Integrating new methods into practice

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Declaration of Interests

- Honorary Honorary Professor of Pathology, Institute of Ophthalmology, University College London, UK
- Director, CanTech Ltd, Northamptonshire, UK
- Former Head of the WHO Classification of Tumours Programme and the Section of Evidence Synthesis and Classification at the International Agency for Research on Cancer, part of the World Health Organisation, Lyon, France.
- Previously implemented a number of molecular pathology methods, and the GE Omnyx digital pathology system for reporting histopathology
- Previously Director of the UK NIHR EME translational research programme.
- Founding member of the UK National Institute for Healthcare Excellence (NICE) Diagnostics Advisory Committee.

- All opinions expressed are personal, and not those of any of the organisations above.

Learning points

- Understand the role of the pathologist in leading innovation within the laboratory to meet the needs of patients.
- Understand the key features of the processes needed for implementation.
- Realise the need for an implementation team and the key roles involved.
- Appreciate applicable regulations and the benefits of external quality assurance (EQA).

What is pathology?

- Pathology is the study of disease.
- It is the bridge between science and medicine.
- It underpins every aspect of patient care, from diagnostic testing and treatment advice to using cutting-edge genetic technologies and preventing disease.


The Royal College of Pathologists
Pathology: the science behind the cure
19 different specialties
Molecular Pathology
Histopathology
Clinical Biochemistry
Metabolic Medicine
Medical Microbiology
Toxicology
Clinical Embryology
Oral Pathology
Immunology
Dermatopathology
Veterinary Pathology
Haematology
Forensic Pathology
Cytopathology
Virology
Paediatric Pathology
Genetics
Histocompatibility & Immunogenetics
Transfusion Medicine
Neuropathology

Role of Diagnostic Pathology

- Provision of excellent care to patients
- Prevention, diagnosis and treatment of disease
- Research to ensure best practice
- Innovation – implementing research
- Supporting industry and wealth creation

Implementation checklist

- Evaluate the needs
- Establish the evidence
- Write the business case
- Validate the test in your laboratory
- Quality assurance in place
- Audit your results continuously
- Effects on patient pathways?

Pathway analysis

- Analytical and clinical validation sufficient for implementation
- Patient pathway analysis:
- Test ➒ result ➒ action ➒ outcome
- Model early in process to understand likely outcomes.

Evaluate the need

- Horizon scanning
- Scope
- Team
- Clinical and laboratory colleagues
- Patients
- Medical, operational, finance, and personnel managers
- Procurement
- Primary Care
- Commissioners

Clinical Pathology Accreditation

ISO 15189 provides a means to accredit Clinical Pathology Services and External Quality Assessment Schemes (EQA).

It involves an external audit of the ability to provide a service of high quality by declaring a defined standard of practice, which is confirmed by peer review.

https://www.ukas.com/accreditation/

Standards for the Medical Laboratory

ISO 15189 and local regulations cover:

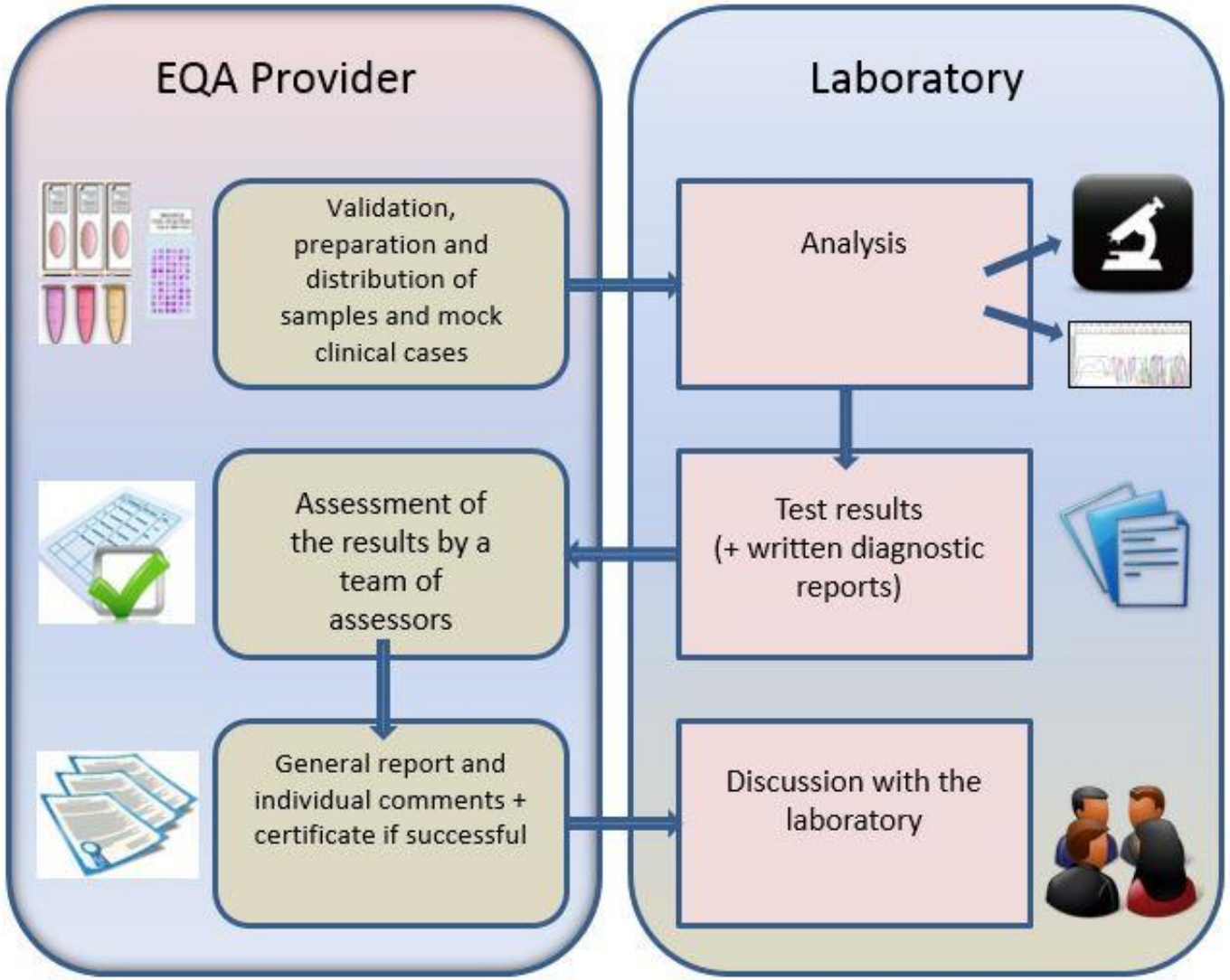
- Organisation and quality management system
- Personnel
- Premises and environment
- Equipment, information systems and materials
- Pre examination process
- Examination process
- The post examination phase
- Evaluation and quality assurance

