CLINICAL UTILITY OF MOLECULAR SIGNATURES

The Emperor's New Clothes?

Rob Stein
DISCLOSURES

• CI of OPTIMA study (uses Prosigna)
  • No financial support of any description from NanoString Inc or any other commercial entity involved in multi-parameter testing
• Provided clinical advice to ScHARR (External Assessment Report for NICE DG10 update)
  • No involvement in the data analysis or conclusions
UTILITY OF MULTI-PARAMETER TESTS

- Improving prognostic information to aid decision making
  - Chemotherapy use
  - (Endocrine therapy duration)
- Predicting treatment benefit
PROGNOSIS AND PREDICTION

• Prognostic factors give information about likely disease outcome
  • lymph node status
• Predictive factors give information about treatment response
  • BRCA mutation & PARP inhibitor therapy
• Some factors are both prognostic and predictive
  • ER & HER2 status
“There is not enough evidence to recommend the routine adoption of EndoPredict, MammaPrint, Oncotype DX Breast Recurrence Score, Prosigna and IHC4+C to guide adjuvant chemotherapy decisions for people with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer with 0 to 3 positive lymph nodes. In particular, more evidence is needed to prove that these tests have a positive effect on patient outcomes. Their cost effectiveness compared with current practice is highly uncertain.”

NICE DG10 update consultation (Jan 2018)
THE LANDSCAPE OF MULTI-PARAMETER TESTS
## MULTI-PARAMETER ASSAYS IN UK & EUROPE

<table>
<thead>
<tr>
<th>Test</th>
<th>Parameters</th>
<th>1(^\circ) Validation</th>
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<tbody>
<tr>
<td>Oncotype DX</td>
<td>16 +5 genes RT-PCR</td>
<td>ER+ (pN0) +ET</td>
<td>Central/ USA</td>
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<tr>
<td>MammaPrint</td>
<td>70 genes array</td>
<td>ER+/-(pN0-1)</td>
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<tr>
<td>IHC4</td>
<td>4 proteins IHC4</td>
<td>ER+ HER2- (pN0-2) +ET</td>
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MPA TESTS ARE ANALYTICALLY "UNIQUE"

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<td>GUS</td>
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<td>PEC1</td>
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# MULTI-PARAMETER ASSAYS OUTPUTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Includes clinical data?</th>
<th>Output</th>
<th>Time horizon</th>
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<tbody>
<tr>
<td>Oncotype DX</td>
<td>No (RSPC optional)</td>
<td>rec score &amp; risk category</td>
<td>10yr DDFS</td>
</tr>
<tr>
<td>MammaPrint</td>
<td>No</td>
<td>risk category</td>
<td>10(5)yr DDFS</td>
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<tr>
<td>Prosigna (PAM50)</td>
<td>Integral pT &amp; pN</td>
<td>rec score &amp; risk category subtype</td>
<td>10yr DDFS</td>
</tr>
<tr>
<td>EndoPredict</td>
<td>Integral clin score</td>
<td>rec score &amp; risk category</td>
<td>10yr DDFS</td>
</tr>
<tr>
<td>IHC4</td>
<td>Integral clin score</td>
<td>rec score &amp; risk category</td>
<td>10yr DDFS</td>
</tr>
</tbody>
</table>
BENEFIT OF ANTHRACYCLINE CHEMOTHERAPY IN EARLY BREAST CANCER


![Graph showing recurrence rates over time for women with early breast cancer, comparing those who received chemotherapy and those who did not.](image)

- 8575 women
- 82% node+ve
- 34.6% recurrence with no chemotherapy at 10 years
- 39.4% recurrence with chemotherapy at 10 years
- 8.0% gain in recurrence-free survival at 10 years

