain significance

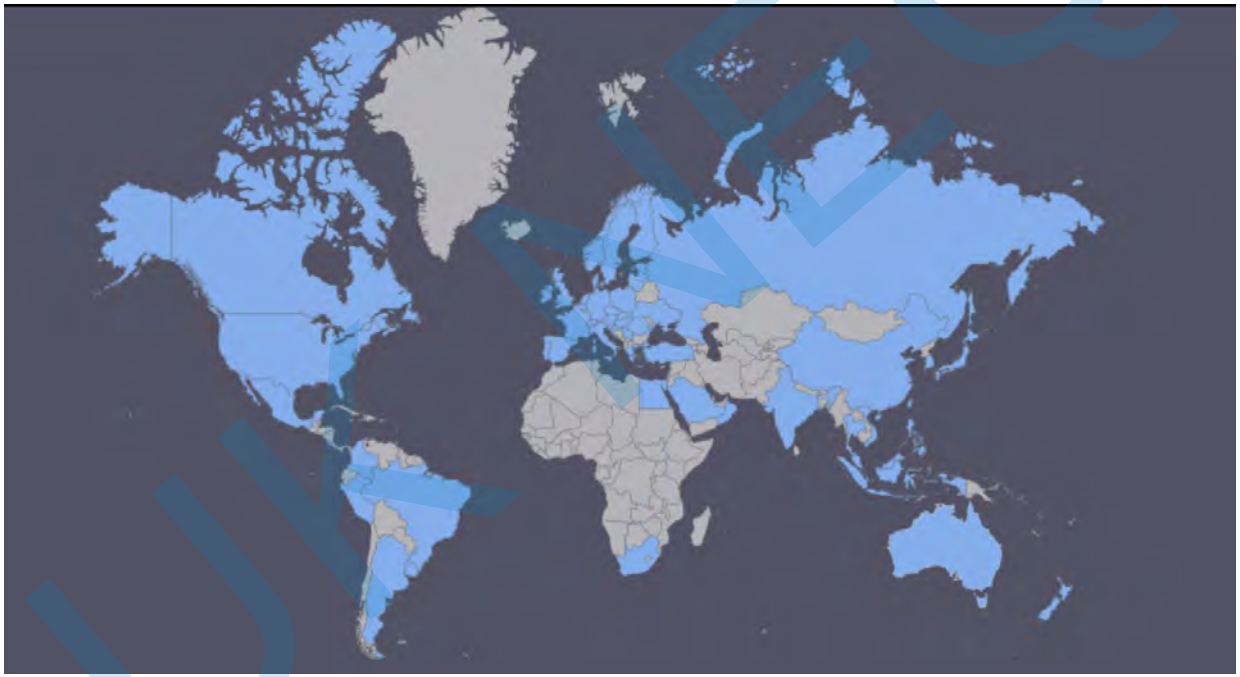
2 Likely benign

1 Benign

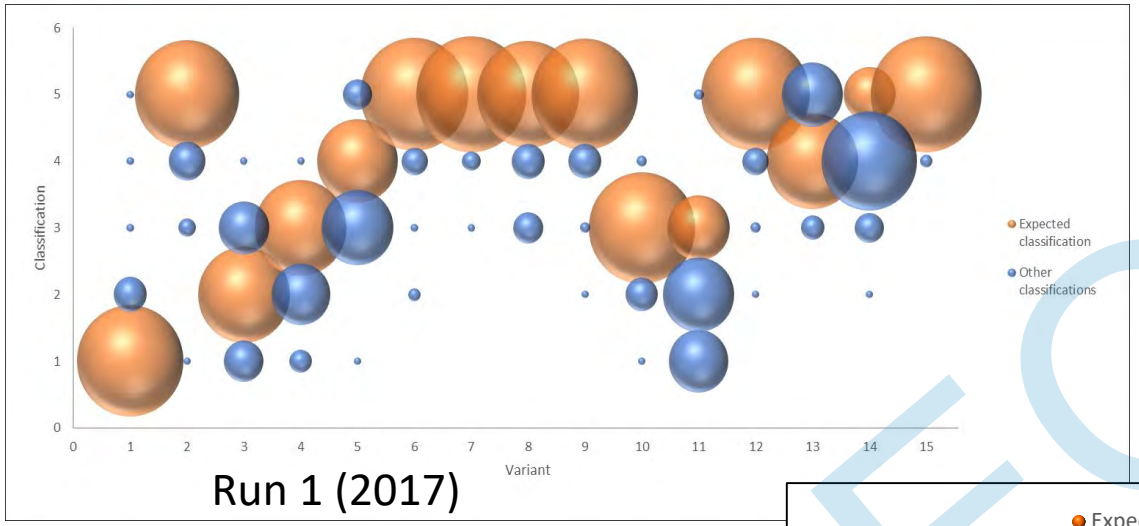
Variant interpretation is not…

BRCA1/BRCA2 variant classification (G-TACT)

- **407 individuals** enrolled in run 1 from **59 countries**
- **271 individuals submitted scenarios**
- 15 *BRCA* variants ➡ Randomised to prevent collusion!
- **Variant classification > Clinical management/treatment options**



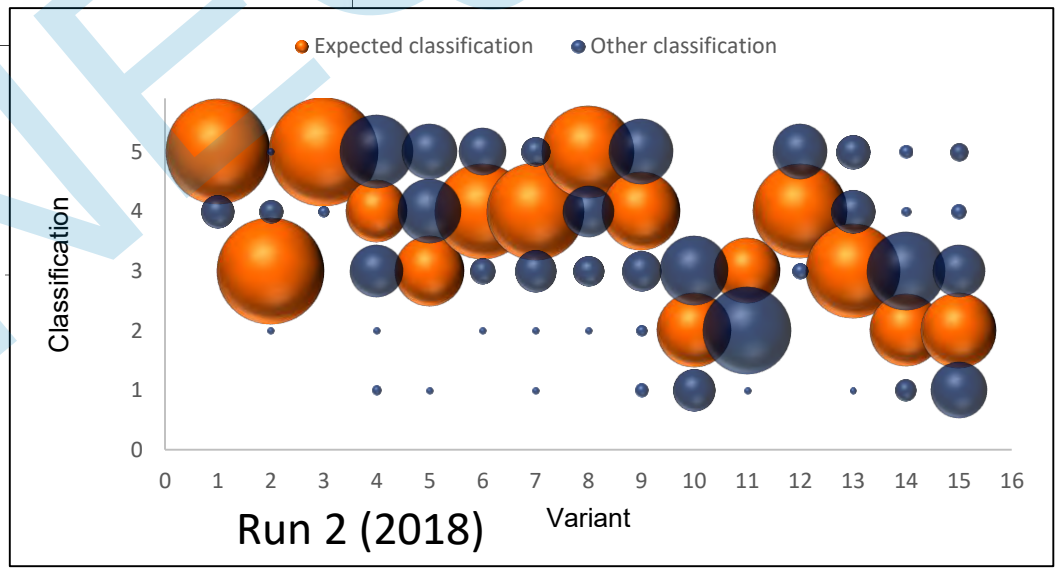
BRCA1/BRCA2 variant classification (G-TACT)



Run 1 (2017)

Classification variation is of greater concern where it crosses the pathogenic/ benign categories.

Run 3 (2019) has just closed.



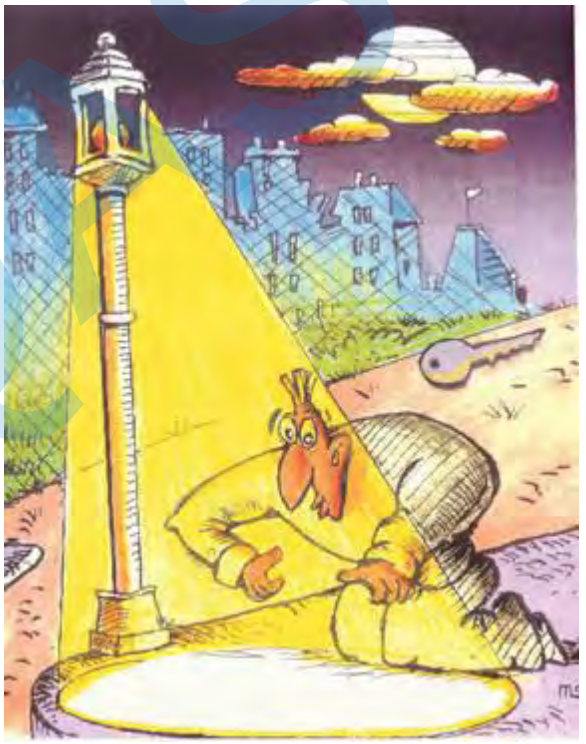
Run 2 (2018)

Variant classification EQAs:

- Disease based EQAs
- Pathogenicity of Sequence Variants EQA (germline and somatic)
- GTACT: Variant interpretation

EQA for Variant Validation

WES/Trio analysis for ultra rare conditions

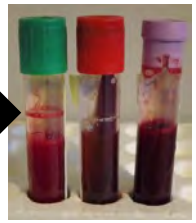


- Variants detected in novel genes
- Genes not yet linked to the phenotype
- Poorly sequenced genes
- Issues with pseudogenes
- Mosaicism
- Variant types not detected (structural rearrangements, tandem repeats, deep intronic splicing and regulatory variants)

End to End testing

Pre-test consultation/ Referral | Sample | Analysis | Interpretation | Reporting | MDT | Consultation

Pre-test referral



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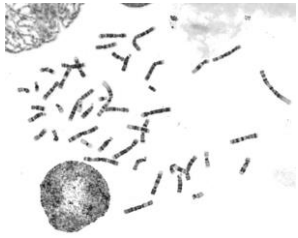
DNA extraction DNA quality

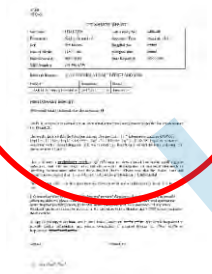
DNA quantity



Analysis – online images/ genotyping accuracy /technical

Interpretation

Reporting



Consultation

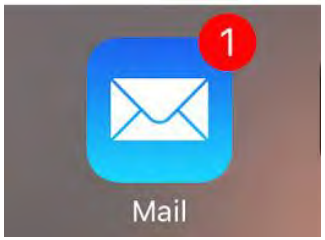
Reporting EQAs

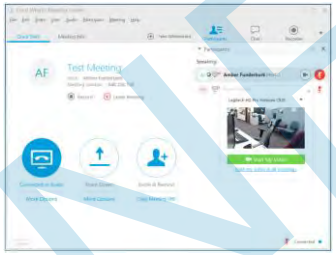
Producing a clear, concise clinical report

- Length of report
- Comprehensive details of technology used, panel details, use of websites
- Limitations of test
- Details of variants included (benign and VUS)

Genomic MDT meetings

Does this variant in this gene fit this patient's phenotype?





Scientific knowledge of gene structure, function, previously identified variants and disease mechanism.

+

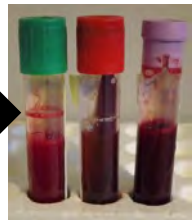
Clinical knowledge of the patient and their family's medical history.

End to End testing

Pre-test consultation/ Referral | Sample | Analysis | Interpretation | Reporting | MDT | Consultation

Pre-test referral

Consultation



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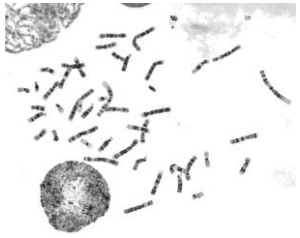
DNA extraction DNA quality

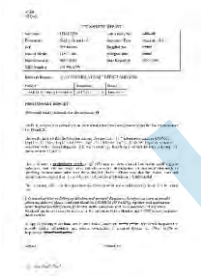
DNA quantity



Analysis – online images/ genotyping accuracy /technical

Interpretation

Reporting



Consultation: Clinical Genetics EQAs

- **Pre- & Post- test** clinical genetics case scenarios
- **Referral letter** from general practitioner or clinician
- **Clinical information given sequentially** with questions online

- **Images of patients** and **family history**
- **Test results with interpretation** (for post-test counselling)

- **Monogenic**
- **Oncogenetic**
- **Dysmorphology**
- **Cardiovascular**

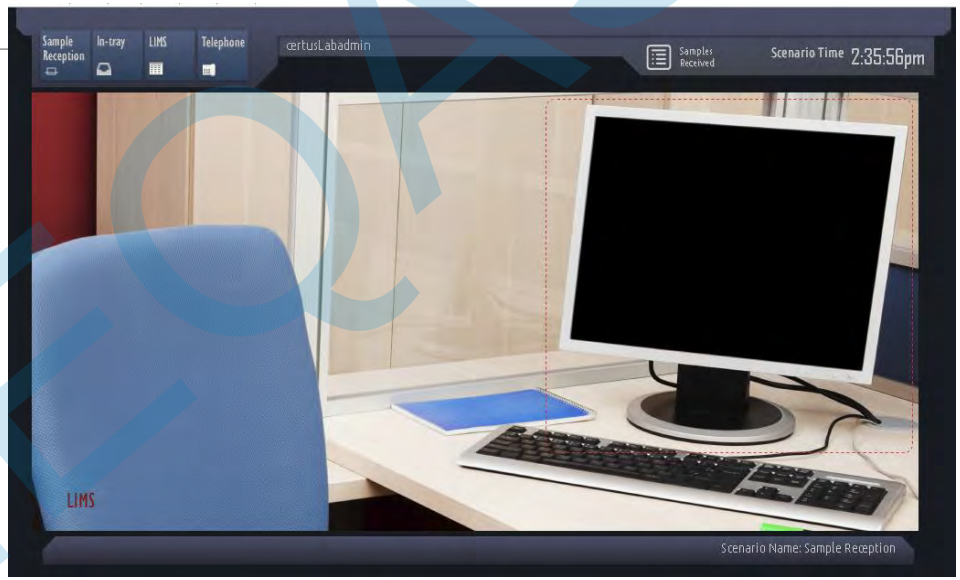
- **All based on a real patient referral.**

Individual Genomics Training, Assessment and Competence Tool

GTACT

Laboratory based

Clinician based

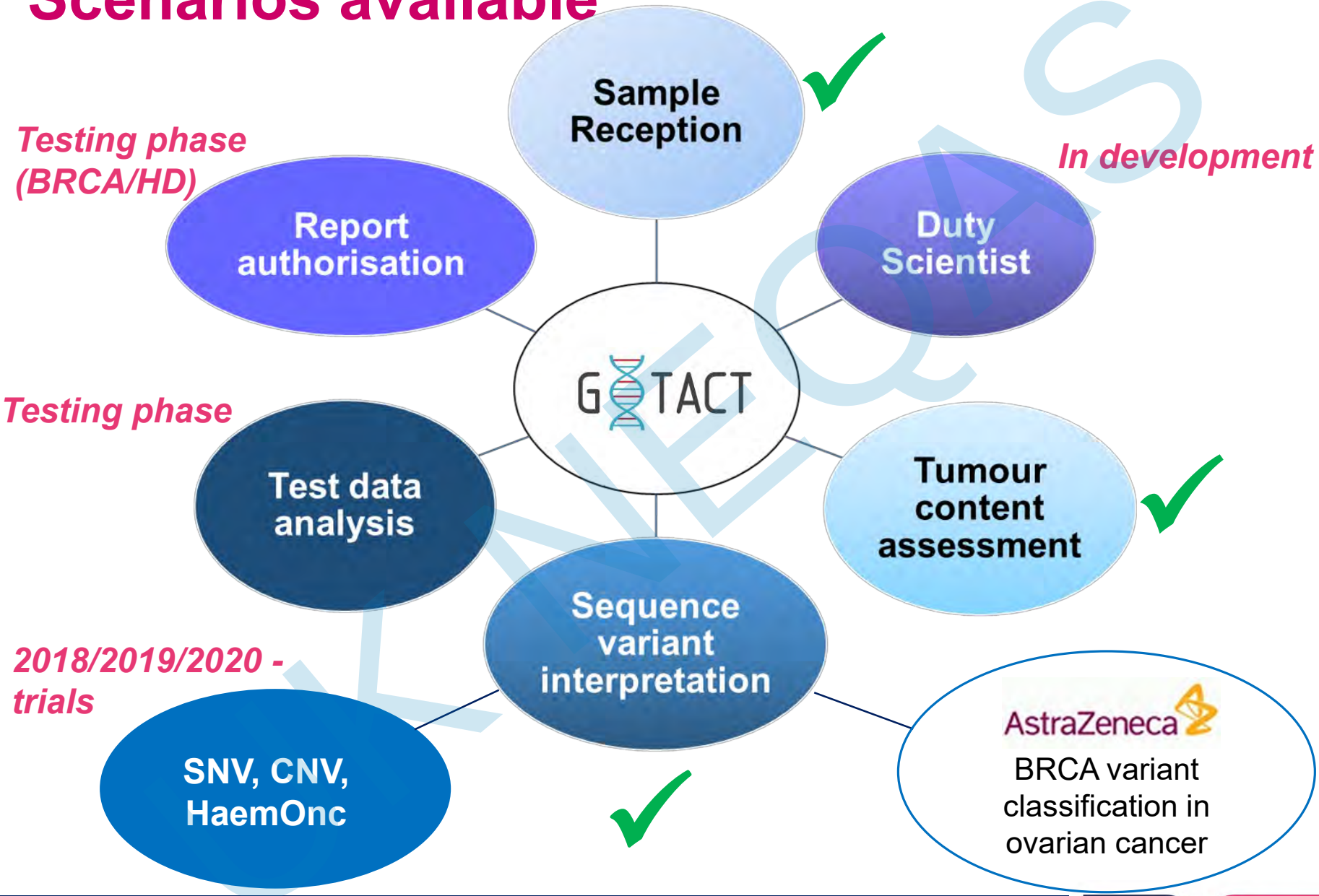


Interactive

- Click on in tray to view samples
- …Or the door to leave

GenQA GENOMICS QUALITY ASSESSMENT

Scenarios available



GTACT going forward

Fixed modules:

- ***BRCA* variant assessment run 4**
  Determining if genetic changes in *BRCA1 and BRCA2* gene are causing ovarian cancer
- **SNV Trial Run 2**
  Second free trial for determining if small genetic changes are disease causing
- **HaemOnc Trial Run 1**
  Determining genomic cause of Haematological Malignancies
- **CNV Trial Run 1**
  Determining if deletions or duplications of the genome are disease causing.

Expanding scope:

- **Sample reception:** increase sample types and referrals
- **Variant Analysis:** increase number of variants
- **Data analysis:** increase data types e.g. FraX, arrays, karyotyping
- **Report Authorisation:** add other disorders e.g CF
- **Cytogenomic** modules for karyotyping and other cytogenomic techniques e.g. FISH
- **Genetic counselling** modules e.g. pedigrees

Genomics EQA future and expanding scope

- **How do we cover all genomic tests?**
  - Provide more panel EQAs defined by clinical indication rather than genetic disorder.
  - Increase number of online assessments

- **Direct to Consumer testing**
- **Point of Care Testing (POCT)**
- **Whole Exome Sequencing/trio analysis (interpretation)**
- **Multifactorial disorders and polygenic risk scores**

Collaborations:

UKNEQAS LI:	CLL TP53 variant detection (pilot)
	CLL IGHV mutation status (pilot)
IQNPath:	cfDNA testing for *EGFR* in lung cancer
	Tumour mutation burden
Biorad:	ddPCR (droplet-digital PCR) - to measure DNA concentration

UK NEQAS Leucocyte Immunophenotyping

IQNPath International Quality Network for Pathology

BIO-RAD

GenQA GENOMICS QUALITY ASSESSMENT

EQA news for 2020

We are modifying our EQAs to adapt to the needs of our participants and the implementation of gene panel testing, so they are based on clinical indications rather than single gene test.

GenQA GENOMICS QUALITY ASSESSMENT
Member of UK NEQAS consortium

New for 2020

- **Disorders of Sexual Development (DSD)**
  (Congenital adrenal hypoplasia, Androgen insensitivity, *SHOX*)
- **Epilepsy Disorders**
  (includes tuberous sclerosis, Rett syndrome, Dravet syndrome)
- **Respiratory disorders**
  (*FLCN*-related disorders and Pulmonary Arterial Hypertension)
- **Renal Disorders**
  (Alport syndrome and Polycystic kidney disease)
- **Osteogenesis Imperfecta (OI)**
- **Infertility (CF, POF, Ydel)** (interpretation only)
- **Pathogenicity of Somatic Variants** (classification only)
- **NGS Copy Number Variant (CNV)**
- **SCID new-born screening** (TREC detection)
- **CLL *TP53* variant detection** (In collaboration with UK NEQAS LI)
- **CLL IGHV mutation status** (In collaboration with UK NEQAS LI)
- **Microdeletion syndromes**
- ***NTRK* fusions**
- **Endocrine tumours (somatic)**
- **Tumour mutation burden**
- **Genetic Counselling** (If interested please contact GenQA)
- **Linkage analysis for HD, CF and DMD** (interpretation only)

Updated EQA for 2020

- **Cardiac Disorders** (previously Arrhythmia/Cardiomyopathies)
  (also includes aortic dissection e.g. Marfan syndrome)
- **Neurodegenerative Disorders** (previously Dementia and ALS)
  (also includes Parkinson disease)
- **Muscular Dystrophies** (previously DMD/BMD)
  (also includes Limb-girdle, Emery Dreifuss and Congenital muscular dystrophies)
- **Inherited Colorectal Cancer and Polyposis syndromes**
  (combined Lynch syndrome and Polyposis syndromes)
- **Inborn Errors of Metabolism** (previously Fabry disease)
  (Fabry disease, Tay Sachs and Gaucher syndrome)
- **Neurofibromatosis type 1 and Rasopathies** (previously NF1/NF2)
  (Neurofibromatosis types 1/2 and Noonan syndrome)
- **Eye Disorders** (previously Retinopathies)
  (retinopathies, structural eye disorders and albinism)
- **Imprinting Disorders** (previously UPD/Imprinting)
  (Beckwith Wiedemann, Angelman and Silver Russell syndromes)
- **Lung Cancer/Additional Lung Cancer** choose one of:
  1) *EGFR* only, 2) core (*EGFR, ALK and ROS1*, 3) comprehensive (*EGFR, ALK, ROS1, KRAS, BRAF, PIK3CA, RET, MET*), 4) fusions (*ALK, ROS1, RET, MET*)
- **Colorectal Cancer** - choose one of:
  1) core (*KRAS, NRAS, BRAF*, 2) Mismatch repair (core + *MLH1* promoter methylation), 3) Extended mismatch repair (mismatch repair + MSI)
- **Pathogenicity of Sequence Variants** – choose either:
  Classification only: submit a proforma
  Classification and clinical interpretation: submit a clinical report

Further details on these EQAs, and the complete list of GenQA 2020 EQAs, is available at www.genqa.org/eqa

Acknowledgements

UK NEQAS
International Quality Expertise

- Sample sourcing & validation laboratories
- Scientific advisory groups (SAGs)
- Peer assessors
- GenQA team

Public Health England

UK Newborn Screening Laboratories Network

IQNPath
International Quality Network for Pathology

Genomics england

The participants

NHS England

CDC
Centers for Disease Control and Prevention

AstraZeneca

BIO-RAD

EMQN
The European Molecular Genetics Quality Network

Contact us on info@genqa.org

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GenQA GENOMICS QUALITY ASSESSMENT

UK NEQAS
International Quality Expertise

50 Years as World Leaders in EQA 1969–2019

External Quality Assessment and the Patient's Journey

Representatives from UK NEQAS Schemes

Sanjiv Rughooputh:	UK NEQAS for Microbiology
Andrew Dodson:	UK NEQAS for Immunocytochemistry & In-Situ Hybridisation
Jenni Fairley:	GenQA – Genomics External Quality Assessment
Tony O' Grady:	UK NEQAS ICC & ISH Assessor

Our Patient

Male

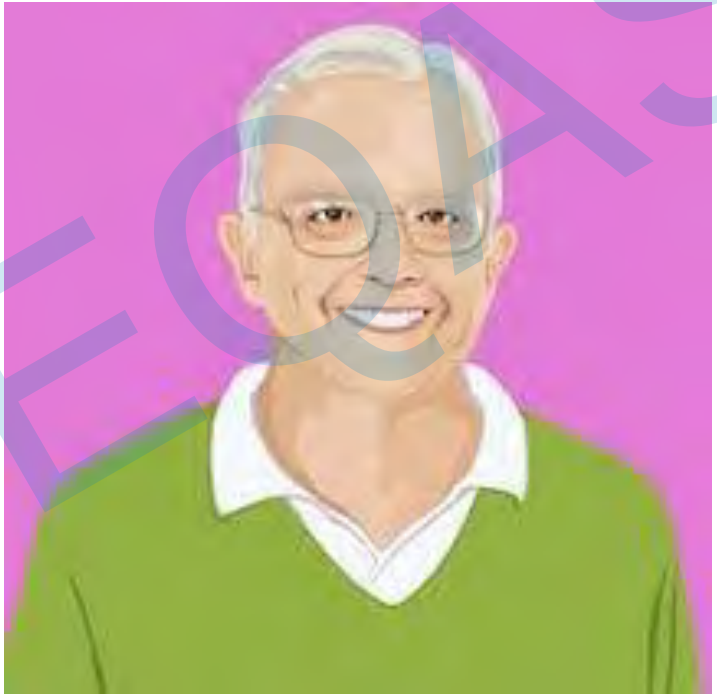
55 years of age

Light smoker

Persistent cough >1 month

GP

- Sputum & Blood
- X-ray



UK NEQAS
International Quality Expertise

50 Years as World Leaders in EQA 1969–2019

UK NEQAS for Microbiology

Dr Sanjiv Rughooputh
Director

UK NEQAS
International Quality Expertise

50 Years as World Leaders in EQA 1969–2019

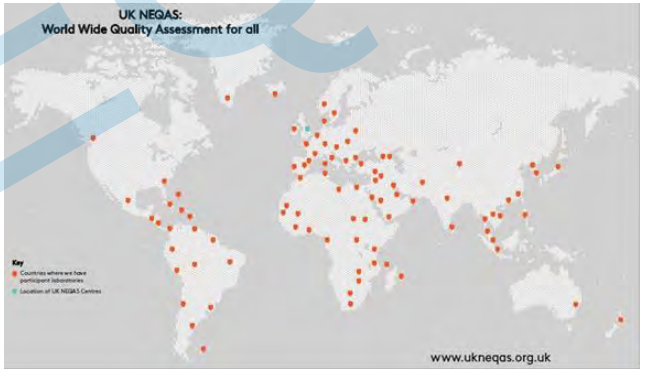
United Kingdom National External Quality Assessment Service

UK NEQAS
International Quality Expertise

50 Years as World Leaders in EQA 1969–2019

Worldwide excellence

- 26 Centres
- 390 Schemes
- Over 8,000 participants worldwide
- Qualitative, quantitative and interpretative investigations in reproductive science, cellular pathology, clinical chemistry, genetics, haematology, immunology and Microbiology



UK NEQAS
International Quality Expertise

50 Years as World Leaders in EQA 1969–2019

UK NEQAS for Microbiology

50 accredited schemes

80 countries worldwide

174 different specimen designed

189 Different reports generated

11181 subscriptions

~ 200,000 specimens annually

If stacked ~ 8000m Height of Broad peak

UK NEQAS
International Quality Expertise

Microbiology

50 Years as World Leaders in EQA 1969–2019

UK NEQAS for Microbiology, P O Box 63003, NW9 1GH
Tel: +44 (0)20 8905 9890 Fax: +44 (0)20 8205 1488 email: organiser@ukneqasmicro.org.uk web: http://www.ukneqasmicro.org.uk

Schemes Available

Bacteriology
AAFB microscopy
Antimicrobial susceptibility
C. difficile
Community medicine
Faecal pathogens (Overseas only)[11]
General bacteriology
General bacteriology & Antimicrobial susceptibility
Genital pathogens
MRSA screening
Mycobacteria culture
Syphilis serology
Urinary antigens[1]

Molecular
CMV DNA quantification
EBV DNA quantification
HBV DNA quantification
Hepatitis C RNA detection[2]
HIV1 RNA quantification
Molecular detection of *C. trachomatis & N. gonorrhoeae*
Molecular detection of HEV RNA[12]
Molecular detection of HPV
Molecular detection of mycobacteria
Molecular detection of respiratory viruses
Molecular detection of viruses in CSF[3]

Mycology
Antifungal susceptibility
Cryptococcal antigen detection[13]
Fungal biomarkers
Mycology culture

Mycology Teaching Programme
Mycology teaching[14]

Parasitology
Blood parasitology
Faecal parasitology
Malaria rapid
Molecular detection of malaria
Parasite serology
Toxoplasma serology[4]

Parasitology Teaching Scheme
Blood programme
Faecal programme

Virology
Anti-HBs detection
Blood Borne viruses[5]
Blood Donor screen[6]
Diagnostic serology (hepatitis screen)[9]
Hepatitis B serology
Hepatitis C serology
Hepatitis E serology[15]
HIV Point of Care
HIV serology
Immunity screen[7]
Measles & mumps IgG serology
Parvovirus B19 and Rubella serology[8]
Respiratory rapid: RSV
Rubella IgG serology
Viral gastroenteritis[10]
Virus identification

1 Includes legionella and pneumococcal antigens
2 Qualitative detection, quantitation and genotype
3 Detection of HSV DNA, VZV DNA and Enterovirus RNA
4 Includes Toxoplasma IgM, IgG and avidity
5 Blood Borne viruses includes screening for HBsAg, HIV Ag/Ab and HCV Ag/Ab (6 distributions)
6 Blood Donor screen includes screening for HBsAg, anti-HBc, HIV Ag/Ab, HCV Ag/Ab, anti-HTLVI/II and *T. pallidum*
7 Parvovirus B19 and Rubella serology includes Parvovirus B19 IgM/IgG and Rubella IgM/IgG serology
8 Hepatitis screen includes HAV IgM, CMV IgM, acute EBV markers
9 Detection of IgG antibodies to HAV, CMV and VZV
10 Suitable for both nucleic acid and antigen detection methods
11 Trial distribution suitable for participants new to EQA participation
12 New for 2018-19: Molecular detection of HEV RNA (scored on qualitative, (quantitative/genotype can be reported but not scored))[14]
13 New for 2018-19: Cryptococcal antigen detection (qualitative detection)
14 New for 2018-19: Mycology teaching, one day course for one person
15 New for 2018-19: Hepatitis E serology (IgM and IgG)

Please see UKAS Reference No. 4715 for full schedule of accreditation for Microbiology
Please see UKAS Reference No. 7512 for full schedule of accreditation for Parasitology

Published: 11.04.2018 Expires: NA

Possible aetiology?

A man, 55-years of age consults his GP because he has been suffering with a persistent cough for more than one month. The cough is becoming worse despite treatments advised by pharmacist.

The GP takes sputum and blood samples and orders an x-ray.

Pneumonia

- Bacterial causes - *Streptococcus pneumoniae*, *Haemophilus influenzae*
- Viral causes: Influenza viruses, parainfluenza viruses, adenoviruses,
- Atypical – Mycoplasma, Chlamydia, Coxiella
- Fungal - *Aspergillus fumigatus*

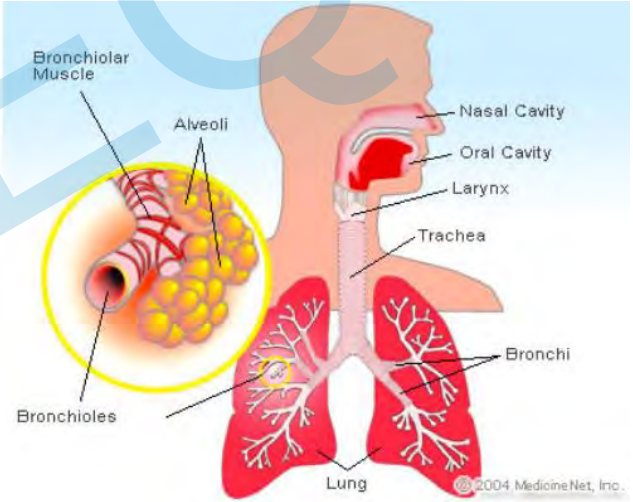
COPD infective exacerbation:

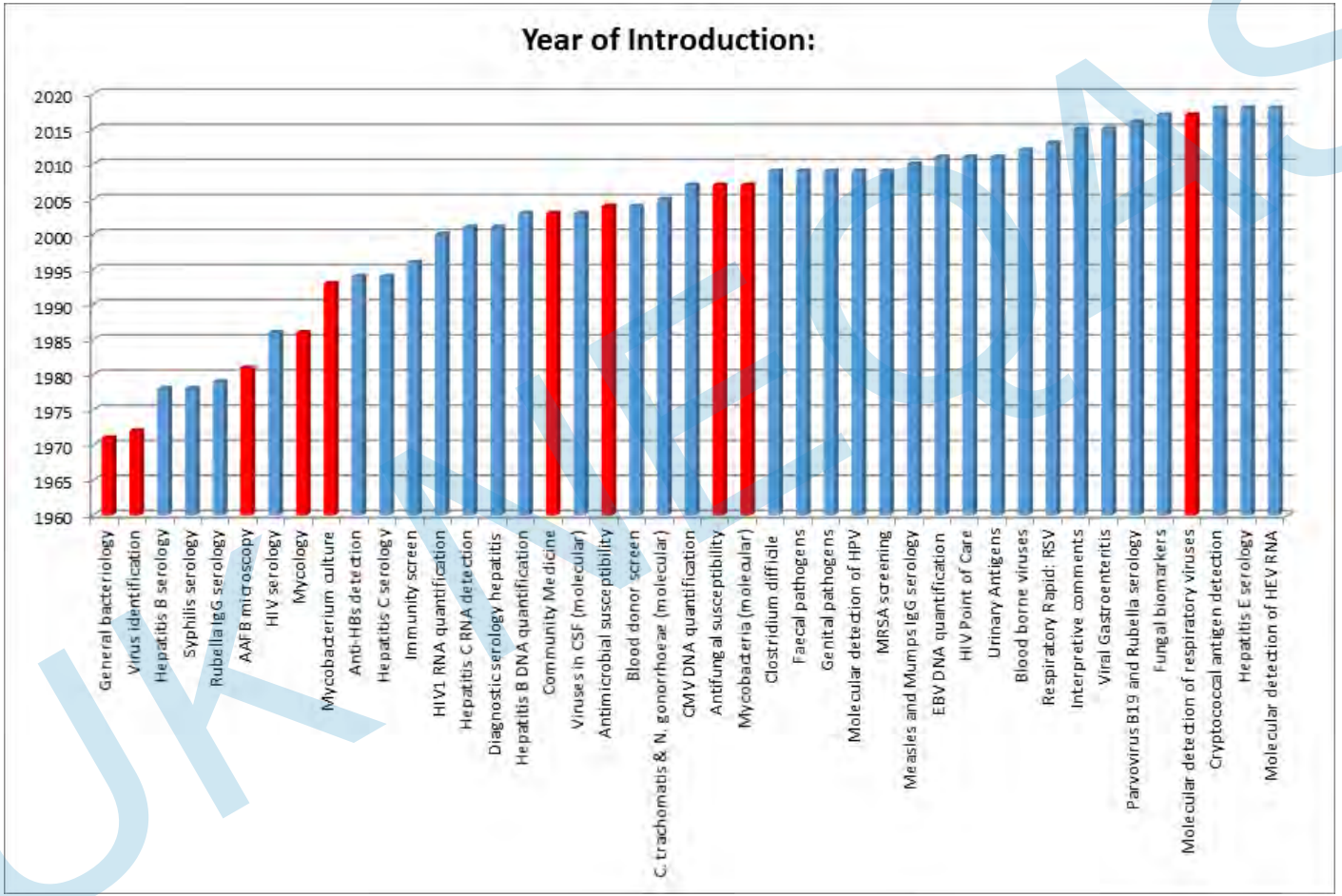
- *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella cattarhalis*

Bronchiectasis

- Variable NB. *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Staphylococcus aureus*

Tuberculosis?

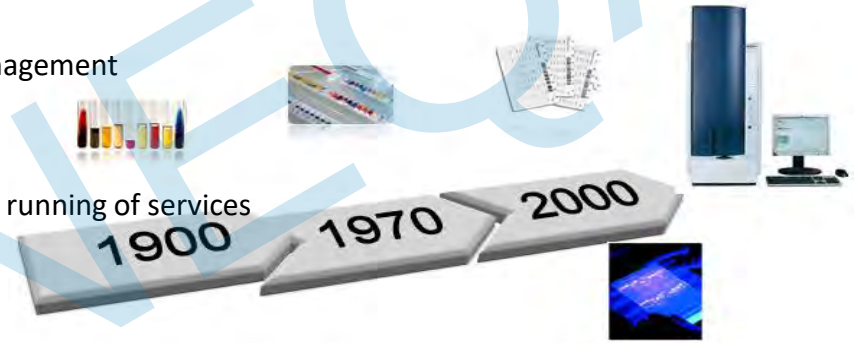



Year of Introduction:
2020
2015
2010
2005
2000
1995
1990
1985
1980
1975
1970
1965
1960
General bacteriology
Virus identification
Hepatitis B serology
Syphilis serology
Rubella IgG serology
AAFB microscopy
HIV serology
Mycology
Mycobacterium culture
Anti-HBs detection
Hepatitis C serology
Immunity screen
HIV1 RNA quantification
Hepatitis C RNA detection
Diagnostic serology hepatitis
Hepatitis B DNA quantification
Community Medicine
Viruses in CSF (molecular)
Antimicrobial susceptibility
Blood donor screen
C. trachomatis & N. gonorrhoeae (molecular)
CMV DNA quantification
Antifungal susceptibility
Mycobacteria (molecular)
Clostridium difficile
Faecal pathogens
Genital pathogens
Molecular detection of HPV
MRSA screening
Measles and Mumps IgG serology
EBV DNA quantification
HIV Point of Care
Urinary Antigens
Blood borne viruses
Respiratory Rapid: RSV
Interpretive comments
Viral Gastroenteritis
Parvovirus B19 and Rubella serology
Fungal biomarkers
Molecular detection of respiratory viruses
Cryptococcal antigen detection
Hepatitis E serology
Molecular detection of HEV RNA

Evolution of microbial Identification

This paradigm shift poses a challenge to the laboratories to ensure that the results are:

- Rapid – impact on patient management
- Cost effective – impact on running of services
- Meaningful – impact on treatment
- Accurate for microbial identification – antimicrobial stewardship



Molecular approach

- **Multiple pathogens assays are pushing towards syndromic panel based testing in microbiology**
- EQA for POCT devices in near patient testing set up that can adapt to different technologies
- Design and develop new molecular based EQA for aetiological agents
- Viral causes: Influenza viruses, RSV, parainfluenza viruses, adenoviruses

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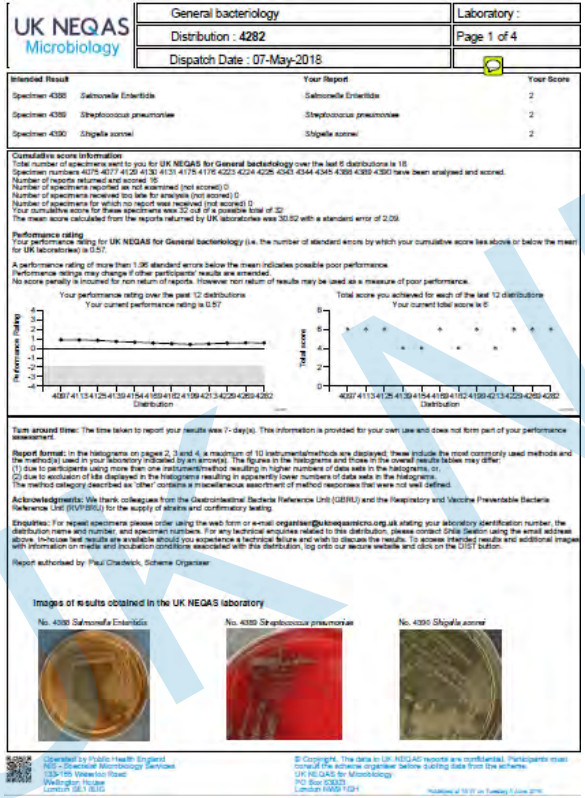
Helping hands for your peace of mind



UK NEQAS Microbiology

General bacteriology	Laboratory :
Distribution : 4282	Page 1 of 4
Dispatch Date : 07-May-2018	

Intended Result		Your Report	Your Score
Specimen 4388	*Salmonella* Enteritidis	*Salmonella* Enteritidis	2
Specimen 4389	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	2
Specimen 4390	*Shigella sonnei*	*Shigella sonnei*	2

Cumulative score information
Total number of specimens sent to you for **UK NEQAS for General bacteriology** over the last 6 distributions is 18.
Specimen numbers 4075 4127 4129 4130 4131 4175 4176 4223 4224 4225 4343 4344 4345 4388 4389 4390 have been analysed and scored.
Number of reports returned and scored: 16
Number of specimens reported as not examined (not scored) 0
Number of specimens received too late for analysis (not scored) 0
Number of specimens for which no report was received (not scored) 0
Your cumulative score for these specimens was 32 out of a possible total of 32.
The mean score calculated from the reports returned by UK laboratories was 30.82 with a standard error of 2.09.

Performance rating
Your performance rating for **UK NEQAS for General bacteriology** (i.e. the number of standard errors by which your cumulative score lies above or below the mean for UK laboratories) is 0.57.

A performance rating of more than 1.96 standard errors below the mean indicates possible poor performance.
Performance ratings may change if other participants' results are amended.
No score penalty is incurred for non return of reports. However, non return of results may be used as a measure of poor performance.

Your performance rating over the past 12 distributions
Your current performance rating is 0.57

Total score you achieved for each of the last 12 distributions
Your current total score is 6

Turn around time: The time taken to report your results was 7- day(s). This information is provided for your own use and does not form part of your performance assessment.

Report format: In the histograms on pages 2, 3 and 4, a maximum of 10 instruments/methods are displayed, these include the most commonly used methods and the method(s) used in your laboratory indicated by an arrow(s). The figures in the histograms and those in the overall results tables may differ:
(1) due to participants using more than one instrument/method resulting in higher numbers of data sets in the histograms, or,
(2) due to exclusion of kits displayed in the histograms resulting in apparently lower numbers of data sets in the histograms.
The method category described as 'other' contains a miscellaneous assortment of method responses that were not well defined.

Acknowledgments: We thank colleagues from the Gastrointestinal Bacteria Reference Unit (GBRU) and the Respiratory and Vaccine Preventable Bacteria Reference Unit (RVPBRU) for the supply of strains and confirmatory testing.

Enquiries: For repeat specimens please order using the web form or e-mail organisers@ukneqasmicro.org.uk stating your laboratory identification number, the distribution name and number, and specimen numbers. For any technical enquiries related to this distribution, please contact Shila Seaton using the email address above. In-house test results are available should you experience a technical failure and wish to discuss the results. To access intended results and additional images with information on media and incubation conditions associated with this distribution, log onto our secure website and click on the DIST button.

Report authorised by: Paul Chadwick, Scheme Organiser

Images of results obtained in the UK NEQAS laboratory

No. 4388 *Salmonella* Enteritidis

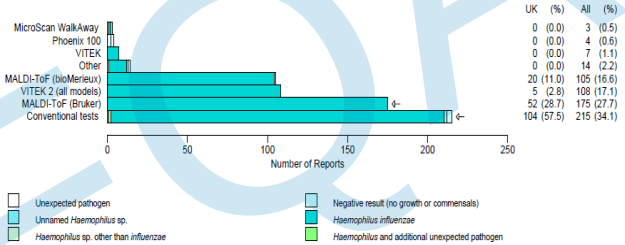
No. 4389 *Streptococcus pneumoniae*

No. 4390 *Shigella sonnei*

Operated by Public Health England
NIS - Standard Microbiology Services
133-155 Waterloo Road
Wellington House
London SE1 8UG

© Copyright. The data in UK NEQAS reports are confidential. Participants must consult the scheme organiser before quoting data from the scheme.
UK NEQAS for Microbiology
PO Box 53325
London NW9 1GH

Specimen : 2970 Sputum: Chest infection in patient with chronic obstructive pulmonary disease (COPD). The presence of significant pathogens was queried. Specimen contained *Haemophilus influenzae*, *Streptococcus mitis* and *Streptococcus salivarius*.



	UK	(%)	All	(%)
	0	(0.0)	3	(0.5)
	0	(0.0)	4	(0.6)
	0	(0.0)	7	(1.1)
	0	(0.0)	14	(2.2)
	20	(11.0)	105	(16.6)
	5	(2.8)	108	(17.1)
	52	(28.7)	175	(27.7)
	104	(57.5)	215	(34.1)

Your Report : *Haemophilus influenzae*
Your Score : 2

Overall Results	UK	All	Score
Unexpected pathogen	0	3	-1
Negative result	2	6	0
Unnamed *Haemophilus* sp.	0	2	0
Haemophilus influenzae	175	572	2
Incorrect *Haemophilus* sp.	0	4	0
Haemophilus & unexpected pathogen	0	3	-1
Total	177	590	
% Correct	98.9	96.9	

Unexpected pathogens with/without *Haemophilus influenzae*:
Burkholderia mallei 1
Moraxella catarrhalis 1
Pasteurella pneumotropica 1
Streptococcus pneumoniae 3

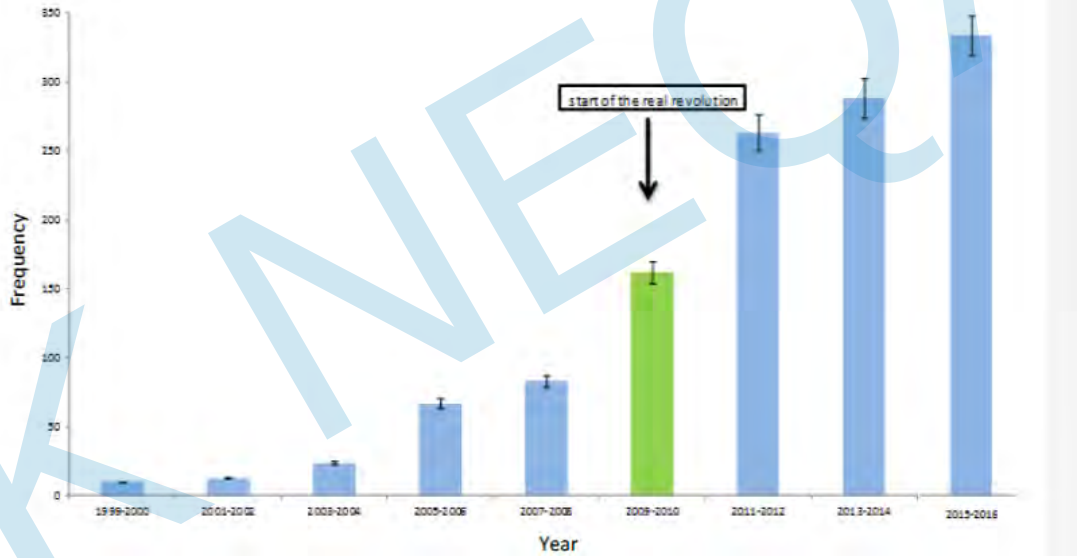
Incorrect species:
H. haemolyticus 1
H. parahaemolyticus 1
H. parainfluenzae 2

Category: Core

Specimen 2970

This specimen contained a *Haemophilus influenzae*.