How does EQA help with testing quality?

External Quality Assessment

(WHO definition)

A system for objectively checking the laboratory's performance using an external agency or facility



Picture by Veronique Tack, ESP EQA

Benefits of External Quality Assurance

- allows laboratory self-checking and comparison of performance to other laboratories
- provides early warning system for possible problems with tests, processes or operations
- provides insights into test results among different test sites
- allows continuous improvement and can highlight areas needing attention
- identifies training needs

Participation in EQA, where available, is required for accreditation

(ISO 15189:2022)

Questions to ask of any new test…

- Is it CE marked?
  - ➢If not, you'll need analytical validation.
  - ➢If it is, then verification is sufficient
- Do the results mean anything?
  - ➢Clinical validation required?
- Do the clinicians want it, and will they use it?
  - ➢Clinical Utility
- Is it cost-effective?
  - ➢NICE, FDA or local assessment as appropriate

OK….then you can start – who do you need involved?

Validation

- Confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled.

Verification

- Provision of objective evidence that a given item fulfils specified requirements.

- ISO15189 - see https://www.iso.org/obp/ui/en/#iso:std:iso:15189:ed-4:v1:en

The implementation team

- Lead - can be anyone, but for laboratory tests the pathologist is usually best placed to do this.
- Technical expert(s) who understand the test, its limitations, and what is needed for implementation
- Clinical pathway expertise - how will the test be used in practice from biopsy to use of the results
- Management/budget expertise
- Others depending on context - e.g. pharmacist, radiologist, surgeon, endoscopist, cytologist

Establish the Evidence

- Systematic reviews can be very helpful, but be aware of differences between healthcare systems and potential bias.
  - National Institute for Health and Clinical Excellence (NICE)
  - US NCCN
  - Health technology assessment programmes
- Consensus documents - for example ESMO, ASCO, or other large international organisations
- Do it yourself…

Business planning

- Background
- Technology
- Potential benefits to patients
- Cost - capital and recurrent
- Cost effectiveness
- Procurement
- Training
- Validation
- External quality assurance
- Milestones and Gantt chart
- Detailed costing

Help?

- National Institute for Health and Clinical Excellence (www.nice.org.uk)
- NHS Technology Adoption Centre (now part of NICE)
- CPA - now part of UKAS (http://www.ukas.com/services/accreditation-services/clinical-pathology-accreditation/)
- UKNEQAS (www.ukneqas.org.uk)
- Molecular pathology guidance - http://jcp.bmj.com/content/early/2014/07/10/jclinpath-2014-202404
- NOTE CHANGES…..

The CMD-ImPACT collaboration

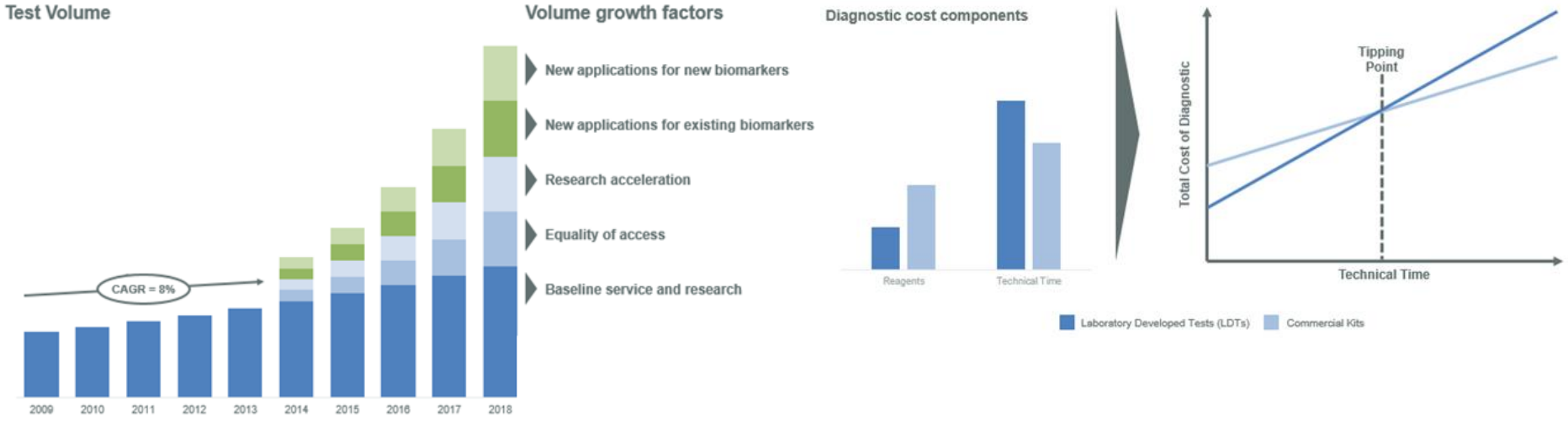
The ambition is to improve cancer outcomes by making sure that patients with cancer have access to the stratified medicines they need.