# OTHER MULTI-PARAMETER ASSAYS

<table>
<thead>
<tr>
<th>Test</th>
<th>Parameters</th>
<th>Output</th>
<th>Time horizon</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCI (central, USA)</td>
<td>7 gene RT-PCR</td>
<td>rec score &amp; risk category</td>
<td>5 &amp; 10yr DDFS</td>
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<tr>
<td>NPI plus (in development)</td>
<td>10 protein IHC</td>
<td>subtype</td>
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<tr>
<td>OICR 95 gene (in development)</td>
<td>95 gene NanoString</td>
<td>rec score</td>
<td>5 &amp; 10yr DDFS</td>
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<tr>
<td>MammaTyper (central, DE)</td>
<td>4 gene RT-PCR</td>
<td>subtype</td>
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MOLECULAR SIGNATURES AS PROGNOSTIC TESTS
A CASE OF UNCERTAINTY UNRESOLVED

• 46 yr old GP referred for 2nd opinion re adjuvant chemo - 11mm node-negative G3 ductal carcinoma, ER-pos, HER2 neg – NPI score 4.2

• PREDICT v2.0 – 10yr OS 84.9%, ET benefit +3.7%, 3gen chemo benefit +2.9%

• Oncotype DX RS = 21 – 10yr DDFS with tam for 5 yrs 86%
  • Benefit of 3G chemo = c.+4.5% (makes various untestable assumptions)
  • Benefit of CMF chemo from report = c.+3% - translates into 3gen benefit ?+5%

• Oncotype DX RSPC – 10yr DDFS with tam for 5yrs 81% (with AI 84%)
  • Benefit of 3G chemo = c.+6% (makes various untestable assumptions)

• Final decision = no chemo, OFS + AI + bisphosphonate
<table>
<thead>
<tr>
<th>Test</th>
<th>Data sets</th>
<th>Patient group &amp; treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncotype DX</strong></td>
<td>7 RCT re-analysis</td>
<td>ER+ve (included HER2+) +ET</td>
</tr>
<tr>
<td></td>
<td>2 prospective cohort (no chemo)</td>
<td>6 studies included a no chemo group</td>
</tr>
<tr>
<td></td>
<td>4 retrospective cohort</td>
<td></td>
</tr>
<tr>
<td><strong>MammaPrint</strong></td>
<td>1 prospective RCT</td>
<td>ER+/± ET</td>
</tr>
<tr>
<td></td>
<td>1 RCT re-analysis</td>
<td>5 studies included a no chemo group</td>
</tr>
<tr>
<td></td>
<td>10 retrospective cohort</td>
<td></td>
</tr>
<tr>
<td><strong>Prosigna (PAM50)</strong></td>
<td>6 RCT re-analysis</td>
<td>ER+ve, +ET</td>
</tr>
<tr>
<td></td>
<td>3 retrospective cohort</td>
<td>5 studies included a no chemo group</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td><strong>EndoPredict</strong></td>
<td>3 retrospective cohort</td>
<td>ER+ve, +ET</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 studies included a no chemo group</td>
</tr>
<tr>
<td><strong>IHC4</strong></td>
<td>6 RCT re-analysis</td>
<td>ER+ve, +ET</td>
</tr>
<tr>
<td></td>
<td>6 routine data</td>
<td>2 studies included a no chemo group</td>
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ONCOTYPE DX: RS AS CONTINUOUS PREDICTOR IN TAM TREATED PATIENTS

data from NSABP B14: Paik NEJM 2004, 351:2817
RISK OF RECURRENCE IS INFLUENCED BY BOTH TUMOUR BIOLOGY AND STAGE

Nottingham Prognostic Index = sum of:
- grade (grade 1 =1, grade 2 =2, grade 3 =3)
- node status (0 nodes =1, 1-3 nodes =2, ≥4 nodes = 3)
- tumour diameter (cm) x 0.2

Overall Survival (Kaplan–Meier) by NPI in the ONCOPOOL data set

To a 1st approximation tumour grade and stage are independent and equal risk factors

the first multi-parameter test

INFLUENCE OF NODAL STATUS ON ENDOPredict RISK SCORE

928 patients from transATAC

EPClin = combined EP score + node status + tumour size

Combined analysis of ABCSG-8 and ATAC using PAM50 intrinsic subtype

Gnant, Ann Oncol 2015; 26:1685
PROGNOSTIC VALUE OF INTRINSIC SUBTYPES ACCORDING TO NODE STATUS

Additional prognostic information of luminal A versus luminal B compared with Clinical Treatment Score alone as difference in log-likelihood ($\Delta LR \chi^2$)