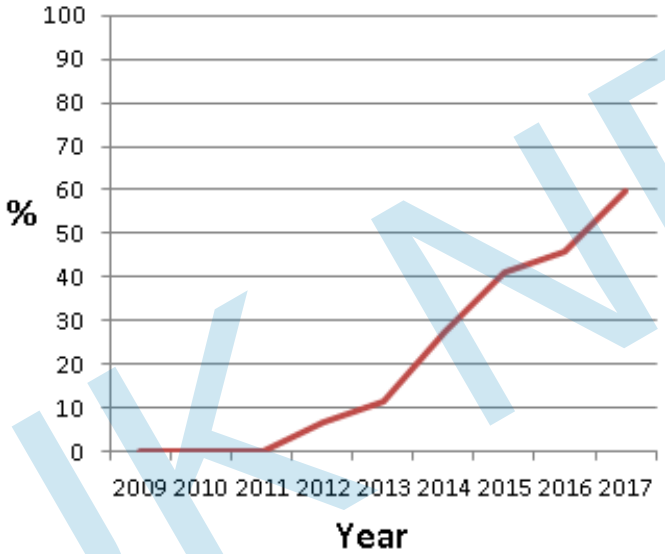
Publications relating to MALDI- ToF in clinical Microbiology



Flaudrops *et al*, 2017

What's in a name?

General Bacteriology



% of UK NEQAS for Microbiology participants using MALDI-ToF for bacterial identification

- Twelve distributions per year of 3 specimens
- Specimens cover different infections
  - include normal flora where applicable
- Challenging
- Educational
- Fit for purpose
- Meet need of participants
- Provide detailed analysis of methods used
- Compare methods

Pneumonia

- Bacterial causes –
  - *Streptococcus pneumoniae*
  - *Haemophilus influenza*
- Fungal -
  - *Aspergillus fumigatus*

COPD infective exacerbation:

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella cattarhalis*

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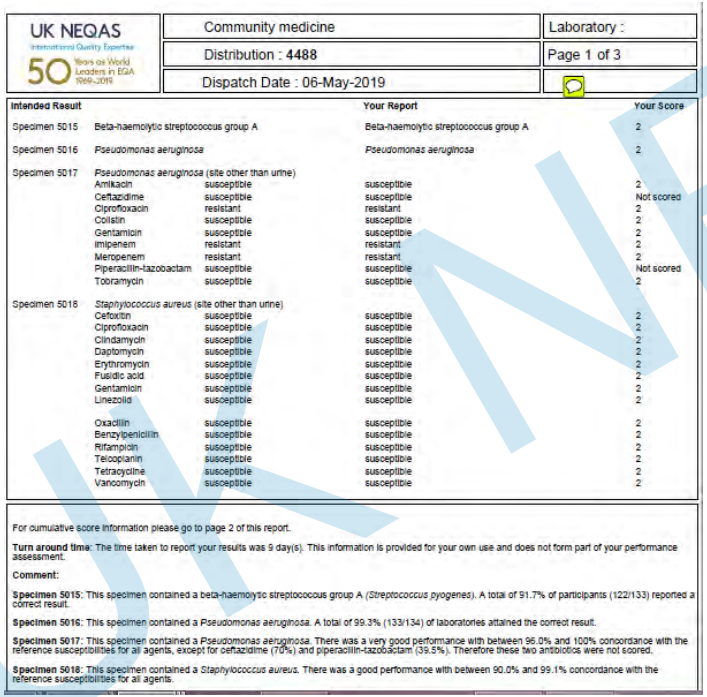
Community medicine



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Community medicine	Laboratory :
Distribution : 4488	Page 1 of 3
Dispatch Date : 06-May-2019	

Intended Result			Your Report		Your Score
Specimen 5015	Beta-haemolytic streptococcus group A		Beta-haemolytic streptococcus group A		2
Specimen 5016	*Pseudomonas aeruginosa*		*Pseudomonas aeruginosa*		2
Specimen 5017	*Pseudomonas aeruginosa* (site other than urine)				
	Amikacin	susceptible	susceptible		2
	Ceftazidime	susceptible	susceptible		Not scored
	Ciprofloxacin	resistant	resistant		2
	Colistin	susceptible	susceptible		2
	Gentamicin	susceptible	susceptible		2
	Imipenem	resistant	resistant		2
	Meropenem	resistant	resistant		2
	Piperacillin-tazobactam	susceptible	susceptible		Not scored
	Tobramycin	susceptible	susceptible		2
Specimen 5018	*Staphylococcus aureus* (site other than urine)				
	Cefoxitin	susceptible	susceptible		2
	Ciprofloxacin	susceptible	susceptible		2
	Clindamycin	susceptible	susceptible		2
	Daptomycin	susceptible	susceptible		2
	Erythromycin	susceptible	susceptible		2
	Fusidic acid	susceptible	susceptible		2
	Gentamicin	susceptible	susceptible		2
	Linezolid	susceptible	susceptible		2
	Oxacillin	susceptible	susceptible		2
	Benzylpenicillin	susceptible	susceptible		2
	Rifampicin	susceptible	susceptible		2
	Teicoplanin	susceptible	susceptible		2
	Tetracycline	susceptible	susceptible		2
	Vancomycin	susceptible	susceptible		2

For cumulative score information please go to page 2 of this report.

Turn around time: The time taken to report your results was 9 day(s). This information is provided for your own use and does not form part of your performance assessment.

Comment:

Specimen 5015: This specimen contained a beta-haemolytic streptococcus group A (*Streptococcus pyogenes*). A total of 91.7% of participants (122/133) reported a correct result.

Specimen 5016: This specimen contained a *Pseudomonas aeruginosa*. A total of 99.3% (133/134) of laboratories attained the correct result.

Specimen 5017: This specimen contained a *Pseudomonas aeruginosa*. There was a very good performance with between 96.0% and 100% concordance with the reference susceptibilities for all agents, except for ceftazidime (70%) and piperacillin-tazobactam (39.5%). Therefore these two antibiotics were not scored.

Specimen 5018: This specimen contained a *Staphylococcus aureus*. There was a good performance with between 90.0% and 99.1% concordance with the reference susceptibilities for all agents.

- EQA for laboratories providing clinical diagnostic bacteriology services at the community laboratory level
- a laboratory type more common on mainland Europe;
- Isolation and identification of potential pathogens, and determination of antimicrobial susceptibilities of various genera of micro organisms, by conventional and molecular methodologies
- Four distributions of 4 (2+2) specimens

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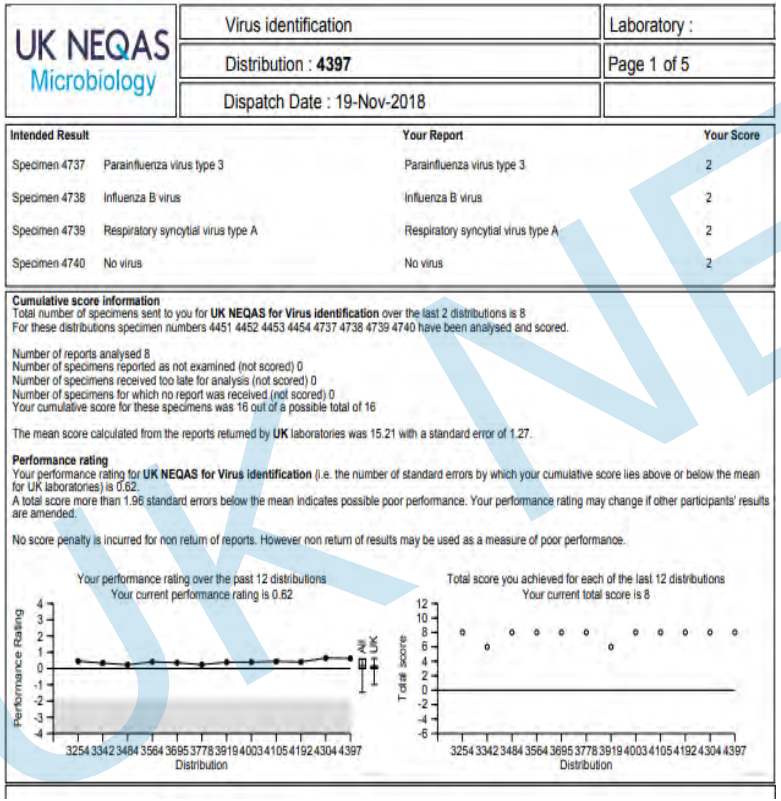
Viral identification



UK NEQAS Microbiology

Virus identification | Laboratory :
Distribution : **4397** | Page 1 of 5
Dispatch Date : 19-Nov-2018

Intended Result		Your Report	Your Score
Specimen 4737	Parainfluenza virus type 3	Parainfluenza virus type 3	2
Specimen 4738	Influenza B virus	Influenza B virus	2
Specimen 4739	Respiratory syncytial virus type A	Respiratory syncytial virus type A	2
Specimen 4740	No virus	No virus	2

Cumulative score information
Total number of specimens sent to you for **UK NEQAS for Virus identification** over the last 2 distributions is 8
For these distributions specimen numbers 4451 4452 4453 4454 4737 4738 4739 4740 have been analysed and scored.

Number of reports analysed 8
Number of specimens reported as not examined (not scored) 0
Number of specimens received too late for analysis (not scored) 0
Number of specimens for which no report was received (not scored) 0
Your cumulative score for these specimens was 16 out of a possible total of 16

The mean score calculated from the reports returned by **UK** laboratories was 15.21 with a standard error of 1.27.

Performance rating
Your performance rating for **UK NEQAS for Virus identification** (i.e. the number of standard errors by which your cumulative score lies above or below the mean for UK laboratories) is 0.62.
A total score more than 1.96 standard errors below the mean indicates possible poor performance. Your performance rating may change if other participants' results are amended.

No score penalty is incurred for non return of reports. However non return of results may be used as a measure of poor performance.

- Established 1972
- EQA for laboratories determining the presence of cultivable virus in clinical samples.
- Identity of the virus/es present by :
  - culture
  - molecular
  - immunofluorescence
- The scheme has two distributions of 4 specimens annually.
- The winter distribution mostly include respiratory viruses such as influenza, parainfluenza, RSV etc
- The summer distributions include: measles, enteroviruses, CMV,HSV

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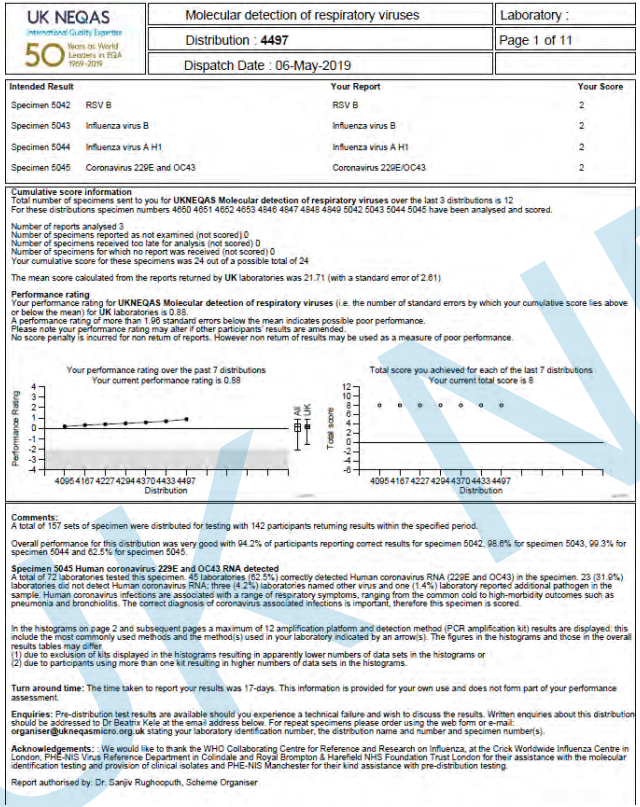
Molecular detection of respiratory viruses



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Molecular detection of respiratory viruses	Laboratory :
Distribution : **4497**	Page 1 of 11
Dispatch Date : 06-May-2019	

Intended Result		Your Report	Your Score
Specimen 5042	RSV B	RSV B	2
Specimen 5043	Influenza virus B	Influenza virus B	2
Specimen 5044	Influenza virus A H1	Influenza virus A H1	2
Specimen 5045	Coronavirus 229E and OC43	Coronavirus 229E/OC43	2

Cumulative score information
Total number of specimens sent to you for **UKNEQAS Molecular detection of respiratory viruses** over the last 3 distributions is 12
For these distributions specimen numbers 4650 4651 4652 4653 4646 4647 4648 4649 5042 5043 5044 5045 have been analysed and scored.

Number of reports analysed 3
Number of specimens reported as not examined (not scored) 0
Number of specimens received too late for analysis (not scored) 0
Number of specimens for which no report was received (not scored) 0
Your cumulative score for these specimens was 24 out of a possible total of 24

The mean score calculated from the reports returned by **UK** laboratories was 21.71 (with a standard error of 2.61)

Performance rating
Your performance rating for **UKNEQAS Molecular detection of respiratory viruses** (i.e. the number of standard errors by which your cumulative score lies above or below the mean) for **UK** laboratories is 0.88.
A performance rating of more than 1.96 standard errors below the mean indicates possible poor performance.
Please note your performance rating may alter if other participants' results are amended.
No score penalty is incurred for non return of reports. However non return of results may be used as a measure of poor performance.

Comments:
A total of 157 sets of specimen were distributed for testing with 142 participants returning results within the specified period.

Overall performance for this distribution was very good with 94.2% of participants reporting correct results for specimen 5042, 98.6% for specimen 5043, 99.3% for specimen 5044 and 62.5% for specimen 5045.

Specimen 5045 Human coronavirus 229E and OC43 RNA detected
A total of 72 laboratories tested this specimen. 45 laboratories (62.5%) correctly detected Human coronavirus RNA (229E and OC43) in the specimen. 23 (31.9%) laboratories did not detect Human coronavirus RNA; three (4.2%) laboratories named other virus and one (1.4%) laboratory reported additional pathogen in the sample. Human coronavirus infections are associated with a range of respiratory symptoms, ranging from the common cold to high-morbidity outcomes such as pneumonia and bronchiolitis. The correct diagnosis of coronavirus associated infections is important, therefore this specimen is scored.

In the histograms on page 2 and subsequent pages a maximum of 12 amplification platform and detection method (PCR amplification kit) results are displayed: this include the most commonly used methods and the method(s) used in your laboratory indicated by an arrow(s). The figures in the histograms and those in the overall results tables may differ
(1) due to exclusion of kits displayed in the histograms resulting in apparently lower numbers of data sets in the histograms or
(2) due to participants using more than one kit resulting in higher numbers of data sets in the histograms.

Turn around time: The time taken to report your results was 17-days. This information is provided for your own use and does not form part of your performance assessment.

Enquiries: Pre-distribution test results are available should you experience a technical failure and wish to discuss the results. Written enquiries about this distribution should be addressed to Dr Beatrix Kele at the email address below. For repeat specimens please order using the web form or e-mail: **organiser@uknegasmicro.org.uk** stating your laboratory identification number, the distribution name and number and specimen number(s).

Acknowledgements: : We would like to thank the WHO Collaborating Centre for Reference and Research on Influenza, at the Crick Worldwide Influenza Centre in London, PHE-NIS Virus Reference Department in Colindale and Royal Brompton & Harefield NHS Foundation Trust London for their assistance with the molecular identification testing and provision of clinical isolates and PHE-NIS Manchester for their kind assistance with pre-distribution testing.

Report authorised by: Dr. Sanjiv Rughooputh, Scheme Organiser

- **Suitable for Molecular testing**
- **Suitable for POCT devices for Flu, RSV and other respiratory viruses in near patient testing settings**
- **Multi viral pathogens**
- 3 distributions per year with 4 specimens each
- Cover different respiratory specimens
- First 3 specimens contain any of these:
  - **Respiratory syncytial virus**
  - **Influenza A (H1, H3)**
  - **Influenza B**
- The fourth specimen can contain any of the following respiratory viruses: adenoviruses, human enteroviruses, rhinoviruses, human metapneumovirus, human parechoviruses, bocavirus, human coronaviruses and human parainfluenza viruses
- In collaboration with worldwide influenza centre
- Based on WHO vaccine consultations
- Vaccine candidates included in EQA
- Viral causes: Influenza viruses, RSV, parainfluenza viruses, adenoviruses

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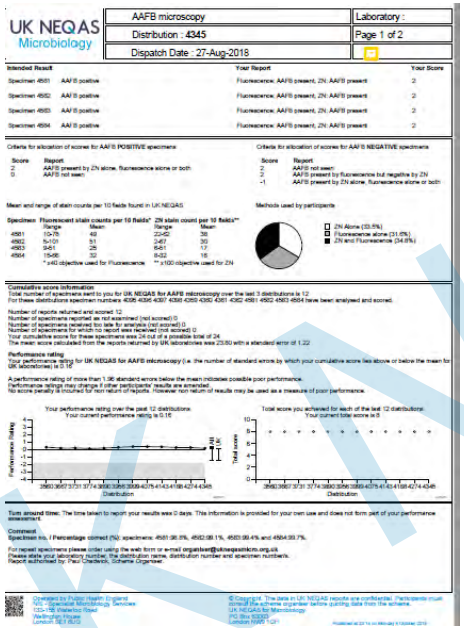
Mycobacterium tuberculosis



UK NEQAS Microbiology

AAFB microscopy | Laboratory :
Distribution : 4345 | Page 1 of 2
Dispatch Date : 27-Aug-2018

Intended Result | Your Report | Your Score

Specimen 4581 AAFB positive | Fluorescence: AAFB present, ZN: AAFB present | 2
Specimen 4582 AAFB positive | Fluorescence: AAFB present, ZN: AAFB present | 2
Specimen 4583 AAFB positive | Fluorescence: AAFB present, ZN: AAFB present | 2
Specimen 4584 AAFB positive | Fluorescence: AAFB present, ZN: AAFB present | 2

Criteria for allocation of scores for AAFB POSITIVE specimens

Score	Report
2	AAFB present by ZN alone, fluorescence alone or both
0	AAFB not seen

Criteria for allocation of scores for AAFB NEGATIVE specimens

Score	Report
2	AAFB not seen
0	AAFB present by fluorescence but negative by ZN
-1	AAFB present by ZN alone, fluorescence alone or both

Mean and range of stain counts per 10 fields found in UK NEQAS

Specimen	Fluorescent stain counts per 10 fields* Range	Mean	ZN stain count per 10 fields** Range	Mean
4581	10-76	49	22-62	39
4582	5-101	51	2-67	30
4583	3-61	25	0-61	17
4584	15-66	32	8-52	16

* x40 objective used for Fluorescence ** x100 objective used for ZN

Methods used by participants

Cumulative score information
Total number of specimens sent to you for UK NEQAS for AAFB microscopy over the last 3 distributions is 12
For these distributions specimen numbers 4586 4587 4588 4585 4581 4582 4583 4584 have been analysed and scored.

Number of reports returned and scored 12
Number of specimens reported as not examined (not scored) 0
Number of specimens received too late for analysis (not scored) 0
Number of specimens for which no report was received (not scored) 0
Your cumulative score for these specimens was 24 out of a possible total of 24
The mean score calculated from the reports returned by UK laboratories was 23.60 with a standard error of 1.22

Performance rating
Your performance rating for UK NEQAS for AAFB microscopy (i.e. the number of standard errors by which your cumulative score lies above or below the mean for UK laboratories) is 0.16

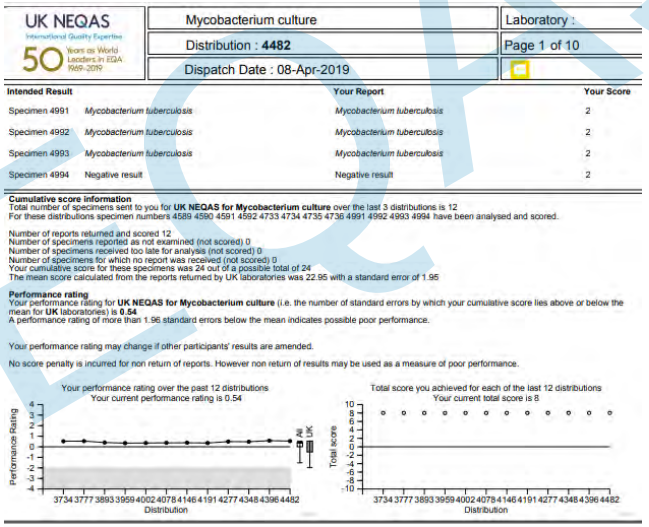
A performance rating of more than 1.96 standard errors below the mean indicates possible poor performance.
Performance ratings may change if other participants' results are amended.
No score penalty is incurred for non return of reports. However non return of results may be used as a measure of poor performance.

Turn around time: The time taken to report your results was 0 days. This information is provided for your own use and does not form part of your performance assessment.

Comment
Specimen No. / Percentage correct (%): specimens: 4581 (96.8%, 4582 88.1%, 4583 99.4% and 4584 99.7%.

For repeat specimens please order using the web form or e-mail organiser@ukneqasmicro.org.uk
Please state your laboratory number, the distribution name, distribution number and specimen numbers.
Report authorised by: Paul Chadwick, Scheme Organiser.

- Established in 1981
- EQA for the detection of AAFB in simulated sputum smears,
- Requires staining and microscopy.
- Three distributions of 4 specimens



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Mycobacterium culture | Laboratory :
Distribution : 4482 | Page 1 of 10
Dispatch Date : 08-Apr-2019

Intended Result	Your Report	Your Score
Specimen 4991 *Mycobacterium tuberculosis*	*Mycobacterium tuberculosis*	2
Specimen 4992 *Mycobacterium tuberculosis*	*Mycobacterium tuberculosis*	2
Specimen 4993 *Mycobacterium tuberculosis*	*Mycobacterium tuberculosis*	2
Specimen 4994 Negative result	Negative result	2

Cumulative score information
Total number of specimens sent to you for **UK NEQAS for Mycobacterium culture** over the last 3 distributions is 12
For these distributions specimen numbers 4589 4590 4591 4592 4733 4734 4735 4736 4991 4992 4993 4994 have been analysed and scored.

Number of reports returned and scored 12
Number of specimens reported as not examined (not scored) 0
Number of specimens received too late for analysis (not scored) 0
Number of specimens for which no report was received (not scored) 0
Your cumulative score for these specimens was 24 out of a possible total of 24
The mean score calculated from the reports returned by UK laboratories was 22.95 with a standard error of 1.95

Performance rating
Your performance rating for **UK NEQAS for Mycobacterium culture** (i.e. the number of standard errors by which your cumulative score lies above or below the mean for **UK** laboratories) is **0.54**
A performance rating of more than 1.96 standard errors below the mean indicates possible poor performance.

Your performance rating may change if other participants' results are amended.

No score penalty is incurred for non return of reports. However non return of results may be used as a measure of poor performance.

- Established in 1993
- EQA for the isolation and identification of Mycobacterial species by:
  - conventional
  - semi automated systems
  - molecular methodologies
  - Three distributions of 4 specimens

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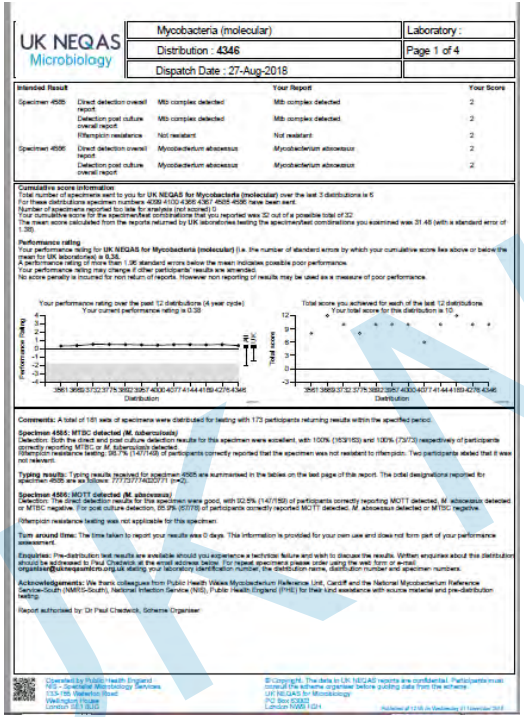
Mycobacteria (molecular)



UK NEQAS Microbiology

Mycobacteria (molecular)	Laboratory :
Distribution : 4346	Page 1 of 4
Dispatch Date : 27-Aug-2018	

Intended Result			Your Report	Your Score
Specimen 4585	Direct detection overall report	Mtb complex detected	Mtb complex detected	2
	Detection post culture overall report	Mtb complex detected	Mtb complex detected	2
	Rifampicin resistance	Not resistant	Not resistant	2
Specimen 4586	Direct detection overall report	Mycobacterium abscessus	Mycobacterium abscessus	2
	Detection post culture overall report	Mycobacterium abscessus	Mycobacterium abscessus	2

Cumulative score information

Total number of specimens sent to you for UK NEQAS for Mycobacteria (molecular) over the last 3 distributions is 6

For these distributions specimen numbers 4099 4100 4366 4367 4585 4586 have been sent.

Number of specimens reported too late for analysis (not scored) 0

Your cumulative score for the specimen/test combinations that you reported was 32 out of a possible total of 32.

The mean score calculated from the reports returned by UK laboratories testing the specimen/test combinations you examined was 31.48 (with a standard error of 1.38).

Performance rating

Your performance rating for UK NEQAS for Mycobacteria (molecular) (i.e. the number of standard errors by which your cumulative score lies above or below the mean for UK laboratories) is 0.38.

A performance rating of more than 1.96 standard errors below the mean indicates possible poor performance.

Your performance rating may change if other participants' results are amended.

No score penalty is incurred for non return of reports. However non reporting of results may be used as a measure of poor performance.

Your performance rating over the past 12 distributions (4 year cycle)
Your current performance rating is 0.38

Performance Rating

Distribution

Total score you achieved for each of the last 12 distributions.
Your total score for this distribution is 10

Total score

Distribution

Comments: A total of 181 sets of specimens were distributed for testing with 173 participants returning results within the specified period.

Specimen 4585: MTBC detected (M. tuberculosis)

Detection: Both the direct and post culture detection results for this specimen were excellent, with 100% (163/163) and 100% (73/73) respectively of participants correctly reporting MTBC or M. tuberculosis detected.

Rifampicin resistance testing: 96.7% (147/149) of participants correctly reported that the specimen was not resistant to rifampicin. Two participants stated that it was not relevant.

Typing results: Typing results received for specimen 4585 are summarised in the tables on the last page of this report. The total designations reported for specimen 4585 are as follows: 777737774422771 (n=2).

Specimen 4586: MOTT detected (M. abscessus)

Detection: The direct detection results for this specimen were good, with 92.5% (147/159) of participants correctly reporting MOTT detected, M. abscessus detected or MTBC negative. For post culture detection, 85.9% (67/78) of participants correctly reported MOTT detected, M. abscessus detected or MTBC negative.

Rifampicin resistance testing was not applicable for this specimen.

Turn around time: The time taken to report your results was 0 days. This information is provided for your own use and does not form part of your performance assessment.

Enquiries: Pre-distribution test results are available should you experience a technical failure and wish to discuss the results. Written enquiries about this distribution should be addressed to Paul Chadwick at the email address below. For repeat specimens please order using the web form or e-mail organiser@ukneqasmicro.org.uk stating your laboratory identification number, the distribution name, distribution number and specimen numbers.

Acknowledgements: We thank colleagues from Public Health Wales Mycobacterium Reference Unit, Cardiff and the National Mycobacterium Reference Service-South (NMRS-South), National Infection Service (NIS), Public Health England (PHE) for their kind assistance with source material and pre-distribution testing.

Report authorised by: Dr Paul Chadwick, Scheme Organiser

Operated by Public Health England
NEQAS Specialist Microbiology Services
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Wellington House
London SE1 8UG

UK NEQAS for Microbiology
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Published at 12:00 on Wednesday 21 November 2018

- Established in 2007
- EQA to establish the absence or presence of
  - *M. tuberculosis*
  - MOTT (Mycobacteria other than tuberculosis)
  - Detection of rifampicin resistance by molecular methods
  - from simulated sputum specimens.
  - Three distributions with 4 specimens

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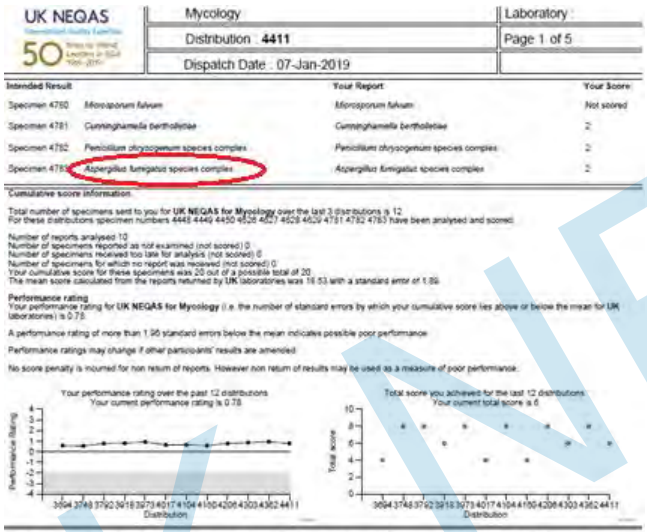
Mycology and antifungals



UK NEQAS | Mycology | Laboratory :
Distribution : 4411 | Page 1 of 5
Dispatch Date : 07-Jan-2019

Intended Result		Your Report	Your Score
Specimen 4780	*Microsporum fulvum*	*Microsporum fulvum*	Not scored
Specimen 4781	*Cunninghamella bertholletiae*	*Cunninghamella bertholletiae*	2
Specimen 4782	*Penicillium chrysogenum* species complex	*Penicillium chrysogenum* species complex	2
Specimen 4783	*Aspergillus fumigatus* species complex	*Aspergillus fumigatus* species complex	2

Cumulative score information

Total number of specimens sent to you for **UK NEQAS for Mycology** over the last 3 distributions is 12
For these distributions specimen numbers 4448 4449 4450 4526 4527 4528 4529 4781 4782 4783 have been analysed and scored.

Number of reports analysed 10
Number of specimens reported as not examined (not scored) 0
Number of specimens received too late for analysis (not scored) 0
Number of specimens for which no report was received (not scored) 0
Your cumulative score for these specimens was 20 out of a possible total of 20.
The mean score calculated from the reports returned by **UK** laboratories was 16.53 with a standard error of 1.89.

Performance rating
Your performance rating for **UK NEQAS for Mycology** (i.e. the number of standard errors by which your cumulative score lies above or below the mean for UK laboratories) is 0.75.

A performance rating of more than 1.96 standard errors below the mean indicates possible poor performance.

Performance ratings may change if other participants' results are amended.

No score penalty is incurred for non return of reports. However non return of results may be used as a measure of poor performance.

Your performance rating over the past 12 distributions
Your current performance rating is 0.75

Performance Rating

Distribution

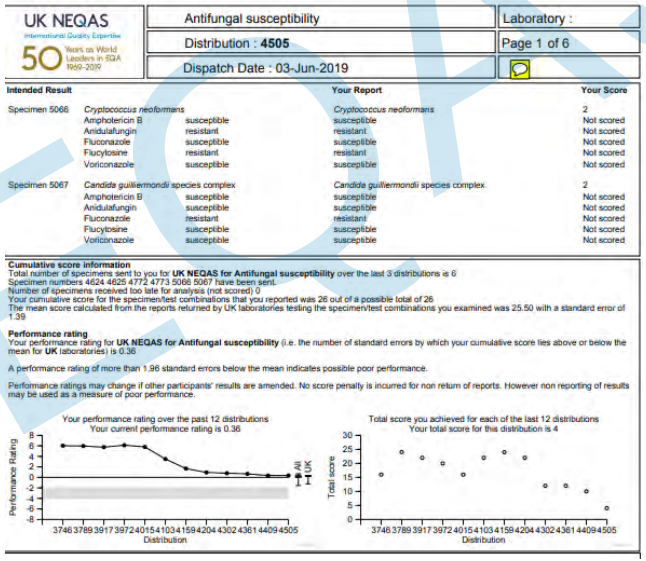
Total score you achieved for the last 12 distributions
Your current total score is 6

Total score

Distribution

Turn around time: The time taken to report your results was 0 days. This information is provided for your own use and does not form part of your performance assessment.

- Established 1986
- EQA for the isolation and identification of various strains of fungi from each phylum, by conventional and molecular methodologies
- Three distributions of 4 specimens
- **Aetiological agent: *Aspergillus fumigatus***



UK NEQAS | Antifungal susceptibility | Laboratory :
Distribution : 4505 | Page 1 of 6
Dispatch Date : 03-Jun-2019

Intended Result			Your Report		Your Score
Specimen 5066	*Cryptococcus neoformans*		*Cryptococcus neoformans*		2
	Amphotericin B	susceptible	susceptible		Not scored
	Anidulafungin	resistant	resistant		Not scored
	Fluconazole	susceptible	susceptible		Not scored
	Flucytosine	resistant	resistant		Not scored
	Voriconazole	susceptible	susceptible		Not scored
Specimen 5067	*Candida guilliermondii* species complex		*Candida guilliermondii* species complex		2
	Amphotericin B	susceptible	susceptible		Not scored
	Anidulafungin	susceptible	susceptible		Not scored
	Fluconazole	resistant	resistant		Not scored
	Flucytosine	susceptible	susceptible		Not scored
	Voriconazole	susceptible	susceptible		Not scored

Cumulative score information
Total number of specimens sent to you for **UK NEQAS for Antifungal susceptibility** over the last 3 distributions is 6
Specimen numbers 4624 4625 4772 4773 5066 5067 have been sent.
Number of specimens received too late for analysis (not scored) 0
Your cumulative score for the specimen/test combinations that you reported was 26 out of a possible total of 26
The mean score calculated from the reports returned by UK laboratories testing the specimen/test combinations you examined was 25.50 with a standard error of 1.39

Performance rating
Your performance rating for **UK NEQAS for Antifungal susceptibility** (i.e. the number of standard errors by which your cumulative score lies above or below the mean for **UK** laboratories) is 0.36

A performance rating of more than 1.96 standard errors below the mean indicates possible poor performance.

Performance ratings may change if other participants' results are amended. No score penalty is incurred for non return of reports. However non reporting of results may be used as a measure of poor performance.

Your performance rating over the past 12 distributions
Your current performance rating is 0.36

Performance Rating

All
UK

Distribution

Total score you achieved for each of the last 12 distributions
Your total score for this distribution is 4

Total score

Distribution

- Established in 2007
- EQA for determination of antifungal susceptibilities from clinically significant yeasts and filamentous fungi such as *Aspergillus spp*, using various AST methodologies
- **Three distributions of 2 specimens**

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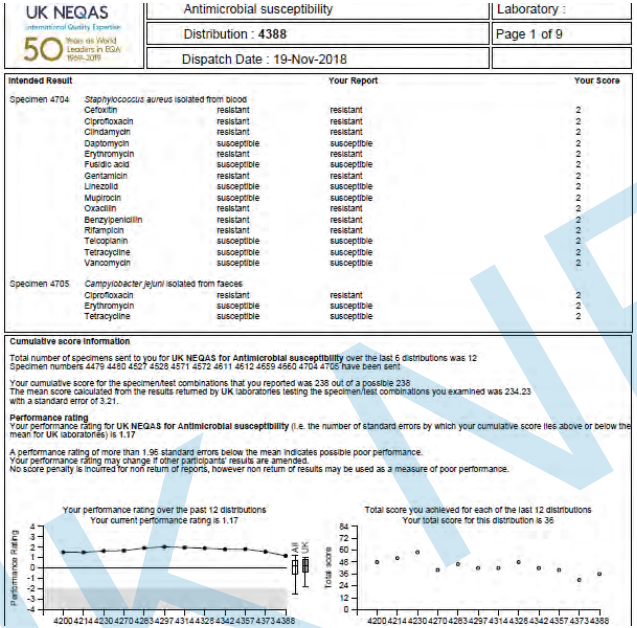
And if the patient had a bacterial infection?



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Antimicrobial susceptibility	Laboratory :
Distribution : 4388	Page 1 of 9
Dispatch Date : 19-Nov-2018	

Intended Result			Your Report	Your Score
Specimen 4704	*Staphylococcus aureus* isolated from blood			
	Cefoxitin	resistant	resistant	2
	Ciprofloxacin	resistant	resistant	2
	Clindamycin	resistant	resistant	2
	Daptomycin	susceptible	susceptible	2
	Erythromycin	resistant	resistant	2
	Fusidic acid	susceptible	susceptible	2
	Gentamicin	resistant	resistant	2
	Linezolid	susceptible	susceptible	2
	Mupirocin	susceptible	susceptible	2
	Oxacillin	resistant	resistant	2
	Benzylpenicillin	resistant	resistant	2
	Rifampicin	resistant	resistant	2
	Teicoplanin	susceptible	susceptible	2
	Tetracycline	susceptible	susceptible	2
	Vancomycin	susceptible	susceptible	2
Specimen 4705	*Campylobacter jejuni* isolated from faeces			
	Ciprofloxacin	resistant	resistant	2
	Erythromycin	susceptible	susceptible	2
	Tetracycline	susceptible	susceptible	2

Cumulative score information

Total number of specimens sent to you for **UK NEQAS for Antimicrobial susceptibility** over the last 6 distributions was 12
Specimen numbers 4479 4480 4527 4528 4571 4572 4611 4612 4659 4660 4704 4705 have been sent.

Your cumulative score for the specimen/test combinations that you reported was 238 out of a possible 238.
The mean score calculated from the results returned by UK laboratories testing the specimen/test combinations you examined was 234.23 with a standard error of 3.21.

Performance rating
Your performance rating for **UK NEQAS for Antimicrobial susceptibility** (i.e. the number of standard errors by which your cumulative score lies above or below the mean for UK laboratories) is 1.17.

A performance rating of more than 1.96 standard errors below the mean indicates possible poor performance.
Your performance rating may change if other participants' results are amended.
No score penalty is incurred for non return of reports, however non return of results may be used as a measure of poor performance.

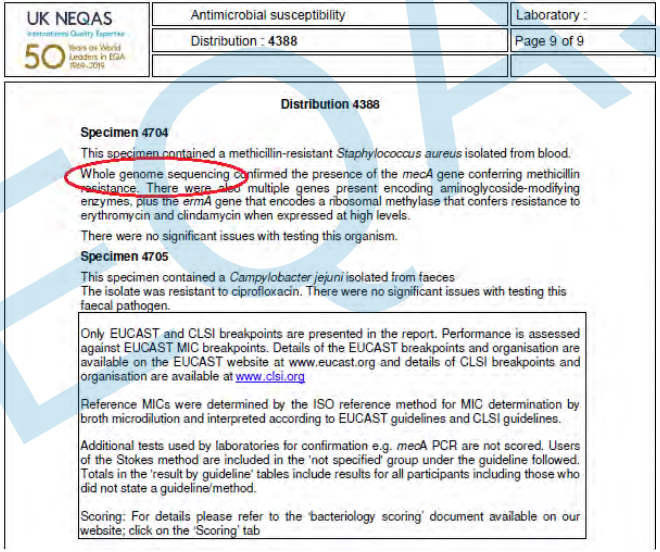
Your performance rating over the past 12 distributions
Your current performance rating is 1.17

Performance Rating

Total score you achieved for each of the last 12 distributions
Your total score for this distribution is 36

Total score

4200 4214 4230 4270 4263 4297 4314 4326 4342 4357 4373 4388



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Antimicrobial susceptibility	Laboratory :
Distribution : 4388	Page 9 of 9

Distribution 4388

Specimen 4704

This specimen contained a methicillin-resistant *Staphylococcus aureus* isolated from blood.

Whole genome sequencing confirmed the presence of the *mecA* gene conferring methicillin resistance. There were also multiple genes present encoding aminoglycoside-modifying enzymes, plus the *ermA* gene that encodes a ribosomal methylase that confers resistance to erythromycin and clindamycin when expressed at high levels.

There were no significant issues with testing this organism.

Specimen 4705

This specimen contained a *Campylobacter jejuni* isolated from faeces
The isolate was resistant to ciprofloxacin. There were no significant issues with testing this faecal pathogen.

Only EUCAST and CLSI breakpoints are presented in the report. Performance is assessed against EUCAST MIC breakpoints. Details of the EUCAST breakpoints and organisation are available on the EUCAST website at www.eucast.org and details of CLSI breakpoints and organisation are available at www.clsi.org

Reference MICs were determined by the ISO reference method for MIC determination by broth microdilution and interpreted according to EUCAST guidelines and CLSI guidelines.

Additional tests used by laboratories for confirmation e.g. *mec*A PCR are not scored. Users of the Stokes method are included in the 'not specified' group under the guideline followed. Totals in the 'result by guideline' tables include results for all participants including those who did not state a guideline/method.

Scoring: For details please refer to the 'bacteriology scoring' document available on our website; click on the 'Scoring' tab

- Established in 2004
- EQA for determining antimicrobial susceptibilities in various genera of microorganisms using conventional and semi automated systems and following international Guidelines
- EUCAST
- CLSI
- 12 Distributions of 2 specimens

Expert commentary explaining antimicrobial resistance mechanisms.

Whole genome sequencing is used to correlate genotypic and phenotypic data.

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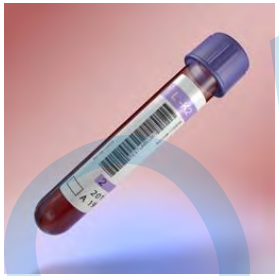
External Quality Assessment and the Patient's Journey

Representatives from UK NEQAS Schemes

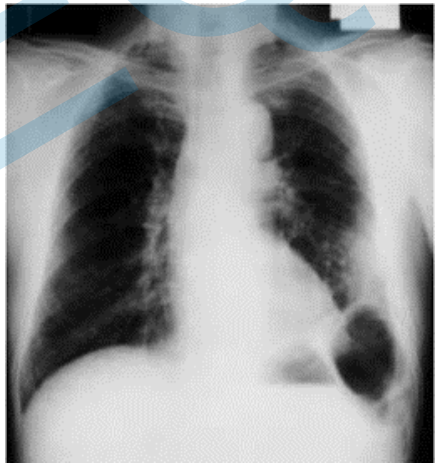
Blood Tests

- No adverse haematological findings



X-Ray

- Shadow on left lung



Follow-up

- CT Scan
- Bronchial biopsy

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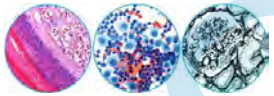
UK NEQAS
Cellular Pathology Technique

Chantell Hodgson

Scheme Manager

UK NEQAS in Partnership

Improving Patient Outcomes:
Non-small cell lung cancer tumour case study



X-ray reveals a shadow on the left lung

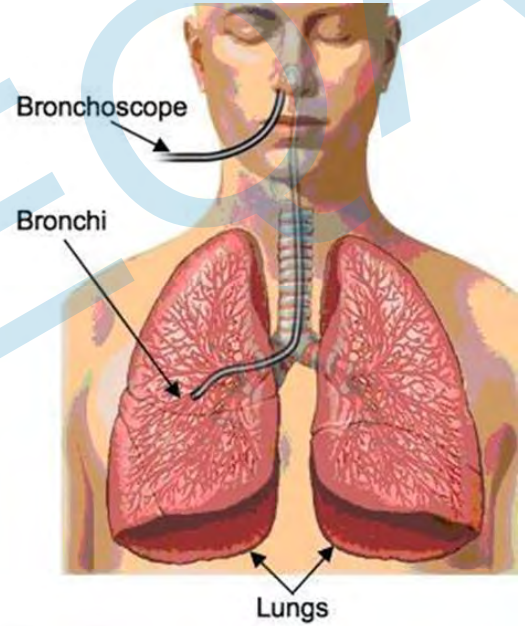
Follow up

- CT scan
- **transbronchial biopsy**

What is a transbronchial biopsy?

- A bronchoscope through the nose and down into the lungs to examine the bronchi
- Small forceps fed down through the bronchus into the lung

Samples taken for **Histological examination**



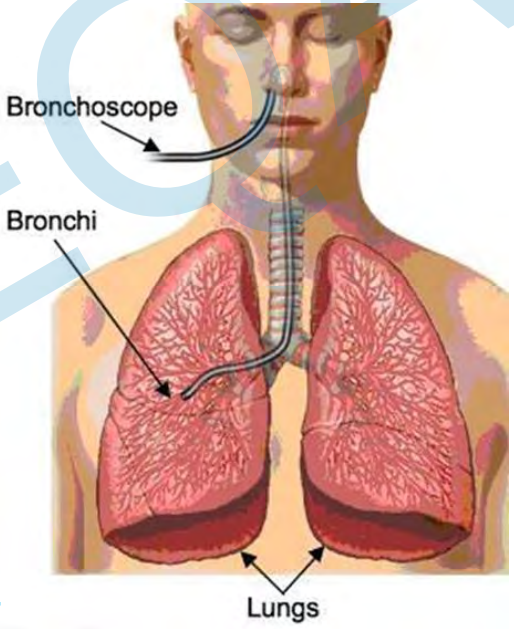
What is a transbronchial biopsy?