The CMD project started in mid-2013:

Cancer
Molecular
Diagnostics
Implementation
Planning
And
Commissioning
Toolkit

CMD ImPACT business planning tool
www.rcpath.org/cmd-impact

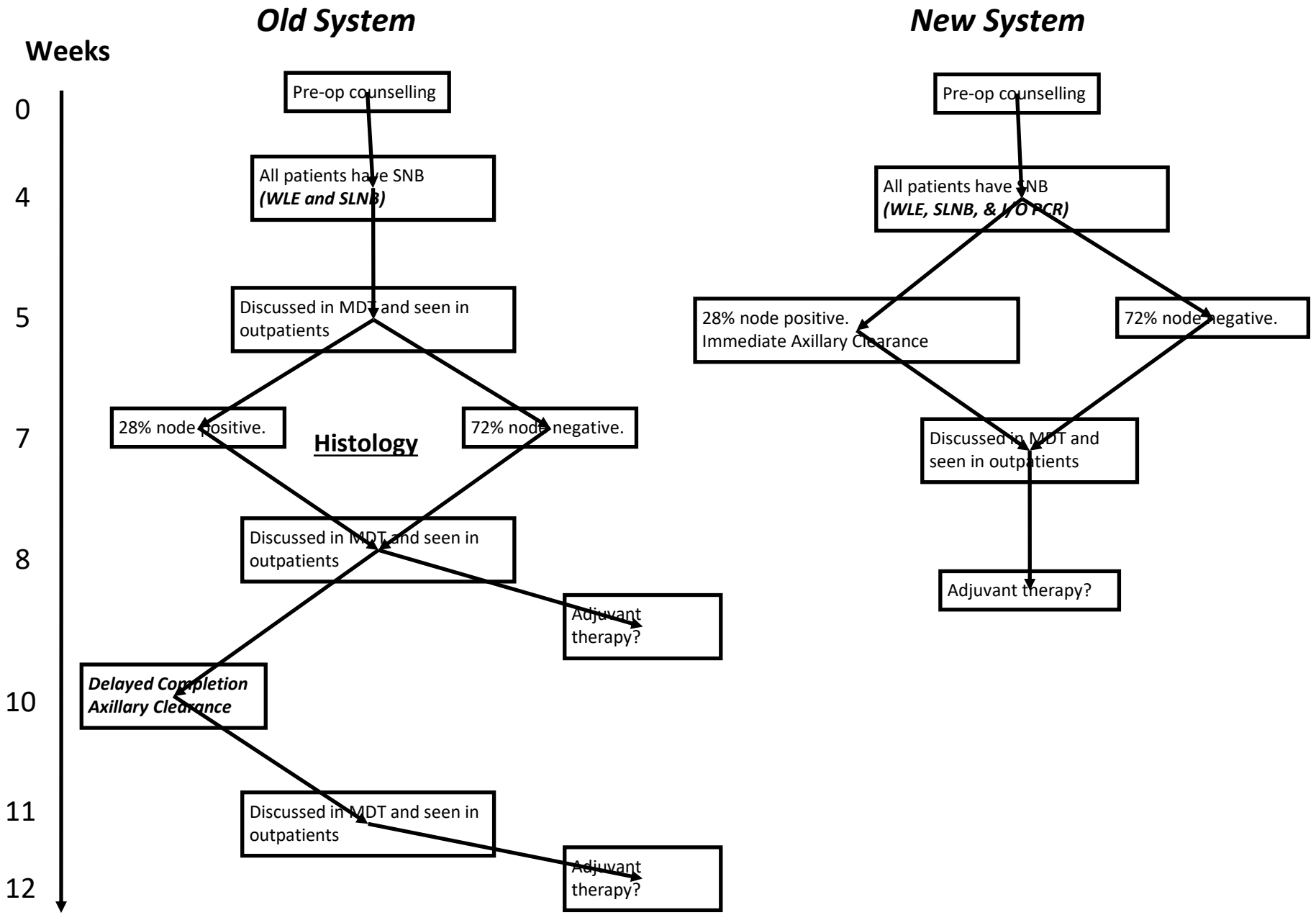
The tool is a simple Microsoft Excel programme that allows the costs and income to be modelled against a wide range of funding or demand scenarios, from current requirements to expansion of existing molecular diagnostic services.