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<th>Patients</th>
<th>Events</th>
<th>$\Delta LR \chi^2$</th>
<th>p-Value</th>
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<td>26.10</td>
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<td>1N+</td>
<td>320</td>
<td>42</td>
<td>12.16</td>
<td>0.0005</td>
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<td>2–3N+</td>
<td>201</td>
<td>45</td>
<td>8.58</td>
<td>0.0034</td>
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<tr>
<td>1–3N+</td>
<td>521</td>
<td>87</td>
<td>20.48</td>
<td>&lt;0.0001</td>
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Combined analysis of ABCSG-8 and ATAC using PAM50 intrinsic subtype

after Gnant, Ann Oncol 2015; 26:1685
• TAILORx pN0 cohort study (RS <11) Sparano 2015 NEJM 373:2005
• PlanB pN0-1 (RS ≤11) Nitz 2017 BCRT 165:573

• Excellent outcome: confirms prognostic utility of ODX (small pN1 cohort)

TAILORx Five-year DFS pN0 (n=1626) 93.8% [92.4–94.9%]
PlanB Five-year DFS ET alone: pN0 (n=238) 94.2% [90.4–98.0%]; pN1 (n=110) 94.4%;[89.5–99.3%]
DEcision Impact
The Emperor’s New Clothes

Oncologists' Pre-Test and Post-Test Recommendations for Chemotherapy and Actual Treatment (Oncotype DX)

972 Patients from Ontario - 92% pN0/ 7% pN1mi
9.7% more/ 18% less chemo advised
after Levine 2016 J Clin Oncol 34:1065

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>N (%)</th>
<th>Actual Treatment</th>
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<td>No post-test</td>
<td>370 (85)</td>
<td>46 (73)</td>
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<tr>
<td>Yes pretest</td>
<td>63 (15)</td>
<td>17 (27)</td>
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<tr>
<td>Yes post-test</td>
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<td>17 (27)</td>
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<td>Yes pre-test</td>
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<td>77 (82)</td>
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<td>No post-test</td>
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<td>115 (98)</td>
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<td>No post-test</td>
<td>249 (76)</td>
<td>9 (3.6)</td>
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<tr>
<td>Yes post-test</td>
<td>79 (24)</td>
<td>67 (85)</td>
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- Demonstrate that clinicians believe in the tests
- Consistently show change in treatment recommendation (less chemo)
- Vulnerable to unregulated information from commercial interests
- Only meaningful if include disease outcome data
AGREEMENT BETWEEN MULTI-PARAMETER TESTS

Do the tests tell us the same thing?
DIFFERENT SIGNATURES PROVIDE SIMILAR AMOUNTS OF INFORMATION

ROC Curves for “In Silico” Signatures from TEAM Pathology Study

from Bayani 2017 npj Breast Cancer 3:3
AGREEMENT BETWEEN TESTS FOR INDIVIDUAL TUMOURS IN OPTIMA PRELIM

Oncotype DX25 vs. Prosigna

HR = pre-defined “high risk” boundary
LR = pre-defined “low risk” boundary

Stein 2016 Health Technol Assess 20(10)
Bartlett 2016 J Natl Cancer Inst 108(9)
### 2 X 2 Comparisons Between Tests in Optima Prelim (High vs Not High Risk)

<table>
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<tr>
<th>Test</th>
<th>Prosigna (ROR_PT)</th>
<th>MammaPrint</th>
<th>IHC4</th>
<th>IHC4 - AQUA</th>
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<td>%</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>High risk</td>
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<td>N=297</td>
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<td>&quot;Low&quot; risk</td>
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<td>19</td>
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<td>High risk</td>
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<td>15</td>
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<td>Prosigna ROR_PT</td>
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<td>&quot;Low&quot; risk</td>
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<td>54</td>
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<td>High risk</td>
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## Kappa Stats for Tests Providing Risk Predictions (High vs Not High)

