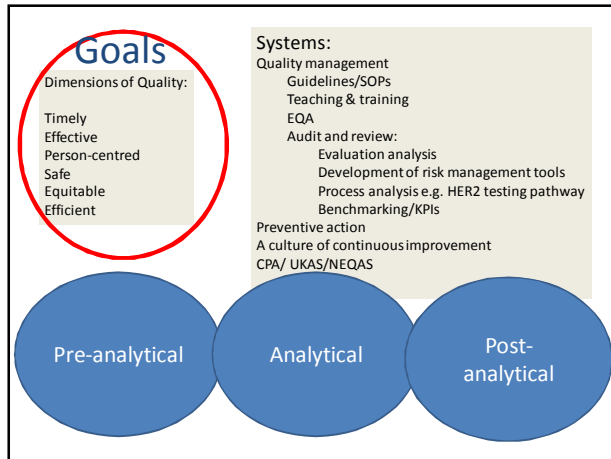


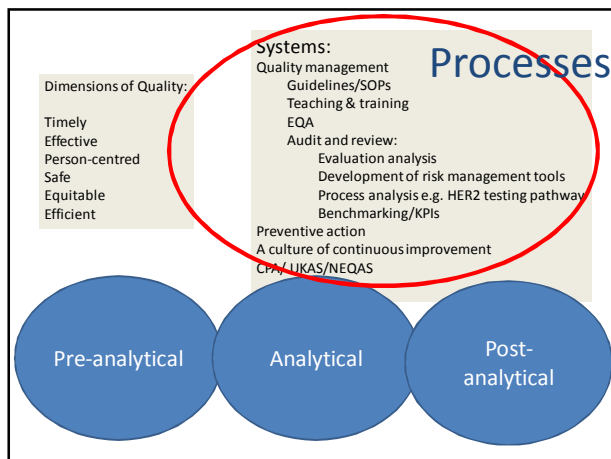
## High Quality Breast Pathology of Today and Challenges for Tomorrow

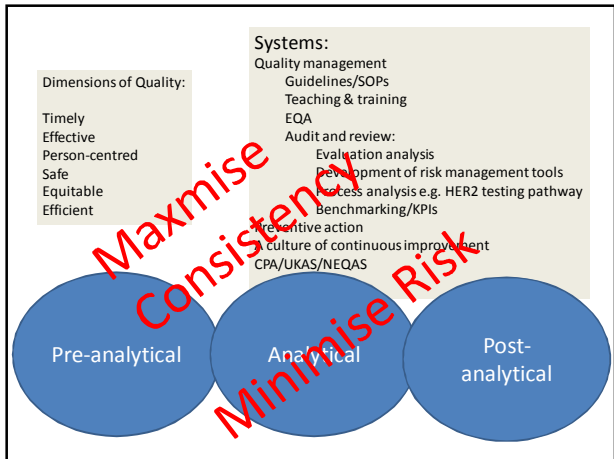
Dr Jeremy Thomas  
Western General Hospital  
Edinburgh



### Disclosures/Conflicts of Interest

“ None to declare



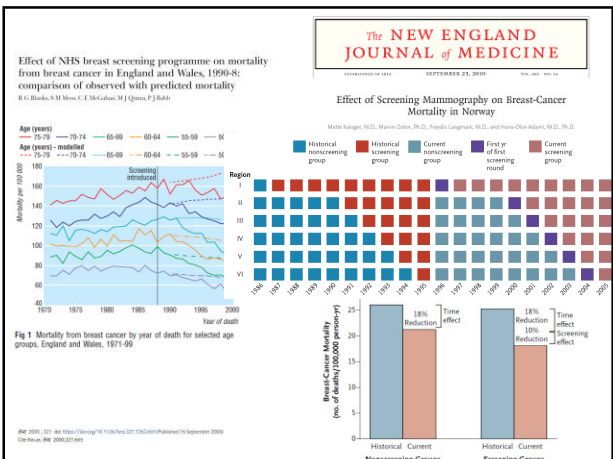


### Breast Screening

- “ Multidisciplinary working
  - . Seeing other professional groups and their work
  - . Breaking down professional silos
  - . Patient-focused
- “ Rigorous audit and accountability
  - . Benchmarking
- “ Education and training