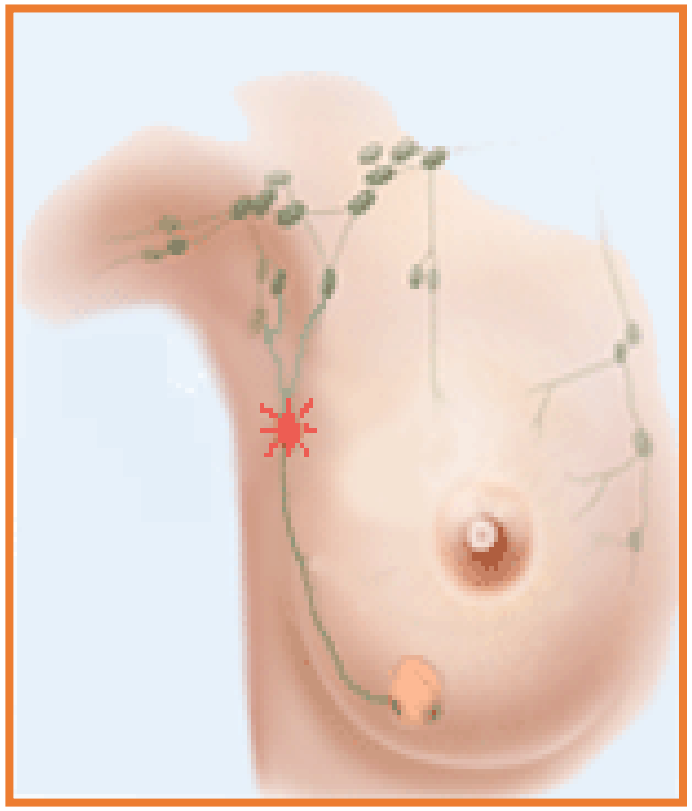
The contributions of different diagnostic specialties to diagnosis:

Breast cancer in a high or low income setting?

PORTSMOUTH


Old System
New System
Weeks
0
4
5
7
8
10
11
12
Pre-op counselling
All patients have SNB
(WLE and SLNB)
Discussed in MDT and seen in outpatients
28% node positive.
72% node negative.
Histology
Discussed in MDT and seen in outpatients
Adjuvant therapy?
Delayed Completion Axillary Clearance
Discussed in MDT and seen in outpatients
Adjuvant therapy?
Pre-op counselling
All patients have SNB
(WLE, SLNB, & I/O PCR)
28% node positive.
Immediate Axillary Clearance
72% node negative.
Discussed in MDT and seen in outpatients
Adjuvant therapy?

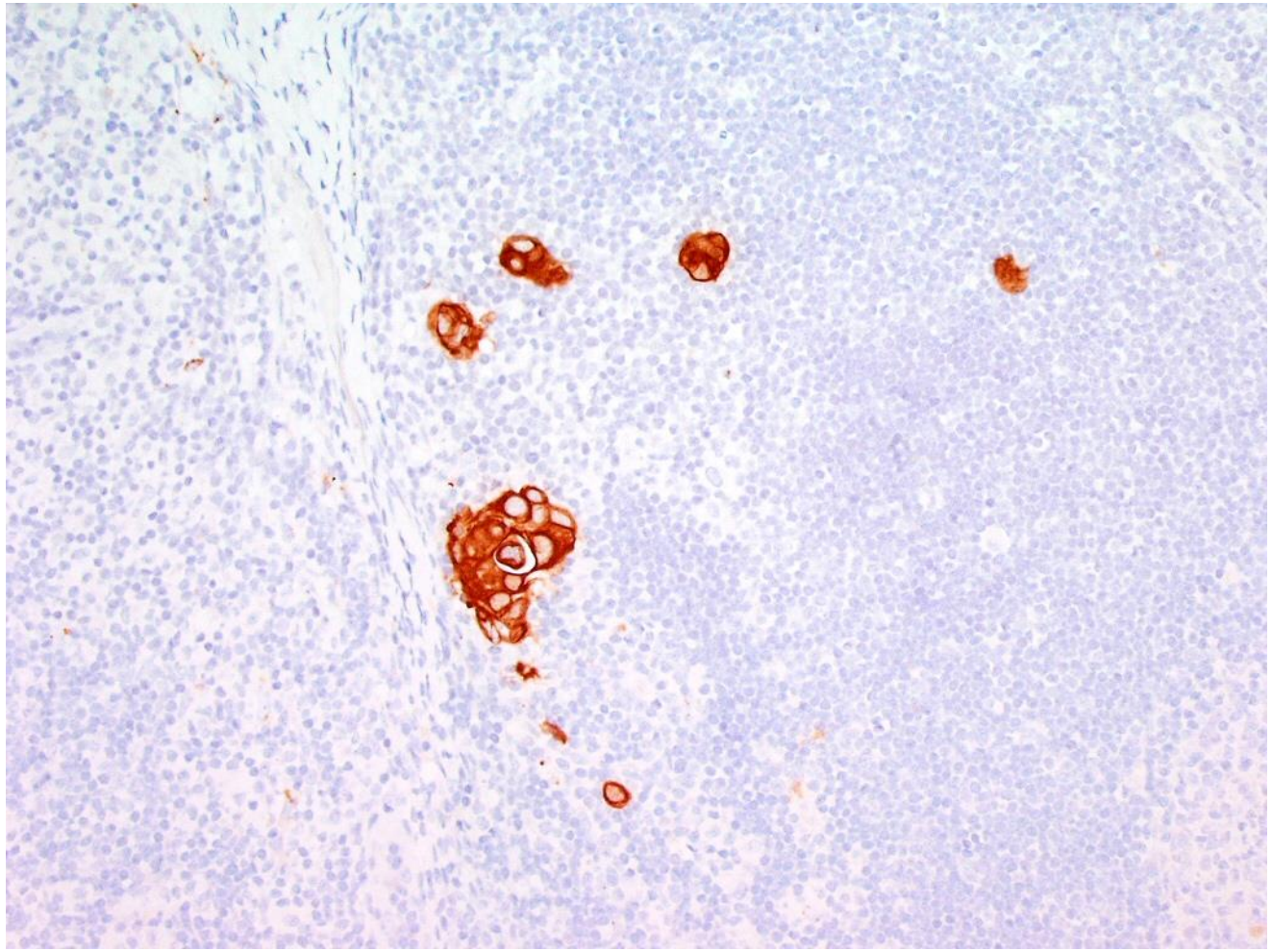
Sentinel lymph node



- **Lymphatic drainage and metastasis is to one node before the rest – the sentinel node (SLN).**
- **SLN sampling has a sensitivity of 83.4-100%**
- **Only patients with positive SLNs go on to have axillary dissection**
- **Significantly less morbidity and cost to health service**
- **Enhanced detection of positive nodes**