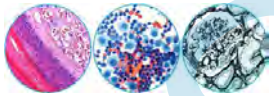
Area of suspected malignancy can also be

- washed and /or brushed
- fine-needle aspiration cytology (FNAC)
- Rapid On-Site Evaluation (ROSE)

Cellular preparation, slide and/or cell blocks for

Non Gyn Cytology examination





UK NEQAS Cellular Pathology Techniques

Includes both cytological and histological specimens

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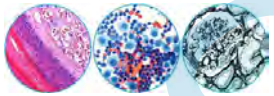
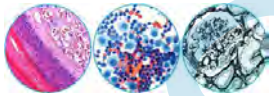
History



- UK NEQAS Cellular Pathology Technique (CPT) formed in 1991
- Merger of a group of regional EQA schemes
- Overseen by a national coordinating group (16 biomedical scientists and original schemes regional coordinators)
- As a result, the group joined the national consortium of EQA schemes, UK NEQAS

UK NEQAS
Cellular Pathology Technique



Lead UK centre for all aspects of General and Specialist Cellular Pathology external quality assessment

Provide worldwide external quality assessment and proficiency testing for all aspects of tissue diagnostics

~900 participant laboratories
International coverage

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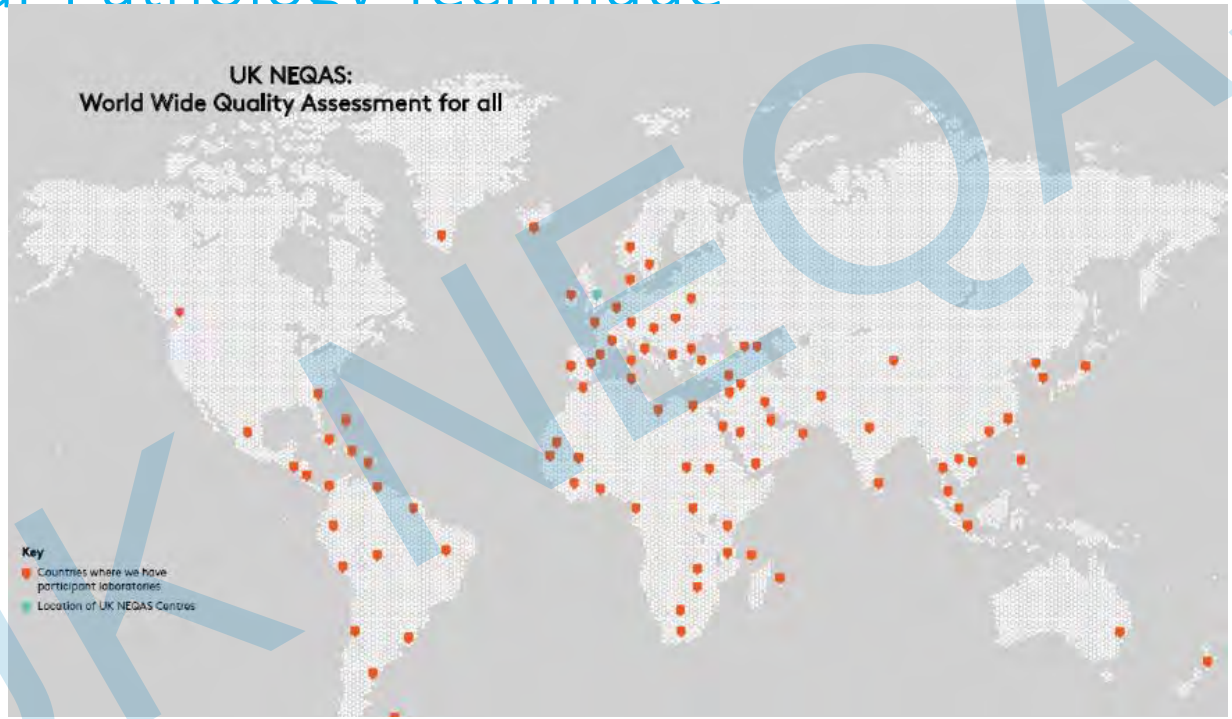
International Quality Expertise

UK NEQAS
Cellular Pathology Technique



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ISO 17043

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proficiency testing provider

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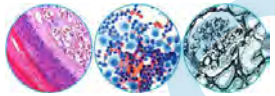
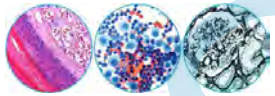


EQA - Why and How?

- Why?
  - To improve quality of testing and interpretation for diagnostic purposes
- How?
  - Providing feedback to laboratories on performance
  - Find innovative ways to promote best practice
  - Driving standards by sharing learning / best practice and education
  - Identifying and resolving problems



Delivering Confidence in Quality

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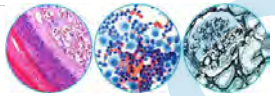
Participation is a continuous assessment of quality and feedback on performance



Remember to make note of the resubscription date

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UK NEQAS

Cellular Pathology Technique

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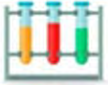
6 annual assessment runs, issued bi-monthly with instructions for participation

Access Reports on-line via UK NEQAS CPT website

Look out for your email notification when these are made available

Select and submit your in house / archival material and / or stain any distributed material



Remember to make note of the return date to avoid late submissions

Submitted material assessed according to designated criteria

Material assessed by specialist experts in the field of cellular pathology

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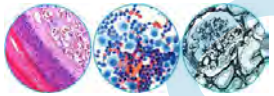
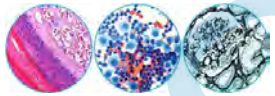


Measurable Quality
=
Improvable Quality

- What you can't measure you don't know
- What you don't know you can't improve
- Without observation and measurement there is no improvement

UK NEQAS
Cellular Pathology Technique



Slide Based Schemes

- General Pathology (Routine Histopathology)
- Neuropathology
- Renal Biopsy
- Muscle Histochemistry
- Diagnostic Non Gyn Cytology
- Bone Marrow Trephine biopsies (BMT)
- Mohs' Procedure

Web Based Schemes

- Transmission Electron Microscopy (TEM)
- Direct Immunofluorescence (DIF) ***(Pilot)***

Interpretive Web Based Schemes

- Diagnostic Digital Non Gyn Cytology ***(Pilot)***

Companion Schemes

- Frozen Sections
- Mega Blocks

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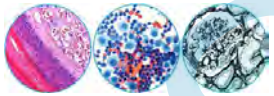
International Quality Expertise

UK NEQAS
Cellular Pathology Technique



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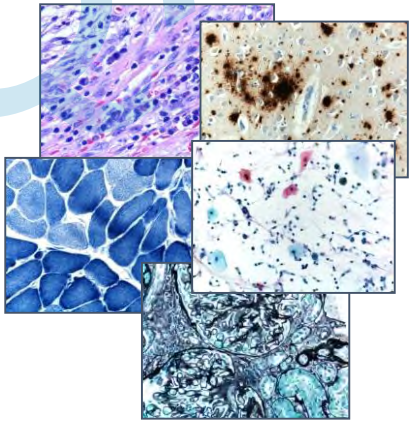
Cellular Pathology Technique

No. of assessment runs: **Slide Based**

General Pathology (Routine Histopathology)

6 distributions over a 12 month period



Stains assessed:

Selected / In-house Material

Haematoxylin and Eosin (H&E) *(all runs)*

Distributed Material

Special A

Diastase / PAS
Elastin / van Gieson
Gram
Perls' Prussian blue
Reticulin (silver method for)
Ziehl-Neelsen

Special B

Alcian blue / PAS
Amyloid (method for)
Grocott
Haematoxylin / van Gieson
Masson-Fontana
Martius-scarlet-blue (MSB)
Copper Associated Protein (method for)
Trichrome

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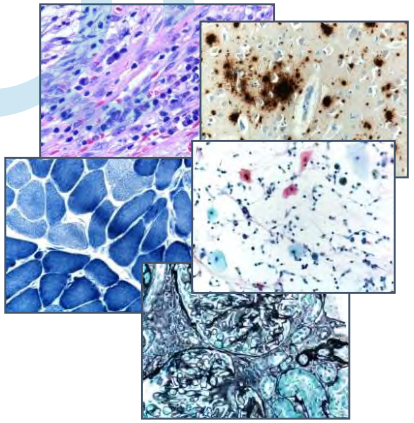

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Cellular Pathology Technique

Diagnostic Non Gynaecological Cytology

6 distributions over a 12 month period

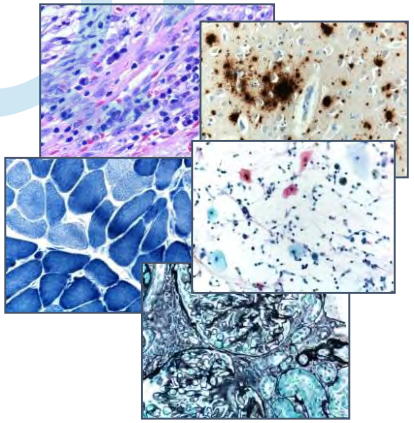
Stains assessed

Selected ~~/ In-house~~ Material *(all runs)*

- Papanicolaou
- Romanowsky

Specimen Types:

- Serous Fluid
- Head and Neck
- Respiratory
- Urine



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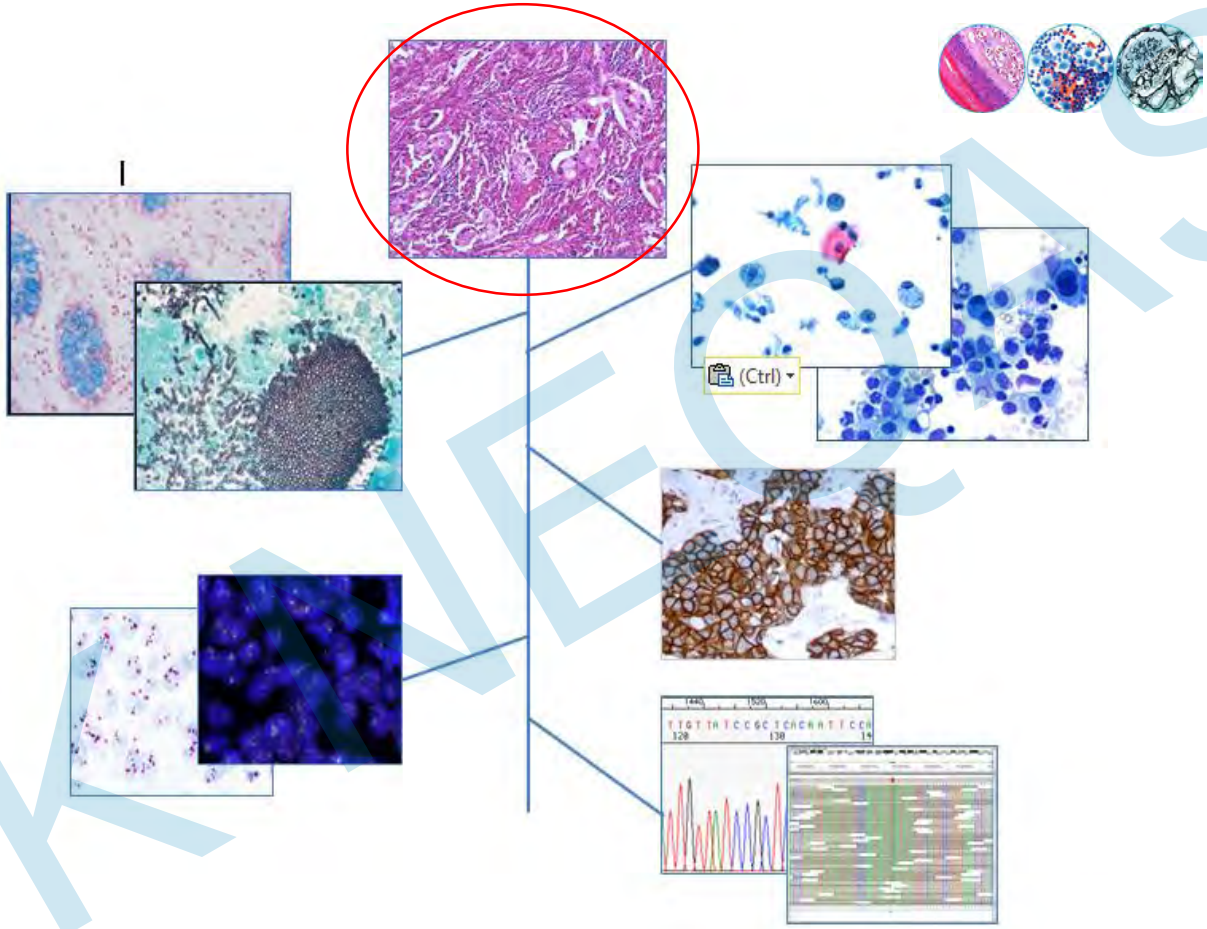

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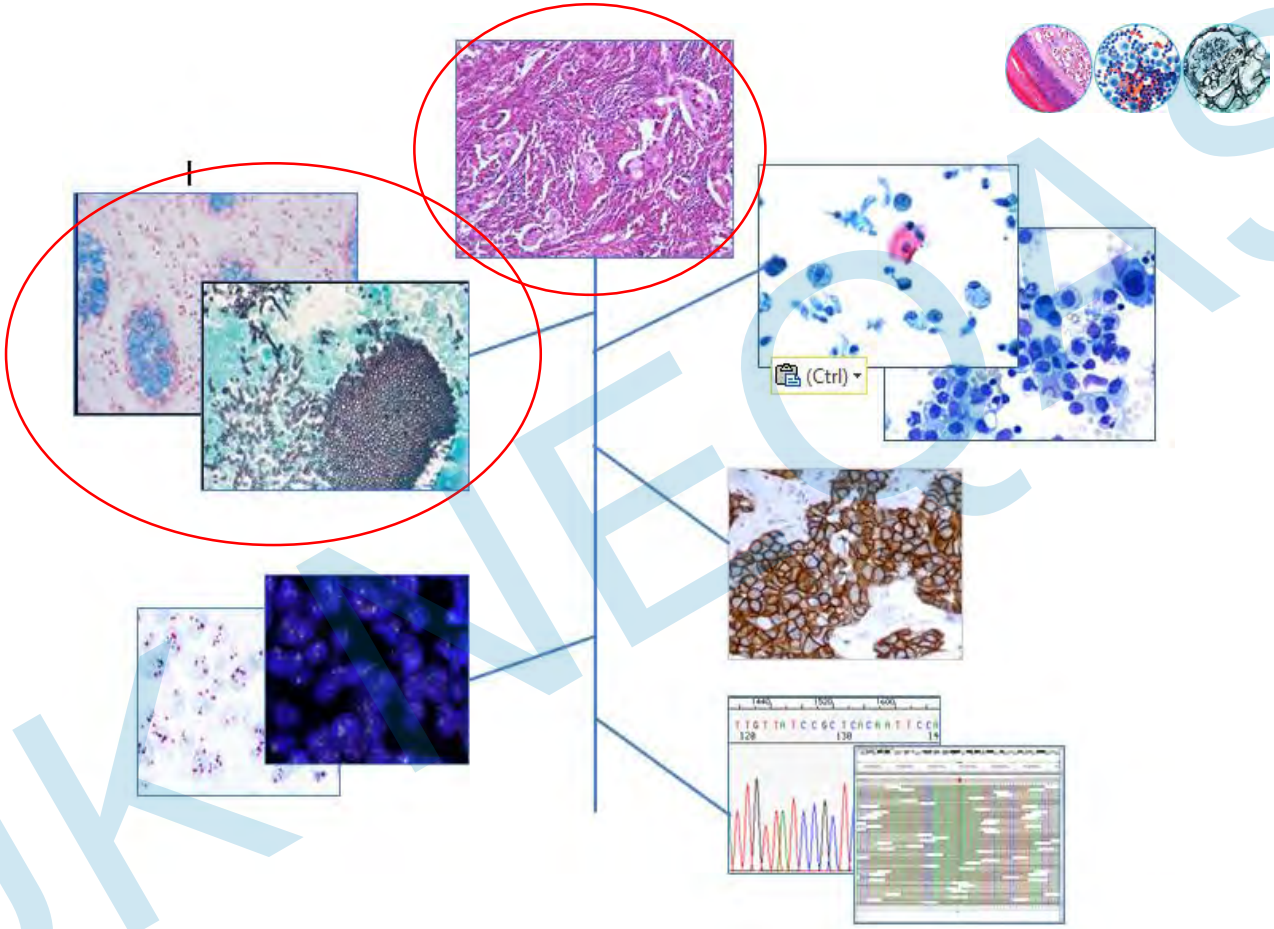

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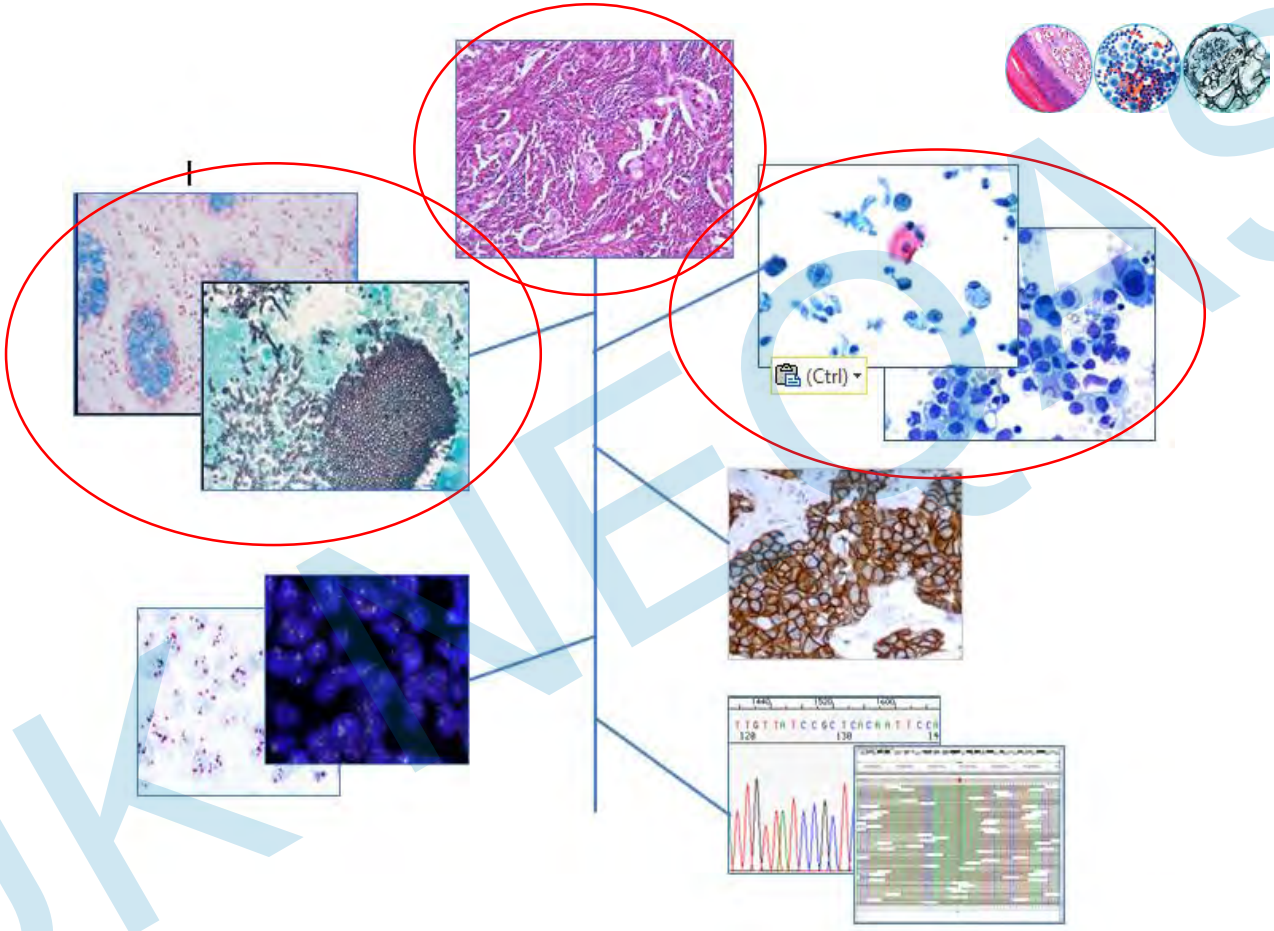

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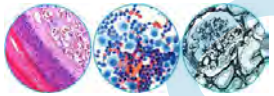


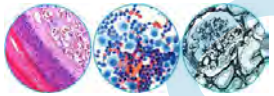
Transbronchial biopsy

Most patients with suspected lung cancer require a tissue-based diagnosis.

- Small samples up to 2mm
- Increasing demand on these samples due to growing diagnostic repertoire

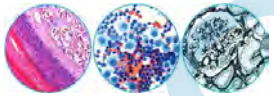
Clinical urgency

- Histological diagnosis is based on morphology and staining pattern
  - Key stages, fixation & processing not compromised
  - Sectioning H&E & special stains



Cytological Diagnosis

- Cytology is increasingly used for the evaluation and diagnosis of pulmonary malignancies
- Cytology sampling techniques available include;
  - bronchial brushing / washing
  - bronchioalveolar lavage (BAL)
  - fine-needle aspiration cytology (FNAC)
- Samples prepared as cellular smears, stained with Papanicolou (PAP)
- Utilised to accurately diagnose lung adenocarcinoma, alongside tissue biopsies

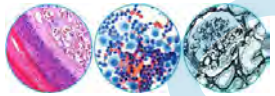


Histological Diagnosis

Haematoxylin and Eosin (H&E)

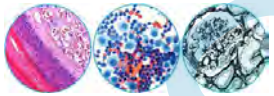
- Most commonly used stain for diagnostic work throughout the world.
  - Cell morphology
  - Atrophy, hypertrophy, inflammation
  - Staining patterns, new growth
  - benign or malignant?

- 95% of all specimens taken for histology are diagnosed by using (H&E) and special stains only



Features of a Good H&E

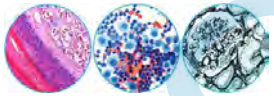
- **Haematoxylin**
  - nuclei blue-black
  - adequate differentiation
  - chromatin detail clearly visible
- **Eosin**
  - cytoplasm - various shades of pink
  - muscle fibres - deep pink / red
  - RBCs – orange / red
  - fibrin - pink



Histological Diagnosis

Special Stains

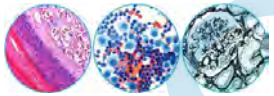
- Used in conjunction on daily basis with H&E
  - Many rely on basic chemical reactions for microscopic visualisation and general identification of various tissues and components
  - Others rely on molecular dye size and composition of the tissue or structure
- Provide “full “ picture for diagnosis
- Provide valuable and cost effective role in diagnosing and monitoring cancer



Histological Diagnosis

Special Stains for Cancer Diagnostic

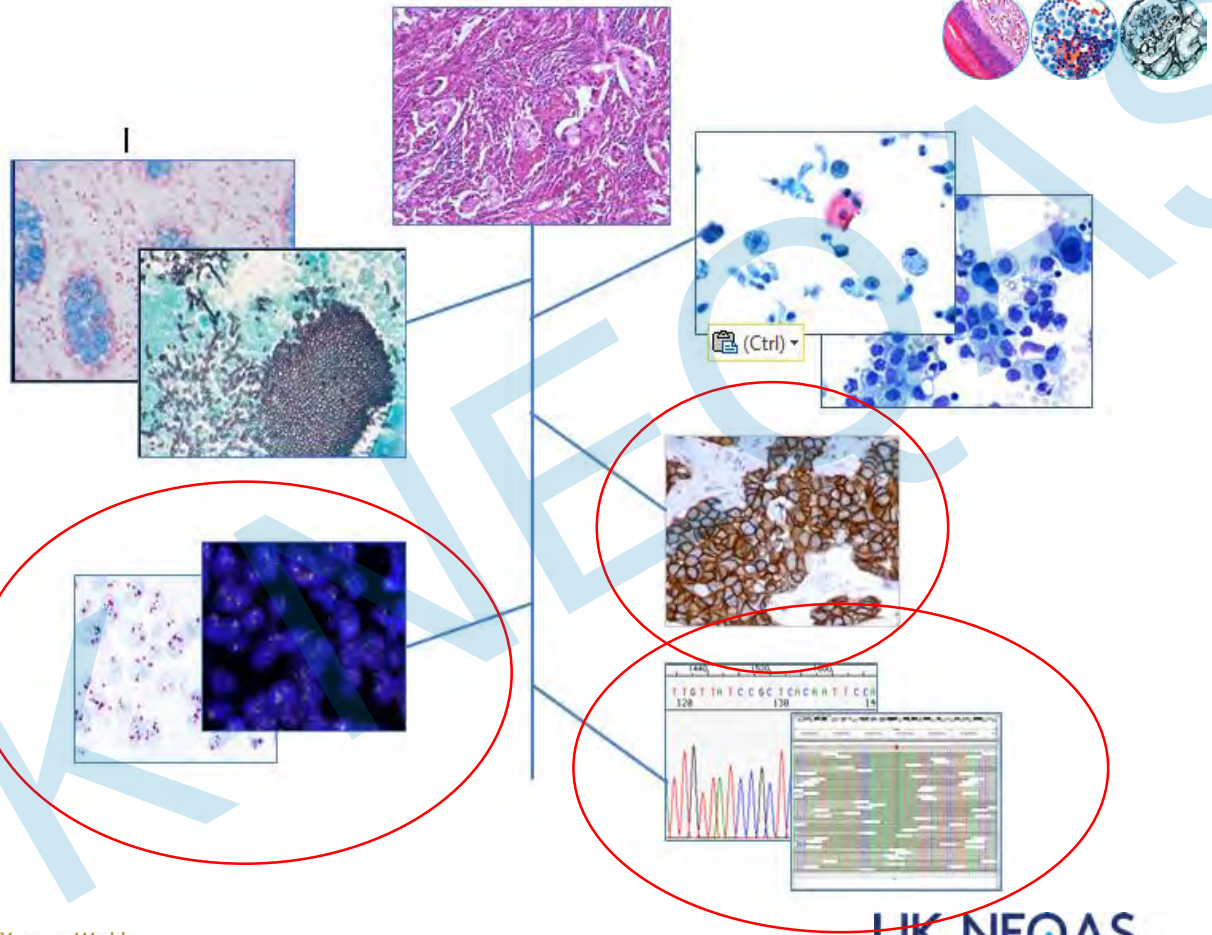
- Mucin staining with Alcian Blue (AB) / Diastase-Periodic Acid Schiff (DPAS) are invariably performed
  - Allows correlation of the mucin content / amount and types for differential cancer identification
  - The sensitivity and specificity of the mucin staining indicates the presence or absence of particular mucins
  - allows diagnosis to be determined



The goal

to provide the primary morphological diagnosis…

whilst still retaining sufficient material
for subsequent ICC and molecular studies



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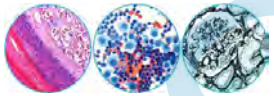
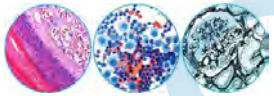


Cellular Pathology Diagnosis

- Primary lung cancers are considered to be of two types:
  - Small cell lung cancer (SCLC)
  - Non-small cell lung cancer (NSCLC)

- The aims of cellular sampling include
  - confirmation of diagnosis (e.g. adenocarcinoma vs squamous cell carcinoma), prior to further molecular testing



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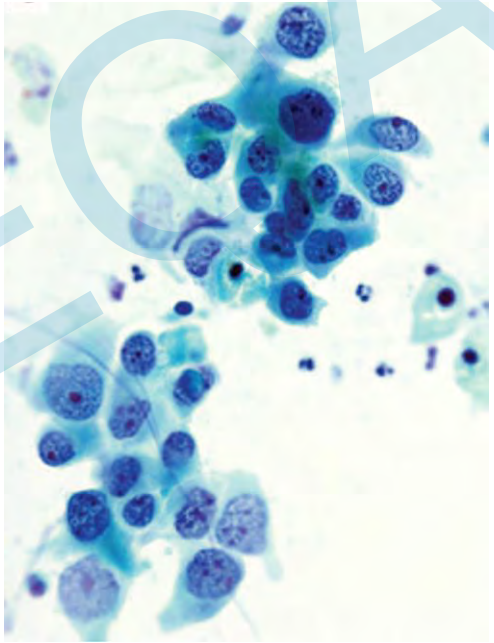
Adenocarcinoma

Cytology

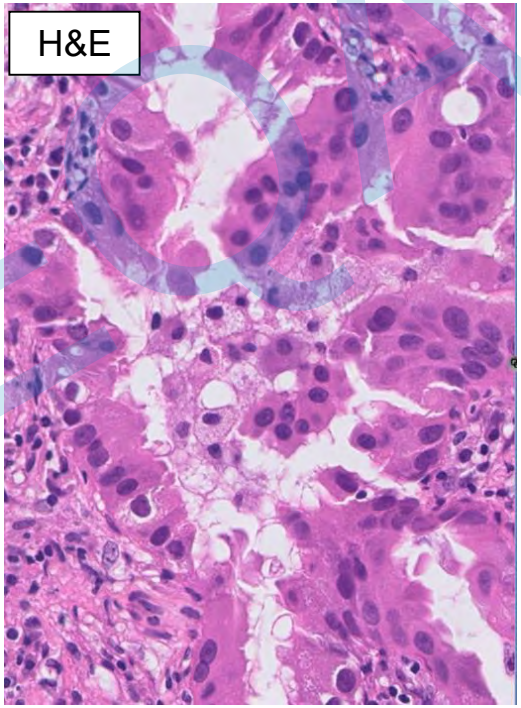
- Staining with PAP allows visualisation of;
  - large malignant cells
  - cells show abundant cytoplasm and prominent nuclei
  - Growth is in an acinar structure



Adenocarcinoma

H&E

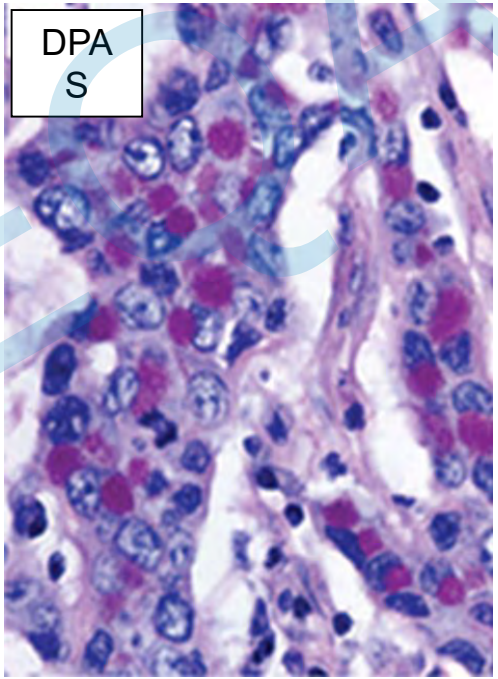
- Nearly 40% of lung cancers are adenocarcinomas
- Usually grow in the peripheral part of the lung
- Consist of glandular tumour cells
- Derived from the mucus-producing glands of the lungs



Adenocarcinoma

Special Stains

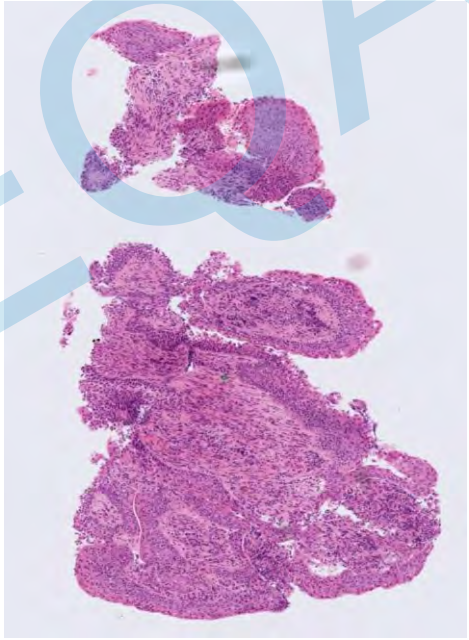
- To detect neutral mucins diagnostic of adenocarcinomas - DPAS staining is performed
- Characteristic positive staining can be seen
- Visualised as numerous intracytoplasmic droplets of mucin



Transbronchial Biopsy Tumour Case

Initial investigation

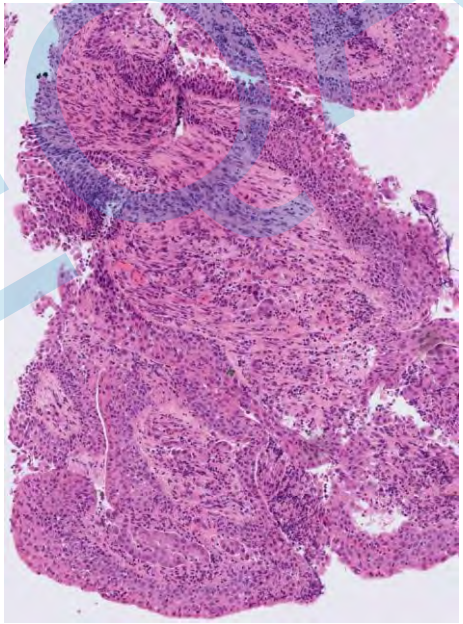
- Primary microscopic visualisation of the morphology with an H&E stained section
  - Shows features typical of non-small cell carcinoma infiltration



Transbronchial Biopsy Tumour Case

Further investigation

- additional levels through the tissue block
- characteristic features shown via special stains
- Confirmation alongside cytology samples

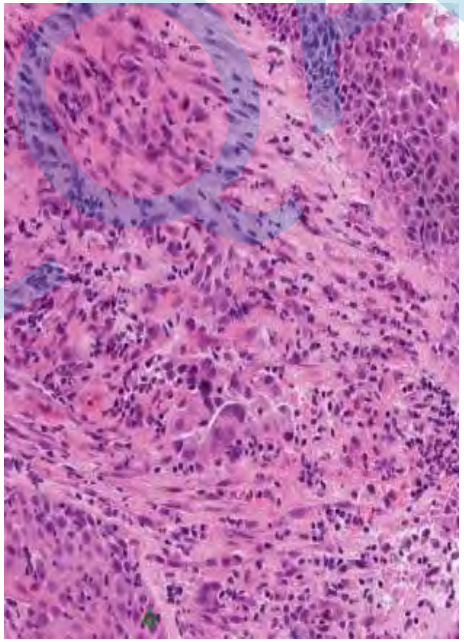


Transbronchial Biopsy Tumour Case

Diagnosis

Non-small cell carcinoma favouring adenocarcinoma

- Tissue referred for further testing to confirm diagnosis and inform treatment and prognosis



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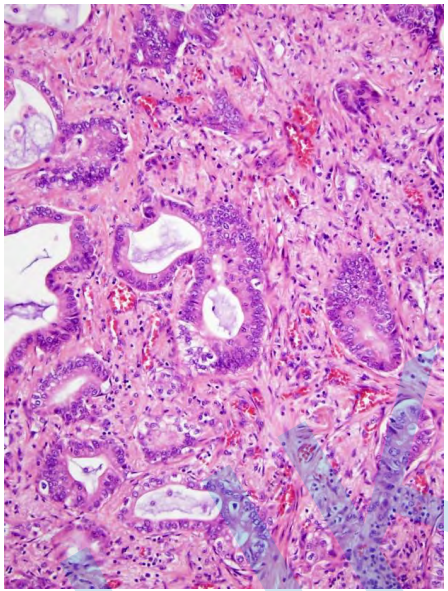
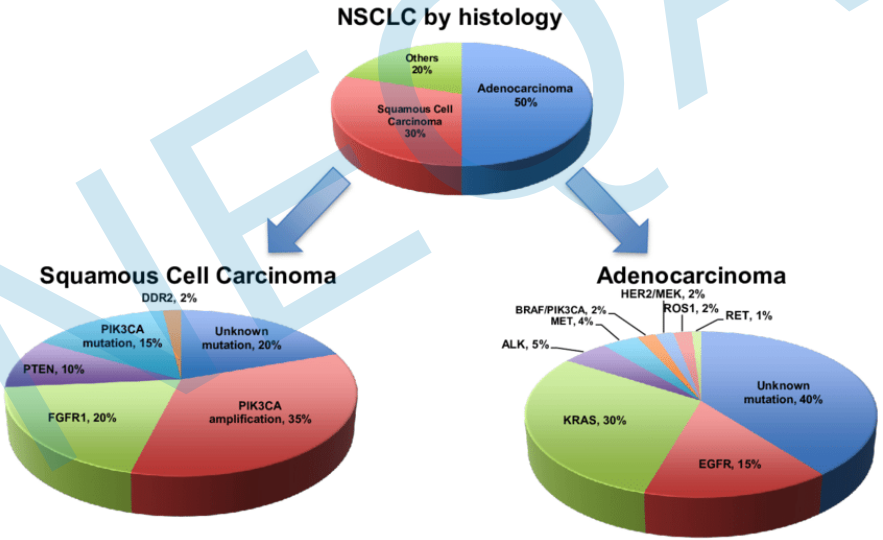
External Quality Assessment and the Patient's Journey

Representatives from UK NEQAS Schemes

Carcinoma – probable non small cell lung cancer (NSCLC)





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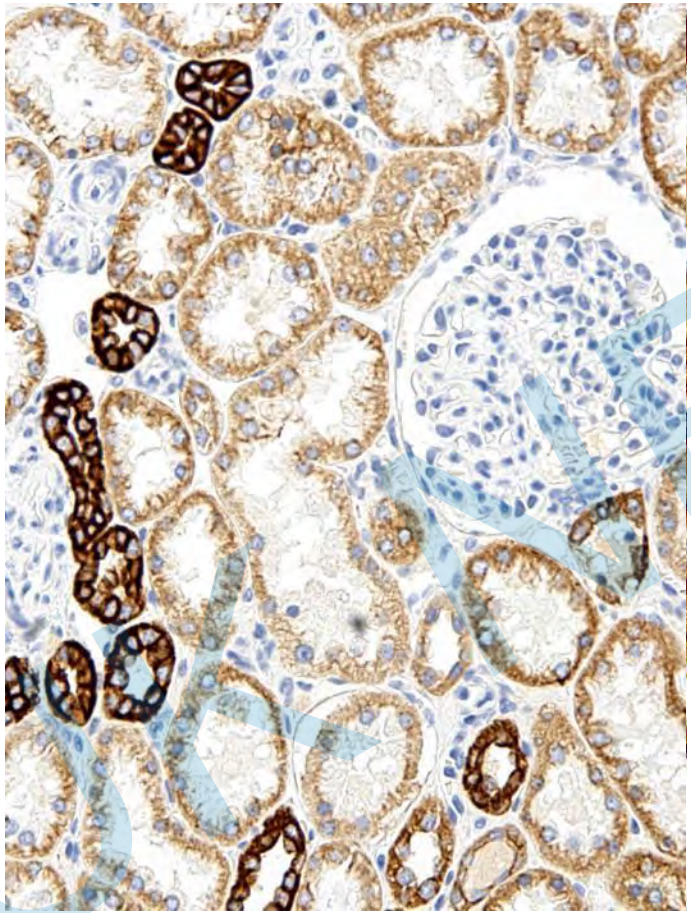
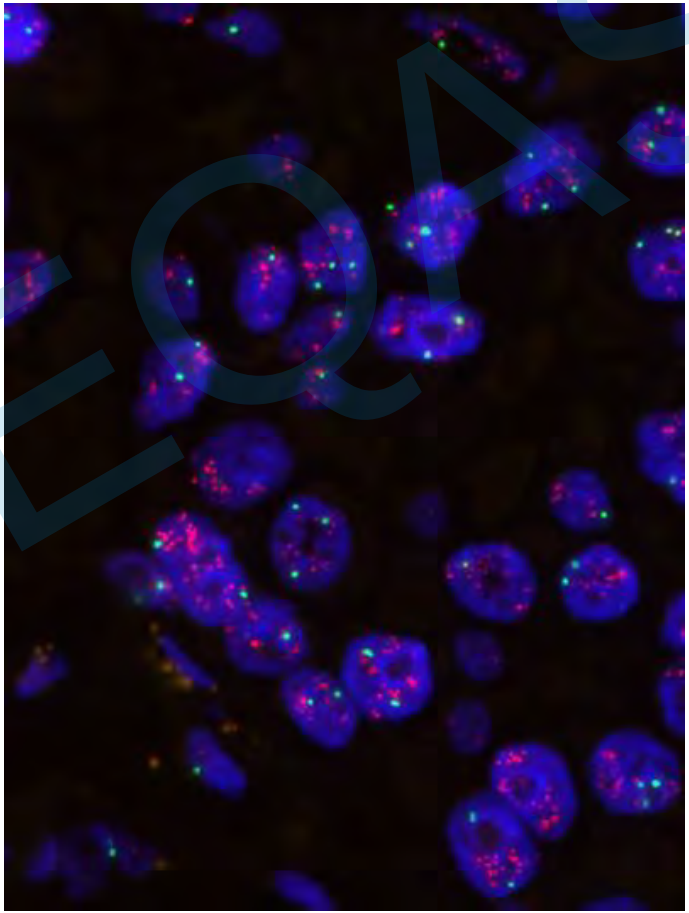
UK NEQAS for Immunocytochemistry & In-Situ Hybridisation

Andrew Dodson
Scheme Director

ICC

Normal kidney tissue: stained with an antibody to cytokeratins (wide spectrum)



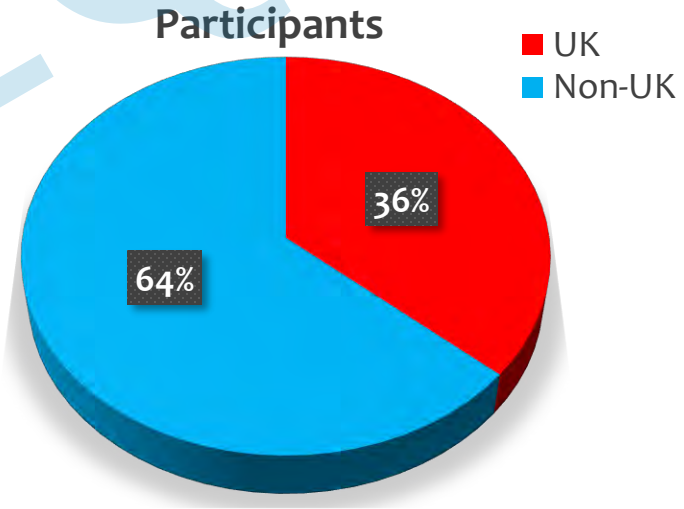


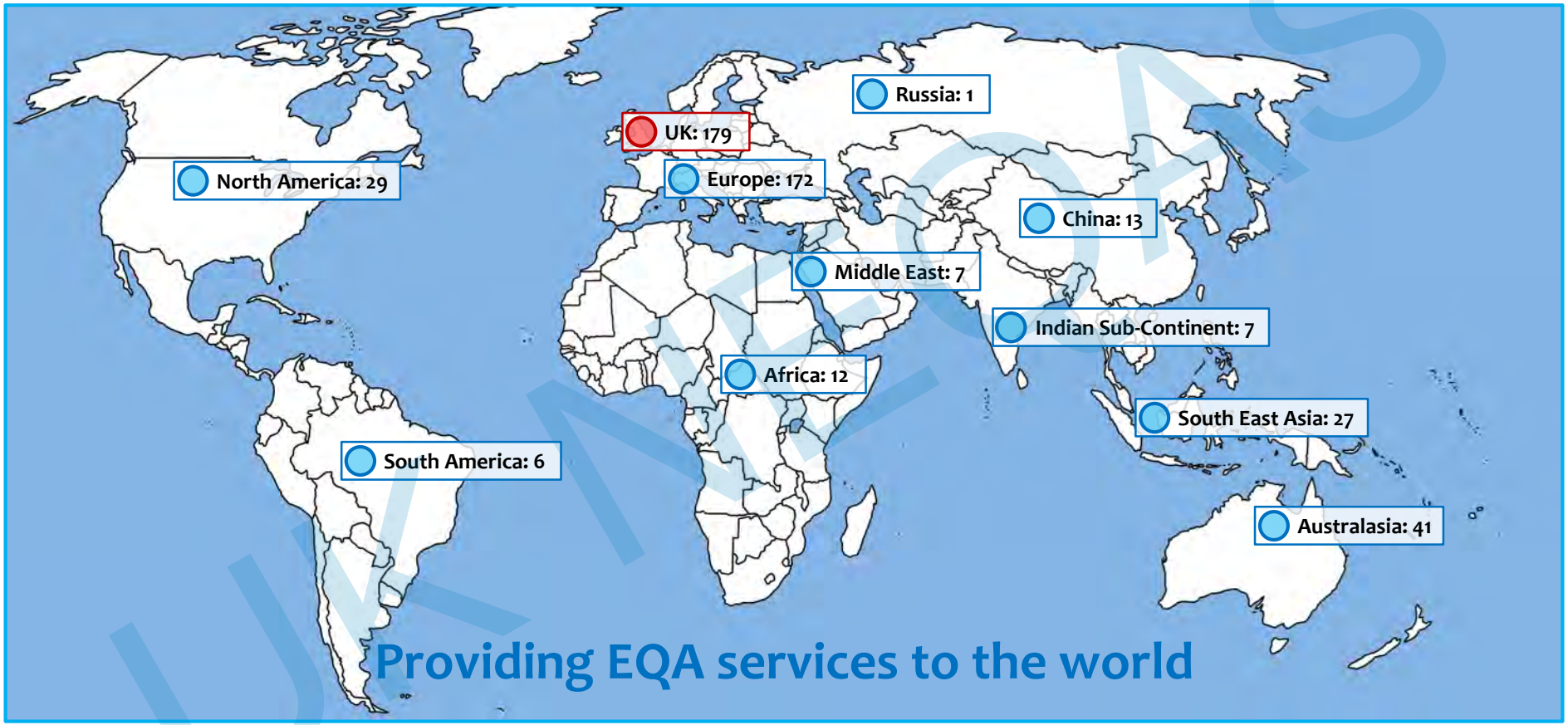
FISH

Breast cancer: tumour cell nuclei stained with probes against HER2 (red) and CEP17 (green)