### Influences on the Quality Agenda

- “ Breast Screening
- “ Benchmarking
- “ Clinical Trials
- “ Tumour heterogeneity
- “ Molecular/Multigene testing



**Bimodal Frequency Distribution of Estrogen Receptor Immunohistochemical Staining Results in Breast Cancer**  
 An Analysis of 825 Cases  
 Laura C. Collins, MD, Maria L. Batono, MD, and Stuart J. Schmitt, MD  
 Key Words: Breast cancer; Estrogen receptor; Immunohistochemistry  
 DOI: 10.1093/ajcp/17.02

~ 825 primary breast cancers:  
 ~19% completely negative  
 ~80% positive (70% of cells)

~1% (8 cases) intermediate  
 ~All core biopsies

Collins LC et al; Am J Clin Pathol 2005

**Histopathology**  
 Further evidence to support bimodality of oestrogen receptor expression in breast cancer  
 Abir A Muftah,<sup>1,2</sup> Mohammed Aleskandary,<sup>1</sup> Sultan N Sonbul,<sup>1</sup> Christopher C Nolan,<sup>1</sup> Maria Diaz Rodriguez,<sup>2</sup> Carlos Caldas,<sup>1</sup> Ian O Ellis,<sup>1</sup> Andrew R Green<sup>1</sup> & Emdad A Rakha<sup>1</sup>

IHC

ESR 1 mRNA

Transcriptomic

3649 CNB 2008-14  
 1892 TMA 1988-98  
 1980 METABRIC (262 N'ham)

Muftah AA et al. Histopathology 2017; 70: 456-465

VOLUME 25 NUMBER 17 JUNE 10 2007  
 JOURNAL OF CLINICAL ONCOLOGY CORRESPONDENCE

Bimodal Population or Pathologist Artifact?

650 cases  
 Fluorescence calibrated using cell lines  
 Fluorescence data  
 IHC data

Rimm D et al. J Clin Oncol 2007

ER – UK Screeners 2008 - 11

ER – Scottish Screeners 2008 - 11

Al-Mohtaseb A et al; J Pathol 2013

**CQC launches urgent inspection at Sherwood Forest Hospital NHS Foundation Trust**  
 Published: 8 October 2012  
 Provider: Sherwood Forest Hospitals NHS Foundation Trust  
 Category: Health

**The Royal College of Pathologists**  
 Pathology: the science behind the cure

**Review of cellular pathology governance, breast reporting and immunohistochemistry at Sherwood Forest Hospitals NHS Foundation Trust**

A report prepared for the Care Quality Commission in respect of diagnostic and screening procedures

28 February 2013

**2010-11 BSP QA data**

Region	Performance (%)
East of England	~95%
London	~90%
North of England	~85%
South of England	~80%
West Midlands	~75%
Yorkshire	~70%
North of Scotland	~65%
East of Scotland	~60%

**Regional Confidence Interval**

- Regional Confidence Interval: 90%
- 6% Boundary
- 10% Boundary
- Not an outlier @ 8%
- Not an outlier @ 10%
- Outlier @ 10%

### Pathology QA in Clinical Trials

- HERA Trial:
  - Central review of ER & HER2
  - 3 erroneous HER2 results in >4000 patients
- ARTEMIS:
  - No difference between report review and central path review for pCR
- SUPREMO Trial
  - Substantial differences in grade and Lvi
- BIG 1-98
  - Tamoxifen v Aromatase Inhibitor
- ALTO Trial
  - Phase 3 trial for adjuvant Lapatinib & Trastuzumab for HER2 +ve disease:

### MODERN PATHOLOGY

**Assessing HER2 testing quality in breast cancer: variables that influence HER2 positivity rate from a large, multicenter, observational study in Germany**

Josef Ritschhoff<sup>1</sup>, Annette Lebeau<sup>2</sup>, Hans Kreipe<sup>3</sup>, Peter Sinn<sup>4</sup>, Claus Dieter Gerhartz<sup>5</sup>.