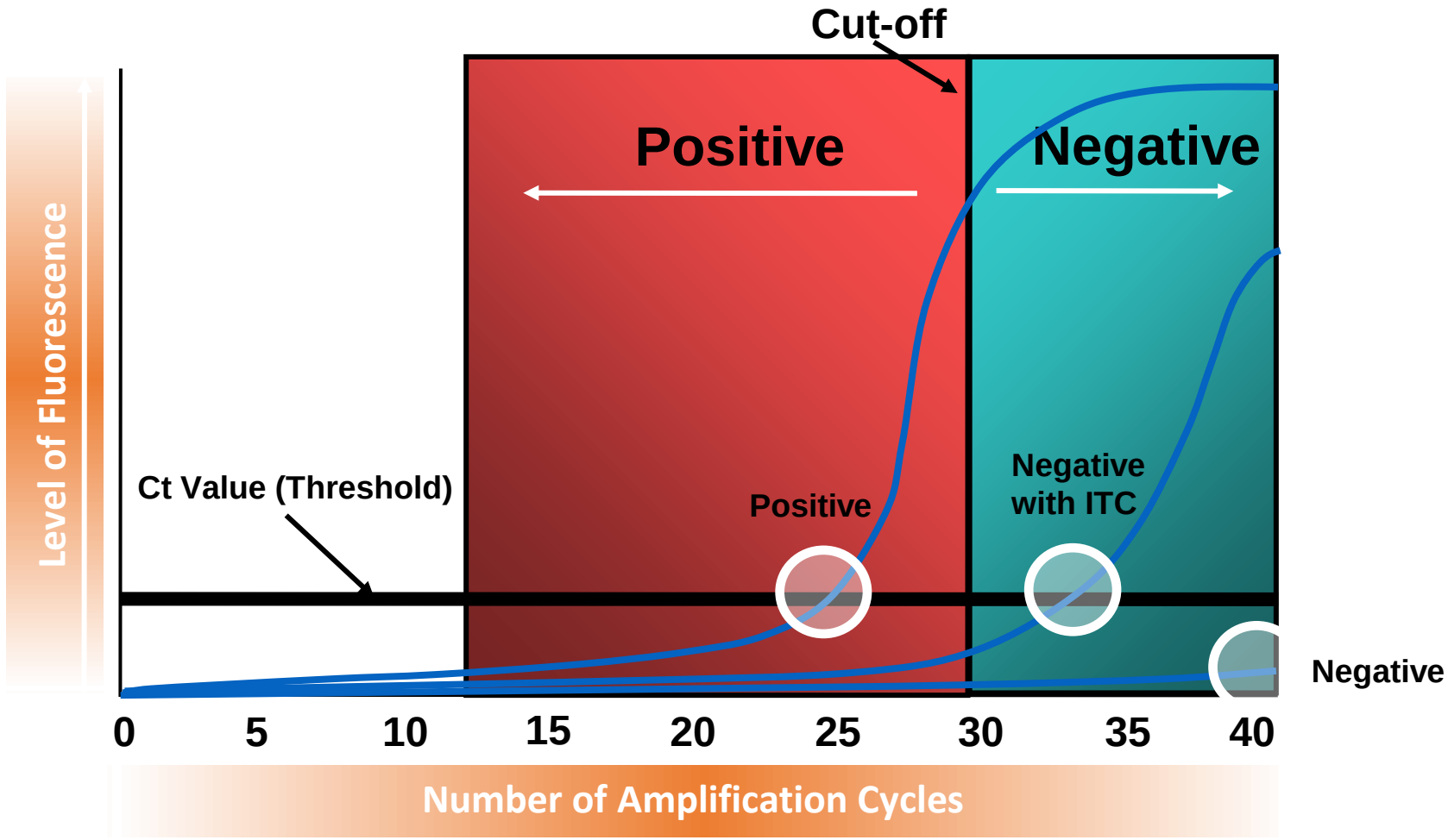
SLN Biopsy – Histology

- Expensive - nodes processed, sectioned and evaluated by H&E histology and immunohistology.
- Results take 10 days sometimes longer.
- Then, if positive - patient has to be informed and further surgery arranged.
- Frozen section or imprint cytology lack sensitivity and only sample part of node, and require a pathologist.




Medica Brush
NITRILE
DELL
Fire door keep shut

GeneSearch™ BLN Assay: Interpretation



Intra-operative SLN - Patients

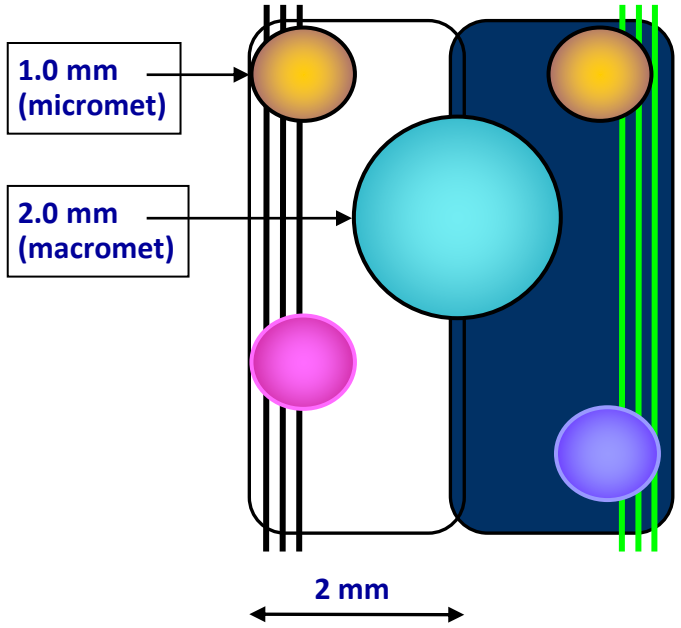
- **932 patients treated with intra-operative sentinel lymph node assessment**
- **676 (73%) negative, 254 (27%) positive**