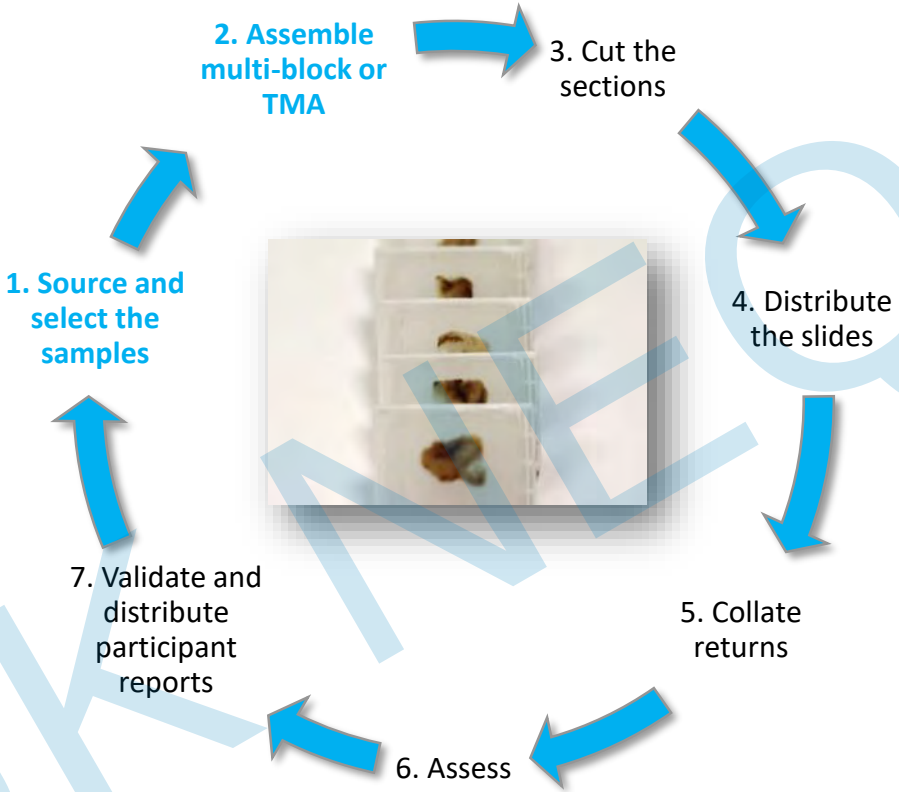
Well-established with a large participant base

- Established in 1985 and have operated continuously since then
  - ✓ First to be established in the field
- Currently have more than 500 participating laboratories
  - ✓ Most comprehensive
  - ✓ Most frequent
- Accredited to UKAS ISO17043:2010

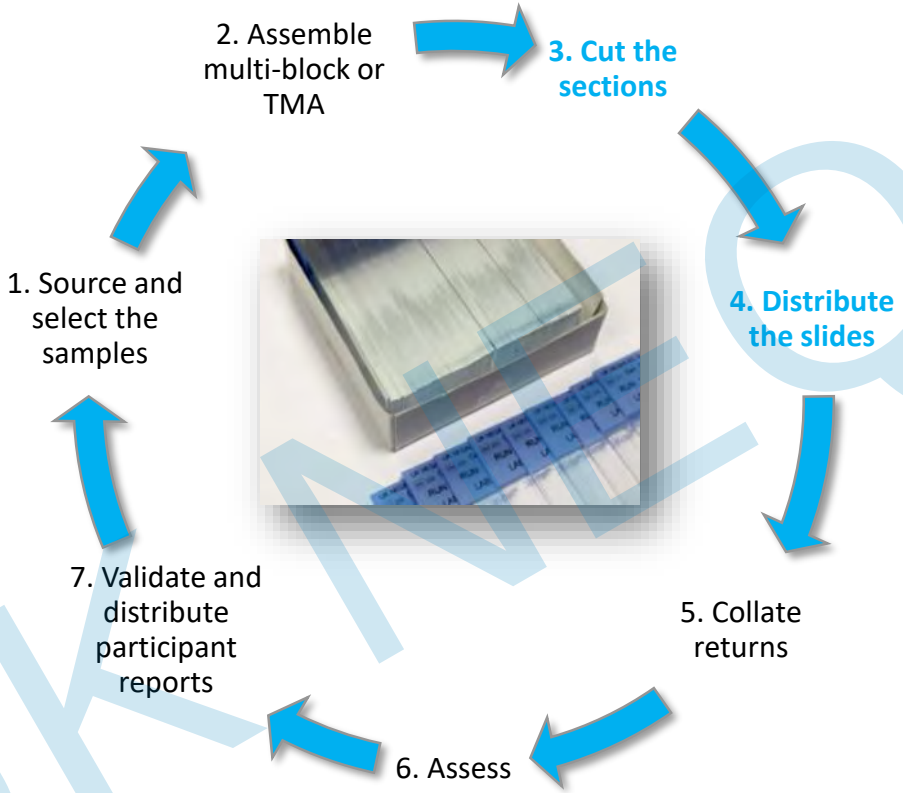




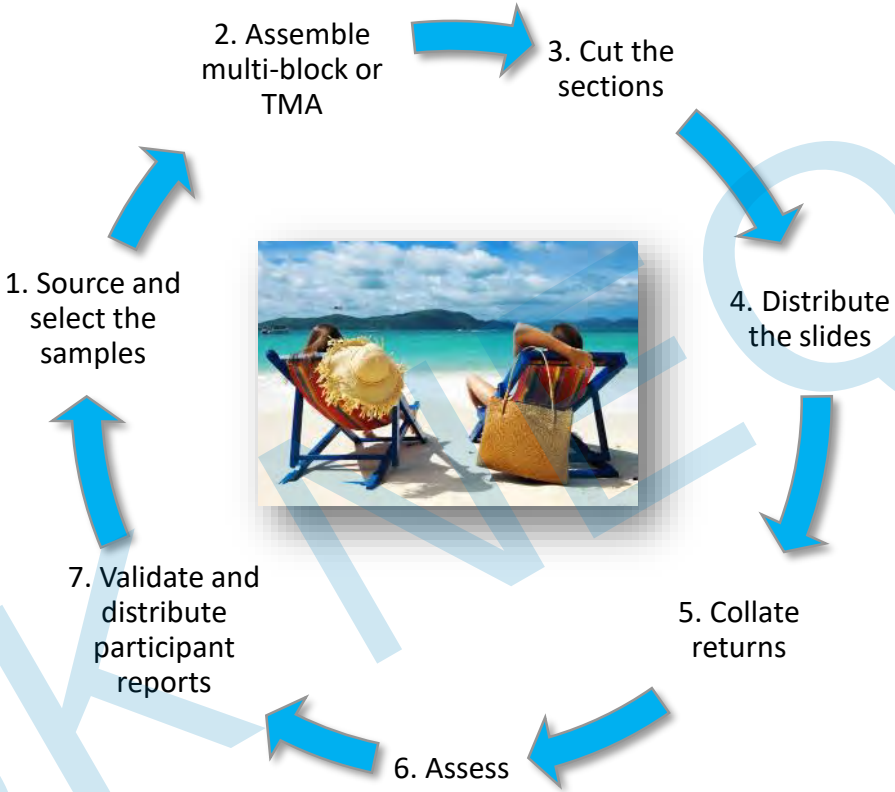
How Do We Work? The EQA cycle



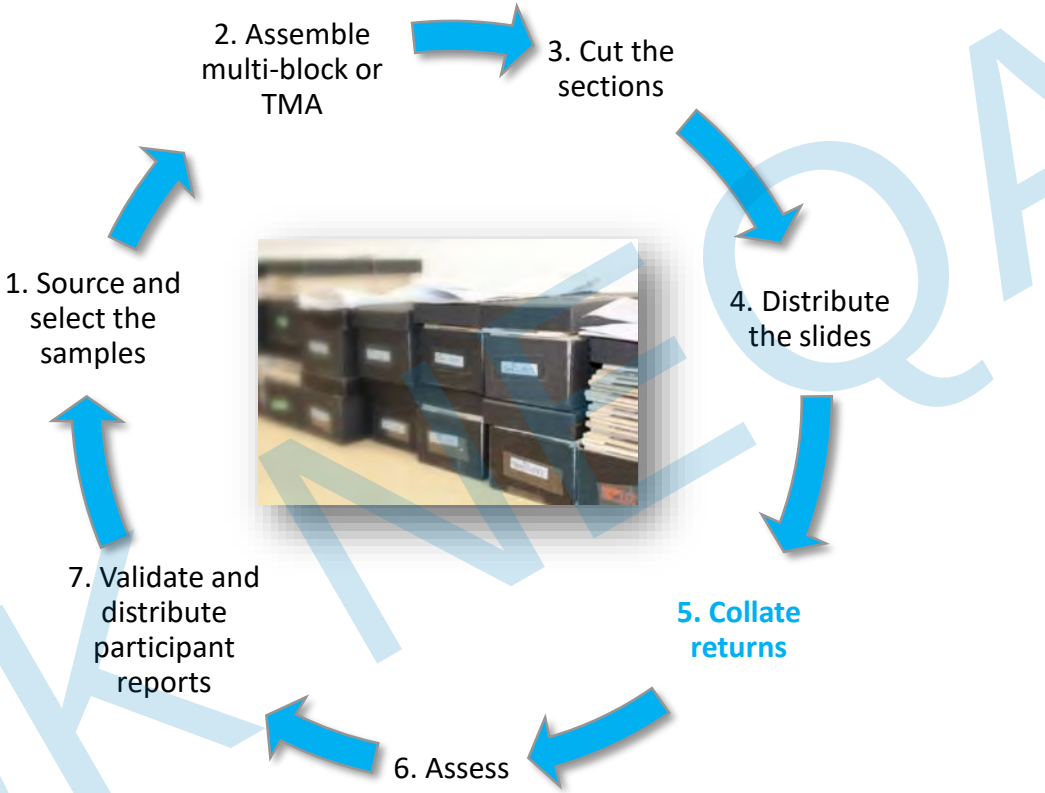
How Do We Work? Prepare the materials for distribution



How Do We Work? Four week window



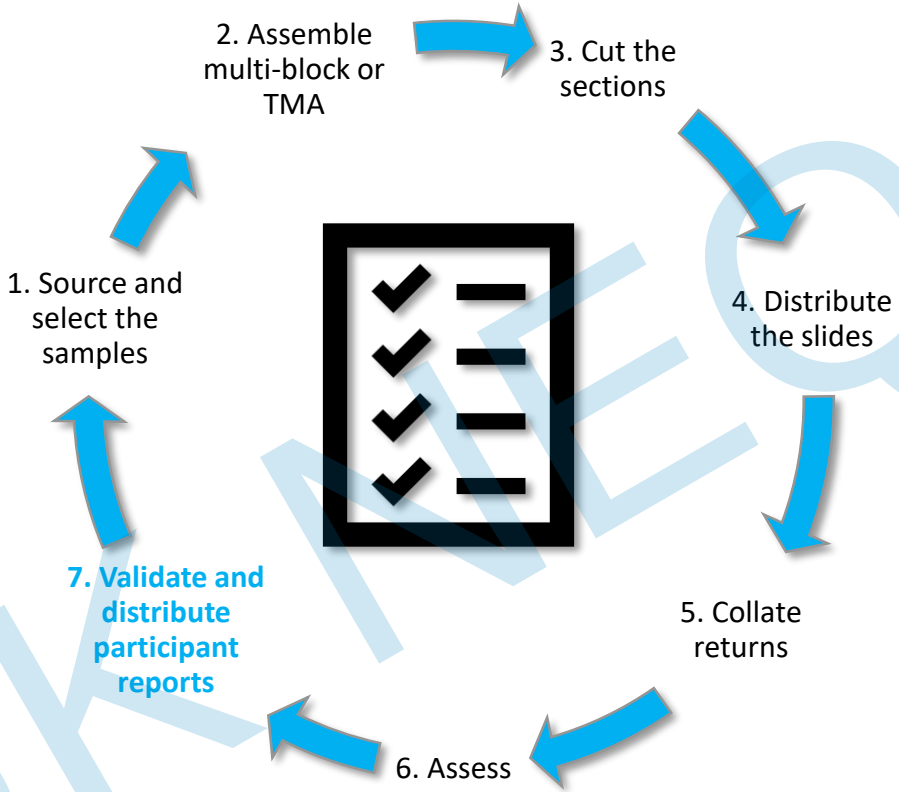
How Do We Work? Prepare the assessment materials



How Do We Work? The assessment process

1. Source and select the samples
2. Assemble multi-block or TMA
3. Cut the sections
4. Distribute the slides
5. Collate returns
6. Assess
7. Validate and distribute participant reports

How Do We Work? The assessment process



UK NEQAS ICC & ISH Modules

Module Code	Module Descriptor
1	General Pathology
2A	Breast Pathology (Hormonal Receptors – ER only)
2B	Breast Pathology (Hormonal Receptors – ER and PR)
3	Breast Pathology HER2 IHC
4	Lymphoid Pathology
5	Neuropathology
6	Cytology
7	Alimentary Tract Pathology (Gastro-Intestinal Stromal Tumour, GIST)
8	Gastric HER2 IHC
9	Breast HER2 ISH (Interpretive & Technical)
10	Non-Small Cell Lung carcinoma (NSCLC) ALK IHC
11	Non-Small Cell Lung carcinoma (NSCLC) PD-L1 IHC (Pilot)
12	Non-Small Cell Lung carcinoma (NSCLC) ALK/ROS1 FISH (Pilot)
13	Mismatch Repair (MMR) Proteins

UK NEQAS ICC & ISH Modules

Module Code	Module Descriptor
1	**General Pathology**
2A	Breast Pathology (Hormonal Receptors – ER only)
2B	Breast Pathology (Hormonal Receptors – ER and PR)
3	Breast Pathology HER2 IHC
4	Lymphoid Pathology
5	Neuropathology
6	Cytology
7	Alimentary Tract Pathology (Gastro-Intestinal Stromal Tumour, GIST)
8	Gastric HER2 IHC
9	Breast HER2 ISH (Interpretive & Technical)
10	Non-Small Cell Lung carcinoma (NSCLC) ALK IHC
11	Non-Small Cell Lung carcinoma (NSCLC) PD-L1 IHC (Pilot)
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- **Epithelial Markers**:
  - ✓ Pan-CK, CK7, CK20, EMA
- **Endothelial Markers**:
  - ✓ CD31, CD34, FVIII(Rag)
- **Muscle Markers**:
  - ✓ Smooth Muscle Actin, Desmin
- **Urological & Prostatic Markers:**
  - ✓ PSA, p63
- **Neuroendocrine Markers**:
  - ✓ Chromogranin, Synaptophysin
- **Mesothelial Markers**:
  - ✓ CEA, Ber-EP4, HBME-1, Calretinin
- **Melanoma Markers:**
  - ✓ HMB45, Melan A
- **Lymphoid Markers:**
  - ✓ CD3, CD20, Ig light-chains, Leucocyte Common Antigen (CD45)
- **Miscellaneous:**
  - ✓ Thyroglobulin, Ki-67, Calcitonin, CD56, TTF1, WT1, CDX2, E-Cadherin

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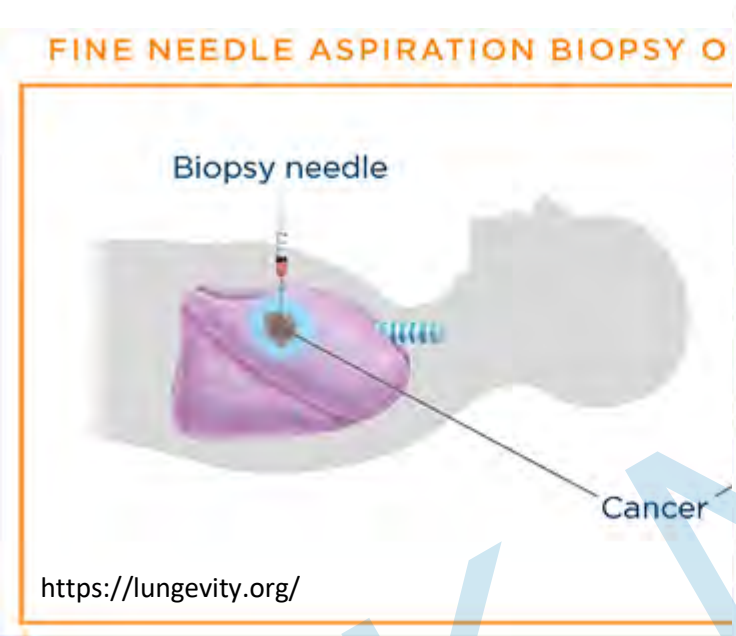
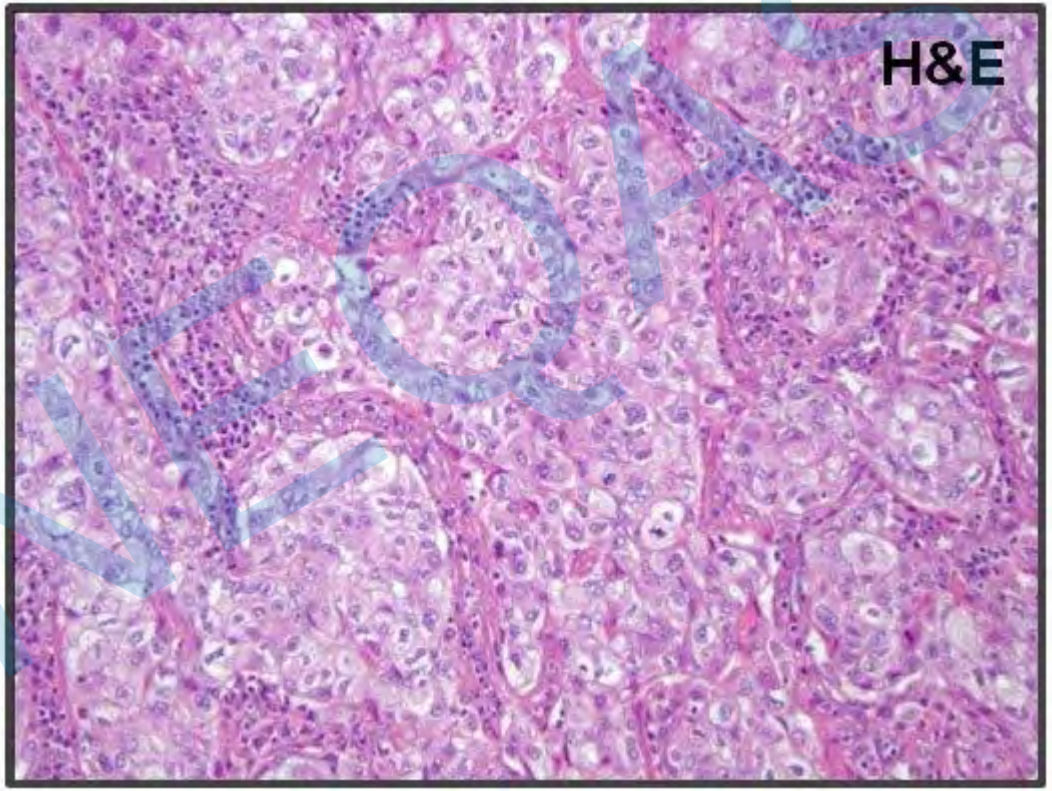
Use of ICC in Pulmonary Pathology



https://lungevity.org/



https://www.medscape.org/viewarticle/757558

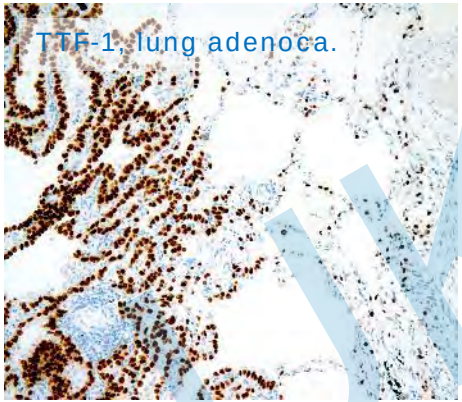
Use of ICC in Pulmonary Pathology

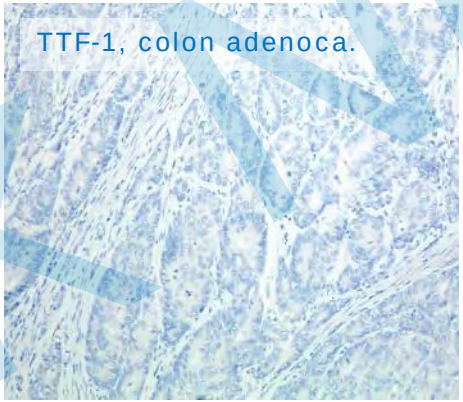
Table 6 Performance of individual marker in primary and metastatic lung adenocarcinomas

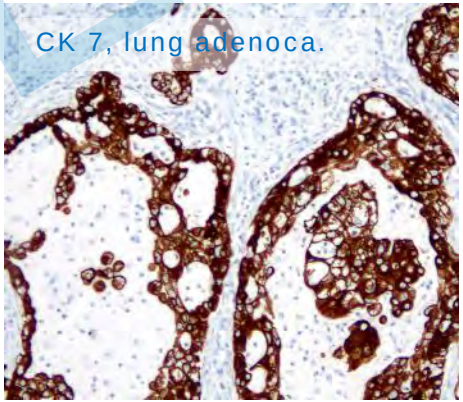
Type	Primary ADC (n = 72) vs Primary SqCC(n = 30)				Metastatic ADC (n = 131) vs Metastatic SqCC(n = 13)			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
TTF-1	84.5%	96.4%	98.4%	71.1%	86.9%	87.5%	99.1%	29.2%
CK7	93.8%	50.0%	86.5%	70.0%	100.0%	25.0%	97.1%	100.0%
Napsin A	92.0%	100.0%	100.0%	80.0%	67.8%	100.0%	100.0%%	13.6%

ADC: adenocarcinoma. SqCC: squamous cell carcinoma. PPV: positive predictive value. NPV: negative predictive value.

Gurdaet al. Clinical and Translational Medicine (2015) 4:16.


TTF-1, lung adenoca.

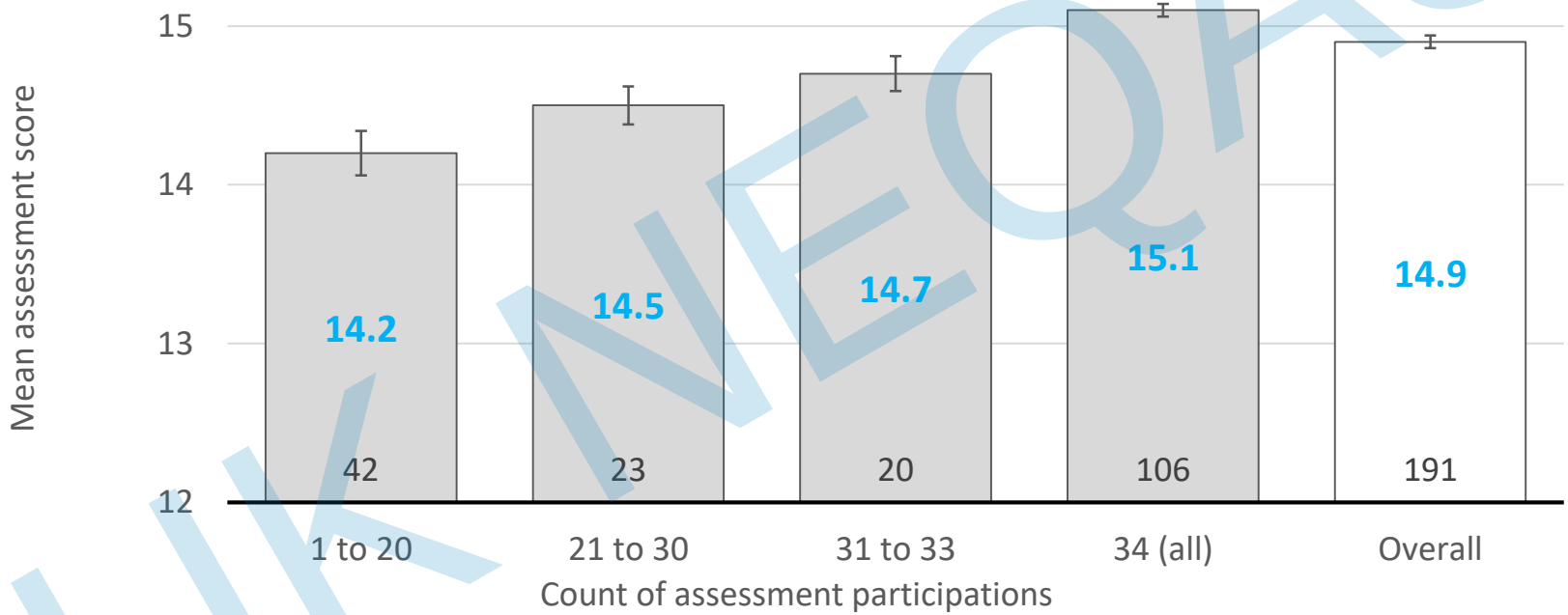

TTF-1, colon adenoca.


CK 7, lung adenoca.


CK 7, colon adenoca.

Why should I take part in EQA?

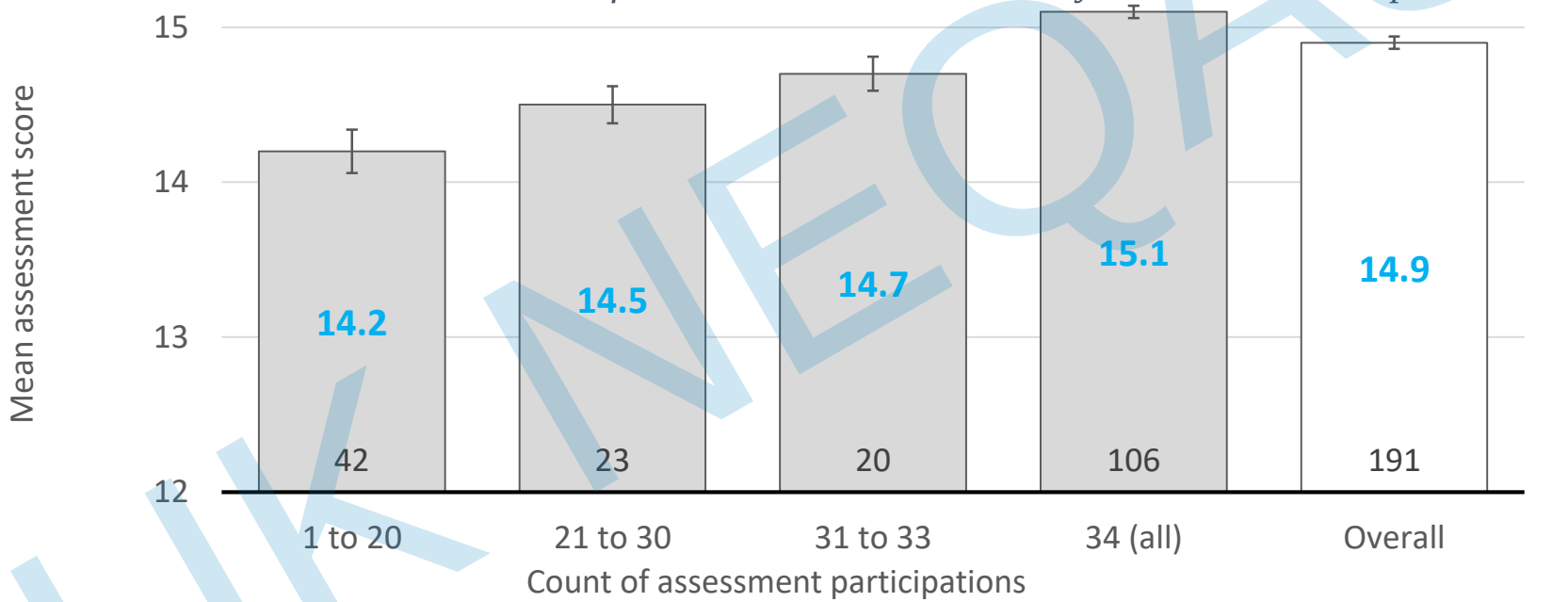
- Participation in EQA improves performance



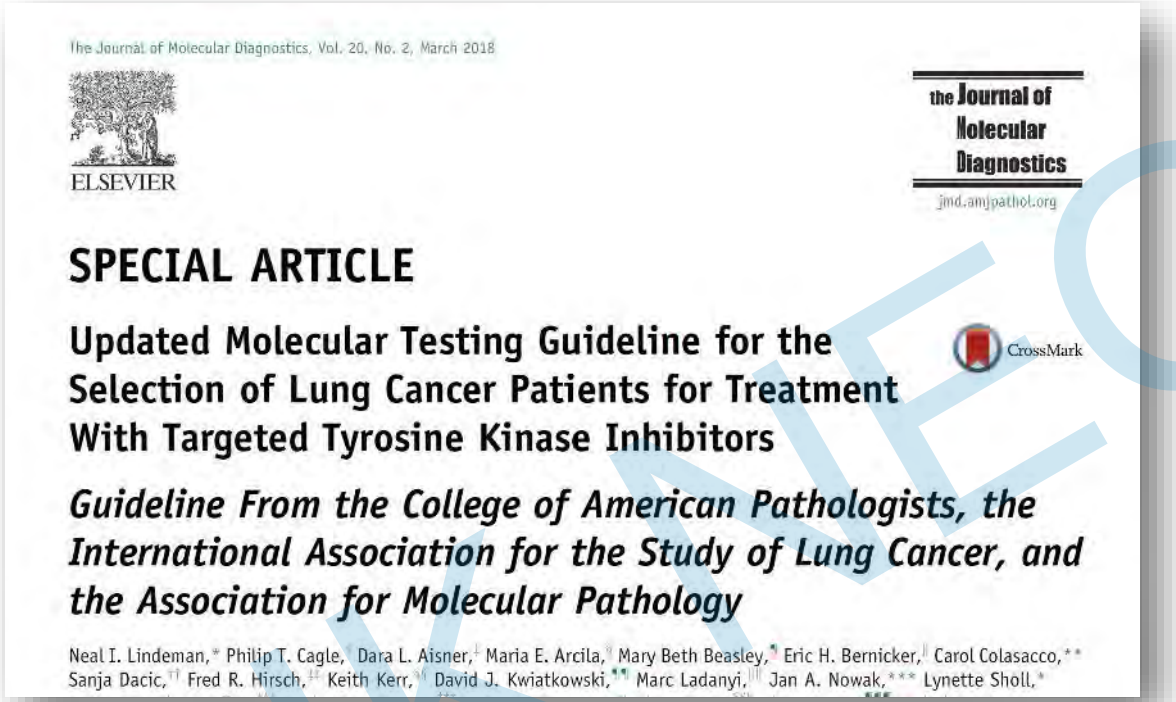
Data taken from Parry *et al*. ECP 2018

'a better test is as good as a better drug…'

Professor Mitch Dowsett, Royal Marsden Hospital, UK



Data taken from Parry *et al*. ECP 2018



The Journal of Molecular Diagnostics, Vol. 20, No. 2, March 2018

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the Journal of Molecular Diagnostics

jmd.amjpathol.org

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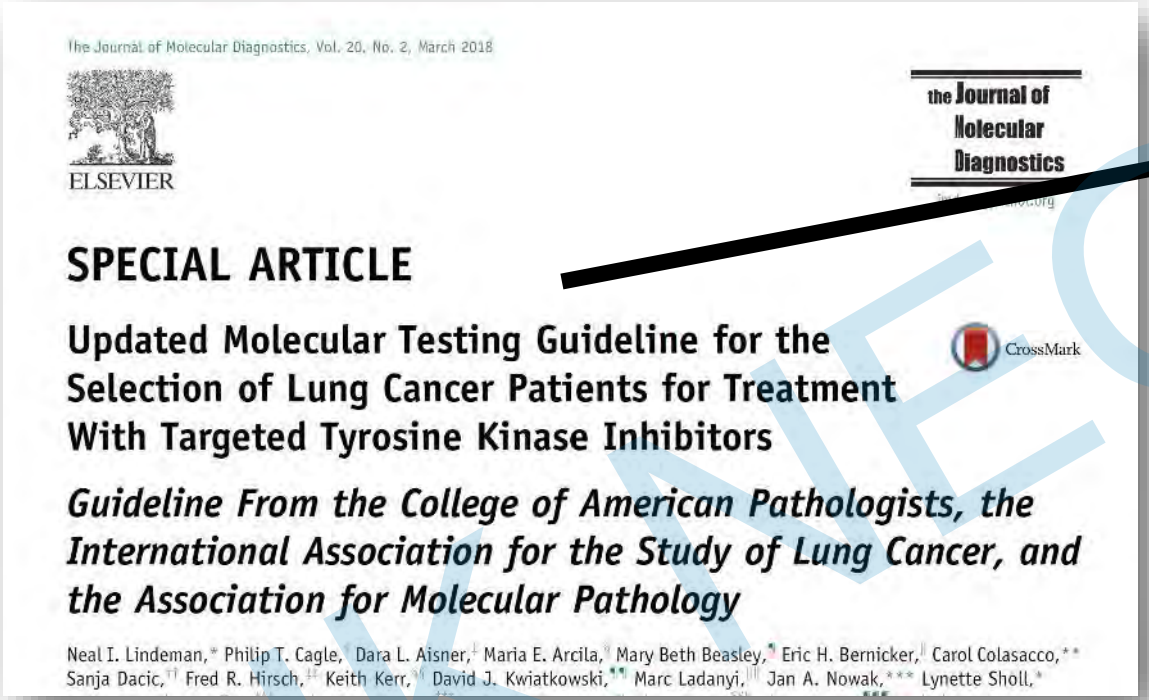

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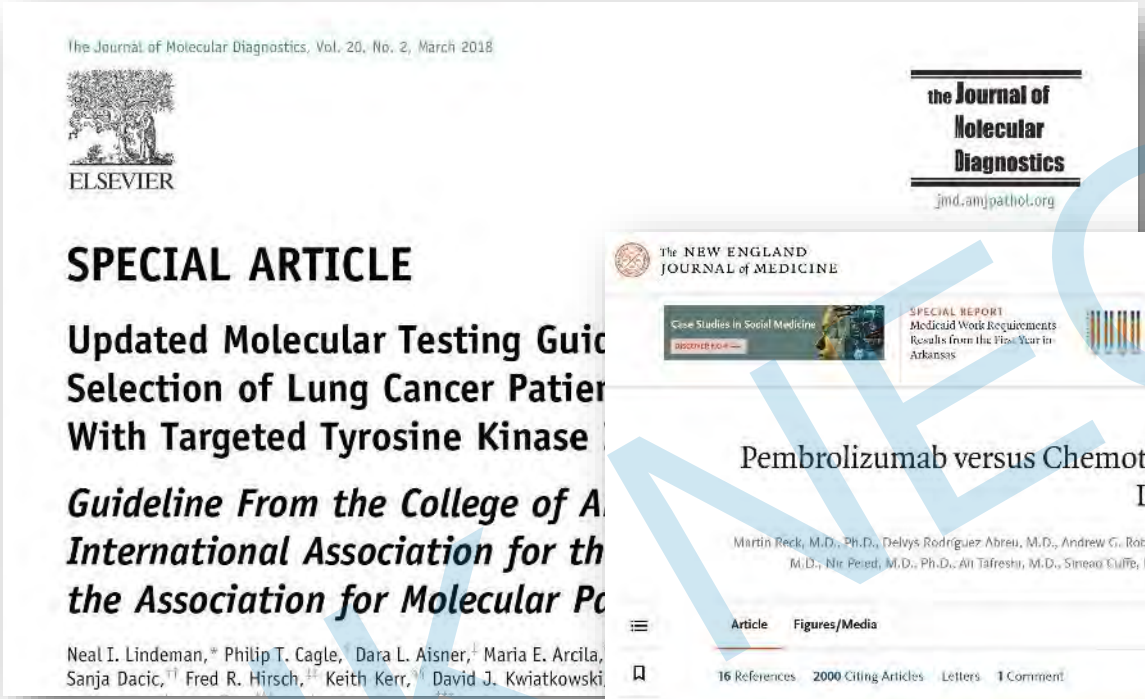
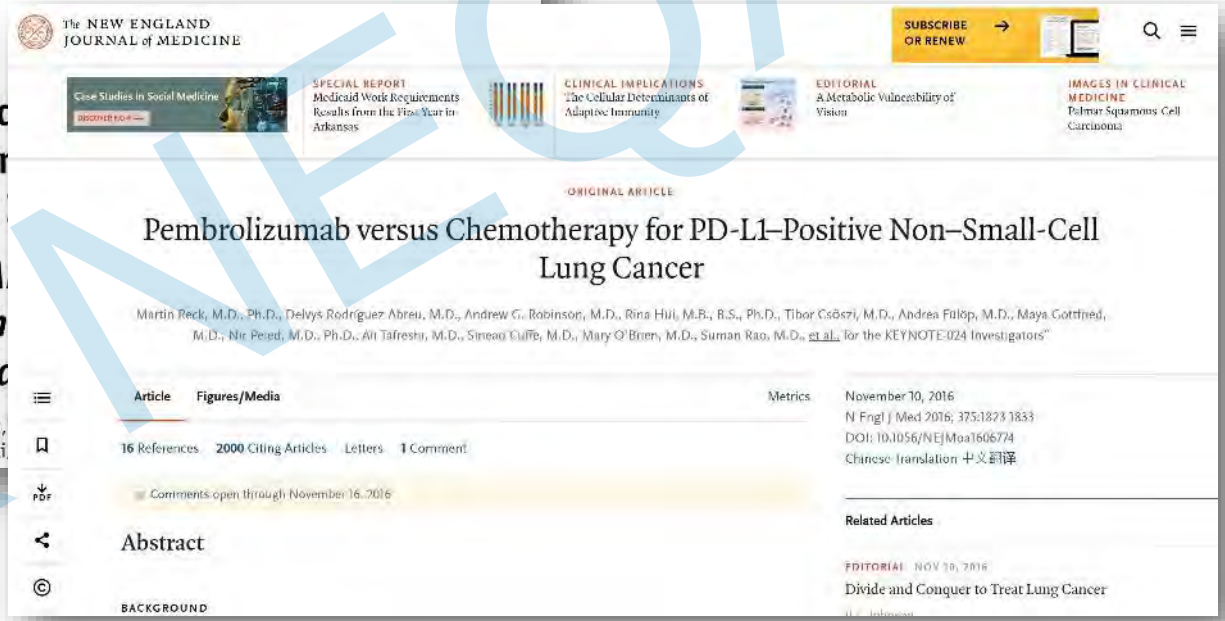
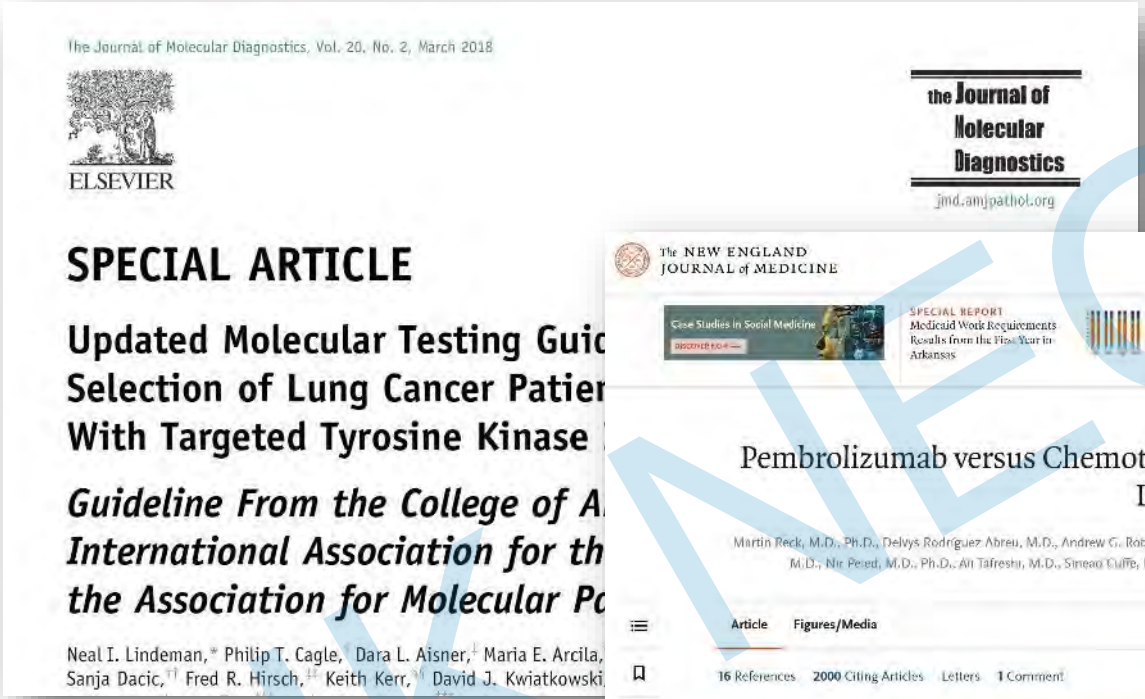
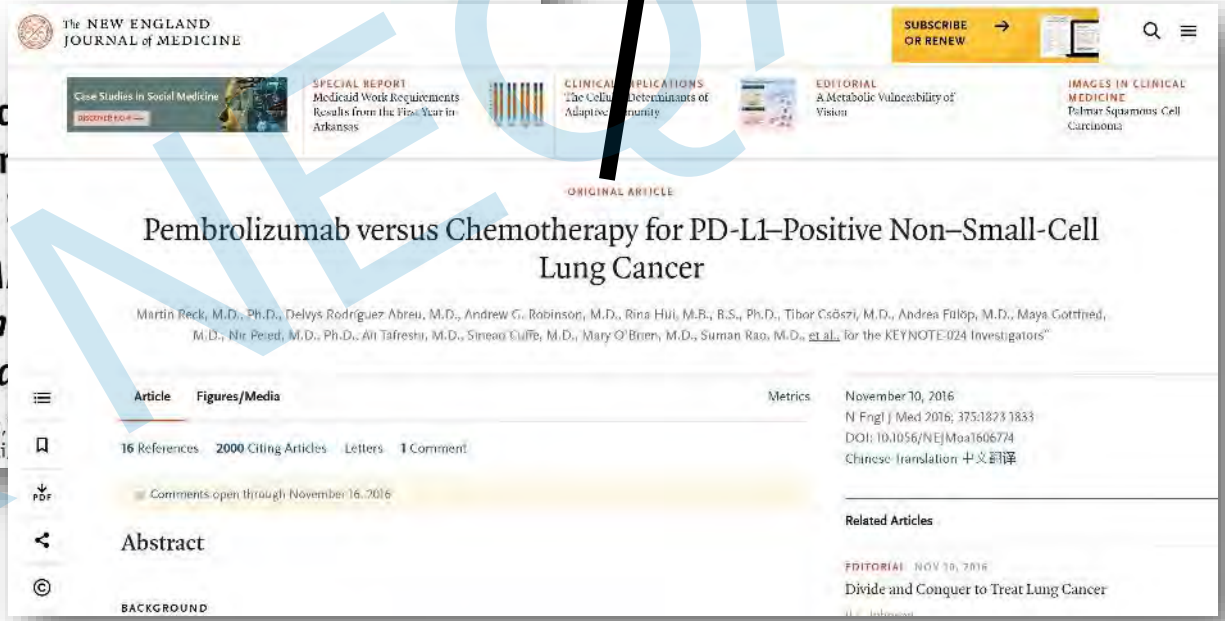
EGFR
ALK
ROS1