57 centres  
 15,332 tests  
 Patient/Tumour effect v Centre effect  
 3 "Centre Effect" instances (P=0.05)  
 3 "7 Centre Effect" instances (P=0.2)

**HER2 positivity**

**G2** Histologic grading

**ER-negative/ PgR-negative** Hormone receptor status

**Ductal** Histologic subtype

**63.5** Age (years)

**(y)pN1** Nodal status

**P=<0.0001**

Ruschoff J et al Modern Pathology (2017) 30, 217-226

### Pathology QA in Clinical Trials

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prognostic and Predictive Value of Centrally Reviewed Expression of Estrogen and Progesterone Receptors in a Randomized Trial Comparing Letrozole and Tamoxifen Adjuvant Therapy for Postmenopausal Early Breast Cancer: BIG 1-98

6291 patients – 10% cut point for positivity  
 Local assessment of ER & PGR compared with central review (Milan)  
 97% confirmed as HR +ve (ER and/or PGR)

Those not confirmed - 66 No Staining; 54 1-9% staining

Discordance more marked for PGR than ER

Patients reclassified as ER negative had a worse DFS

Viale G et al JCO 2007; 25: 3846-52

ALTTO Trial

NIH Public Access Author Manuscript

Central Pathology Laboratory Review of HER2 and ER in Early Breast Cancer: An ALTTO Trial [BIG 2-06 / NCCTG N063D (Alliance)] Ring Study

HER2 FISH ratio (Mayo)

HER2 FISH ratio (Milan)

Locally HER2 +ve:
 

- 5.8% neg (Mayo clinic)
- 14.8% neg (Milan)

Locally ER +ve:
 

- 16.2% neg (Mayo clinic)
- 4.2% neg (Milan)

Locally ER neg:
 

- 3.4% pos (Mayo)
- 21.4% pos (Milan)

McCullough AE et al Breast Cancer Res Treat. 2014; 143(3): 485-492.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prognostic and Predictive Value of Centrally Reviewed Expression of Estrogen and Progesterone Receptors in a Randomized Trial Comparing Letrozole and Tamoxifen Adjuvant Therapy for Postmenopausal Early Breast Cancer: BIG 1-98

Assessable material from 74% of randomized patients **not entirely typical** of the trial population.

Patients whose material was unavailable for review ... had **poorer outcome overall**, showed less or no benefit from letrozole instead of tamoxifen.

Providers of a **lower proportion of specimens for central review - lower concordance of local & central assessment.**

We thus question whether the non-assessable material would also show low concordance with central assessment.

ALTTO Trial

NIH Public Access Author Manuscript

Central Pathology Laboratory Review of HER2 and ER in Early Breast Cancer: An ALTTO Trial [BIG 2-06 / NCCTG N063D (Alliance)] Ring Study

reasons for discrepancies

Lack of agreed methodology:
 

- ER – different antibodies in Mayo and Milan
- HER2 FISH – different counting guidelines
  - Red signal clouds – Mayo = 20; Milan always <20
  - Green signals – Mayo = any cell; Milan always ≥2 greens

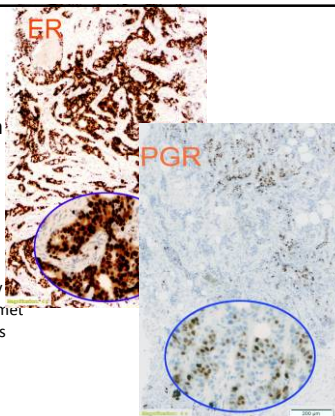
National diff<sup>s</sup> – esp some big German centres