- **Concordance with histology: 94%**

- **Discordance with histology: 6%**
  - **PCR +ve, Histology –ve: 41 patients**
  - **PCR –ve, Histology +ve: 7 patients**
  - **Failed assay: 1 patient**
- **Specificity 97%, (specificity = PCR +ve/Total +ve)**
- **Sensitivity 94% (sensitivity = PCR -ve/Total –ve)**

Sampling of Node
Challenges

Assay samples whole piece – not just "representative" sections



Probable results:

Both + (assay is considered TP)

Only assay + (assay is considered FP)

Only histology + (assay is considered FN)

Only assay + (assay is considered FP)

Histology vs. histology (sampling error)

- **100% detection of macrometastases within sentinel nodes analysed**

What's the difference?

- Introduction of SLN cut the axillary dissection rate to 27% of breast cancer patients in Portsmouth
- Introduction of intra-operative PCR assessment of SLN reduced breast cancer operations by 21%
- Saves patients the risk and anxiety, and the hospital the cost of second operations
- If combined with intra-operative radiotherapy, complete treatment could be done more rapidly, with the exception of adjuvant therapy – which could be hormonal only in many stage 1 patients.

Cutress RI, et al. J Clin Pathol 2010; 63: 522-529

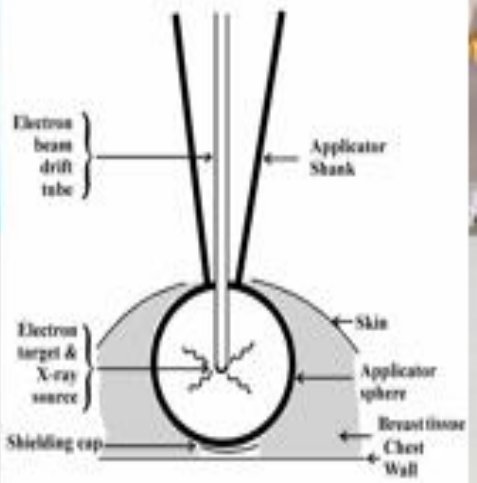
Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial

Jayant S Vaidya, David J Joseph, Jeffrey S Tobias, Max Bulsara, Frederik Wenz, Christobel Saunders, Michael Alvarado, Henrik L Flyger, Samuele Massarut, Wolfgang Eiermann, Mohammed Keshtgar, John Dewar, Uta Kraus-Tiefenbacher, Marc Sütterlin, Laura Esserman, Helle M R Holtveg, Mario Roncadin, Steffi Pigorsch, Marinos Metaxas, Mary Falzon, April Matthews, Tammy Corica, Norman R Williams, Michael Baum