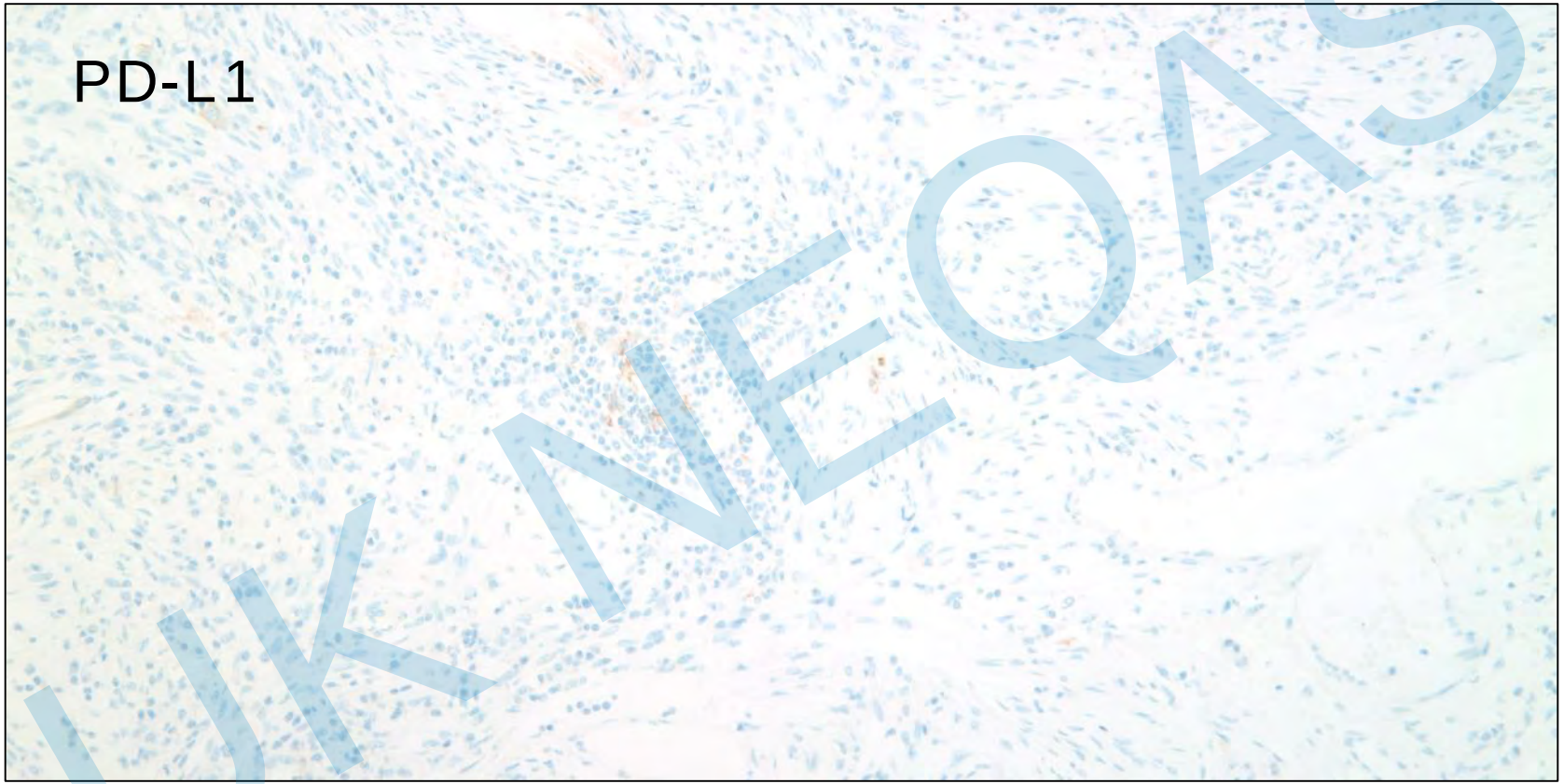


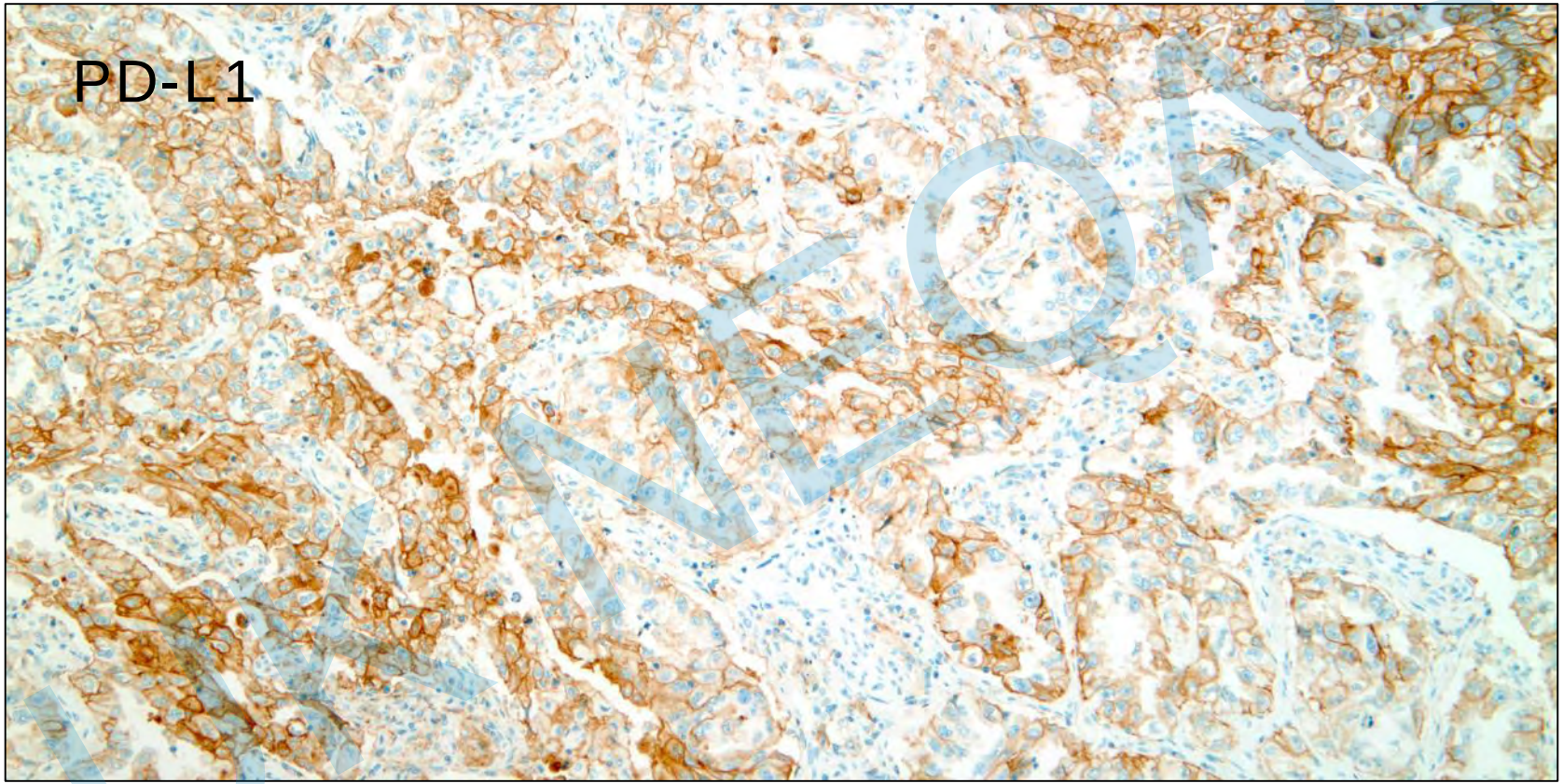


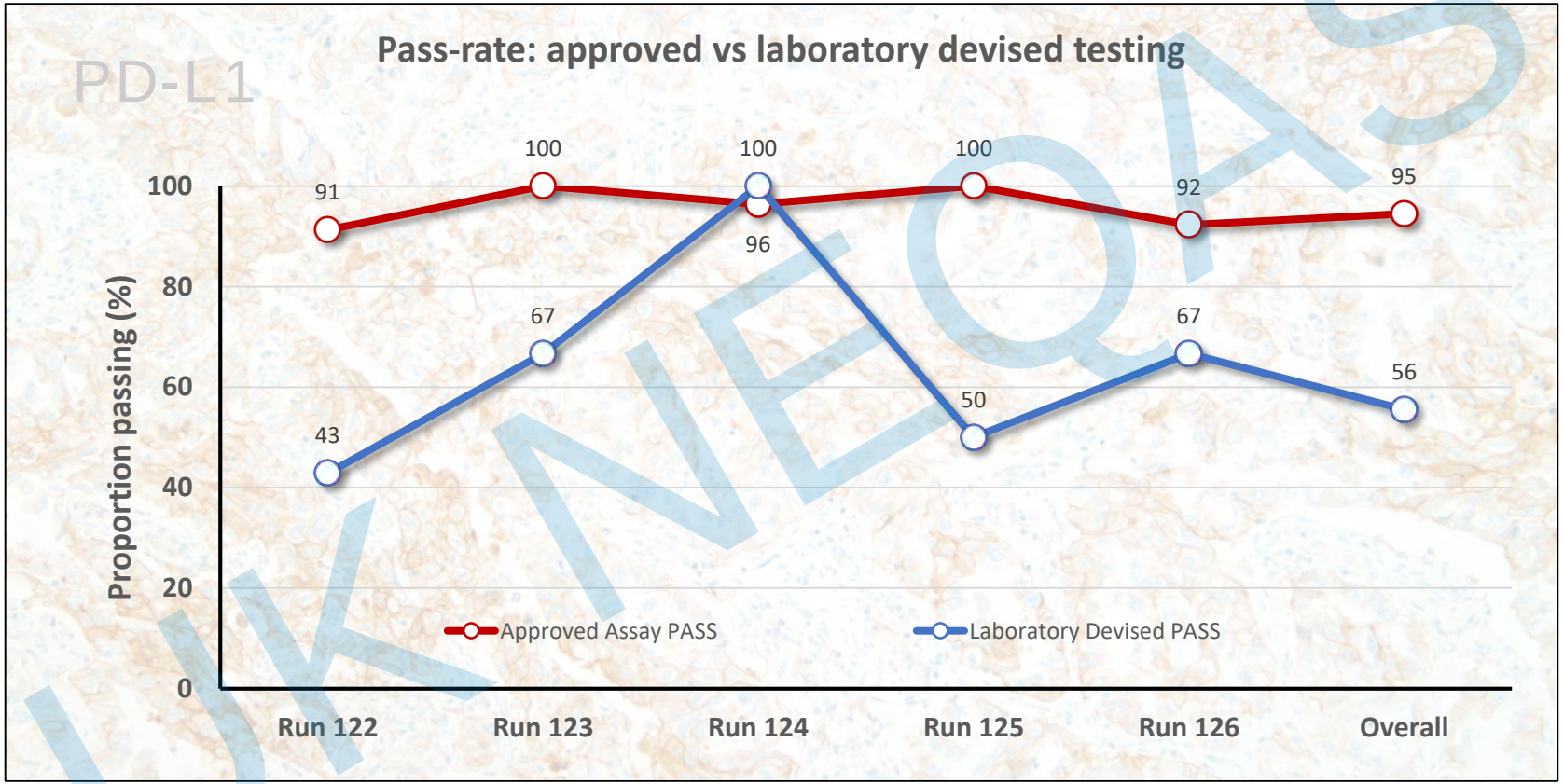


PD-L1



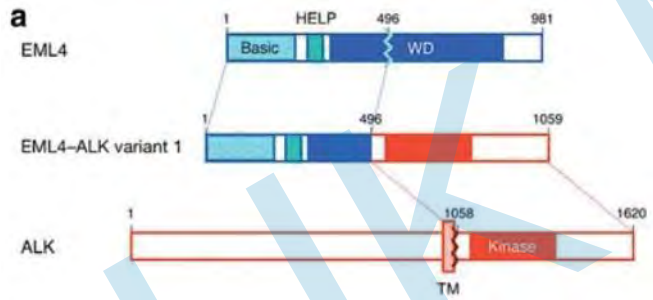


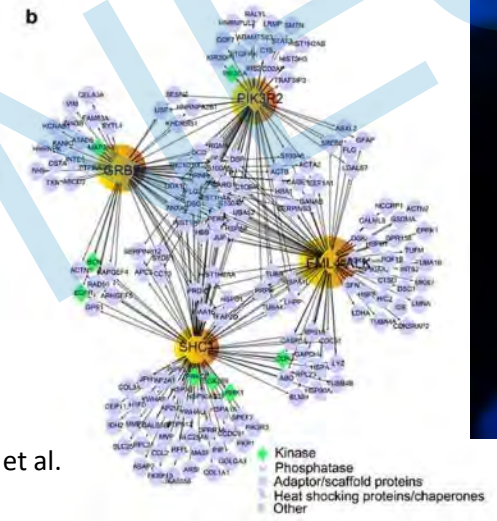


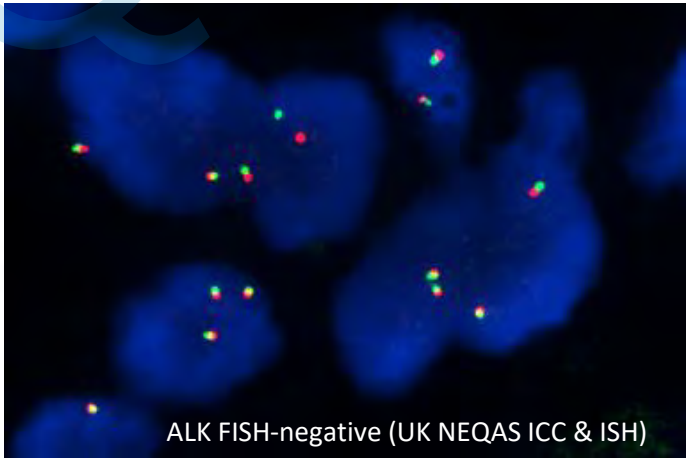


Anaplastic Lymphoma Kinase (ALK)

- Specific translocations involving the *ALK* gene lead to uncontrolled intra-cellular signalling and cell division
- It can be targeted using small molecule tyrosine kinase inhibitors (TKi's) – in particular, *Crizotinib*







Mol Cancer. 2018 Feb 19;17(1):52. Golding B et al.

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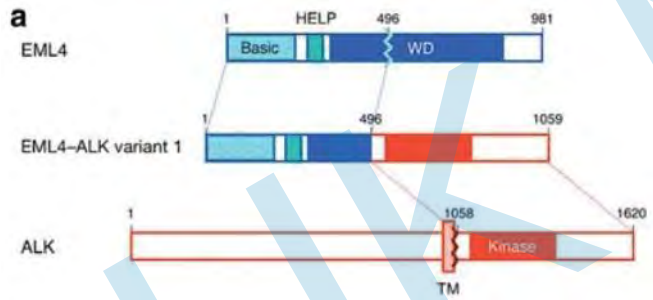
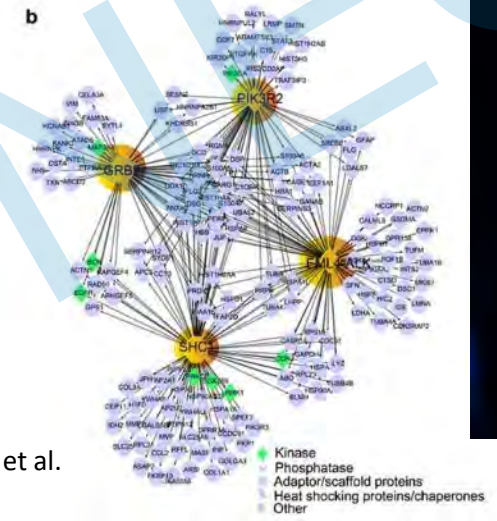
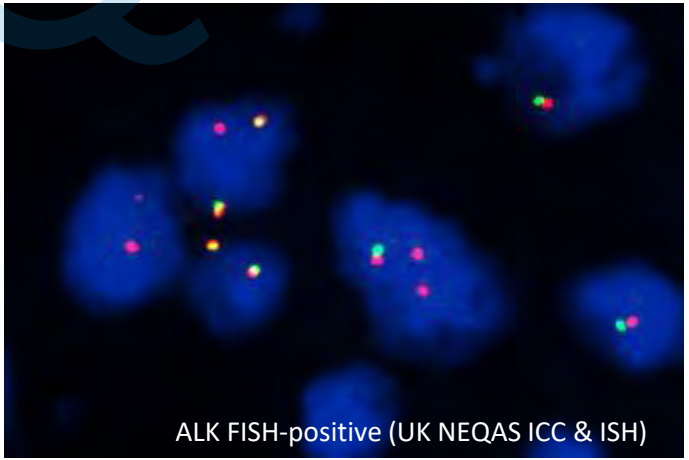


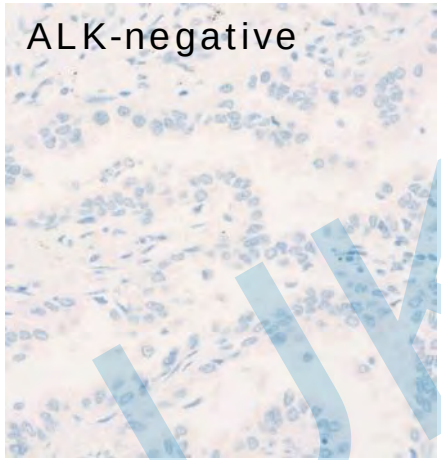


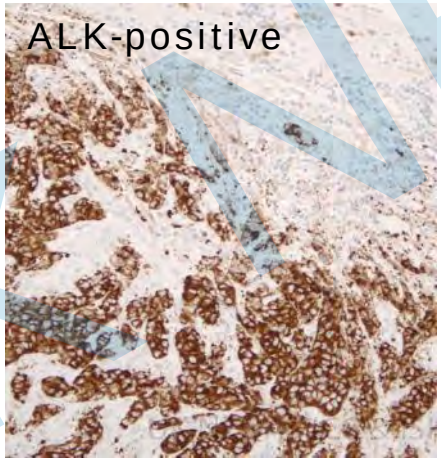

ALK FISH-positive (UK NEQAS ICC & ISH)

Mol Cancer. 2018 Feb 19;17(1):52. Golding B et al.

ALK

- The translocation also causes overexpression of the ALK protein, which can be detected by IHC
- UK NEQAS ICC & ISH has been offering an ALK IHC module since 2015





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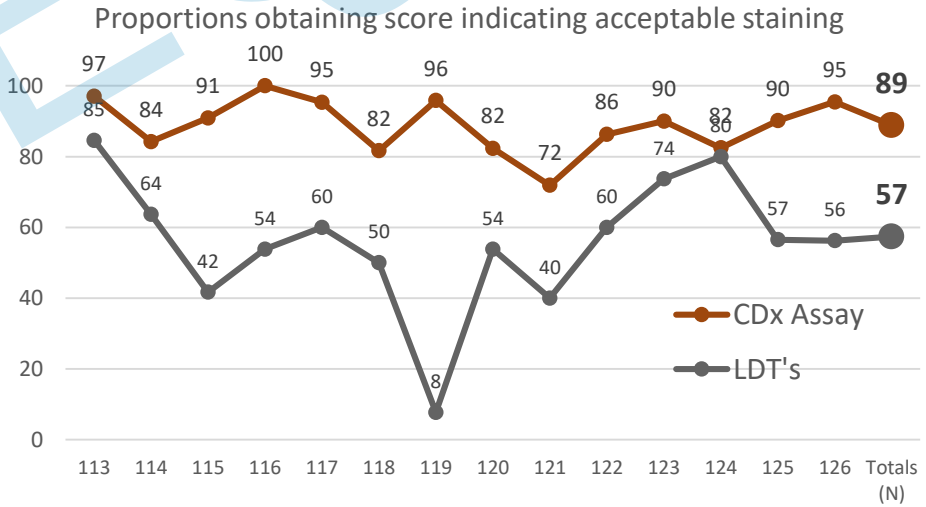

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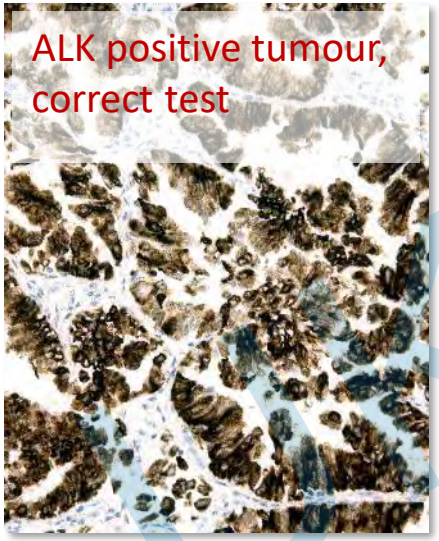
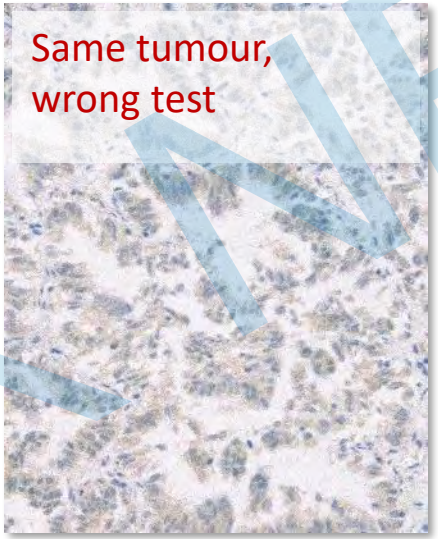
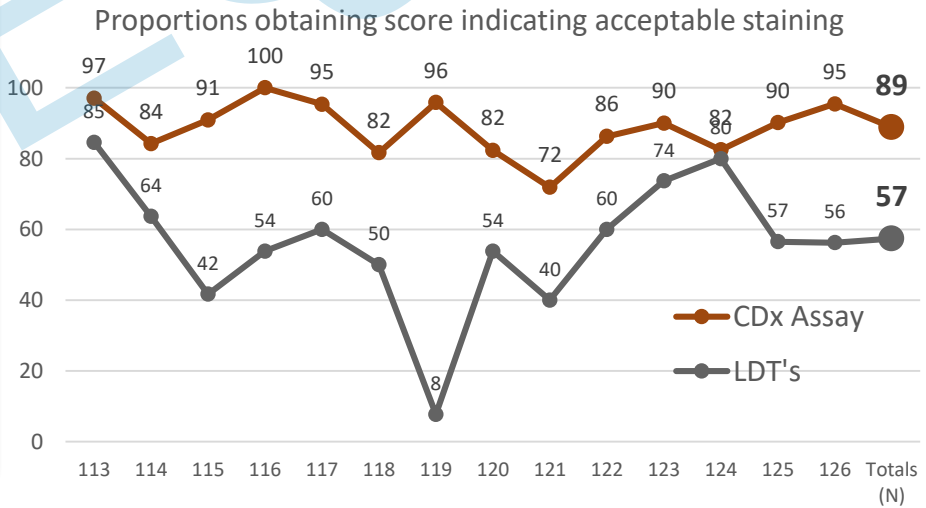
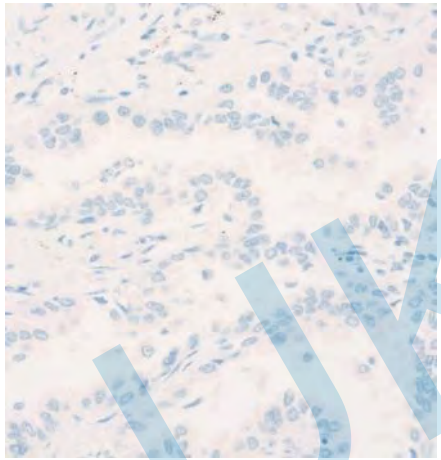


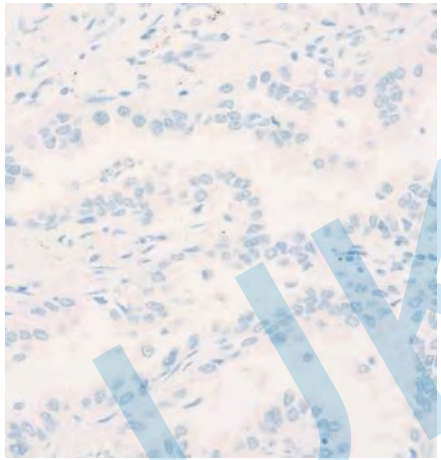




~~Crizotinib~~



William is
ALK negative



William is ALK negative

What's next?

Acknowledgments

Suzanne Parry
Jamie Hughes
Marie Stoddart
Chris-Jude Quaye
Neil Bilbe
Wendy Fernandes
Nick Warrick
Clara Lynch
Lin Rhodes

UK NEQAS
International Quality Expertise

50 Years as World Leaders in EQA 1969–2019

External Quality Assessment and the Patient's Journey

Representatives from UK NEQAS Schemes

Surgery

Complications

- Pneumonia – UK NEQAS Microbiology
- Deep vein thrombosis – UK NEQAS Haematology & UK NEQAS Blood Transfusion Laboratory Practice

UK NEQAS
International Quality Expertise

GenQA GENOMICS QUALITY ASSESSMENT

GenQA – Genomics External Quality Assessment

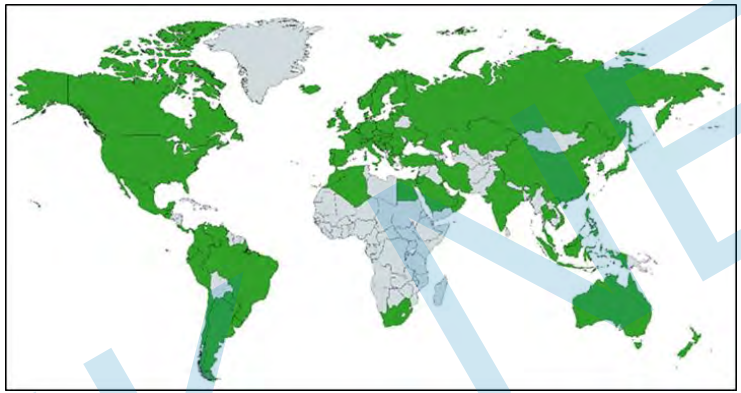
Dr Jenni Fairley
Deputy Director, GenQA, Edinburgh, UK

UK NEQAS
Molecular Genetics

CEQAS
Cytogenomic External Quality Assessment Service

78

GenQA GENOMICS QUALITY ASSESSMENT
Collaboration between CEQAS and UK NEQAS Molecular Genetics
Member of UK NEQAS consortium

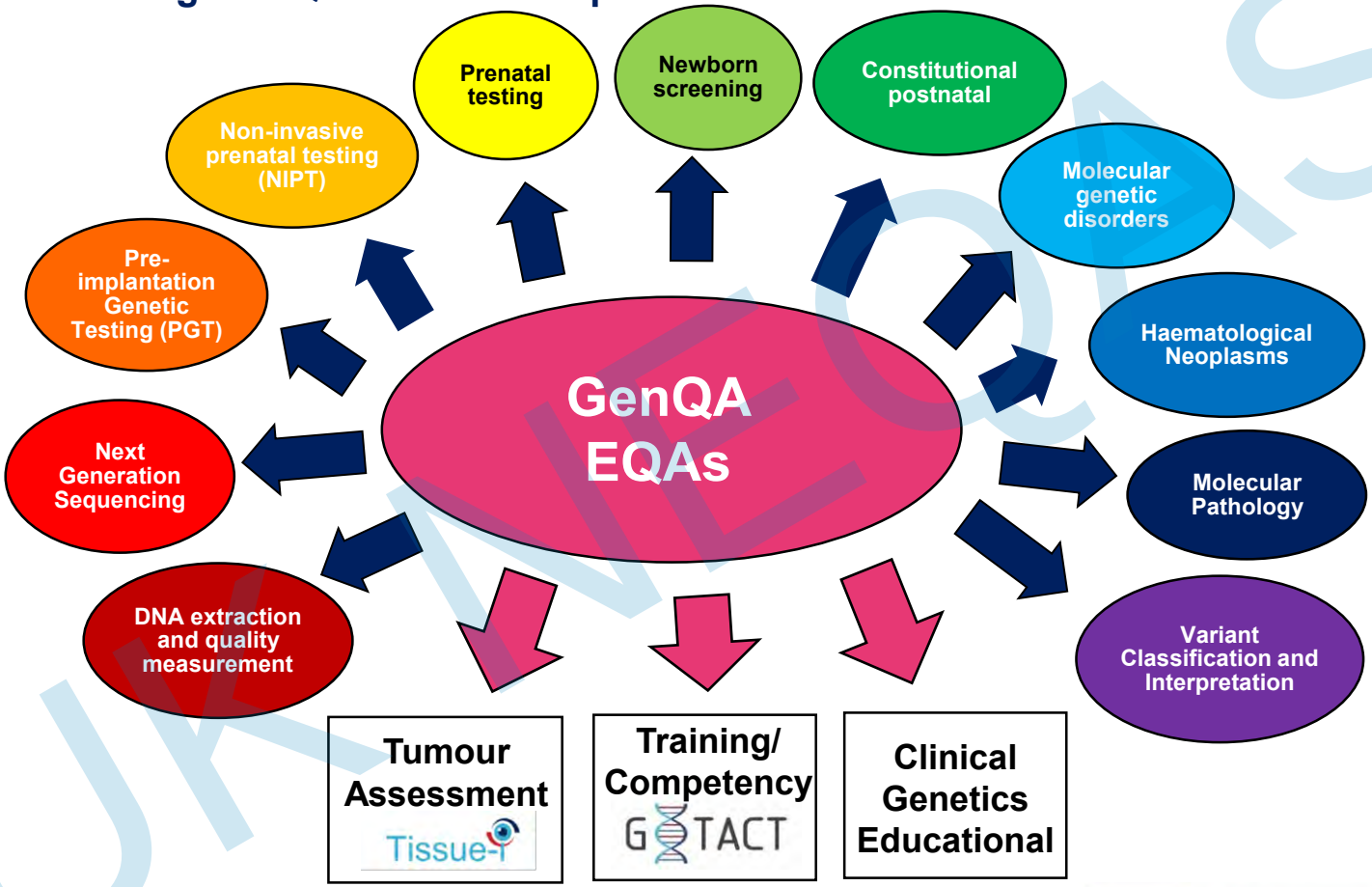


79
Countries

2019
Delivery of 94 EQAs, including:
- EQAs with multiple distributions
- 12 pilot EQAs

2020
98 EQAs planned so far, including:
- EQAs with multiple distributions
- 17 new EQAs

Delivering 98 EQAs across 14 specialities

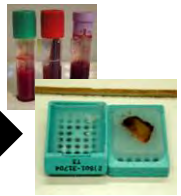


GenQA GENOMICS QUALITY ASSESSMENT

End to End testing

Pre-test consultation /Referral → Sample → Analysis → Interpretation → Reporting → MDT → Consultation

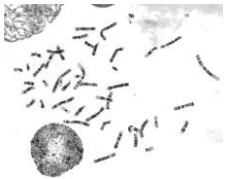
Pre-test referral



Sample handling

DNA extraction
DNA quality

DNA quantity



Analysis – online images/ genotyping accuracy / technical

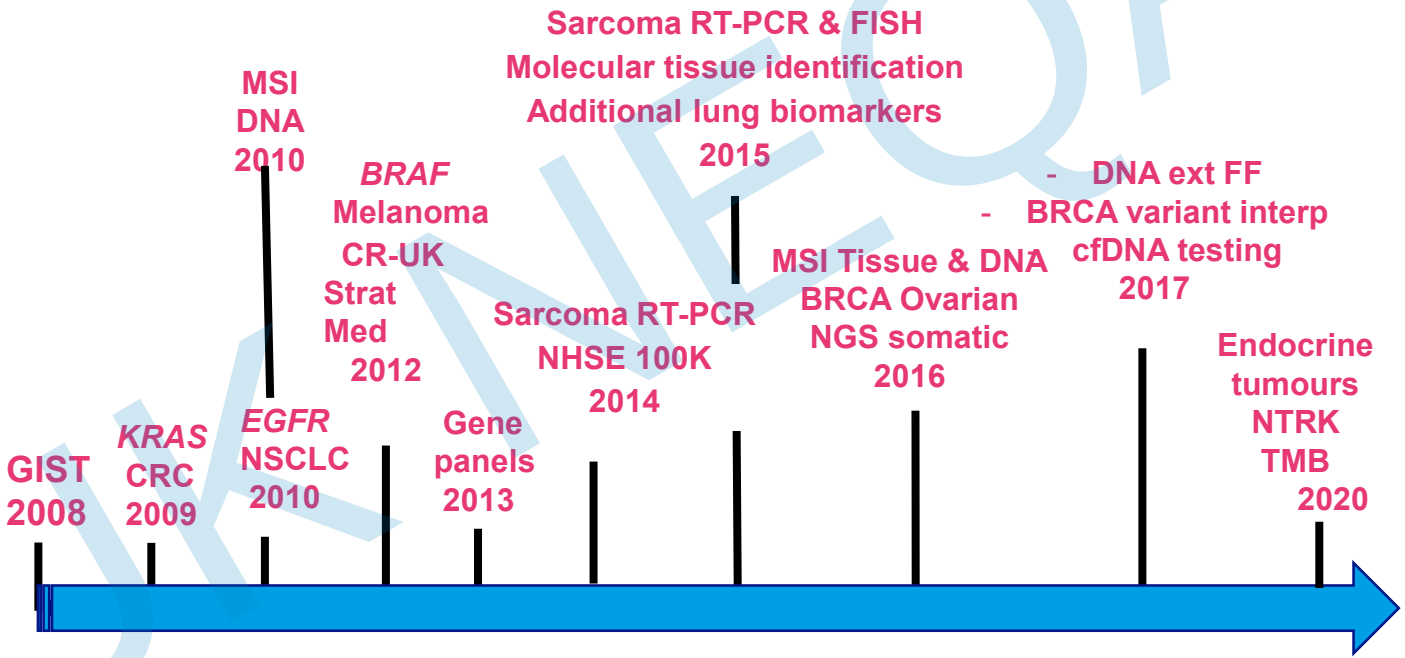
Interpretation

Reporting

Consultation

GenQA GENOMICS QUALITY ASSESSMENT

Molecular Pathology
External Quality Assessment



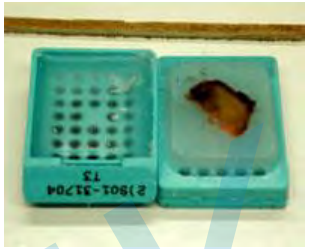
GenQA GENOMICS QUALITY ASSESSMENT

Scheme format

Mutation selected for EQA ✓

EQA sample identified - available and with consent ✓

>1 block from same tumour ✓



Sections prepared for EQA scheme

EQA Distribution

Validating Lab 1
First sections cut Method 1

Validating Lab 2
Last sections cut Method 2

Sections mid block

GenQA GENOMICS QUALITY ASSESSMENT

Scheme format

Assess the whole process involved in the clinical service

Validated tumour samples

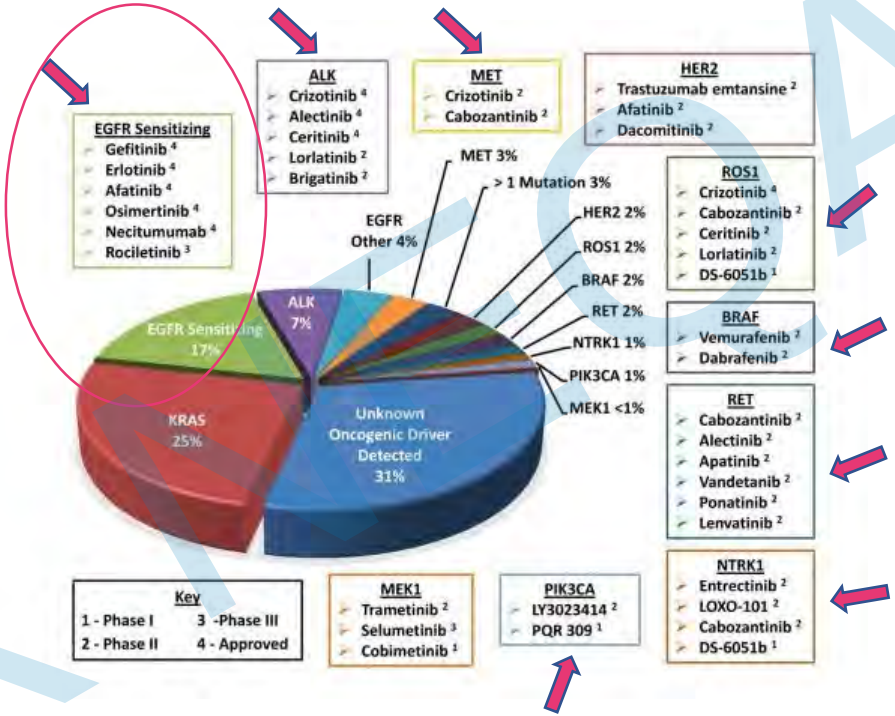
- **Rolled FFPE sections**
- **Slide mounted F**
- **Rolled FFP mounted F**

Test according to routine protocols and report in the context of the clinical case using normal reporting format

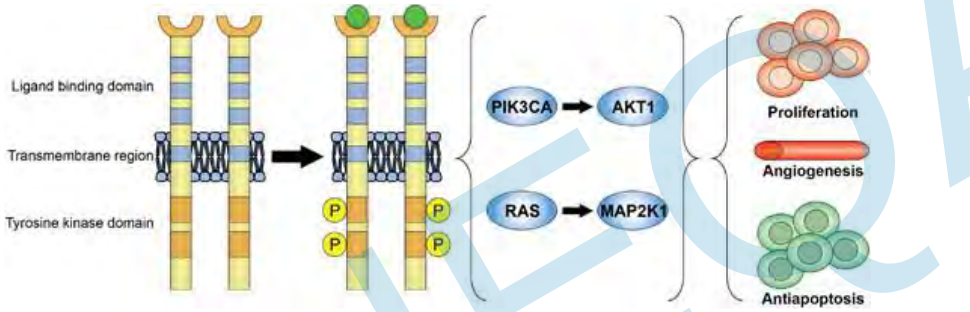
Case 1
Patient name - Mary BROWN
Date of birth - 11/02/1950
BLOCK NUMBER – 50

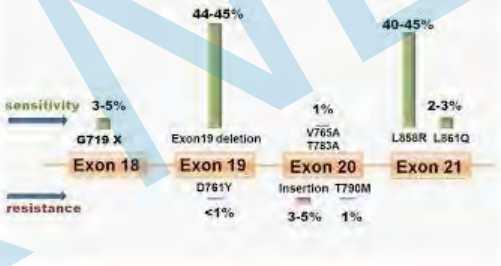
Non-smoker diagnosed with arcinoma on biopsy vent lung resection e cancer and 6 presented with A sample from primary tumour referred for ar testing to determine further treatment options.

Molecular Alterations in Lung Cancer

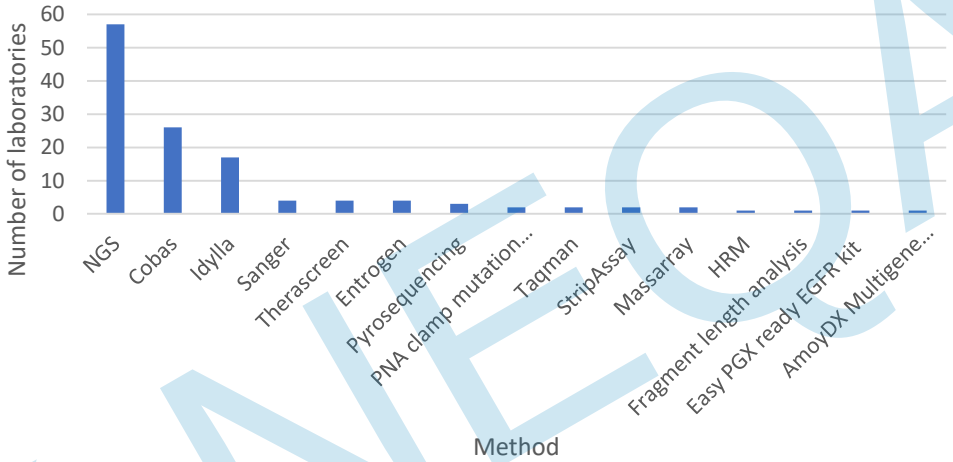


EGFR

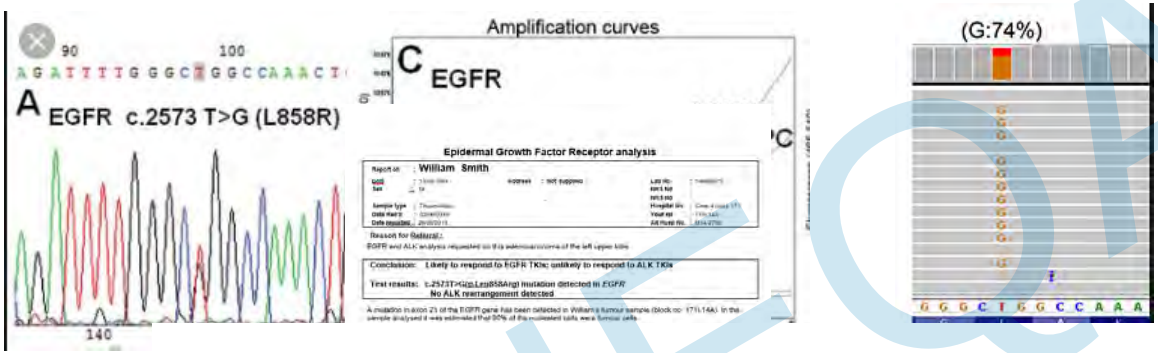




Testing for mutations in *EGFR*



Results



William has a mutation in *EGFR* and therefore may respond to EGFR tyrosine kinase inhibitors

Acknowledgements –

- *Sample sourcing & validation laboratories*
- *Scientific advisory groups (SAGs)*
- *Peer assessors*
- *GenQA team*

The participants

Contact us on info@genqa.org

GenQA GENOMICS QUALITY ASSESSMENT

UK NEQAS
International Quality Expertise

50 Years as World Leaders in EQA 1969–2019

External Quality Assessment and the Patient's Journey

Representatives from UK NEQAS Schemes

Male

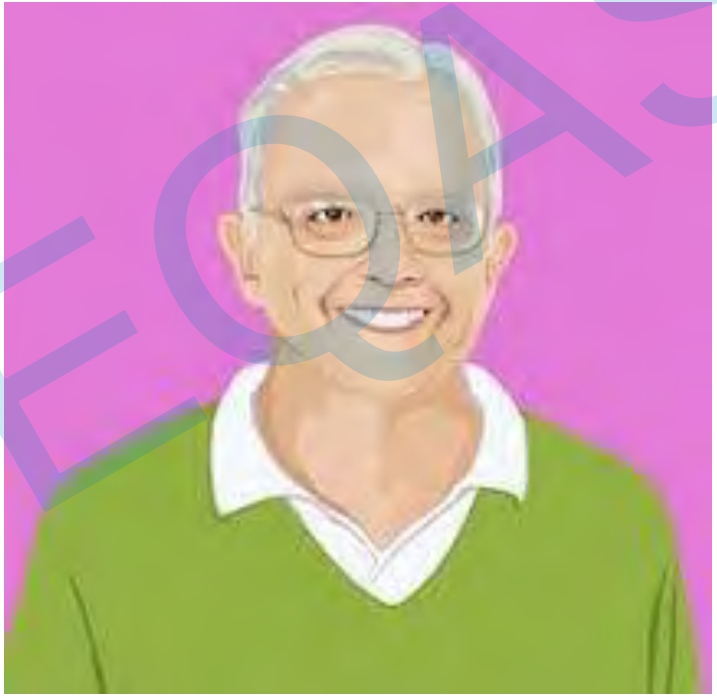
55 years of age

Light smoker

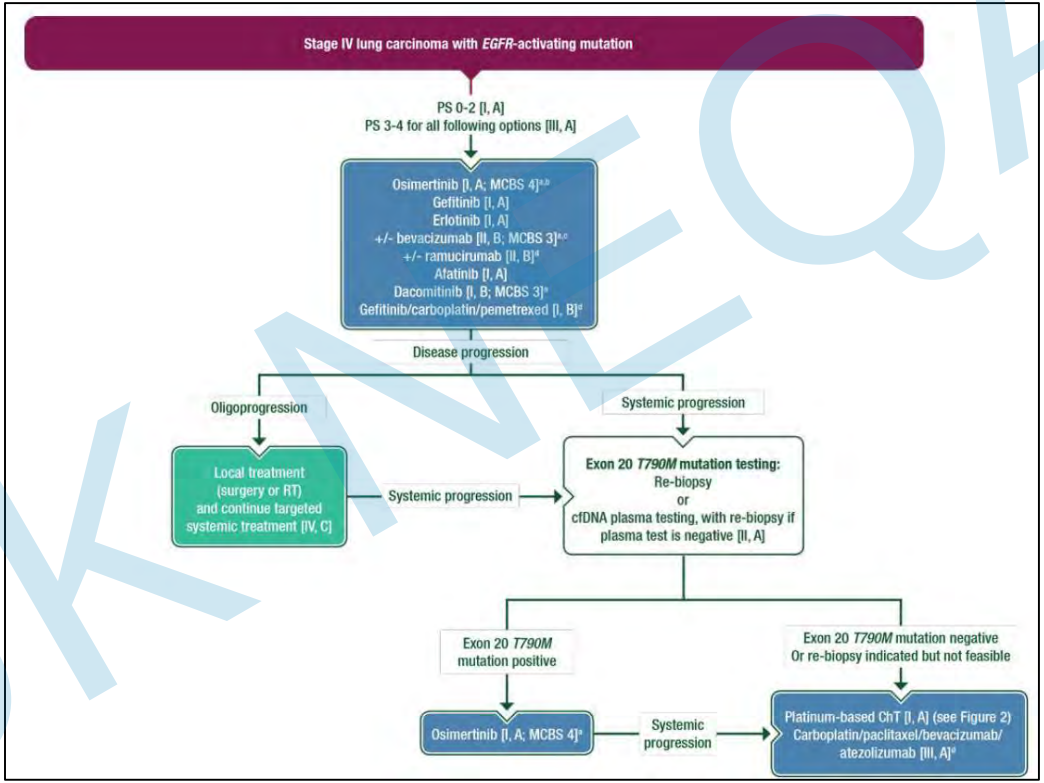
Persistent cough >1 month

GP

- Sputum & Blood
- X-ray

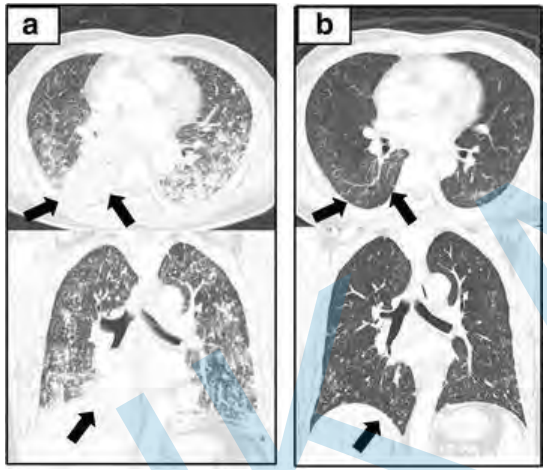


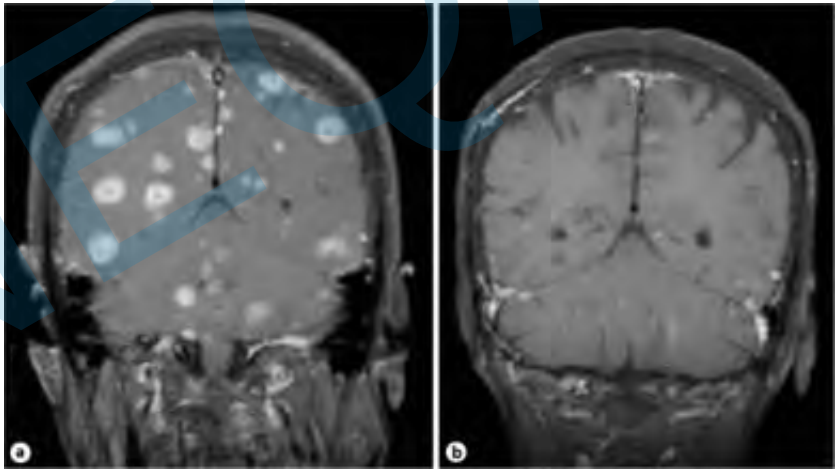
Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (Updated version published 18 September 2019)



EGFR positive

- Afatinib, erlotinib, dacomitinib, gefitinib and osimertinib





UK NEQAS
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Thank You

Back to Top

Keeping Control of Quality

Dr Graham Lee FRCPath
Consultant Clinical Biochemist/UCD Assistant Clinical Professor
Department of Clinical Biochemistry & Diagnostic Endocrinology
Mater Misericordiae University Hospital and
Cappagh National Orthopaedic Hospital, Dublin
Midland Regional Hospital, Mullingar,
University College Dublin

Keeping Control of Quality?

Keeping

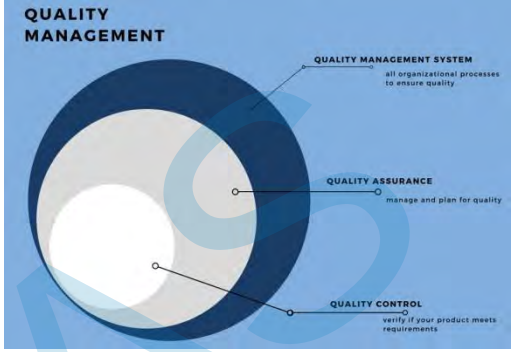
Using time (energy/resource) commensurate to the quality requirement!