Heterogeneity

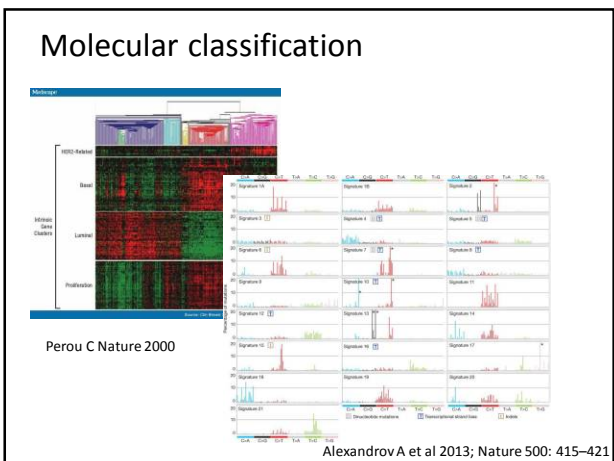
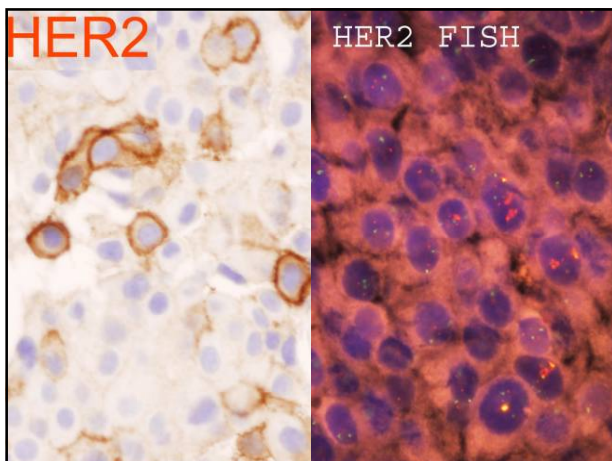
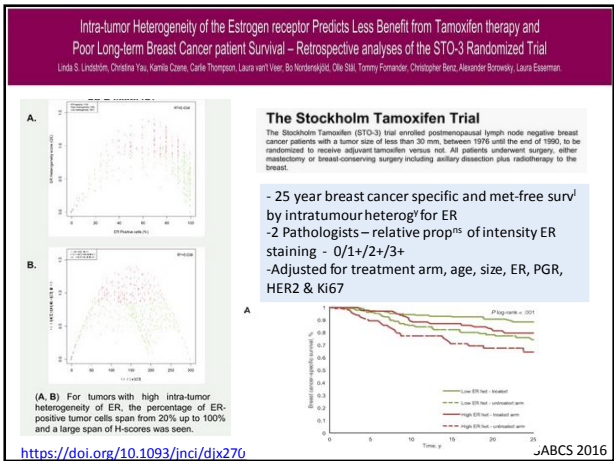


## Heterogeneity

- ~ Intertumour (between patients) – molecular
- ~ Intratumour – ER/PGR/HER2
  - . Spatial
    - ~ E.g. Within the primary
    - ~ Between primary and met
    - ~ Between different mets
  - . Temporal
    - . Spatial & temporal



Zardavos D et al Nature Reviews: Clin Oncol (2015); 12:381-394



“Breast cancer is not a single disease with heterogeneous marker expression and variable histology but a collection of genuinely different cancers that happen to originate from breast epithelium”



THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes

DOI: 10.1056/NEJMoa1804710

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**Data based on local testing**  
**Central review of ER, PGR & HER2 to follow**  
**Opportunity to compare with Oncotype PCR testing**

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes

Table 1. Estimated Survival Rates According to Recurrence Score and Assigned Treatment among Women 50 Years of Age or Younger in the Intention-to-Treat Population.\*

End Point and Treatment Group	Rate at 5 Yr	Rate at 9 Yr
Respective (Median; Range survival)		percent
Score of <20, endocrine therapy	95.1 (1.1)	87.4 (2.0)
Score of 21-25, endocrine therapy	95.1 (1.2)	87.7 (2.2)
Score of 11-25, chemotherapeutic therapy	94.3 (1.3)	89.2 (1.9)
Score of 16-20, endocrine therapy	92.6 (1.9)	86.6 (2.3)
Score of 16-20, chemotherapeutic therapy	94.2 (1.1)	88.6 (1.7)
Score of 21-25, endocrine therapy	96.3 (1.3)	79.2 (1.3)
Score of 21-25, chemotherapeutic therapy	92.1 (1.8)	81.5 (2.0)
Score of ≥26, chemotherapeutic therapy	88.4 (1.8)	80.3 (2.3)

Flowchart showing patient flow from 31,230 patients through various stages of testing and treatment assignment.