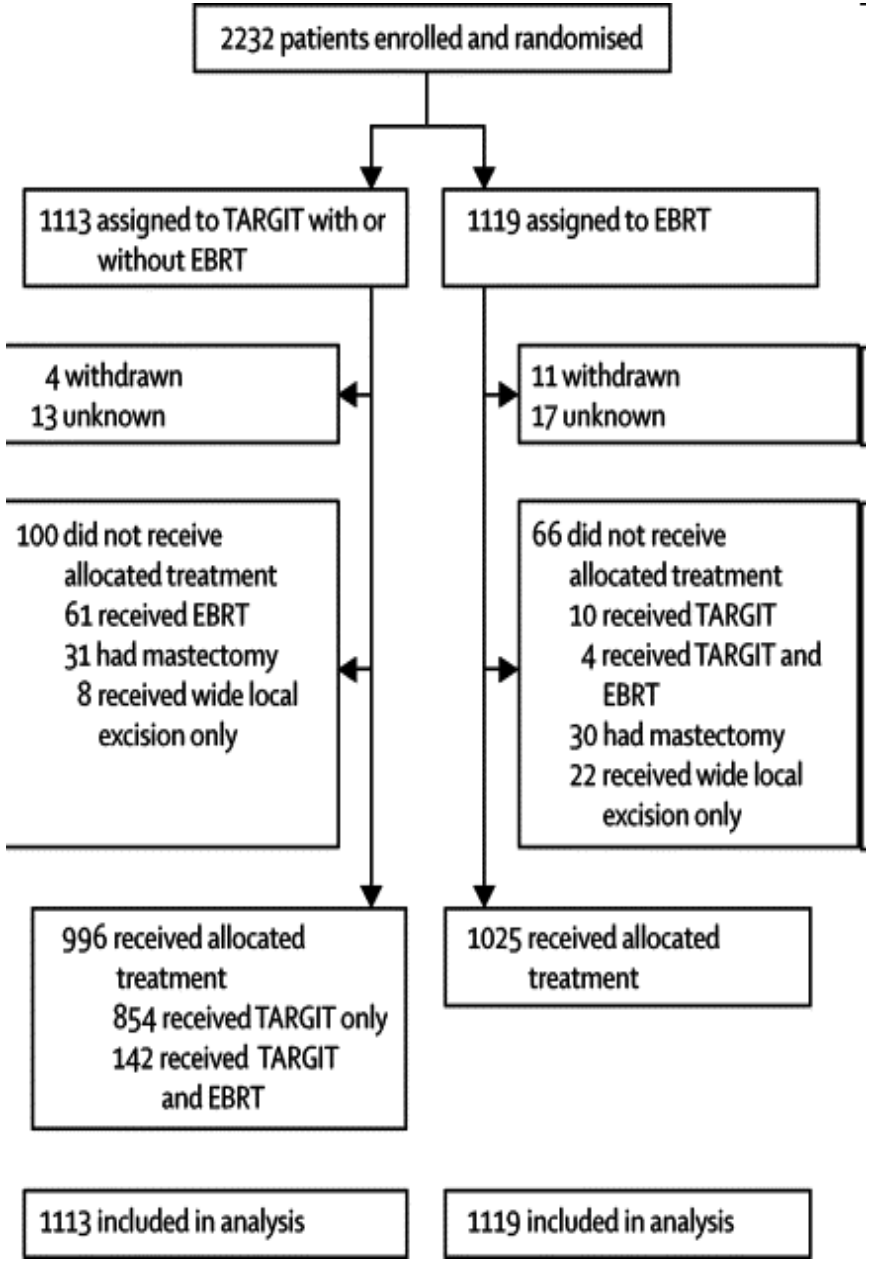
Lancet 2010; 376: 91–102

Interpretation For selected patients with early breast cancer, a single dose of radiotherapy delivered at the time of surgery by use of targeted intraoperative radiotherapy should be considered as an alternative to external beam radiotherapy delivered over several weeks.

Targeted Intraoperative Radiotherapy for Breast Cancer



Vaidya JS et al. Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. BMJ 2020 Aug 19;370:m2836. doi: 10.1136/bmj.m2836. PMID: 32816842



	Targeted intraoperative radiotherapy (n=1113)	External beam radiotherapy (n=1119)
Number of complications per patient		
0	917 (82·4%)	946 (84·5%)
1	151 (13·6%)	139 (12·4%)
2	29 (2·6%)	27 (2·4%)
3	11 (1·0%)	5 (0·4%)
4	3 (0·3%)	0
5	2 (0·2%)	0
6	0	3 (0·3%)
Any complication*	196 (17·6%)	174 (15·5%)

Data are number of patients (%). *χ^2 1·74, p=0·19 comparison between the targeted intraoperative radiotherapy and external beam radiotherapy groups for no complications versus any number of complications, degree of freedom 1.

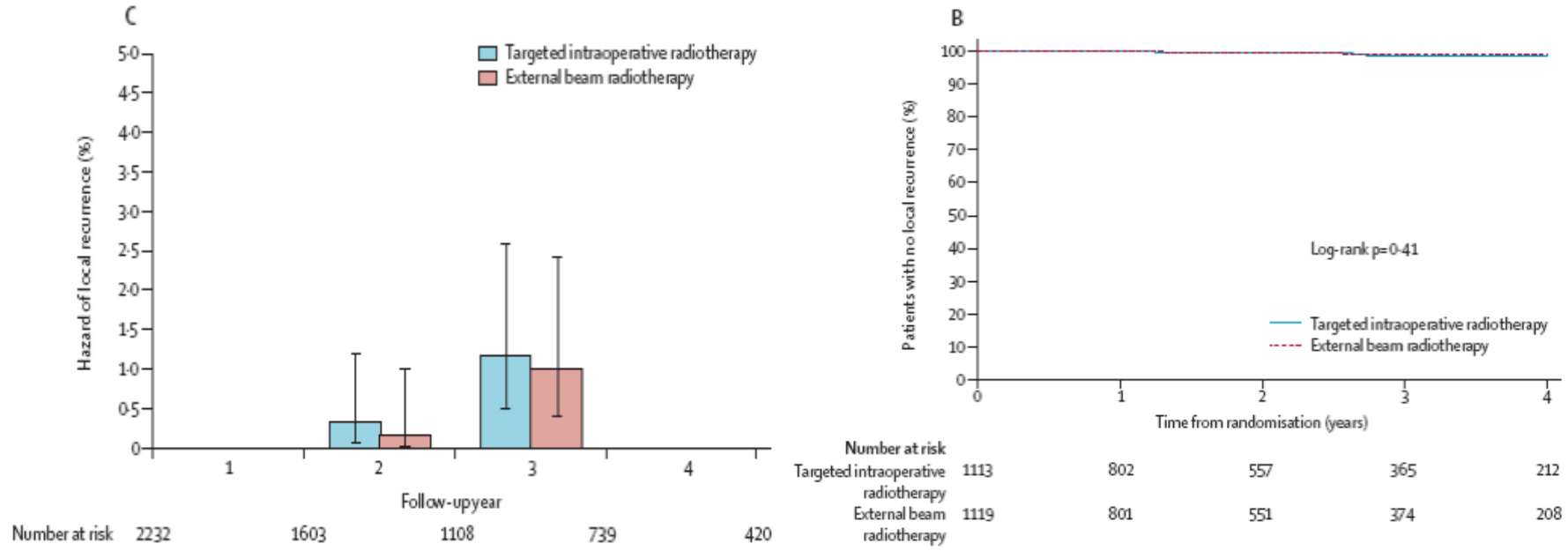
Table 4: All complications

Vaidya JS et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet. 2010 Jul 10;376(9735):91-102. doi: 10.1016/S0140-6736(10)60837-9.PMID: 20570343