Quality Management Definitions

- **Quality**: Degree (e.g. %) to which a set of inherent characteristics fulfils requirements (ISO15189:2012)

e.g. If the *requirement* is to receive all urine samples in the laboratory uncontaminated, the number of contaminated urine samples received as a % of all urine samples received (*the inherent characteristic of the process*) is a *measure* of the quality of the process

Quality Management Definitions definitions continued (ISO9000)



- **Quality <u>Assurance</u>** is **Process** oriented

-Providing confidence that quality requirements <u>will be</u> fulfilled

"**planning** etc. for **ensuring quality**….at the **beginning**"

- **Quality <u>Control</u>** is **Product** oriented

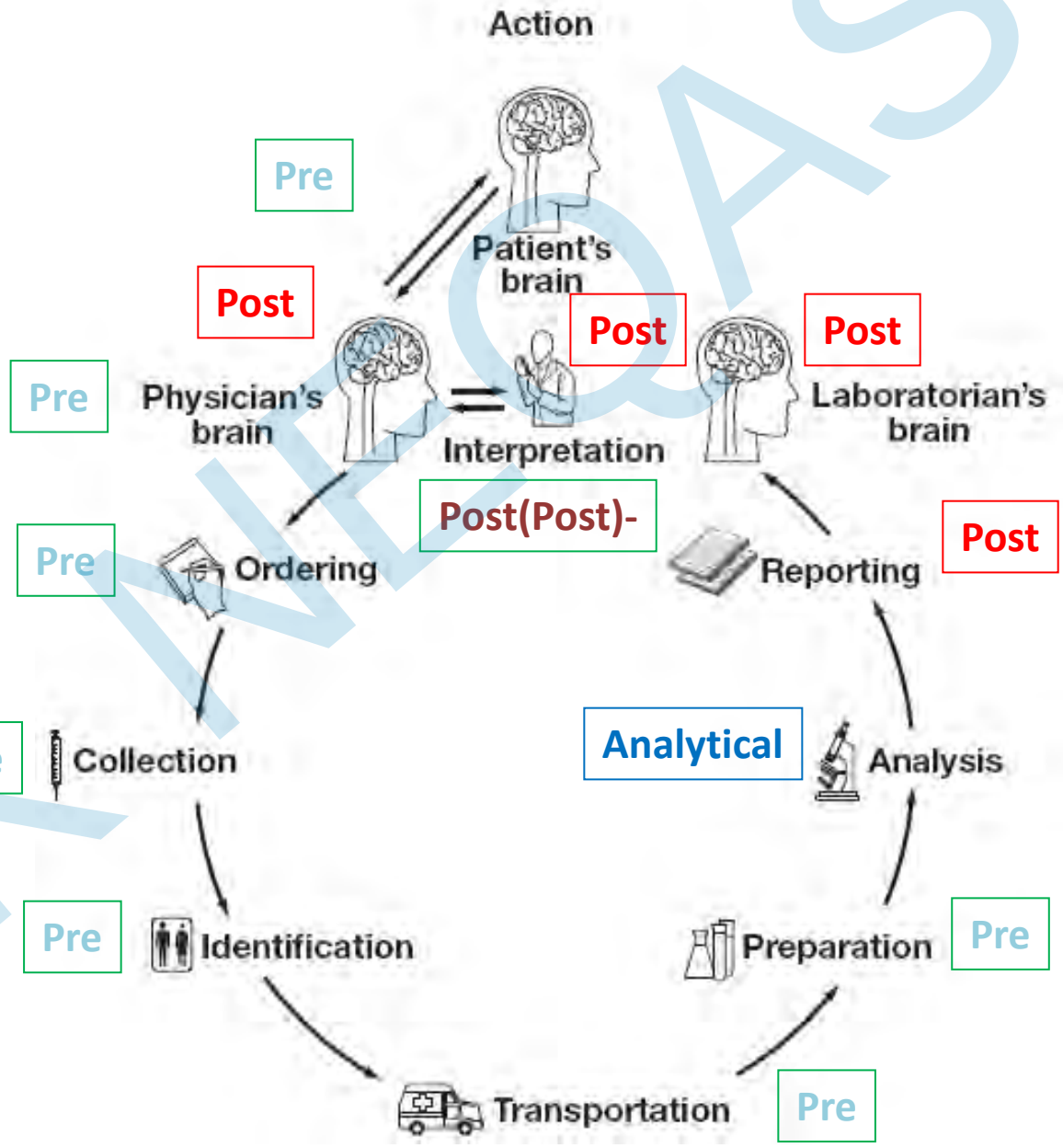
-Fulfilling quality requirements

"**Inspecting** a **product** to **ensure it meets the requirements**….

…reactive… at the **end** of the process".

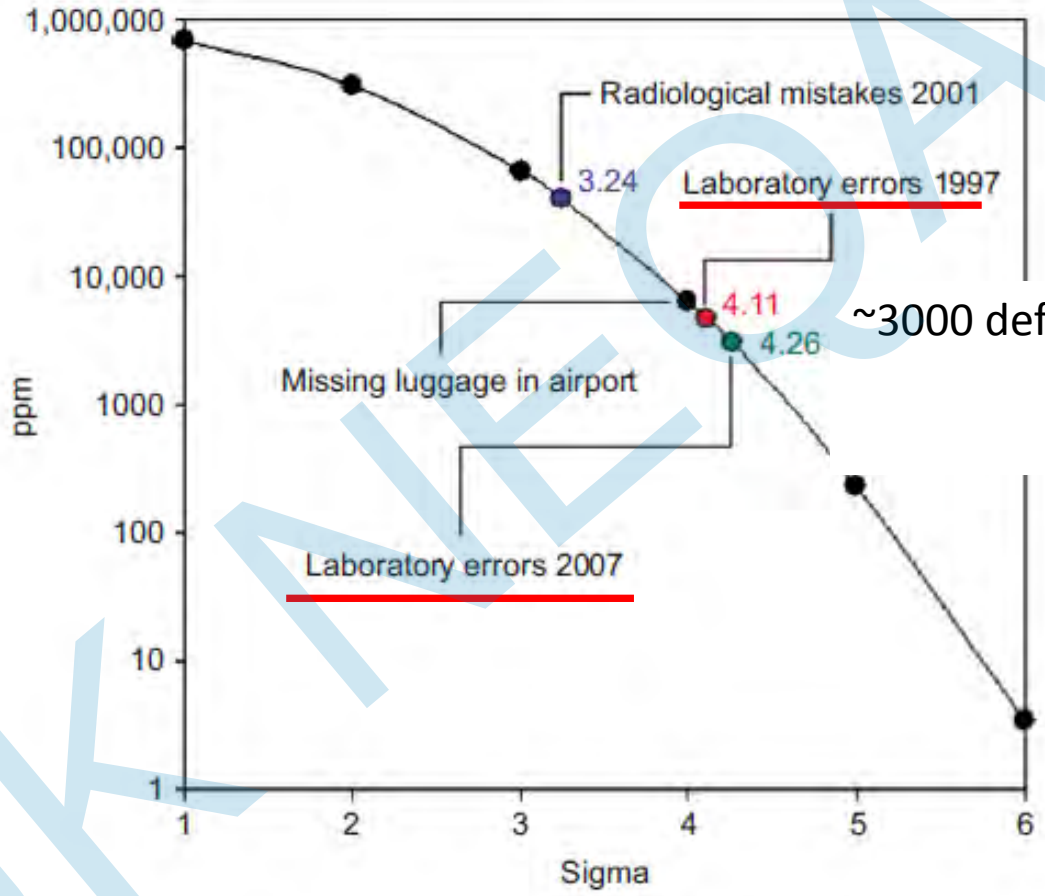
Keeping Control of Quality across the Total Testing Pathway

Lundberg (1981):
Brain to Brain loop
concept for laboratory testing



What is involved in ALL Laboratory testing?

ERROR!



~3000 defects *per* million
1:333

….seems we are possibly getting a little better!

(*presuming ability to detect is not lower*)

Is the degree of error (ppm) in Lab Med acceptable?

Pre-analytical:

*"Processes that start, in chronological order, **from the clinician's request** and include:*
the examination request,
preparation and identification of the patient,
collection of the primary sample(s),
and transportation to and within the laboratory,
*and end **when the analytical examination begins**"*
(ISO15189:2012)

-a focus on Requesting….

Demand Management/Appropriate Testing

Improving quality in the Preanalytical phase through innovation
Lippi *et al*., Clin Chem Lab Med 2017; 55(4): 489–500.,

Over-requesting ↑ costs + may lead to further unnecessary testing + significant adverse effects

"Managing laboratory demand strategies: some actual examples of their usefulness" (supporting appropriate testing):

- Guidelines
- Education
- Diagnostic decision trees

-Stepwise reflex/reflective testing e.g. Depending on the result of Test 1 e.g. Testosterone <RI in male , a prompt is given to do Test 2 e.g. SHBG, therefore avoid doing Test 2 if not required

- Minimum Retest Intervals

Demand Management experiences

-To support appropriate ordering of B12 + Folate

- Routinely requested (B12/Folate/Ferritin/TSH/FT4)
- No/V. little clinical information with requests
- Baseline data showed GP = 86% of B12/Folate requests

The Demand Management Intervention:

- **Step 1**: GP liaison meeting (Sept 2018)

A look across the Total Testing Pathway for B12 + Folate

-Pre-Post analytical limitations

-Need for Appropriate indications, be prepared!

- **Step 2**: Memo (Nov-18) requesting use of a "Clinical Indication form" on B12/Folate requests in Dec-18. **Mandatory in Jan -19**.

Reminder of appropriate indications!

-Phased implementation to GPs at Location 1, then Locations 2+3

Baseline data for B12 and Folate testing

*-**Pre** demand management: GP = 86% of requests*

GP	B12			
	Low B12 (<122)	**Normal (122-626)**	**High (>626)**	**Total**
	n=229 (3%)	n= 7787 (93%)	n= 344 (4%)	**8360**
Low folate <3.1	n=15/174 (9%)	n=189/6219 (3%)	n= 8/229 (3.5%)	6714

- Folate not tested concurrently (Folate only in ~1%)

…You can't have one without the other!

- Low B12 in only 3%:

…Low diagnostic yield, Low Pre-test probability, Appropriate test?

NEED to define Indication for testing…..

PATHOLOGY REGIONAL HOSPITAL MULLINGAR
Longford Road, Mullingar, Co Westmeath Tel: 044 9394330

Vitamin/Folate B12 clinical indication form. Download from
https://www.hse.ie/eng/services/list/3/acutehospitals/hospitals/regional-hospital-mullingar/our-services
(See also laboratory memorandum of MEMO-M/CC/79)

Please complete this form for ALL Vitamin B12/Folate requests and enclose with each sample, to enable timely analysis. From 24/06/2019, if this form is incomplete or not enclosed with the sample, usual analysis will NOT proceed. The sample will instead be retained for 1 week from the date of sample collection and will be analysed only upon receipt of this form by the laboratory (contact details at bottom). During this time if there has been no such correspondence, samples will be discarded without analysis. This form must accompany all requests for Vitamin B12/Folate testing. Lab request form also required. Please affix patient label here or complete box below

Please affix patient label here or complete box below

Patient demographics -
Name:
Gender:
Date of Birth:
Hospital Number:
*SDR Number:
*From 10/06/2019, if the form is not received, the test "SDR" will be reported with a number in the result field. State this number when sending this form

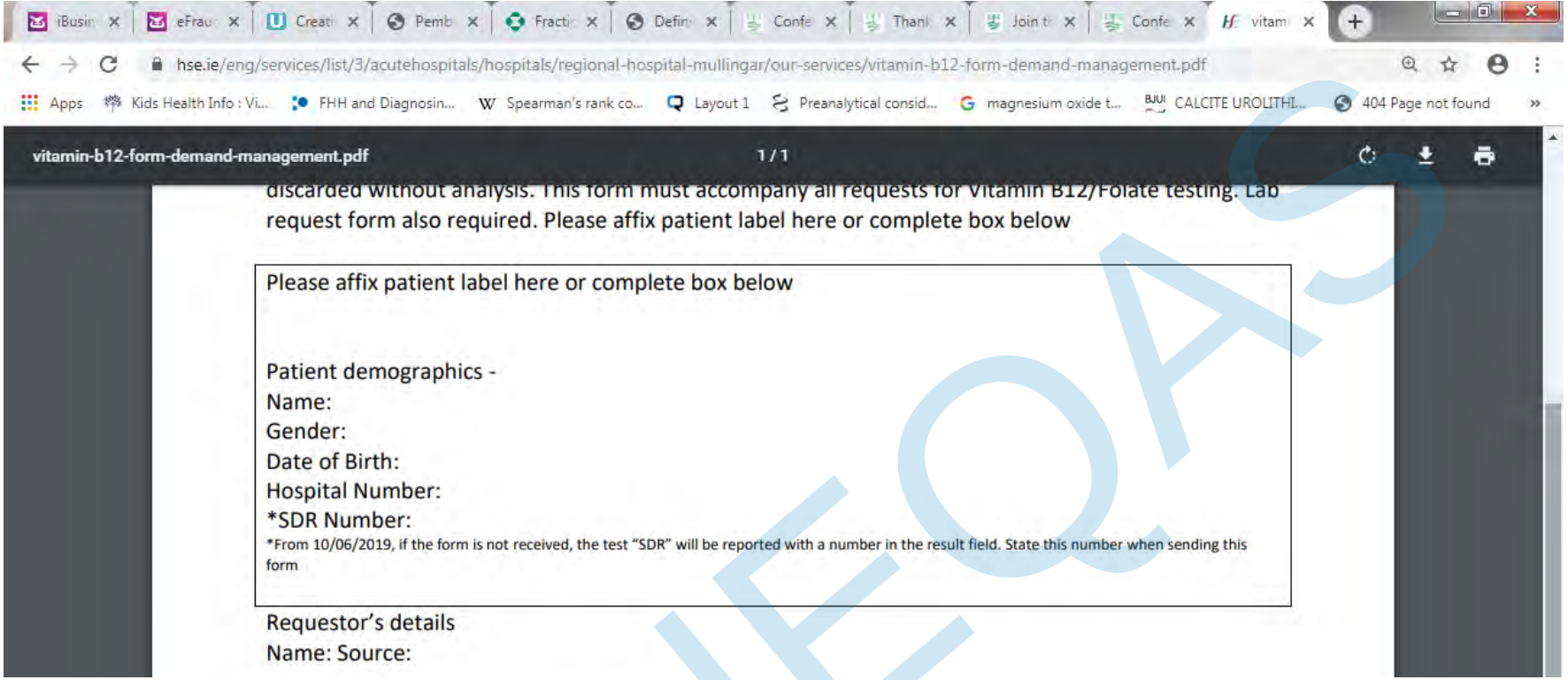
Requestor's details
Name: Source:

*Date and Time stamp LAB USE ONLY:
Request Details

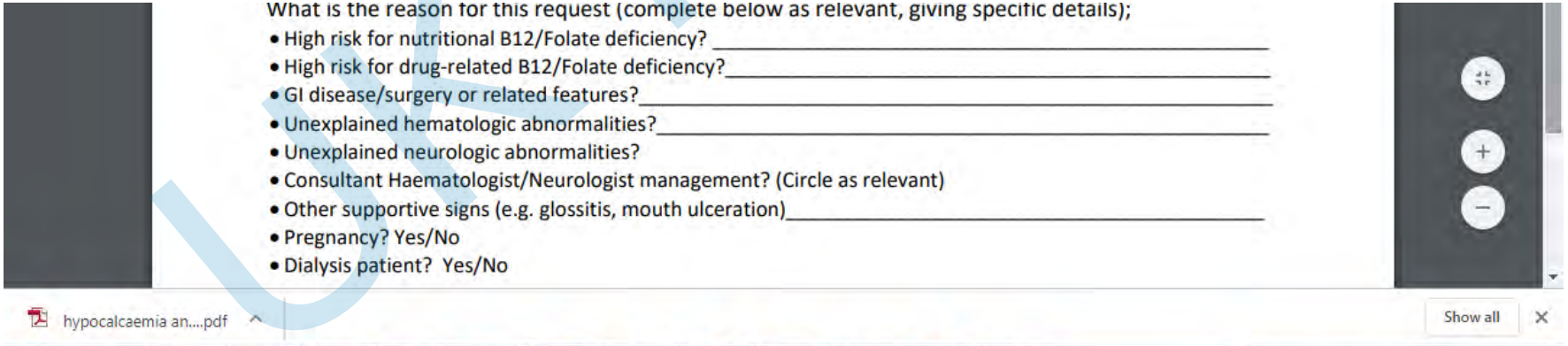
Has Vitamin B12/Folate been requested on this patient before? Yes / No (circle as applicable) If Yes:
*When was the last sample analysed? ____/___/20_____
What is the reason for this request (complete below as relevant, giving specific details);

- High risk for nutritional B12/Folate deficiency? _____
- High risk for drug-related B12/Folate deficiency?_____
- GI disease/surgery or related features?_____
- Unexplained hematologic abnormalities?_____
- Unexplained neurologic abnormalities?
- Consultant Haematologist/Neurologist management? (Circle as relevant)
- Other supportive signs (e.g. glossitis, mouth ulceration)_____
- Pregnancy? Yes/No
- Dialysis patient? Yes/No

Doc. No: ***FORM-M/CC/58***	***Doc Owner: Helen Corrigan***	***Dept & Location: Clinical chemistry*** *Pathology RH, Mullingar*	
Vers. No: 2	***Active Date:*** ***June 2019***	***Doc Title: Vitamin B12 demand management form***	***No. Of Pg:*** *1 of 1*



What has changed using this strategy to support testing based on clinical indication?....



Intervention to support appropriate ordering of B12 + Folate, Post-intervention data:

Vitamin B12		
	2018	**2019**
Jan	9655	6388
Feb	8981	6165
Mar	9062	6254
Apr	9639	6206
May	10792	6721
		4512
July	8848	**3661**
Aug	9859	**3264**
Sept	8986	**3406**
Oct	10542	
Nov	9970	
	6307	

DM for Location 2+3 GPs

DM for Location 1 GPs

Intervention to support appropriate ordering of B12 + Folate, Post-intervention data:

Folate		
	2018	**2019**
Jan	8258	5927
Feb	7728	5500
Mar	7726	5475
Apr	8662	5526
May	9514	5921
		3945
July	7764	**3145**
Aug	8420	**3080**
Sept	7622	**2986**
Oct	9092	
Nov	8713	
	5835	

DM for Location 2+3 GPs

DM for Location 1 GPs

Summary (Jan-Sept 19)

Numbers of each test decreased by 64%

Savings -€38K

Pre (Nov 18) vs Post (Jan 19)

B12 <128		
Nov-18	**Oct-19**	**Comment**
288/8942= 3.2%	172/2681=6.4%	100% ^ yield
SFOL<3.1		**Comment**
114/7392=1.5%	43/2209=1.9%	27% ^ yield

- ↑ in Diagnostic yield
- ↓ Numbers of patients identified with low B12/Folate
- ↓ Reduction in Asymptomatic screening?

-Laboratories have become centres for screening

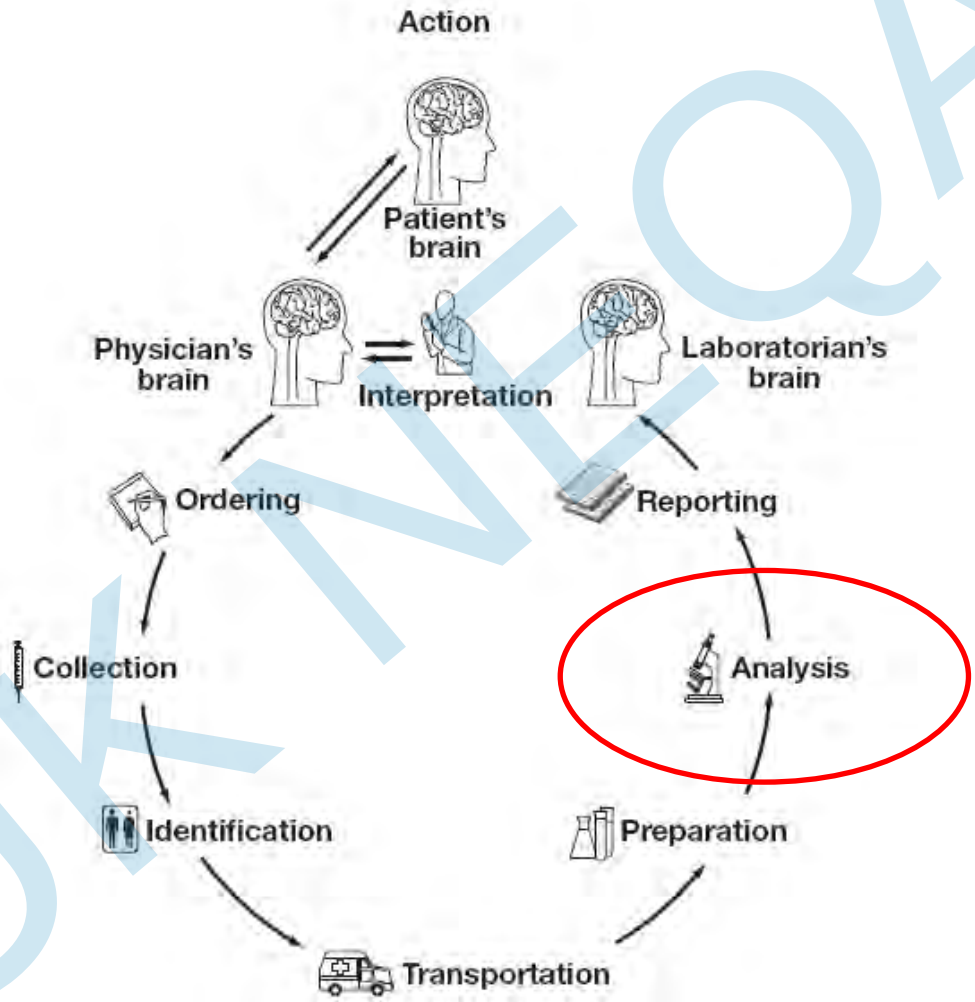
….as well as providing services for diagnosis + monitoring!

Thoughts on Controlling Quality of the "Request"

(% of Appropriate tests received)

- Significant Cost Savings achievable BUT need to consider clinical/diagnostic outcome measures
- Works well if clinical users engaged + it's mutually beneficial e.g. Vit D (↓80%, ↓100K/yr)
- ↓Unnecessary AND ↑Necessary tests
- Can be resource intensive (Start/During)
- Needs to be sustained

Controlling Quality in the Analytical Phase:



Analytical Phase

- A nod to automation for helping to reduce error!
- Improvements in Consistency, Standardisation + Traceability
- Less error than the Extra-analytical phases

..but room for improvement in

quality assurance + control measures….

What's *en vogue* (driven by accreditation)?

What's still not done/understood well/variable?

What's en vogue in Analytical Phase?

-Driven by ISO15189:2012?

5.3.2.1 General

*The laboratory shall have a documented procedure for the reception, storage, **acceptance** testing and inventory management of reagents and consumables.*

5.3.2.3 Reagents and consumables — Acceptance testing

*Each new formulation of examination kits with changes in reagents or procedure, or a new lot or shipment, shall be **verified** for **performance** before use in examinations.*

What do such Verification procedures
look like in your laboratory?
Time/effort well spent?

Reagent ACCEPTANCE testing

-for new lots of reagents, calibrators etc.

The Procedure in brief…

Stage 1 (Receipt):

Quarantine (colour code for **new lots)**

Visual Inspection

Documentation Review (kit insert, new version?)

Stage 2: (Evaluation/*Verification*)

IQC run X ≥1, ≥1 levels, ≥1 analyser, ≥1 day

…Compare IQC result vs Target Mean + SD for given test

>Pass i.e. within Mean ± 2SDs. Accept for use

>Fail. Do Not Accept for use, Quarantine + Non-conformance

***Acceptance** vs Rejection!*

Batch Acceptance (BA) experience Accept > Reject?

- Review of BA for Abbott Architect reagents (1 year)
- Immunoassay-based tests

n=235/237: ACCEPT, n=2/237 (0.8%): REJECT

- Chemistry tests-based tests

n= 261/262: ACCEPT, n=1 (0.4%): REJECT

But issues of subsequent Systematic Error detected in real time/life even where reagents + calibrators have 'Passed' initial BA procedures

BAs procedures good (sensitive) enough to detect clinically meaningful (lot-to-lot) bias?

Clinical Chemistry 59:8
1187–1194 (2013)

Failure of Current Laboratory Protocols to Detect Lot-to-Lot Reagent Differences: Findings and Possible Solutions

Alicia Algeciras-Schimnich,[1] David E. Bruns,[2] James C. Boyd,[2] Sandra C. Bryant,[3] Kristin A. La Fortune,[2] and Stefan K.G. Grebe[1*]

Approaches for acceptance testing/detecting lot-to-lot variability

Analyse samples across reagent lots (current/new) using:

- Patient samples

>Criteria: Regression Slope (0.9-1.1) or Intercept Δ by ≤10%

…using n=20-30 samples over Analytical Range

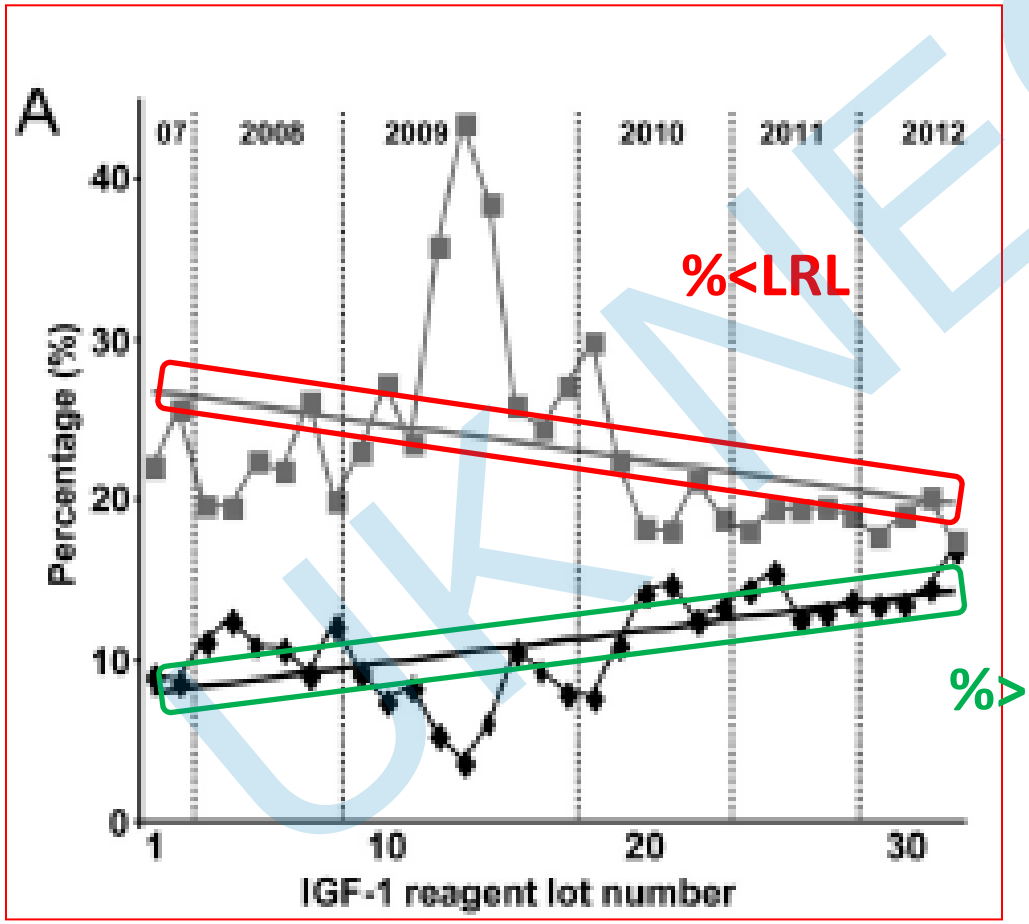
- IQC + EQA

A lot of Lot-to-Lot variability!

(Schimnic et al., 2013)

- ***Increase in No of high IGF-1 results…reported by clinical users!***
- ***Lab retrospectively evaluated 32 previous lots (2007-2012) + examined:***

1. ***Patient data (n = 286av. Per reagent lot)***
2. ***Data used from previous lot-lot comparison studies (n=20 data pairs per lot)***



Over time (lot 1-32):

A 3 fold increase

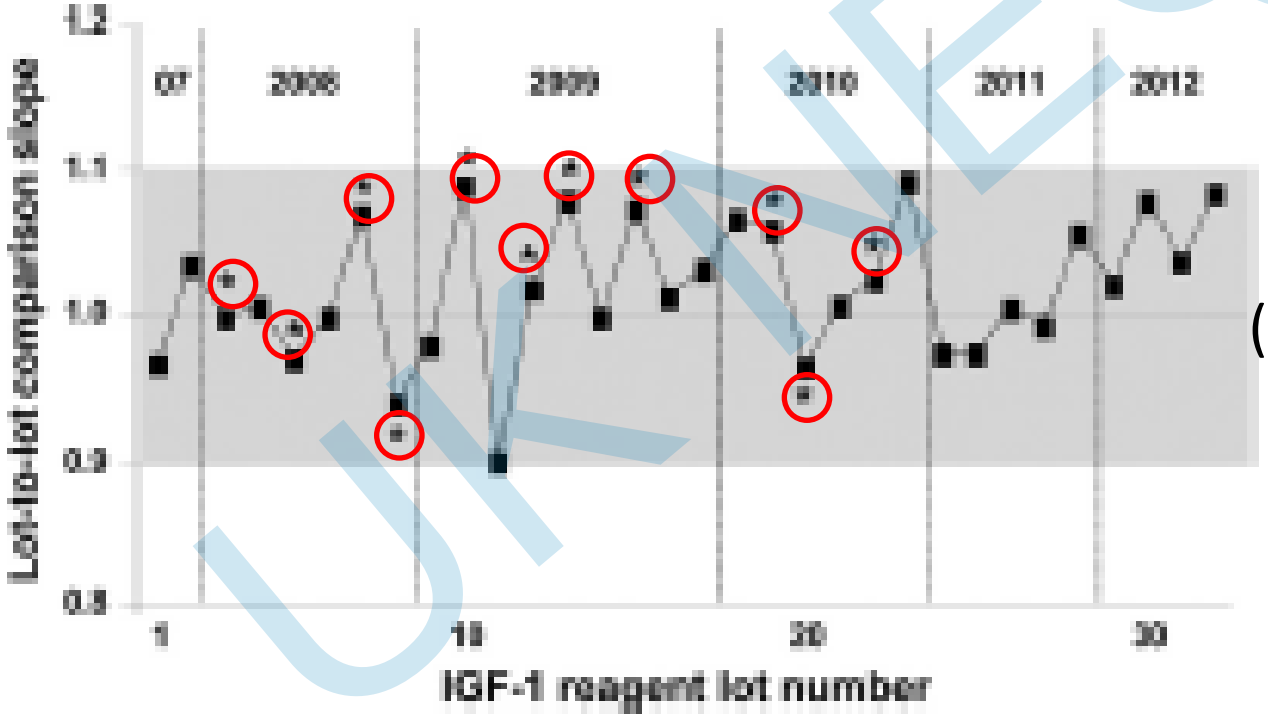
in results (%) above the

Upper Reference limit (URL)

A lot of Lot-to-Lot variability!

All lots "passed" Criteria$_{Acc}$! (Slope 0.9-1.1, within Grey region)

5 year lot-to-lot comparison analysis: ALL Passed!



….But not when evaluated retrospectively using patient data (n=286av/point) for the indicated reagent lots i.e. (*)

A lot of Lot-to-Lot variability!

"n=20 for reagent lot acceptance NOT powered (50%) to detect 10% shift in bias (n=50-100 min needed for 90% power)"

- Practicality/Capability of laboratories to provide adequately powered approaches using patient data (e.g. n=200/1000 *per* lot)?
- Manufacturers?

>Stringency of reagent release/acceptability criteria?

>Procedures may be inadequate at detecting clinically significant shifts in reagent performance

Thaler *et al*. Clinically relevant lot-to-lot reagent difference in a commercial immuno turbidimetric assay for glycated hemoglobin A1c. Clin Biochem 2015;48:1167-70.

A lot of Lot-to-Lot variability!

"The laboratory may take steps to evaluate and detect variation, the ideal is to reduce variation between lots at the point of manufacture. Using appropriate acceptance criteria based on medical need or biological variation requirements instead of some arbitrary percentage may go toward achieving this"

Thompson and Douglas. Lot to Lot Variation. *Clin Biochem* Rev 39 (2) 2018

Detecting Lot-to-Lot Variation -A big data approach?

"Collaboration and **data-sharing between laboratories and manufacturers** also has an important role to play in the detection of **lot-to-lot variation**"……

Thompson and Douglas. Lot to Lot Variation. *Clin Biochem* Rev 39 (2) 2018

NOKLUS
-formerly the Empower Project

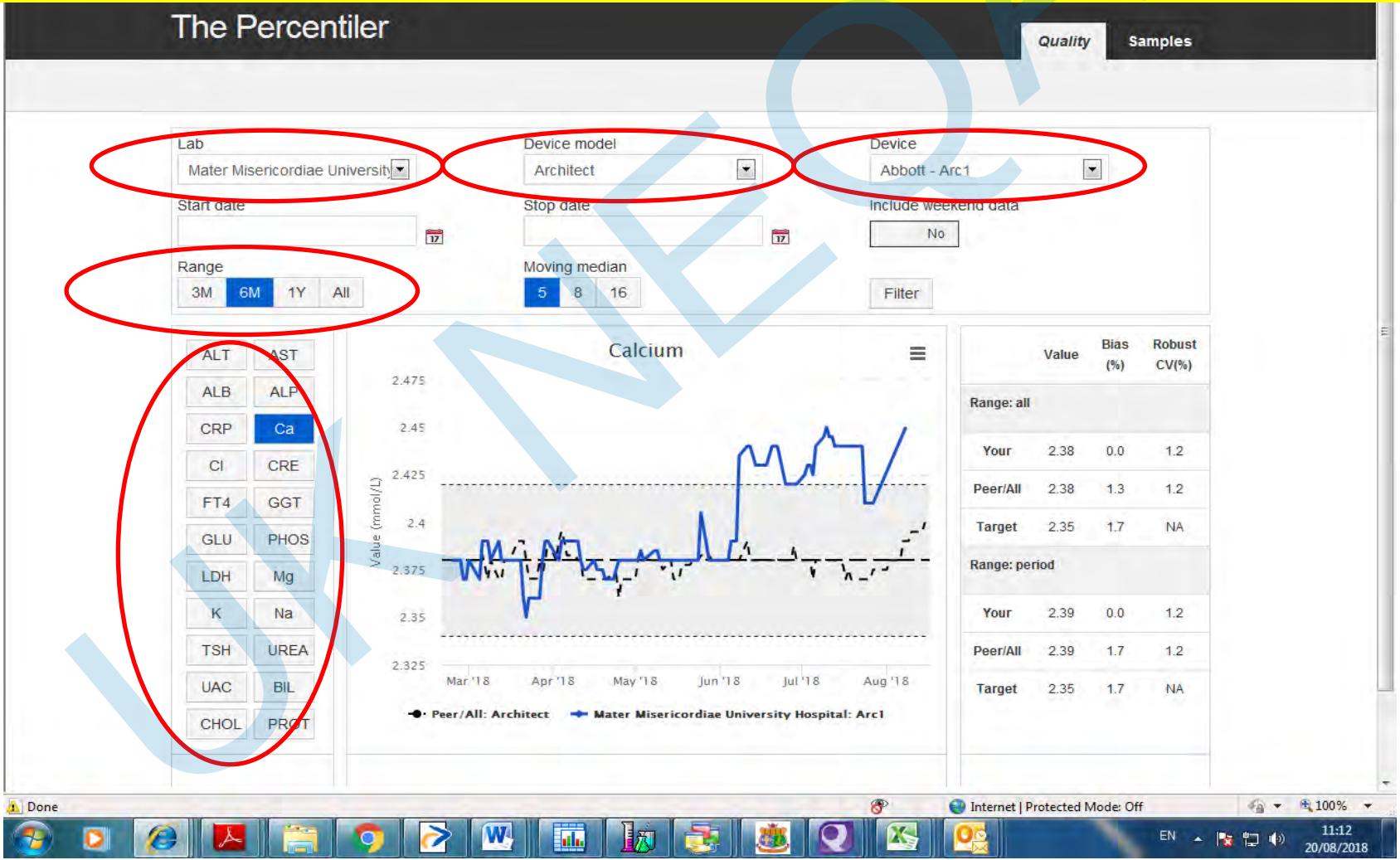
"**Cooperation** between **laboratories and manufacturers** to pursue a common objective of **assessing** and **improving test comparability and stability**"

- Used In MMUH retrospectively for IQC/EQA troubleshooting (currently)
- Patient data used to monitor bias for a set of biochemical analytes (n=22)
- The "**Percentiler**"- Patient Percentile (median) monitoring
- The "**Flagger**" -% of results < and > Reference Limits
- **Daily medians** (GP) extracted from LIS/Middleware by participant Labs.
- Email to Noklus
- **Reports** generated for **Daily medians** *per* **laboratory/analyser** and compared over **time** and with Daily medians from **manufacturer's peer** group or ALL manufacturers

NOKLUS aka the Empower Project

Using data retrospectively (NOT ideal) to confirm anecdotal observations of a +ve shift in Calcium

Shift of ~0.05 NOT observed on "daily" IQC or EQA



Analytical Phase

What's still not done/understood well/Variable?

….Internal Quality Control

"Despite long-standing IQC procedures, considerable variation in practice remains even amongst ISO15189:2012 accredited laboratories (Housley *et al*., 2008)"

IQC

Variability remains….

- Internal Quality Control Survey - Results and Recommendations Joint Working Group on Irish Laboratory Accreditation (JWG ILA) –Sub-group on IQC Procedures (Cunningham S *et al*., May 2016)

Q: On the main analyser(s), what is the frequency of running controls?

A: For routine tests (e.g. U+Es) this varies a lot, from once daily to once hourly.

Q: How did you decide on QC frequency?

A: Analyser performance / analyser stability (10)

A: Historical or previous experience (11)

A: Workload (8)

A: Manufacturer's recommendation (8)

A: Published guidelines / best practice (7)

A: INAB Assessor advice (4)

***A*: Sigma metric (1)**

Sigma metric based IQC

Principles….?Practice

Sigma metrics can be used in designing appropriate IQC procedure“**s”** (QC Frequency, Rules), which may be suitable to ≥1 test if their sigma values (σ) are similar.

$\sigma = (TE_a - B)/CV$ where,

TE_a(%)=quality requirement (tolerance limit) *B*=Bias observed (*B*, %) and CV=imprecision (CV, %)

Example 1:

A test (T) with TE_a=10%, *B*=1% and CV=2% has a $\sigma = [(10 - 1)/2] = 4$

Higher the Sigma = Less IQC (+ other work)
to meet the Quality Requirement for a Test!

Sigma metric based IQC

Principles to Practice

Lessons and limitations to sigma-metric-based IQC procedures

"…a test's sigma-metric involves only three variables, each can be defined in several ways, which can have implications for the sigma-metric magnitude and related IQC procedure"

GR Lee, MC Fitzgibbon and P O'Shea,
International Journal of Health Care Quality Assurance, 2016, Vol. 29 Iss 5 pp.

- In control? IQC consensus and statutory regulation, p492 - 506
- Laboratory services: regaining and maintaining control, International Journal of Health Care Quality Assurance, p507 -522

Sigma metrics –Effect of the TE_a

Lee *et al* 2016. IJHCQA, 29(5): 492-522

$$\sigma = (TE_a - B)/CV$$

Analyte	Quality Requirement (TE_a %, $^aD_{int}$ %)							Assay performance	
	(1) CLIA	(2) $Biol_{Min}$	(3) $Biol_{Des}$	(4) $Biol_{Opt}$	(5) ^{a}Skendzel	(6) RCPA	(7) Rilibak	Imprecision	Bias
Glucose	10	10.5	6.9	3.4	30	8	11	1.4	0.9
fT4	20	12.1	8	4	33	15	15.5	4.3	3.1

Effect of using different definitions of the TE_a

Analyte	(σ)	Quality Requirement (TEa or $^aD_{int}$ %)						
		(1)	(2)	(3)	(4)	^{a}(5)	(6)	(7)
Glucose	σ	6.5	6.9	**4.3**	1.8	20.8	**5.1**	7.2
fT4	σ	3.90	2.10	1.10	0.20	7.00	2.80	2.90

Sigma metrics does though provide opportunity to design IQC procedures with time, effort + resource used commensurately to the Quality Requirement

Defining the Quality Requirement?....

Defining the Quality requirement
TEa (%), Total Error Allowable

- **Quality Control** is focused on fulfilling **quality requirements.**
- Need to **define the quality requirement** before we can achieve/control it!
- Quality requirements for a Test can be defined by **Analytical Performance Specifications** (APS) i.e. Analytical Goals
- APS can be defined by 3 models (EFLM, Milan consensus):

- **Model 1A/B**: Based on effect of test performance on clinical outcomes/classification/decisions: A. Direct, B. Indirect
- **Model 2**: Based on Biological Variation of the measurand
- **Model 3**: Based on State-of-the-art measurement (highest level technically achievable)

Analytical Performance Specifications (APS)
Model choices: 1a/b, 2 and 3

Panteghini *et al*., Clin Chem Lab Med 2017; 55(12): 1849–1856
Strategies to define performance specifications in laboratory medicine: 3years on from the Milan Strategic Conference

- Which one do you choose?

Model 1: If **test** has a **well-defined role (directly)** in **decision making…management…outcome** (V few such tests!)

E.g. HbA1C. In the Diabetes Control and Complications Trial (DCCT), patients with poor or good glycaemic control had HbA1c >64 or <53 mmol/mol

Therefore, to properly classify an individual with an HbA1c value of 58.5 mmol/mol, the **measurement error** should **not exceed ±5.5 mmol/mol**; a relative total error (TE) of ± 9.4% (5.5/58.5)

IF error is >9.4%, a patient with HbA1c of 58.5 mmol/mol could be randomly misclassified into both glycaemic control categories (good or poor)

>Time, Effort + Resource should be spent accordingly to control error to within 9.4% for HbA1C analyses

What APS (Quality Requirement) for What Test?

APS model 1: outcome-based	APS model 2: biological variation	APS model 3: state-of-the-art
P-Cholesterol+ester	P-Sodium Ion	U-Sodium Ion
P-Cholesterol+ester in LDL	P-Potassium Ion	U-Potassium Ion
P-Cholesterol+ester in HDL	P-Chloride	U-Chloride
P-Triglycerides	P-Bicarbonate	U-Calcium Ion
P-Glucose	P-Calcium Ion	U-Magnesium Ion
B-Hemoglobin A_{1c}	P-Magnesium Ion	U-Phosphate (Inorganic)
P-Albumin	P-Phosphate (Inorganic)	U-Creatinine
P-Troponin T and P-troponin I	P-Creatinine	U-Urate
P-Thyrotropin	P-Cystatin C	
B-Hemoglobin	P-Urate	
B-Platelets	P-Proteins	
B-Neutrophil leukocytes	B-Erythrocytes	
	B-Erythrocyte volume fraction	
	B-Erythrocyte volume	
	P-Prothrombin time	
	P-activated partial thromboplastin time	

Criteria for assigning laboratory measurands to models for analytical performance specifications
Cerlotti *et al.*, 2016. CCLM

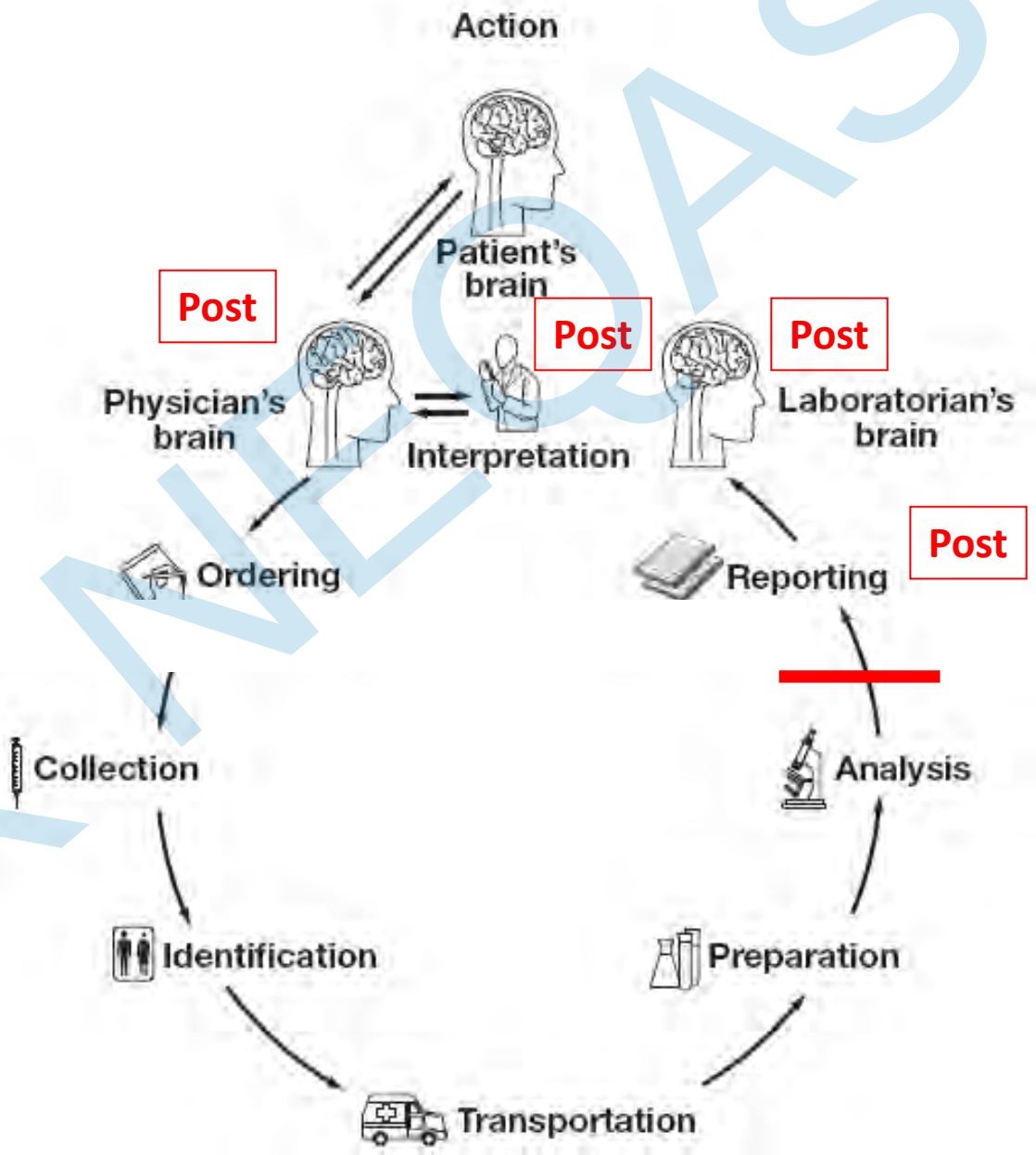
- After defining the quality requirement, define appropriate IQC procedures (Frequency, Rules) *for* ***each*** **test(s)**
- Ongoing work: Many other tests + issues still to be considered
  e.g. Different quality requirements depending on [Analyte]?