DOI: 10.1056/NEJMoa1804710

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ARTICLE

Comparing Breast Cancer Multiparameter Tests in the OPTIMA Prelim Trial: No Test is More Equal Than the Others

John M. S. Bartlett\*, Jane Bayani\*, Andrea Marshall, Janet A. Dunn,

**60% of tumours assigned to different risk categories by different tests.**  
**Discordant subtyping (Luminal A etc) in 41% of tumours**

Table 4. Kappa statistics for tests providing risk predictions\*

Test	MammaPrint (low), Kappa statistic (95% CI)	Prosigna (low/intermediate), Kappa statistic (95% CI)	IHC4 (low/intermediate), Kappa statistic (95% CI)	IHC4-AQUA† (low/low-mid), Kappa statistic (95% CI)
Oncotype DX (recurrence score ≤25)	0.40 (0.30 to 0.49)	0.44 (0.33 to 0.54)	0.53 (0.41 to 0.65)	0.40 (0.30 to 0.51)
MammaPrint (low/intermediate)	-	0.53 (0.43 to 0.63)	0.33 (0.21 to 0.44)	0.42 (0.30 to 0.53)
Prosigna (low/intermediate)	-	-	0.39 (0.27 to 0.50)	0.43 (0.31 to 0.54)
IHC4 (low/intermediate)	-	-	-	0.60 (0.50 to 0.70)

\*Kappa statistics are for agreement between categorisation into combined low and intermediate risk vs high risk. CI = confidence interval. †IHC4-AQUA mid risk and high risk are combined for this analysis.

Bartlett JMS et al J Nat Cancer Inst 2016 108: djw050

### Next generation diagnostic molecular pathology: Critical appraisal of quality assurance in Europe



Hendrikus J. Dubbink<sup>a</sup>, Zandra C. Deans<sup>b</sup>, Bastiaan B.J. Tops<sup>a</sup>, Folbert J. van Kemenade<sup>c</sup>, S. Koljenovic<sup>d</sup>, Han J.M. van Krieken<sup>a</sup>, Willeke A.M. Bloks<sup>e</sup>, Winand N.M. Dinjens<sup>a</sup>, Patricia J.T.A. Groenen<sup>b,c</sup>

MOLECULAR ONCOLOGY 8 (2014) 830–839

#### Challenges from Molecular Testing for a Diagnostic Laboratory:

1. Tissue challenges: FFPE v Fresh; Mixtures of Normal & Tumour
2. Technological challenges: Limited tissue – multiple tests and techniques
3. Mutation detection and chromosomal rearrangements
4. Validation and gold standards
5. QA for diagnostic labs: Internal; Competence of personnel; EQA & proficiency testing
6. Where & how?>

Table 1 – External quality assessment providers for molecular pathology schemes in Europe.

	Name	Abbreviation	Website
European	European Society for Pathology	ESP	<a href="http://www.esp-pathology.org">www.esp-pathology.org</a>
National	European Molecular Genetics Quality Network	EMQN	<a href="http://www.emqn.org">www.emqn.org</a>
	Dutch Foundation for Quality Assessment in Medical Laboratories	SQML	<a href="http://www.stml.nl">www.stml.nl</a>
	UK National External Quality Assurance Services	UK NEQAS	<a href="http://www.ukneqas.org.uk">http://www.ukneqas.org.uk</a>

## Challenges for the future (3)

- “ Tumour heterogeneity
- “ Companion diagnostics
- “ Accurate reproducible (biomarker) measurement
- “ Digital pathology:
  - . Automation
  - . Quantitation
  - . Communication

## Challenges for the future (2)

- “ Automation of background QA systems
- “ Integrating laboratory and outcomes data
- “ Rationalising IT
- “ Centralising testing

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  - Drs Joe Loane
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  - Catriona Cowan
  - Marie O'Donnell
  - Sarah Pinder
  - Andy Hanby
  - Emad Rakha
  - Elena Provenzano
  - Ian Ellis
- . Oncology
  - David Cameron
  - Larry Hayward
  - Frances Yuille
- . International
  - Fraser Symmans
  - David Rimm
  - Stuart Schnitt
- . Surgery
  - Mike Dixon
  - Matthew Barber
- . Lab
  - Scott Maxwell
  - Tim Ingman
  - John Bartlett