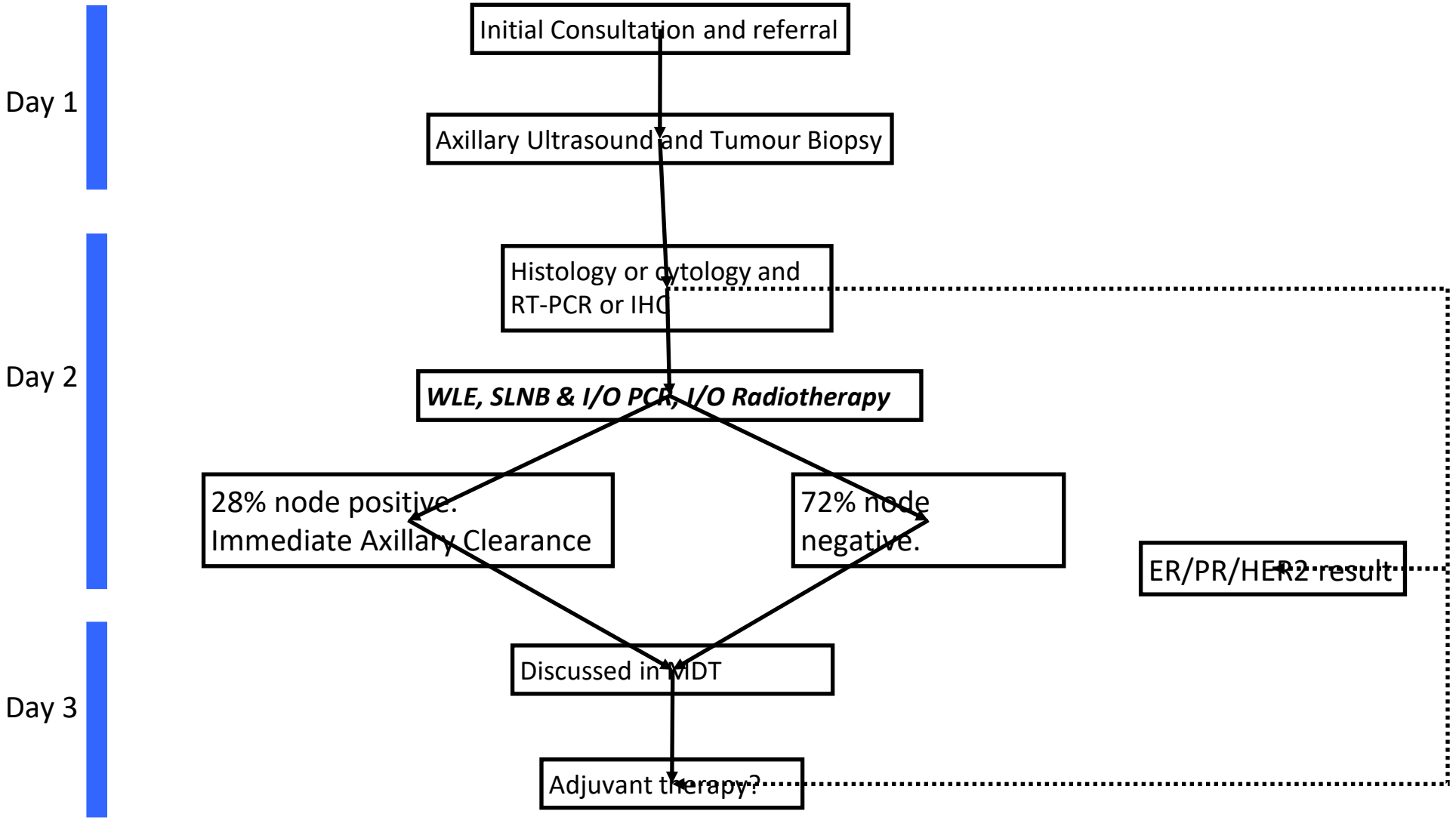
	Targeted intraoperative radiotherapy (n=1113)	External beam radiotherapy (n=1119)	p value
Haematoma needing surgical evacuation	11 (1·0%)	7 (0·6%)	0·338
Seroma needing more than three aspirations	23 (2·1%)	9 (0·8%)	0·012
Infection needing intravenous antibiotics or surgical intervention	20 (1·8%)	14 (1·3%)	0·292
Skin breakdown or delayed wound healing*	31 (2·8%)	21 (1·9%)	0·155
RTOG toxicity grade of 3 or 4†	6 (0·5%)	23 (2·1%)	0·002
Major toxicity‡	37 (3·3%)	44 (3·9%)	0·443

Data are number of patients (%). RTOG=Radiation Therapy Oncology Group. *Some of the patients in the first three rows (haematoma needing surgical evacuation, seroma needing more than three aspirations, infection needing intravenous antibiotics or surgical intervention) could be included in the fourth row (skin breakdown or delayed wound healing). †No patient had grade 4 toxicity. ‡Defined as skin breakdown or delayed wound healing and RTOG toxicity grade of 3 or 4).

Table 5: Clinically significant complications



Vaidya JS et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet. 2010 Jul 10;376(9735):91-102. doi: 10.1016/S0140-6736(10)60837-9.PMID: 20570343


Day 1
Day 2
Day 3
Initial Consultation and referral
Axillary Ultrasound and Tumour Biopsy
Histology or cytology and
RT-PCR or IHC
WLE, SLNB & I/O PCR, I/O Radiotherapy
28% node positive.
Immediate Axillary Clearance
72% node
negative.
ER/PR/HER2 result
Discussed in MDT
Adjuvant therapy?

Conclusions

- Implementation of any test needs careful planning and a comprehensive team approach.
- Laboratories do not act in isolation - so engage with users, including patients, as necessary.
- Continuous improvement is the key - make a change, then audit the results and be prepared to alter your approach.
- Make use of the experience of others - from guidelines, reviews, and EQA schemes.
- The breast cancer example given uses results from large clinical trials, but may not be applicable in all centres, where other clinical pathways or methods may be in use.


Thank you!