Goal: Move from current IQC approaches where same IQC procedure is used for ALL tests

…Enable commensurate use of Time, Effort + Resource

Controlling quality in the Post-analytical phase?....

Lundberg (1981):
Brain to Brain loop
concept for laboratory testing



Controlling **Irregular [individual] analytical Error**

Irregular analytical errors in diagnostic testing – a novel concept. Vogeser and Seger CCLM 2018; 56(3): 386–396

- Not readily detected by *Statistical IQC procedures (*Systematic +Random)
- Erroneous result may be Falsely High or Low
- Error is NOT reproducible on repeat (unlike e.g. error due to interferents)
- *Identified* by

A. Clinical user (lack of clinical correlation)

B. Clinical authorisation (Delta checks, Discordant results e.g.↑FT4/Normal TSH)

Approaches **A + B** Effective (100%)?....***No***

All such errors identified?....***No***

Any **un**identified errors with (inappropriate) Clinical Decisions?...***Likely***

Other approaches for improving effectiveness (added to above)?...**Yes**

Analysis in Duplicate?

.....Are you kidding?**.....No!**

Detecting **Irregular [individual] Analytical Error - Duplicate testing**

- Most dup. studies evaluated error rate for a few Biochem. + Haem. tests

-involving routine testing strategies where tests are repeated ONLY where the first result is critically low or high (</> decision thresholds)

-based on the (*perceived) low* error rate a justification has (generally) been made (*seemingly*) for abandoning such repeat testing for ALL: Biochemistry/Endocrinology + Haematology tests, Instruments, Sample types

- Other studies have formally evaluated the "Flier" rate through duplicate testing (all samples) - Most focus on cardiac Troponin (cTn):

Variability and Error in Cardiac Troponin Testing. An ACLPS Critical Review. *Herman, Kavsak and Greene. Am J Clin Pathol* 2017;148:281-295

"Instrument malfunction can lead to cTn results that are **irreproducible**. One common example of these **"fliers"** are cTn results that are **initially** significantly **elevated**… but on **repeat**…significantly **decreased**…"

Clinical role for Troponin: Diagnosis of MI (4rd universal definition, 2018)

Definition of myocardial infarction

Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

95th, 97.5th, 99th

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.

Troponin (cTn) **False +ve** Fliers

"No cTn immunoassays are immune to outliers, rate varies *per* instruments + manufacturers"

(Herman, Kavsak and Greene, 2017)

Newer (high sensitivity) cTn assays are better……

Transitioning high sensitivity cardiac Troponin I (hs-cTnI) into routine diagnostic use: More than just a sensitivity issue.

Lee *et al*., Prac. Lab. Med. 2016:4;62-75

↓ "Fliers" with newer Troponin assays (Lee *et al*. 2016)

Critical outlier ("Flier") studies (n=1239, 1 month analysis)

Top: cTnI, Bottom: hs-cTnI I (new)

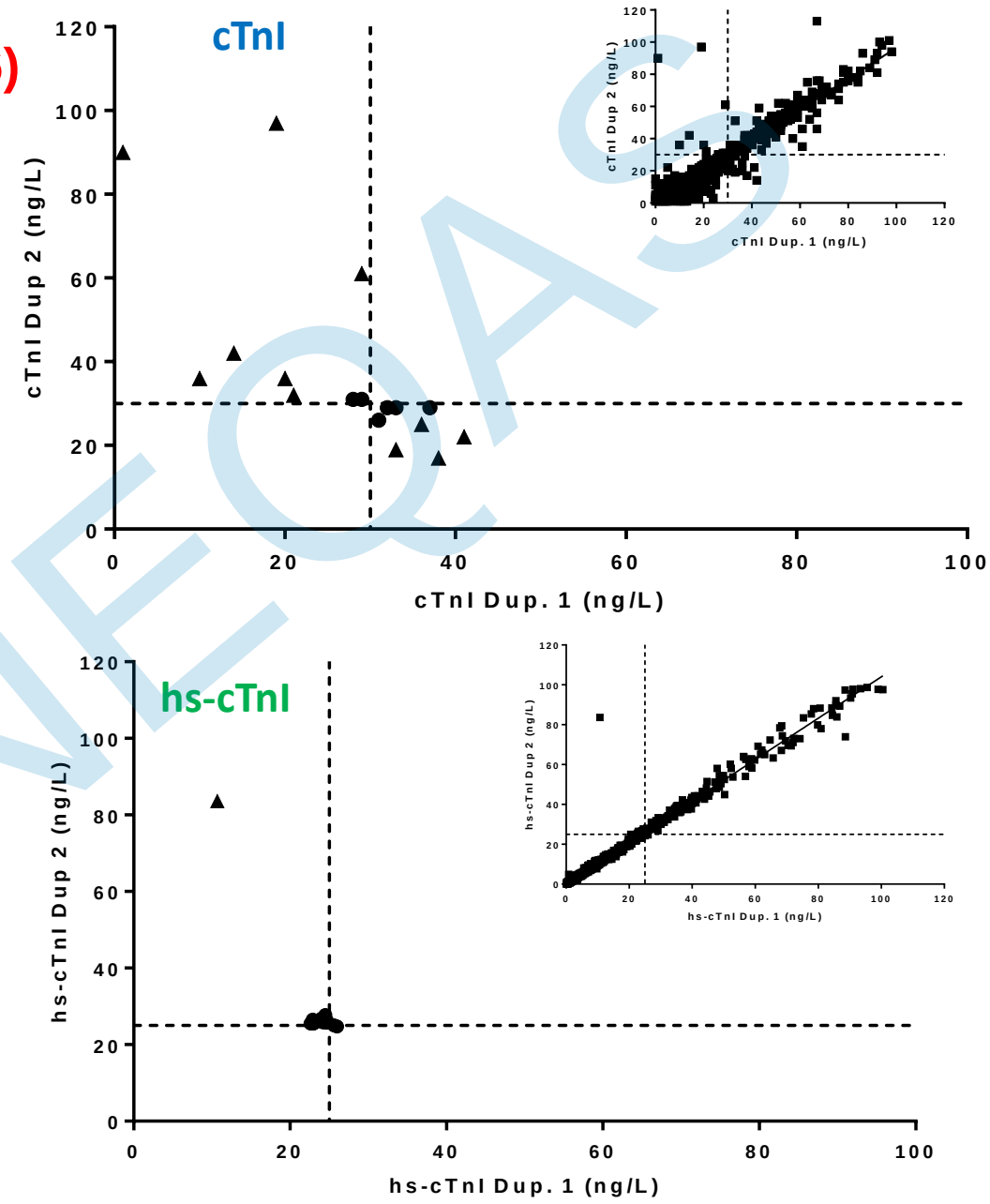
(i) X axis Dup. 1, Y axis Dup 2

(ii) Dashed lines = 99th centiles: 30 ng/L = cTnI, 25 ng/L = hs-cTnI used to evaluate duplicate results

(iii) Duplicate results (●) which were discordant vs respective 99th centile

(iv) Critical Outliers (▲): Discordant duplicates where $\%Diff_{(Dup1-Dup2)} > \%Diff_{Allow.}$

(iv) cTnI: 0.97% hs-cTnI: 0.091%



Lower incidence (↓10x) of Critical Outliers (1:1000) with newer assay hs-cTnI!

What to do with Irregular [individual] Analytical Error - "FLIERS"?

- Some fliers are thought to be due to micro-clots or debris within specimens i.e. Pre-analytical issue

HOWEVER

- Instruments should ideally (in real-time) detect + flag samples with interfering particles i.e. Analytical issue

AND

- Some irreproducible False elevations (Fliers) occur in Quality Control or Blank specimens, without a potential pre-analytical error component (Analytical?...Carry-over , probe block etc.)

IF

- Root cause cannot be identified and corrected AND clinical correlation/ authorisation alone is insufficient for detection, duplicate testing could be considered…….

Do I need to repeat myself?

AD Green & GR Lee, ACBI conference

8th+9th November 2019, Radisson Blu Hotel, Athlone

- Routine duplicates for 4 tests: Sodium, Calcium, ALP, Troponin
- Unacceptable (Analytical) Error (UE) b/n duplicate results (Δ)
- Critical Error = UE with discordant duplicates vs Ref. Limits

Duplicate Testing in 2018-19

Test	Unacceptable Error (UE): Δb/n Duplicates	Total Tests Analysed	Unacceptable Error (UE): Number	Frequency	
Sodium (Na)	$\Delta Na^{2+} \geq 4$mmol/L	21649	6	0.03%	**1:3000**
Calcium (Ca)	[1] $\Delta Ca^{2+} \geq 0.04$mmol/L	14803	678	4.70%	**1:21**
Alkaline Phosphatase (ALP)	ΔALP $\geq 18\%$	19698	44	0.22%	**1:454**
Troponin (cTn)	[2] ΔcTn $\geq 20\%$	17036	196	1.15%	**1:87**

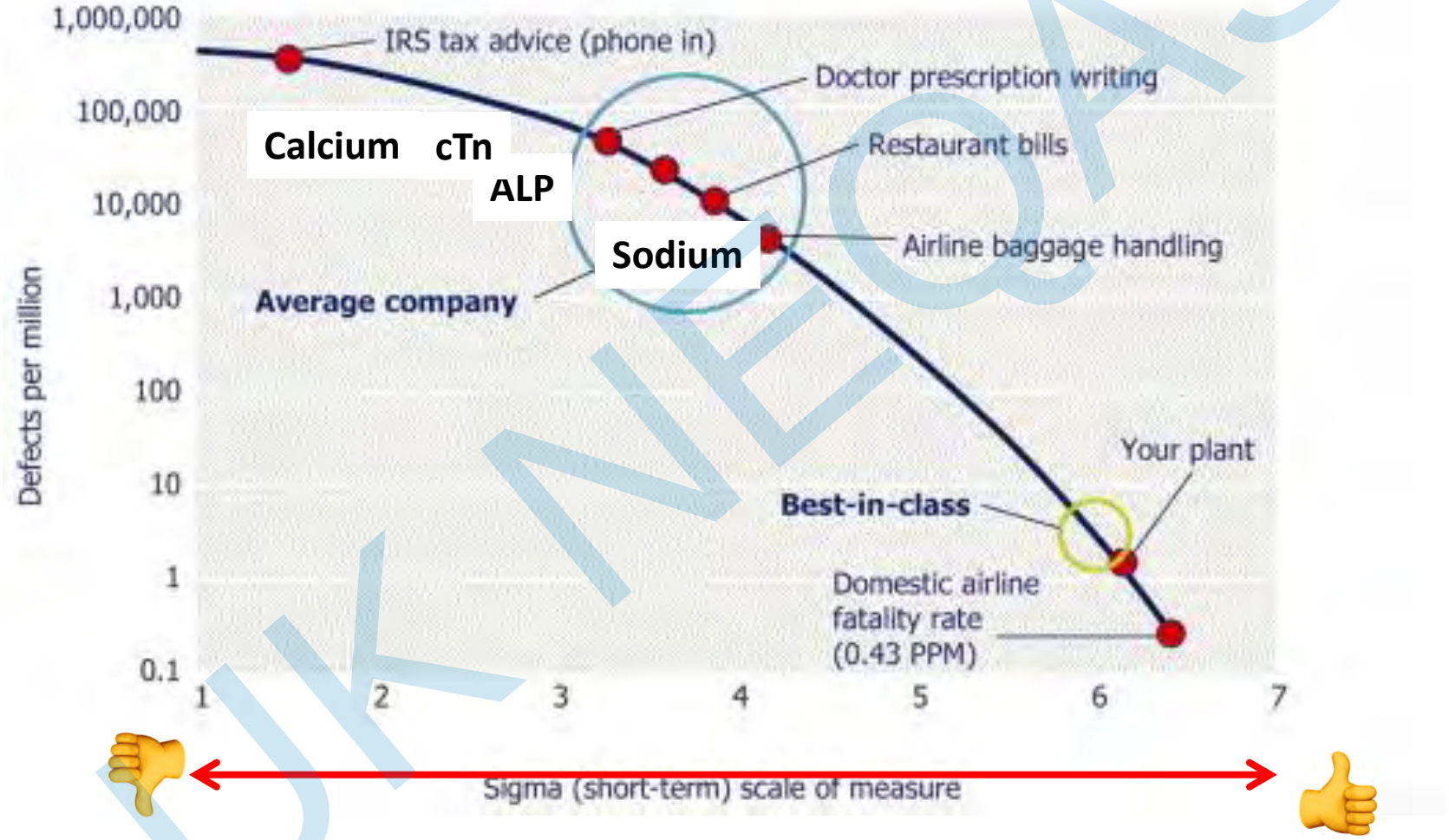
When one duplicate result is: [1] ≤2.25 or ≥2.55 nmol/L, [2] ≥7 ng/L

Critical UE		
Number	Frequency	
2	0.009%	**1:11 111**
125	0.84%	**1:119**
19	0.096%	**1:1042**
19	0.11%	**1:901**

Na: 1/2wks, Ca: 1/day, ALP: 1/wk, cTn: 1/2wks

(Clinically) Acceptable Error rate?...

Duplicate Testing on balance



Duplicate Testing on balance

Advantages: Effective!

Disadvantages:

Cost (Unless cost/reportable test)

TTAT (Unaffected e.g. hs-cTn 92% within TTAT in 2015 AND 2019)

Is duplicate testing a reasonable approach for such tests which could otherwise be undetected + which may cause clinical misclassification and inappropriate treatment?

OR

Can we accept the error + rely on vigilance of our clinical users?

Taking a step back in time, 50y ago to 1969!...

J. clin. Path. **22,** suppl. (Coll. Path.), **3,** 42-50

Discrete analysis systems

B. E. NORTHAM

From the General Hospital, Birmingham

"Various steps either to reduce or reveal random errors"....
"Random errors...revealed with a high degree of probability by duplicating"

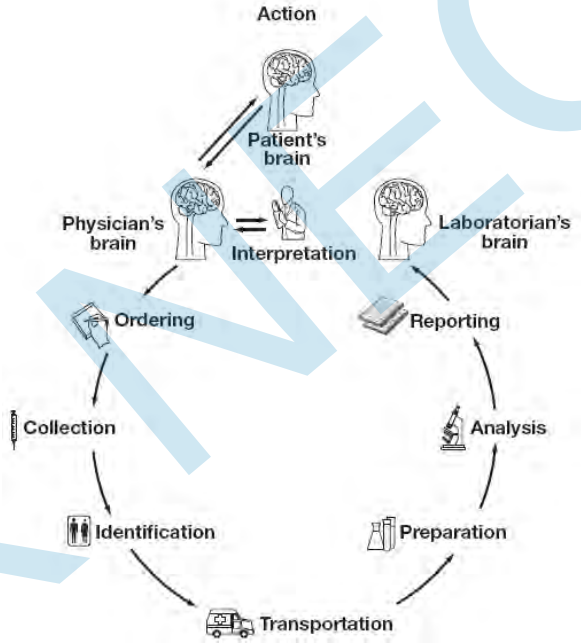
"This may appear to be extravagant...feasible in a high-speed system... increased precision for each determination"

"Computer analysis...essential to detect differences between duplicates greater than would be expected from the analytical error."

"I am indebted to Professor T. P. Whitehead, Dr R. Gaddie, Mr P. M. G. Broughton, Dr G. M. Widdowson and members of the ACB Study Group on Automation in Clinical Chemistry and to many other Biochemists for information and advice freely given."

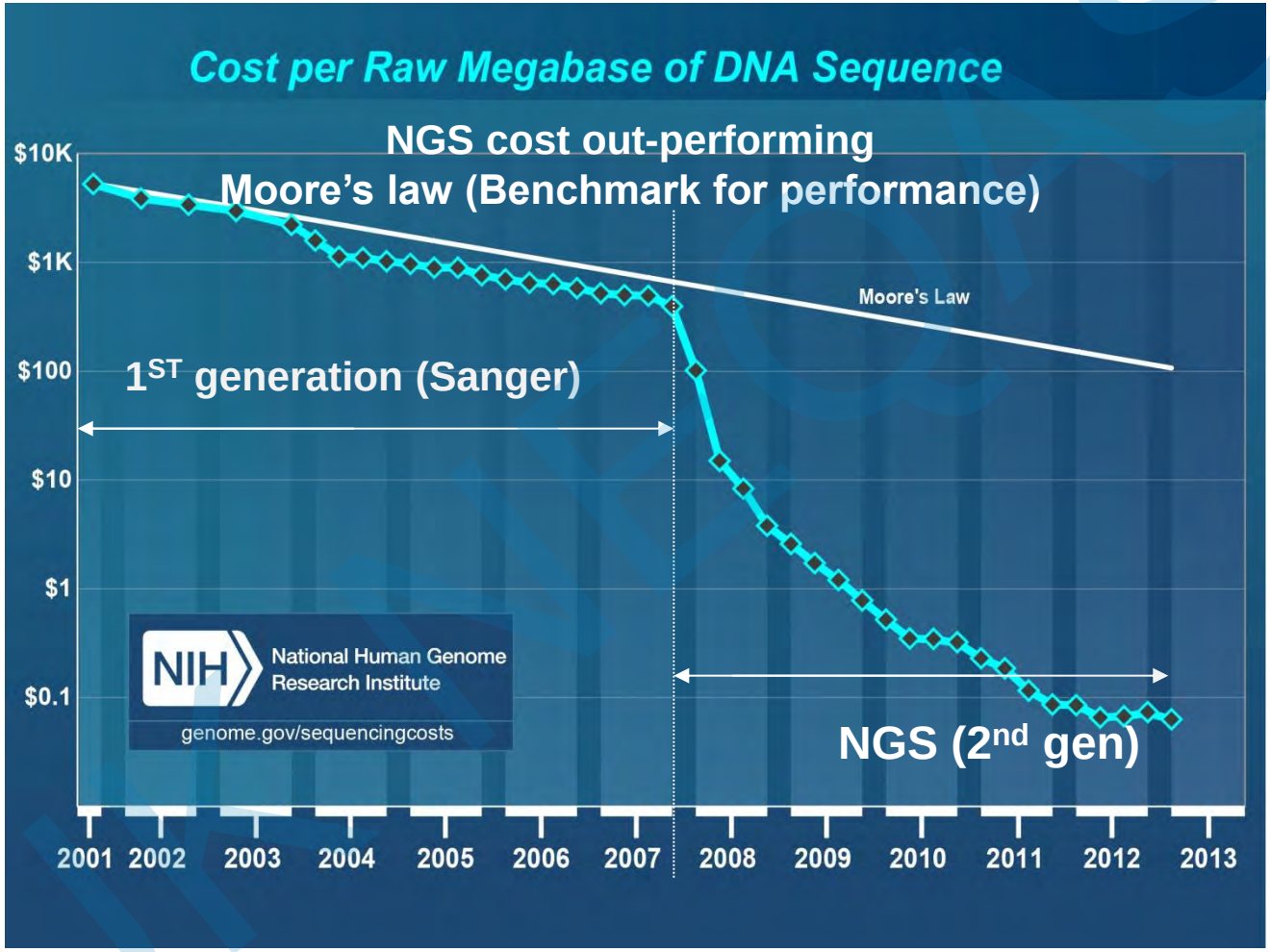
Taking a big step FORWARD in time, 50y to 2069!...

How will the Time (Effort + Resource) be used to control Quality across the Total Testing Pathway in 50y?



*More or **Less** (Human) **Effort** required given (Pre)-Analytical advances?*

Could Duplicate Testing become routine (↓cost/↑speed) for detecting Irregular Analytical Error?



2007: 1 sequencing run = 1GigaBase of data, [$1x10^9$] bases

2011: 1 sequencing run = 1 TB (TeraBase) = 1000 GB ($1x10^{12}$)....Big data!

(Human genome = 3.2 billion bases/3.2GB ($3.2x10^9$)

Conclusion

Controlling quality across the TTP

1. Must consider/define the Quality Requirement for the Test
2. Effort in the TTP must be commensurate to such need
3. Requires collective involvement of many stakeholders: Laboratorians, Clinical users, Clerical + Transport personnel + Patients

…ALL with likely different understanding
+ expectations of the Quality Requirement

4. Adequate control requires efficient data capture + analytics
-also informs efficiency/effectiveness of control measures
5. Evolving/cyclical entity involving 1-4
6. ISO15189:2012 *may*be a driver/catalyst for enhancing quality

….Is ISO15189 really the gift that keeps on giving?

….QMS must evolve

-Effort toward ISO15189 may not yield commensurate gain + MAY not be sufficient to meet the Quality Requirement!

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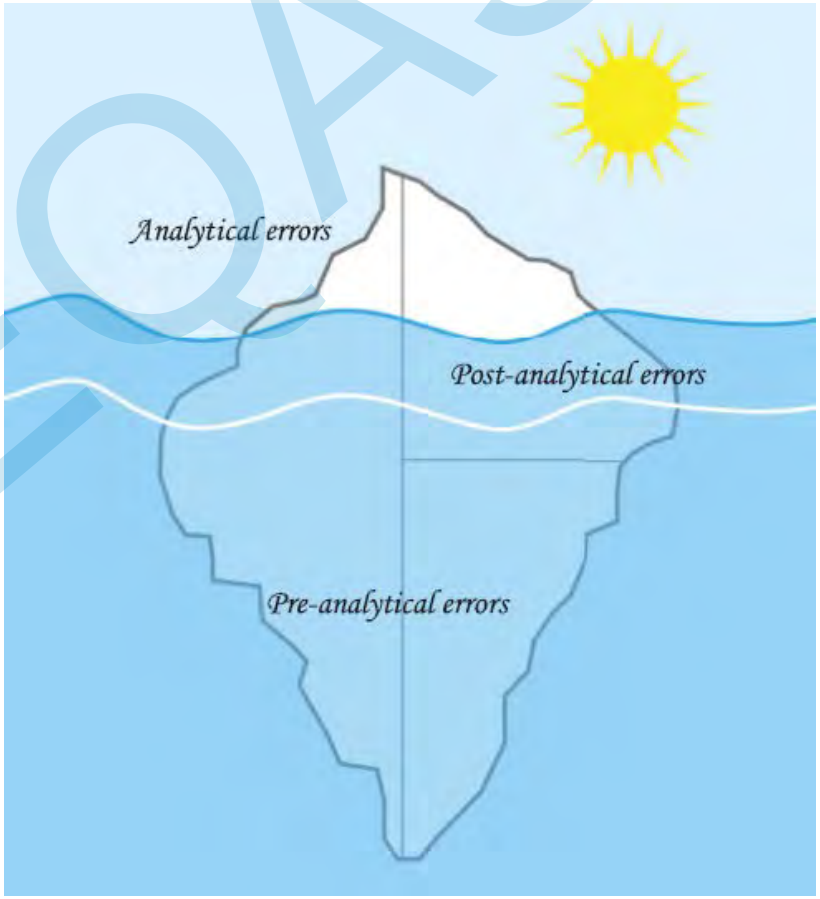
Melting the pre-analytical iceberg of errors

Barbara De la Salle
Director, UK NEQAS Haematology
haem@ukneqas.org.uk

Most errors are not in the analytical phase



The Iceberg of Laboratory Errors

Plebani M *et al*

Clinical Chemistry and Laboratory Medicine (CCLM). Volume 53, Issue 3, Pages 357–370, ISSN (Online) 1437-4331, ISSN (Print) 1434-6621, DOI: 10.1515/cclm-2014-1051, December 2014

Diagnostic errors cause patient harm:

- Incorrect diagnosis
- Missed diagnosis
- Delayed diagnosis and treatment
- Missed opportunity for screening
- Unsatisfactory patient experience
- Wasted resources (=cost!)

- 1/12 Americans experience a diagnostic error and laboratory medicine contributes to this figure *Singh, H.et al, 2014. BMJ Qual Saf, pp.bmjqs-2013*

Pre-analytical requirements of ISO 15189

- Laboratories should establish quality indicators to evaluate performance throughout the pre-examination, examination and post-examination processes
- Laboratories should have documented procedures for pre-examination processes to ensure validity of results

M Cornes, ACB News: issue 635, 2016

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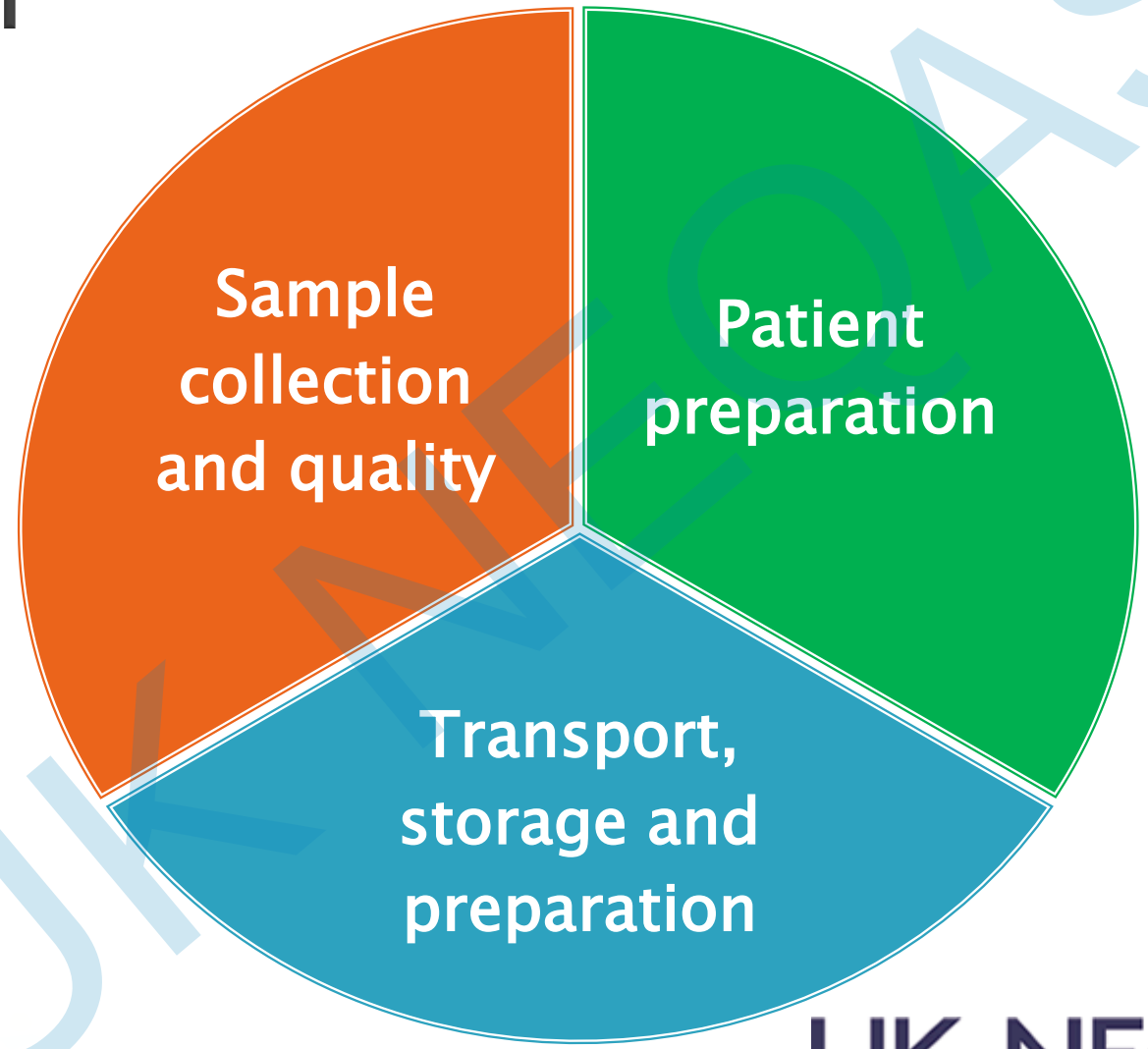
Total testing process

Incidence of errors by phase

TTP phase	Examples of error	Estimated proportion of errors
Pre-preanalytical	Test ordering, patient identification, patient preparation, sample collection, sample quality, transportation, storage	46 – 68%
Preanalytical	Sample sorting, centrifugation, labelling, separation	3-5%
Analytical	Sample analysis	7 – 13%
Postanalytical	Validation, interpretation, turnaround time, critical value reporting	13 – 20%
Post-postanalytical	Interpretation, delayed reaction, lack of follow-up or referral	25- 46%

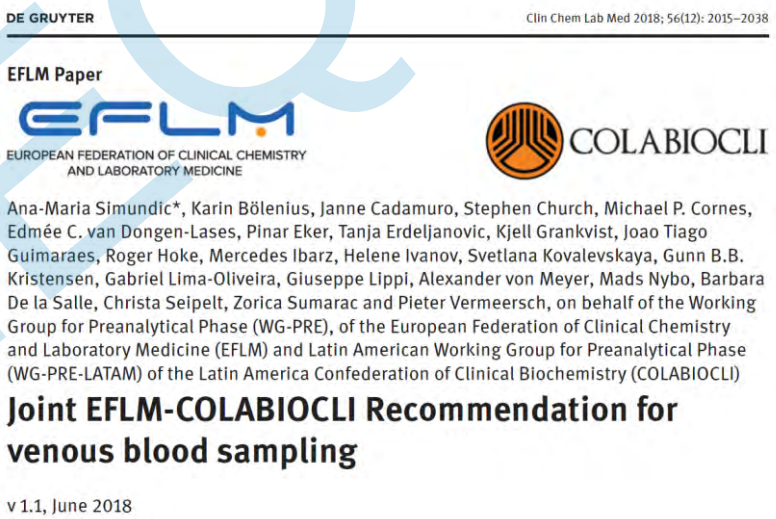
Plebani, M., 2010. Ann Clin Biochem, 47(2), pp.101-110.

From the patient to the laboratory bench



Errors common to all disciplines

- Test selection and ordering
- Patient identification
- Wrong blood in tube
- Sample collection
- Sample labelling
- Patient preparation



DE GRUYTER Clin Chem Lab Med 2018; 56(12): 2015–2038

EFLM Paper

EFLM EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

COLABIOCLI

Ana-Maria Simundic*, Karin Bölenius, Janne Cadamuro, Stephen Church, Michael P. Cornes, Edmée C. van Dongen-Lases, Pinar Eker, Tanja Erdeljanovic, Kjell Grankvist, Joao Tiago Guimaraes, Roger Hoke, Mercedes Ibarz, Helene Ivanov, Svetlana Kovalevskaya, Gunn B.B. Kristensen, Gabriel Lima-Oliveira, Giuseppe Lippi, Alexander von Meyer, Mads Nybo, Barbara De la Salle, Christa Seipelt, Zorica Sumarac and Pieter Vermeersch, on behalf of the Working Group for Preanalytical Phase (WG-PRE), of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) and Latin American Working Group for Preanalytical Phase (WG-PRE-LATAM) of the Latin America Confederation of Clinical Biochemistry (COLABIOCLI)

Joint EFLM-COLABIOCLI Recommendation for venous blood sampling

v 1.1, June 2018

Simundic, A.M., et al., 2018. Joint EFLM-COLABIOCLI Recommendation for venous blood sampling. Clin Chem Lab Med, 56(12), pp.2015-2038.

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Patient preparation

- Unaccustomed or extreme physical exercise
  - To be avoided in the 24 h prior to venepuncture
- Patient posture
  - Seated for 15 minutes prior to venepuncture
- Fasting
  - Lipaemia
  - Post-prandial physiological changes
- Time of day
  - 7 a.m. to 9 a.m. advised

Simundic, A.M., et al., 2018. Joint EFLM-COLABIOCLI Recommendation for venous blood sampling. Clin Chem Lab Med, 56(12), pp.2015-2038.

Patient posture: example

- Elderly patient admitted to ER, no apparent bleeding and not treated with IV fluids
- CBC on admission (taken without resting) was within reference interval
- CBC repeated after 2 hours lying down showed a 10-15% reduction in Hb and Hct

Lippi, G. and Cervellin, G., 2017. Acutely developing, spurious anaemia without actual blood loss. A paradigmatic case report. Biochem Med, 27(2), pp.421-425

Why monitor pre and post-analytical errors

- Because accreditation standards (e.g. ISO15189) say so?
- Managing the errors is more important than monitoring
- Allows the laboratory to identify and prioritise the causes of error and implement corrective actions

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You can't manage what you don't measure

"When you can measure what you are speaking about, and express it in numbers, you know something about it"

"If you can not measure it, you can not improve it"

William Thomson, 1st Baron Kelvin

ACB Pre-analytical WG

developing 'best practice' document on what and how to measure

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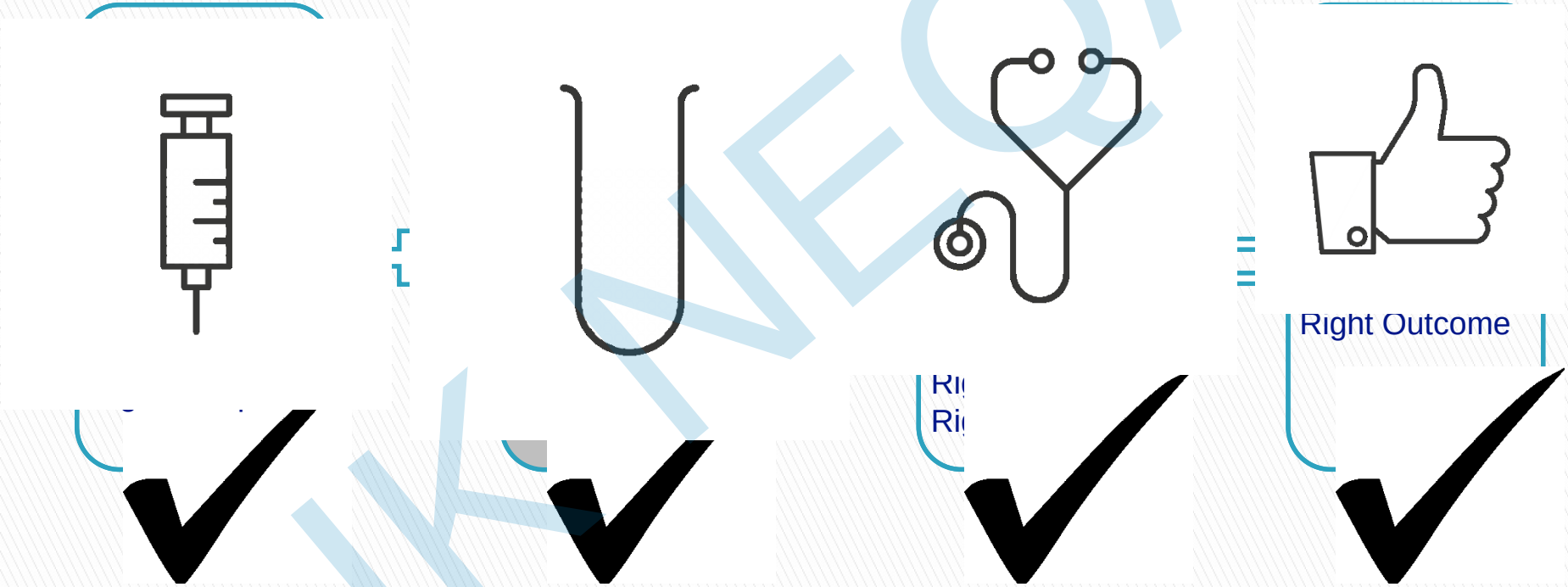
PREPQ

End to End Quality

It's not just about the Quality of the test



A UK NEQAS Pre & Post Analytical Quality Monitoring Service

Background

- Need for Whole Process EQA long recognised
  - various Scheme-based initiatives had been developed
- UK NEQAS Executive confirmed benefits & needs
  - across the organisation
- Timing stimulated by PQAR recommendations
  - "PREPQ WG" set up in early 2014
  - Design and pre-pilot exercise reported at last meeting

- To provide harmonised single facility across UK NEQAS organisation
- To provide extended data collection relevant to UK needs

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Possible design models

- Type I: Registration of procedures
- Type II: Circulation of samples simulating errors
- Type III: Registration of errors/adverse events

Gunn BB Kristensen *et al.* Biochemica Medica 2014; 24 (1): 114–22

- Collate error rates and causes gathered through corrective and preventative actions or root cause analysis investigation

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Quality indicators selected

Table 1. Quality indicators used in the pilot exercise

Phase	Category	Indicator
Pre-analytical	Identification	Patient identification failures
		Sample identification failures
	Sample collection	Sample type / container failures
		Sample volume failures
		Blood science sample quality failures
	Sample transport	Temperature / time critical sample failures
	Microbiology	Microbiology sample quality failures
		Contaminated blood cultures
Post-analytical	Reporting	Turnaround time failures
		Number of corrected reports
		Reporting time critical results failures

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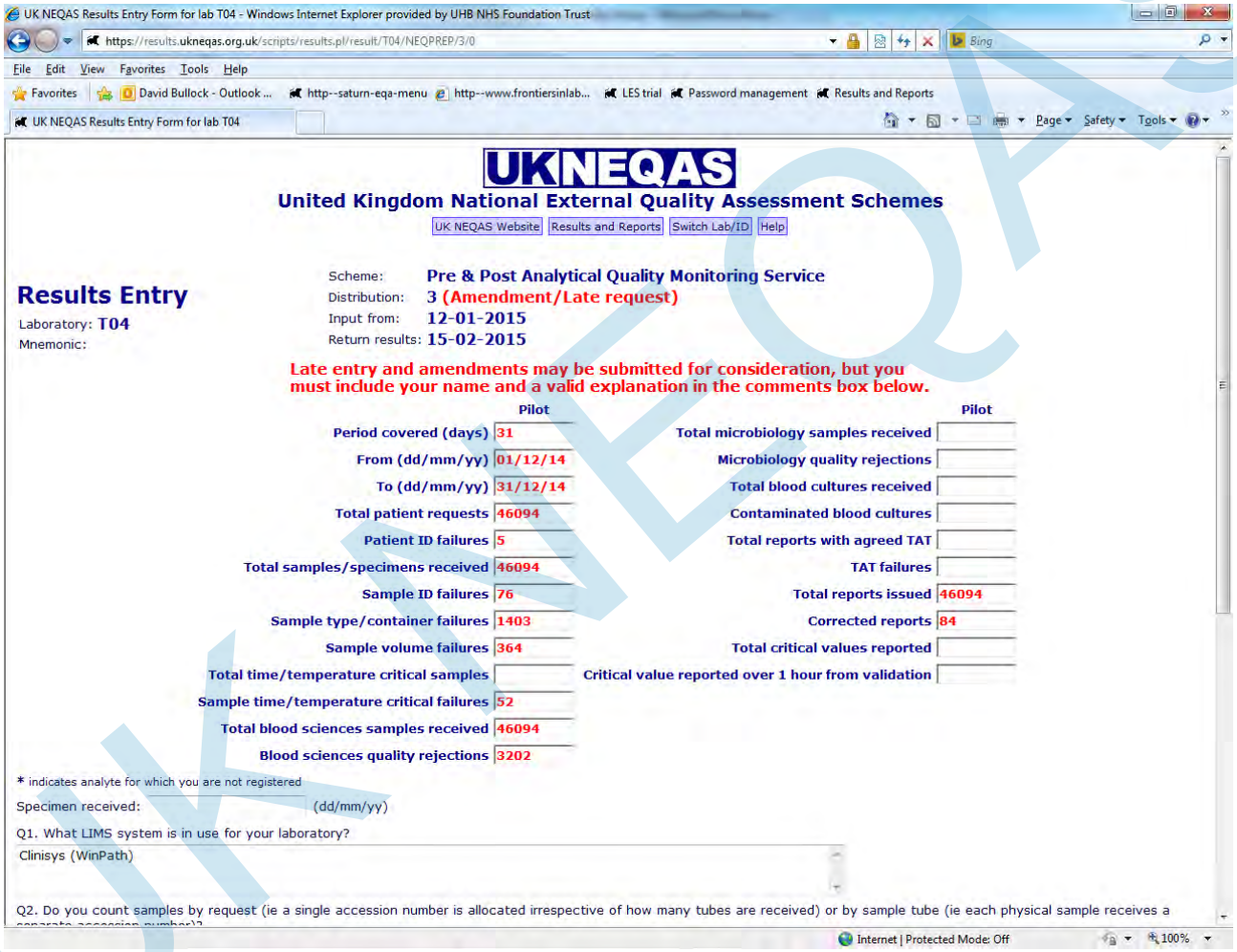
Online data entry



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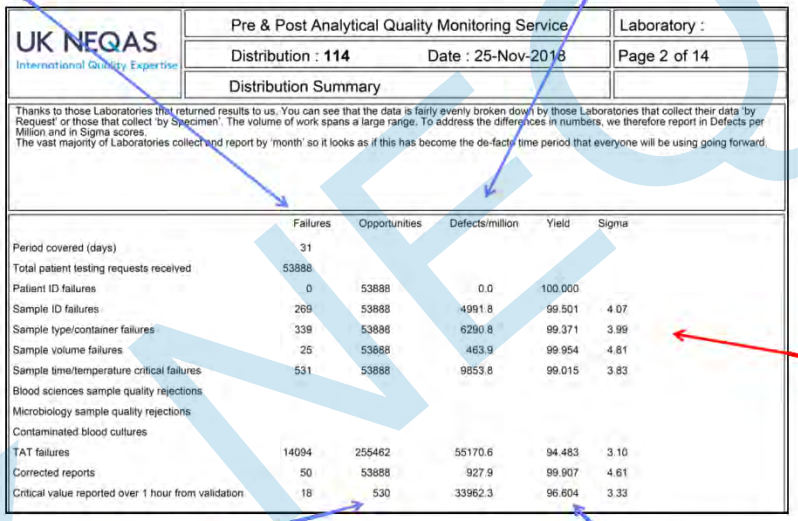
Summary report, including Sigma metrics

Number of **Failures** during time period

Defects/million calculated by normalising data



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Pre & Post Analytical Quality Monitoring Service | Laboratory :

Distribution : **114** Date : 25-Nov-2018 | Page 2 of 14

Distribution Summary

Thanks to those Laboratories that returned results to us. You can see that the data is fairly evenly broken down by those Laboratories that collect their data 'by Request' or those that collect 'by Specimen'. The volume of work spans a large range. To address the differences in numbers, we therefore report in Defects per Million and in Sigma scores.
The vast majority of Laboratories collect and report by 'month' so it looks as if this has become the de-facto time period that everyone will be using going forward.

	Failures	Opportunities	Defects/million	Yield	Sigma
Period covered (days)	31				
Total patient testing requests received	53888				
Patient ID failures	0	53888	0.0	100.000	
Sample ID failures	269	53888	4991.8	99.501	4.07
Sample type/container failures	339	53888	6290.8	99.371	3.99
Sample volume failures	25	53888	463.9	99.954	4.81
Sample time/temperature critical failures	531	53888	9853.8	99.015	3.83
Blood sciences sample quality rejections					
Microbiology sample quality rejections					
Contaminated blood cultures					
TAT failures	14094	255462	55170.6	94.483	3.10
Corrected reports	50	53888	927.9	99.907	4.61
Critical value reported over 1 hour from validation	18	530	33962.3	96.604	3.33

11 Quality Indicators assessed

Sigma score calculated

Number of **Opportunities** during time period (number of requests or number of specimens)

Yield is the ability of the process to be defect free

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Error-monitoring programmes

- CAP Q-Track Monitors
  - *Meier FA, Arch Pathol Lab Med 2015; 139: 762-75*
- IFCC Model of Quality Indicators project
  - *Sciacovelli L, CCLM 2017; 55 (3): 348-357*
- RCPA QAP Key Incident Monitoring and Management System (KIMMS)
  - *Badrick T, CCLM 2018; 56(2): 264-272*
- UK NEQAS PREPQ programme
  - *Established 2017*

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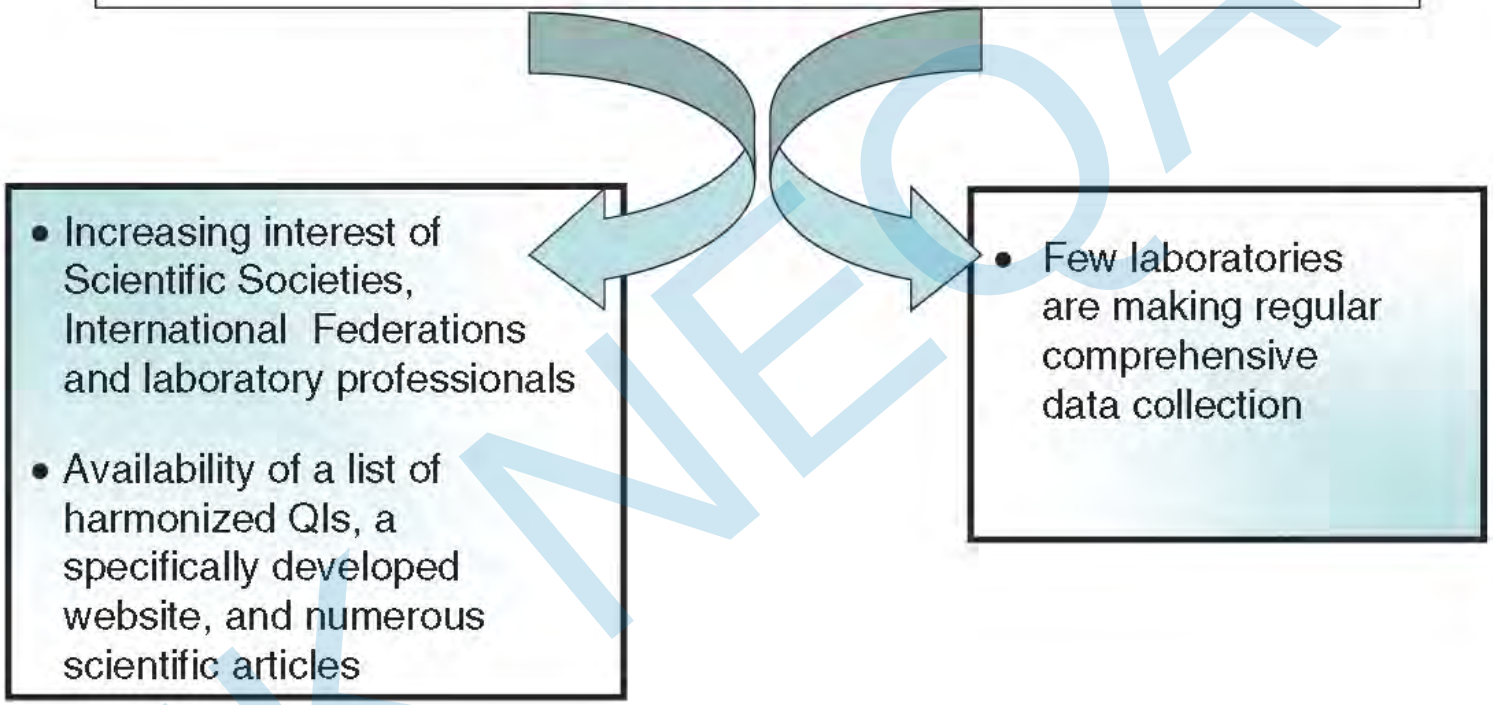
THE QUALITY INDICATORS PARADOX



Plebani M (2015) Clin Chem Lab Med Editorial
DOI 10.1515/cclm-2015-1080

The biggest challenge?

Data collection process

- Discussion with LIMS providers
- Standard specification
- Driven by laboratories?

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Keys to success

- Laboratory culture
  - Responsibility for extra-analytical phase errors
  - Relevance to service improvement
- Interested and committed individual(s)
- Intermediate level of data management knowledge
- Recognising limitations

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PREPQ Current Practice Scenarios

- 24 years old female, admitted post RTA:
  Hb 81 g/L,
  Na 145 mmol/L, K 2.5 mmol/L,
  Urea 0.8 mmol/L, Creatinine 40 umol/L

UK NEQAS
International Quality Expertise

Scenario responses (291 labs)

- Q1. Would you release these results without further investigation? [Y/N]

  286 participants responded. 62 (22 %) responded yes

- Q2. Would you request a repeat specimen? [Y/N]

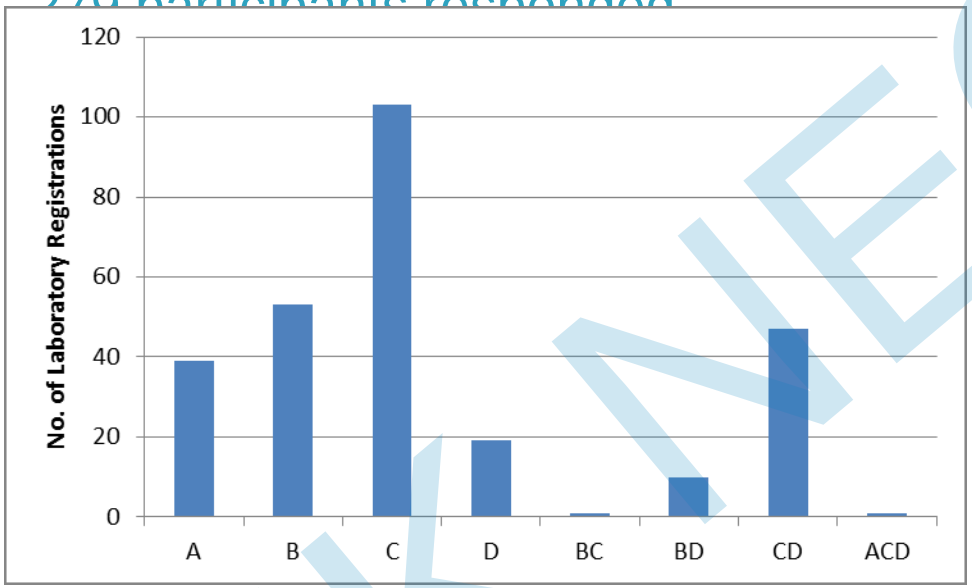
  278 participants responded. 168 (64 %) responded yes

- Q3. At the point of first release would clinical results have gone through a delta check procedure? [Y/N]

  278 participants responded. 244 (88 %) responded yes

Q4. You find a previous result on the patient from one month earlier, with a
Hb concentration of 142 g/L, Na 135 mmol/L, K 4.5 mmol/L, Urea 5.2 mmol/L and Creatinine 78 umol/L. How would you handle this case?

270 participants responded



(A) Would release all the results and report without comment or further action

(B) Would report all the results without investigation but with an advisory comment,

(C) Would investigate the medical history and current treatment

(D) Would review what other tests had been requested.

Q5. What further actions would you take? (Please detail all)

Responses included:

- Discussion with requesting clinician, ? Contamination, ? Drip arm, ? What treatment is the patient on
- Check labelling, check date, check for clots, check sufficient volume, check on another analyser
- Add on additional tests – LFTS, Protein Profile, Glucose
- Possibly add Cortisol, request urine for osmolality
- Request a repeat.

Very few people commented that they would investigate if other specimens were taken at the same time, and therefore liaise with other departments

Classic ‘drip arm’ specimen. May have resulted in unnecessary transfusion – a reportable haemovigilance incident

Summary

- Manage the risks at all phases in the TTP to minimize the contribution of the lab to healthcare risks
- Guidelines to standardise practice in the pre-analytical phase
- Monitoring errors to identify and prioritise the corrective action needed to reduce risk
- Benchmarking and education

Acknowledgements

- Rachel Marrington
- Finlay MacKenzie

- David Bullock
- Bill Egner

- UK NEQAS PREPQ WG

- ACB

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You have got to be Kidding me!

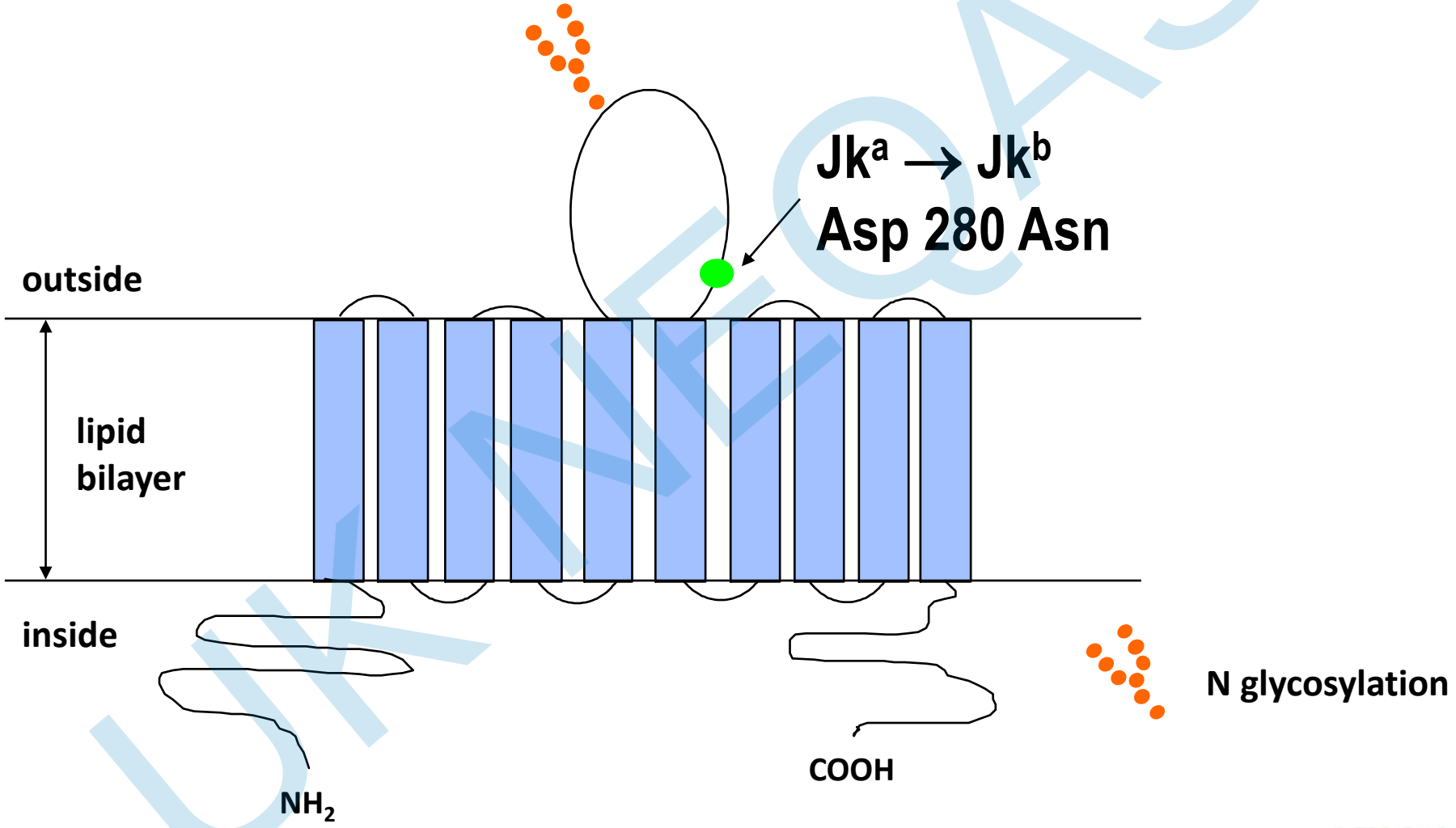
Jenny White

UK NEQAS for Blood Transfusion Laboratory Practice (BTLP)

UK NEQAS
Haematology and Transfusion

Not this…

Model of the Urea Transporter depicting the location of the Jk^a/Jk^b blood polymorphism



Slide courtesy of Joyce Poole

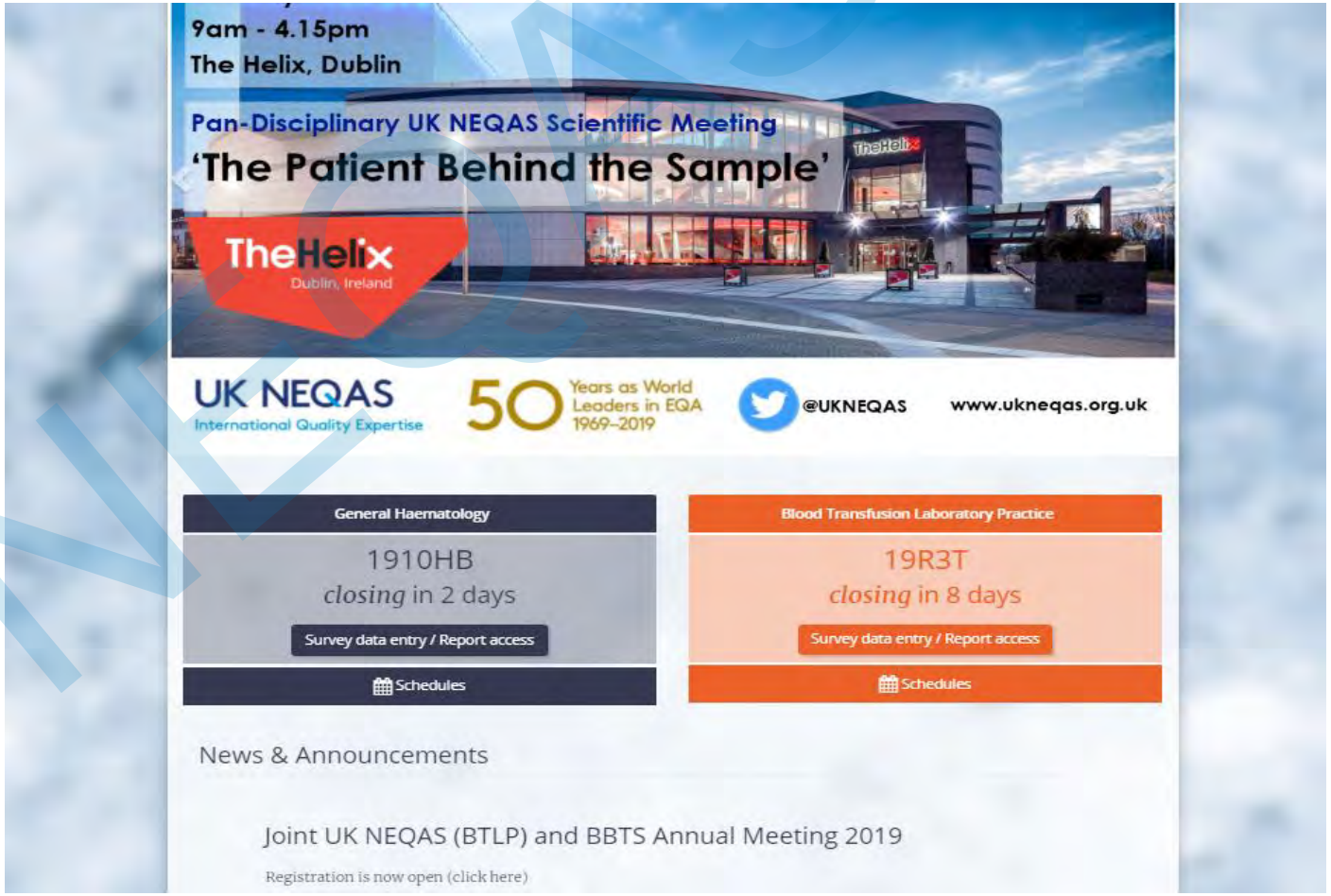
Most UK donors and patients Jk(a+b+), Jk(a+b-) or Jk(a-b+)

Serological red cell phenotyping

- To select antigen negative donations for transfusion
  - Anti-Jk^{a} and anti-Jk^{b} clinically significant
    - Cause both HTR and DHTR
    - Notorious for evanescence, so rely on phenotyping
- To type patients for
  - Completion of antibody identification
  - Extended matching of red cells, e.g. in SCD

UK NEQAS BTLP

- Pre-transfusion testing
  - ABO/D
  - Antibody screening and ID
  - Crossmatching
  - Phenotyping
- FMH
- ABO titration
- Pilot schemes
  - Red cell genotyping
  - DAT
  - Antenatal titration
  - Extended phenotyping

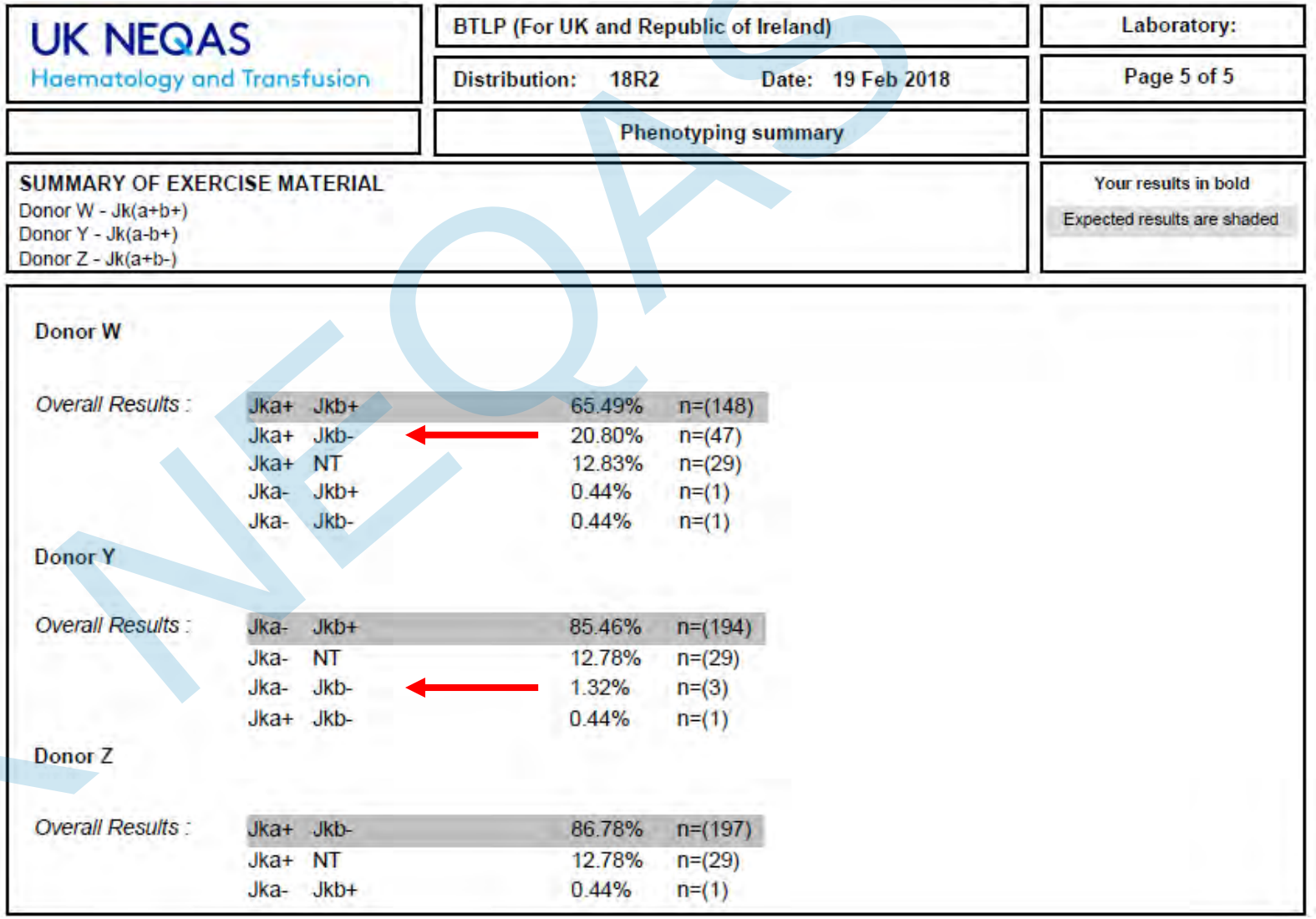


http://www.ukneqasbtlp.org/

UK NEQAS
Haematology and Transfusion

Phenotyping
Error rate in the UK
0.5 – 1%

- Data entry, transposition in testing
- Issues with reagents and/or controls
- Not noticing unlikely results
  - e.g. all 3 ‘donors’ Jk(a-b-)



UK NEQAS
Haematology and Transfusion

BTLP (For UK and Republic of Ireland)

Distribution: 18R2 Date: 19 Feb 2018

Laboratory:

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Phenotyping summary

SUMMARY OF EXERCISE MATERIAL
Donor W - Jk(a+b+)
Donor Y - Jk(a-b+)
Donor Z - Jk(a+b-)

Your results in bold
Expected results are shaded

Donor W

Overall Results :	Jka+	Jkb+	65.49%	n=(148)
	Jka+	Jkb-	20.80%	n=(47)
	Jka+	NT	12.83%	n=(29)
	Jka-	Jkb+	0.44%	n=(1)
	Jka-	Jkb-	0.44%	n=(1)

Donor Y

Overall Results :	Jka-	Jkb+	85.46%	n=(194)
	Jka-	NT	12.78%	n=(29)
	Jka-	Jkb-	1.32%	n=(3)
	Jka+	Jkb-	0.44%	n=(1)

Donor Z

Overall Results :	Jka+	Jkb-	86.78%	n=(197)
	Jka+	NT	12.78%	n=(29)
	Jka-	Jkb+	0.44%	n=(1)

Possible link with one reagent

BIOSCOT®

Anti-Jk^{a} Cell Line: MS-15
Product Code: BI

Anti-Jk^{b} Cell Line: MS-8
Product Code: BE

Monoclonal Human IgM
Blood Grouping Reagents

For Tube Technique

CE 0123

IVD

INTENDED USE

BIOSCOT Anti-Jk^{a} and Jk^{b} are monoclonal human IgM blood grouping reagents which will detect the Jk^{a} and Jk^{b} antigens respectively, when tested according to the tube technique. These reagents are designed for use by operators trained in serological techniques.

PERFORMANCE CHARACTERISTICS

Anti-Jk^{a} (cell line MS-15) monoclonal human IgM blood grouping reagent BI and Anti-Jk^{b} (cell line MS-8) monoclonal human IgM blood grouping reagent BE have been tested by the recommended technique with donor, clinical and neonatal specimens. The sample population represented all major phenotypes. The total number of tests (n), and the calculated sensitivity and specificity for each technique are displayed below:

TECHNIQUE	Anti-Jk^{a} Product Code BI			
	Sensitivity		Specificity	
	n	%	n	%
Tube	726	99.6	205	100

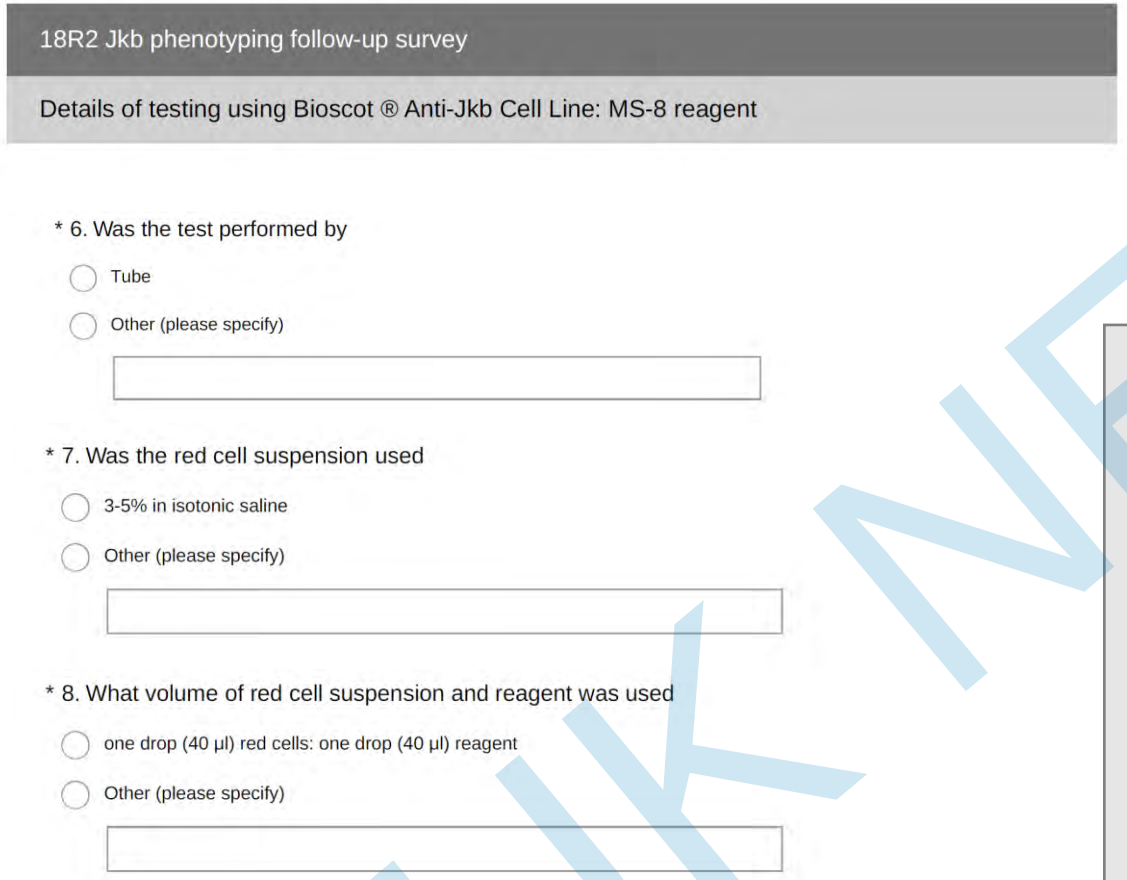
TECHNIQUE	Anti-Jk^{b} Product Code BE			
	Sensitivity		Specificity	
	n	%	n	%
Tube	666	99.5	265	100

Exercise 18R2 investigation

- Reagent
  - Bioscot reagent supplied by a distributor (Lorne laboratories) who had previously been supplying a different anti-Jk^b reagent
  - Instructions for use of new reagent only available on-line
  - Some used Column Agglutination Technology method as for previous anti-Jk^b reagent from Lorne
  - Some others did not exactly follow 'complex' Bioscot instructions for tube testing

- EQA material – Donor W Jk(a+b+)
  - Single donation from NHSBT
  - Within 35 days limit
  - Confirmed by IBGRL to have normal expression of the Jk^b antigen with range of anti-Jk^b reagents, but weak reaction vs. BioScot (MS-8)

Surveyed all UK & ROI phenotyping labs (197)



18R2 Jkb phenotyping follow-up survey

Details of testing using Bioscot ® Anti-Jkb Cell Line: MS-8 reagent

* 6. Was the test performed by

- Tube
- Other (please specify)

* 7. Was the red cell suspension used

- 3-5% in isotonic saline
- Other (please specify)

* 8. What volume of red cell suspension and reagent was used

- one drop (40 µl) red cells: one drop (40 µl) reagent
- Other (please specify)

Survey developed in collaboration with Merck Millipore to investigate details of how their reagent was used and to gather denominator data from all UK labs reporting phenotyping results in 18R2

Additional survey report - 18R2

Reaction grade Donor W	Reagent manufacturer									
	Alba Bioscience	Bio-Rad	Bioscot[1]	Grifols	Immucor	ImuMed	Lorne	Ortho	Quotient	Total
1+	2	0	4	0	0	2	6	1	0	15
2+	2	4	11	0	4	0	1	1	0	22
3+	5	2	8	0	7	3	1	4	1	31
4+	0	2	1	0	3	0	0	3	2	11
negative	1	5	23	0	0	0	2	0	0	31
weak	0	0	2	1	0	0	1	0	0	4
not stated[2]	0	3	1	0	0	0	0	1	0	5
Total	10	16	50	1	14	5	11	10	3	120

- 49% of Bioscot users did not follow the manufacturer's method
- But 29% of those following the correct method still obtained a negative result
- Problem not just one reagent?
- General problems with phenotyping also identified
  - 25% selected a Jk(a-b+) cell as the positive control for Jk^b typing
  - Typing reported on weak reactions obtained for test and/or control

UK NEQAS response to Manufacturer

Discussed survey findings in detail and asked them to consider:

- Potency of reagent
- Change to method (non-standard and too complex)
  - unnecessary 2 step incubation and spin
  - Incubation temperature not optimal for an IgM reagent
- Making instructions available with the reagent

Learning points

1. To reduce the potential for procedural errors, checks are required at critical points in the pre-transfusion process, e.g. sample labelling, performing and interpreting manual tests and transcribing information.

2. When performing red cell phenotyping it is good practice to select a 'positive' control cell with heterozygous expression of the relevant antigen; this demonstrates that the weakest normal antigen expression can be detected on the test cells.

3. It is important that reagent manufacturer's instructions are followed and that the limitations of reagents in use are considered.

4. Commercial phenotyping reagents generally give 'strong' reactions with antigen positive cells, and it is advisable to repeat tests and question results where a weaker than expected reaction is obtained with either the positive control or with an individual test.

Exercise –Final report from Manufacturer

Investigation Outcome

'The complaint is not Justified or confirmed.'

'Investigative testing performed by Merck did not confirm any false negative test results in tests performed using the Donor W cell. Tests performed using the 'Donor W' sample produced positive test results. False negative test results were not confirmed. '

'UK NEQAS confirmed to Merck that a high proportion of laboratories who had participated in exercise 18R2 and who had reported discrepant test results had deviated in some way from the manufacturer's instructions'

'Merck conclude that the most likely reason for the discrepant negative test results reported for exercise 18R2 by UK NEQAS clients are a combination of weak cell reactivity of the 'Donor W' cell, deviation from the recommended test method by the participants and a failure of the analysts to recognize weak positive test results.'

Recommendation 1

Merck recommend that all tests performed using Bioscot anti-Jk^b reagent code BE are performed using the recommended test method which is provided in the product IFU version PI84/g 2013-02:

Recommendation 2

Merck recommend that Lorne Laboratories Ltd provide customers with information on how to obtain the product IFU.

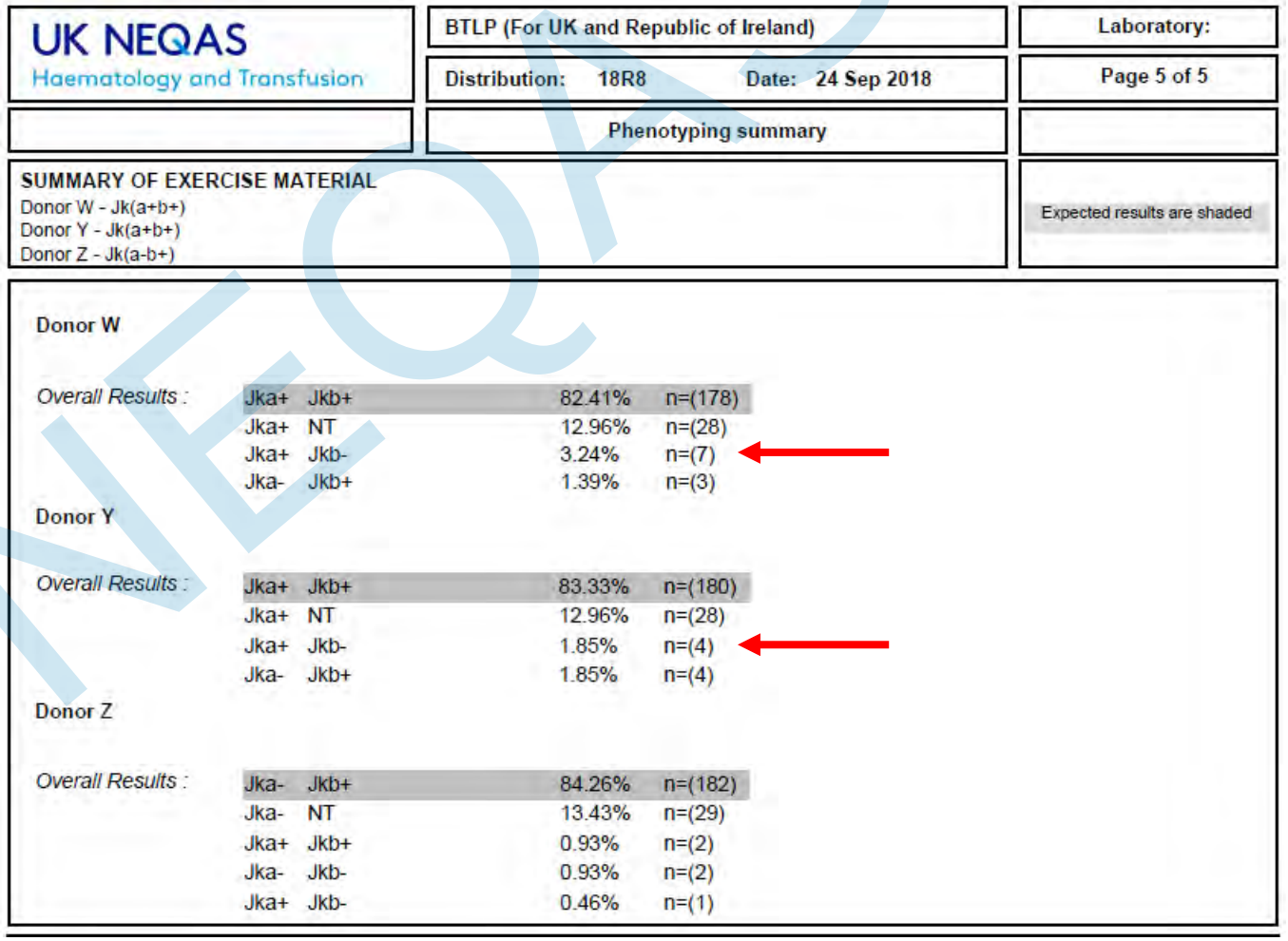
The instructions on how to obtain a copy of the current version of the IFU, free of charge, are provided on the 'Information Sheet' that is supplied by Merck with all Bioscot reagents:
From www.millipore.com/bioscot_ifu

Exercise 18R8

2 x Jk(a+b+) samples

7 labs with false neg Jk^b types

- 5 using same reagent (Bioscot ® Anti-Jk^b Cell Line: MS-8)
  - 3 following manufacturer's instructions
  - 2 not following manufacturer's instructions
- 2 using other reagent
  - 1 not following manufacturer's instructions 1 method unknown



UK NEQAS
Haematology and Transfusion

BTLP (For UK and Republic of Ireland) | Laboratory:

Distribution: 18R8 Date: 24 Sep 2018 | Page 5 of 5

Phenotyping summary

SUMMARY OF EXERCISE MATERIAL
Donor W - Jk(a+b+)
Donor Y - Jk(a+b+)
Donor Z - Jk(a-b+)

Expected results are shaded

Donor W

Overall Results :	Jka+	Jkb+	82.41%	n=(178)
	Jka+	NT	12.96%	n=(28)
	Jka+	Jkb-	3.24%	n=(7)
	Jka-	Jkb+	1.39%	n=(3)

Donor Y

Overall Results :	Jka+	Jkb+	83.33%	n=(180)
	Jka+	NT	12.96%	n=(28)
	Jka+	Jkb-	1.85%	n=(4)
	Jka-	Jkb+	1.85%	n=(4)

Donor Z

Overall Results :	Jka-	Jkb+	84.26%	n=(182)
	Jka-	NT	13.43%	n=(29)
	Jka+	Jkb+	0.93%	n=(2)
	Jka-	Jkb-	0.93%	n=(2)
	Jka+	Jkb-	0.46%	n=(1)

MHRA meeting

- UK NEQAS meeting with MHRA
- Encouraged to report potential issues with IVDs early
- Discussion on mechanism of reporting and weighting of reports from EQA

Reporting Routes – Yellow Card

Who?

Anyone can report

Healthcare professionals

Patients

Members of the public

What?

Medicines

Medical Devices

Defective Medicines

Fake or Counterfeit Devices and Meds

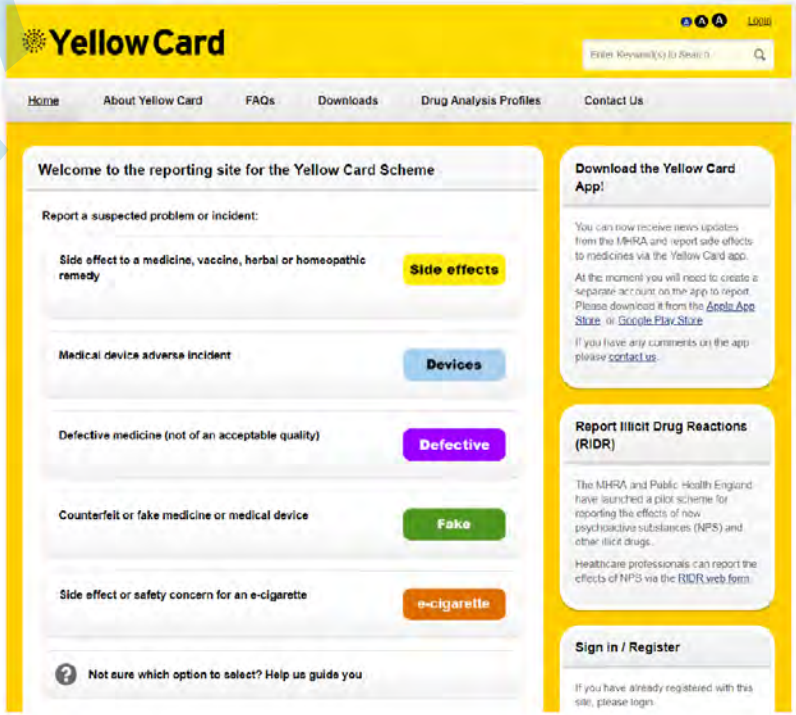
E-cigarette issues

When?

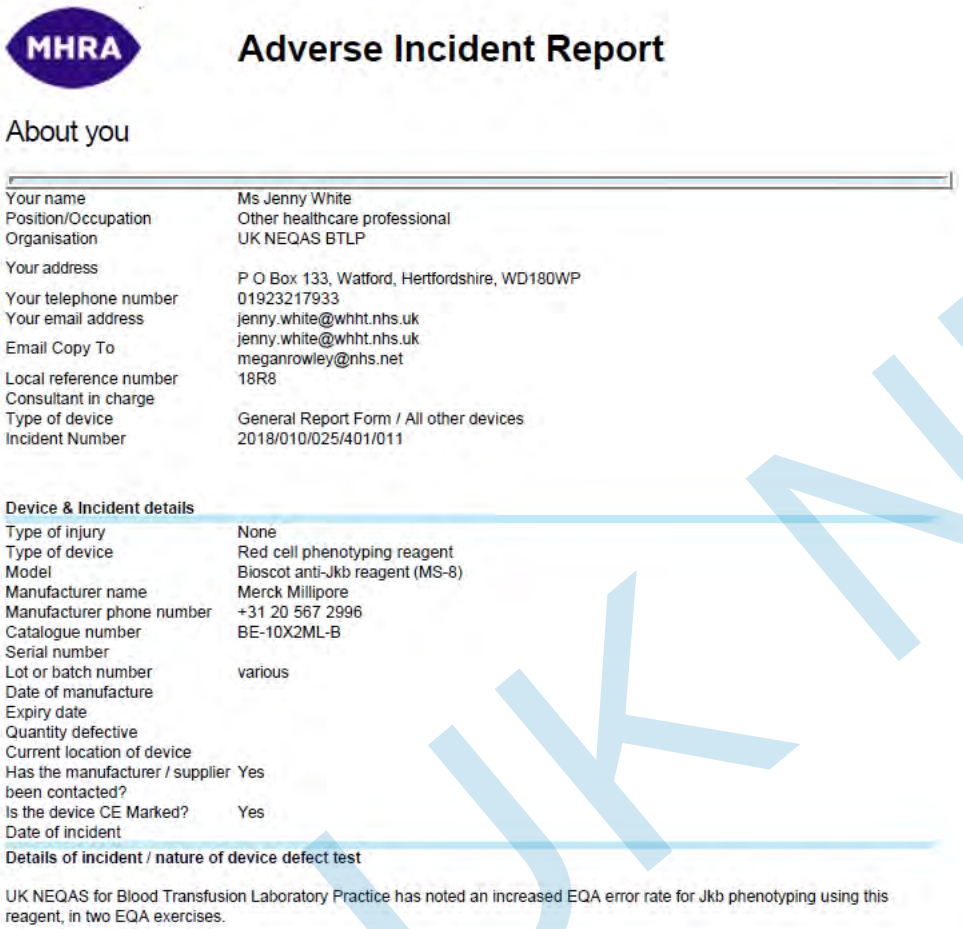
As soon as you can after the event

Where?

https://Yellowcard.mhra.gov.uk



Report to MHRA



MHRA

Adverse Incident Report

About you

Your name	Ms Jenny White
Position/Occupation	Other healthcare professional
Organisation	UK NEQAS BTLP
Your address	P O Box 133, Watford, Hertfordshire, WD180WP
Your telephone number	01923217933
Your email address	jenny.white@whht.nhs.uk
Email Copy To	jenny.white@whht.nhs.uk meganrowley@nhs.net
Local reference number	18R8
Consultant in charge	
Type of device	General Report Form / All other devices
Incident Number	2018/010/025/401/011

Device & Incident details

Type of injury	None
Type of device	Red cell phenotyping reagent
Model	Bioscot anti-Jkb reagent (MS-8)
Manufacturer name	Merck Millipore
Manufacturer phone number	+31 20 567 2996
Catalogue number	BE-10X2ML-B
Serial number	
Lot or batch number	various
Date of manufacture	
Expiry date	
Quantity defective	
Current location of device	
Has the manufacturer / supplier been contacted?	Yes
Is the device CE Marked?	Yes
Date of incident	

Details of incident / nature of device defect test

UK NEQAS for Blood Transfusion Laboratory Practice has noted an increased EQA error rate for Jkb phenotyping using this reagent, in two EQA exercises.

- Reported through yellow card process
- Uploaded 18R2, Q and 18R8 reports
- ? Should have reported before… wanted to be sure – MHRA would say report immediately…
- MHRA ref: 2018/010/025/401/011
  Your ref: 18R8
- We have assessed your report and have asked the manufacturer to investigate. They may contact you for further information and you can release the device to them.
- ‘It can take 3 months or longer to investigate and so you might not hear from us during this time.’!

What happened next

- Re-opened talks with Merck Millipore within a week

….. but no change in Bioscot reagent achieved

- Lorne Laboratories no longer supply the Bioscot reagent

UK NEQAS
Haematology and Transfusion

BTLP (For UK and Republic of Ireland)

Laboratory: xxxxx

Distribution: 19R8 Date: 23 Sep 2019

Phenotyping summary

SUMMARY OF EXERCISE MATERIAL
Donor W - Jk(a+b+)
Donor Y - Jk(a+b+)
Donor Z - Jk(a+b-)

Expected results are shaded

Donor W

Overall Results :	Jka+	Jkb+	85.05%	n=(182)
	Jka+	NT	9.81%	n=(21)
	Jka+	Jkb-	4.21%	n=(9)
	Jka-	Jkb+	0.93%	n=(2)

Donor Y

Overall Results :	Jka+	Jkb+	85.05%	n=(182)
	Jka+	NT	9.81%	n=(21)
	Jka+	Jkb-	3.74%	n=(8)
	Jka-	Jkb+	1.40%	n=(3)

Donor Z

Overall Results :	Jka+	Jkb-	88.68%	n=(188)
	Jka+	NT	9.91%	n=(21)
	Jka+	Jkb+	1.42%	n=(3)

12 labs, 17 false negative reactions vs. anti-Jk^{b}

10 labs repeated testing after the closing date

9/10 using Bioscot reagent

- 2 did not follow manufacturer's instructions
- 7 could not find the cause of the original false negative reactions, including 5 labs with repeat testing giving <2+ reaction

2nd report to MHRA pending

Example CAPA - EQA phenotyping error vs. anti-Jk^{b}

Remedial action

Consider risk of clinical samples typed using this anti-Jk^{b} reagent

? Re-test

Corrective action

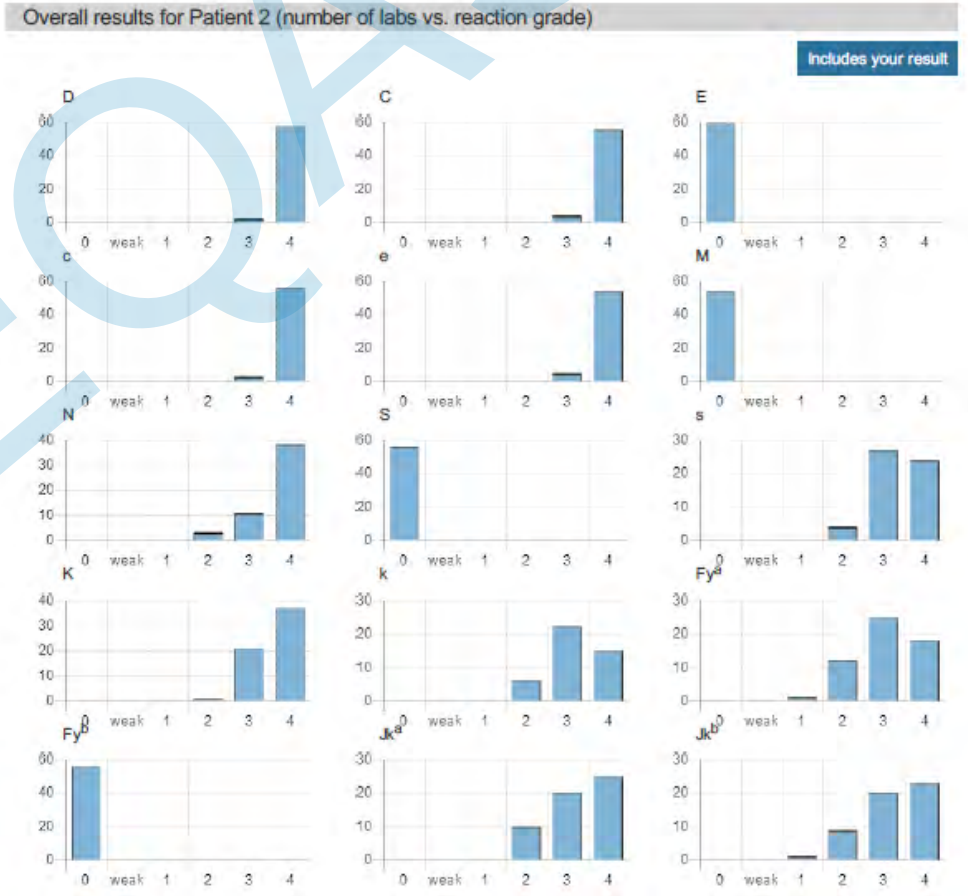
Replace anti-Jk^{b} validate and document method including controls required

Preventive action

Review policy for selecting, validating, receipt, controlling and using all reagents

Extended red cell phenotyping pilot (1920ERP1)

- Jk(a+b+) sample
- Mostly reference labs and large hospitals
- No Jk^b typing errors but range of reaction grades with anti-Jk^b and some other phenotyping reagents



Antibody screening 19E1 – weak anti-E

- 14/370 UK and ROI laboratories reported a negative screen
  - All using the same batch of Ortho screening cells
  - Variable reactions on repeat with Ortho R_2R_2 (cDE/cDE) screening cell
  - Some still negative and some others weaker than other E+ panel cells

- UK NEQAS BTLP – liaised with manufacturer
- Reported to MHRA
- Manufacturer cited EQA material as cause… as all complaints related to EQA
- But agreed to our request to remove that R_2R_2 cell from the screening panel

Feb 2018	Mar 2018	Apr 2018	May 2018	June 2018	Aug 2018	Sep 2018	Nov 2018	**Jan 2019**

EQA

- Highlighting problems with practice
  - Following manufacturer's instructions
  - Selecting and validating reagents
  - Using appropriate IQC
  - Policy for investigating weak and anomalous reactions

- Highlighting reagent problems unlikely to be revealed otherwise
  - Clinical samples – correct result unknown
  - Phenotyping often undertaken to confirm antibody ID (absence of an antigen)
  - Screening – expect majority to be negative

Value of collective and objective EQA data

Enables / speeds up detection of sporadic problems

Scheme support for participating laboratories

Allows laboratories to learn from each other

Never work with kids

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