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<th>Kappa statistic (95% confidence interval)</th>
<th>Prosigna (Low/Int)</th>
<th>MammaPrint (Low)</th>
<th>IHC4 (Low/Int)</th>
<th>IHC4-AQUA (Low/Low-Mid)</th>
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<tbody>
<tr>
<td>Oncotype DX ≤25 (OPTIMA low risk)</td>
<td>0.45 (0.34-0.55)</td>
<td>0.40 (0.30-0.50)</td>
<td>0.52 (0.40-0.64)</td>
<td>0.41 (0.31-0.52)</td>
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<tr>
<td>Prosigna (Low/Int)</td>
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<td>0.53 (0.43-0.63)</td>
<td>0.39 (0.27-0.50)</td>
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DO MOLECULAR SIGNATURES PREDICT CHEMOTHERAPY BENEFIT?
BENEFIT OF ANTHRACYCLINE CHEMOTHERAPY IN EARLY BREAST CANCER

8575 women
82% node+ve

Recurrence (%)

No Chemotherapy

Chemotherapy

Time (years)

34.6%
26.1%
47.4%
39.4%

8.0% gain at 10yrs

BREAST CANCER CHEMO-SENSITIVITY: THE OXFORD META-ANALYSIS

• Oxford Overview demonstrates that patients with ER-positive breast cancer benefit from adjuvant chemotherapy.

• The relative benefits for chemotherapy are the same for all patients.

• No identified factors including ER status predict chemo-sensitivity.
  • Little information on tumour grade in the analysis

• The overall benefit from chemotherapy is modest
  • Patients not destined to relapse cannot benefit
NSABP B-20 – ONCOTYPE DX SUBPOPULATION

N –ve, ER+ve

651/2299 patients
45% < 50

Tam + MF
Tam + CMF
Tam

Chemotherapy arms combined in this analysis

4.4% absolute benefit from tam + chemo at 10 yrs

Patients & outcome consistent with full B-20 population

N       Events
424        33
227        31

P = 0.02
B-20 RESULTS: RELATIVE BENEFIT OF CHEMO ON 10 YEAR DDFS

Issues: 1. Patients in the tamoxifen only arm were included in the Oncotype DX derivation studies
   2. There were undoubtedly patients with HER2-positive tumours included in this study. This data has not been disclosed
It is difficult to estimate the effect of these issues on the conclusions of the study but they do detract from the credibility.
SWOG-8814: DFS by Recurrence Score—Prediction of Benefit from CAF + TAM vs TAM

367 blocks from tam & CAF-T arms (=40% of parent trial), demographics representative of parent;
227 pN1, 140 pN2; 43 tumours (12%) HER2-positive by Oncotype testing

**Low (RS <18)**
- CAF-Tam
- Stratified log-rank $p = 0.97$ at 10 years

**Intermediate (RS 18-30)**
- Tam only
- CAF-Tam
- Stratified log-rank $p = 0.48$ at 10 years

**High (RS ≥31)**
- Tam only
- CAF-Tam
- Stratified log-rank $p = 0.033$ at 10 years

Results suggest that high RS tumours are disproportionally sensitive to chemo

after Albain 2010 Lancet Oncol 11:55-65
I can see your error bars using Google Earth.
PROSPECTIVE CLINICAL TRIALS
EORTC-BIG MINDACT TRIAL DESIGN

6,693 women enrolled: 79% pN0, 81% ER-pos HER2-neg

Evaluate Clinical-Pathological (AoL) risk and MammaPrint risk

41% (10%) Clinical-pathological and 70-gene both LOW risk
N=2745

32% (35%) Discordant
Clin-Path HIGH 70-gene LOW | 72% N=1550
Clin-Path LOW 70-gene HIGH | 28% N=592

27% (55%) Clinical-pathological and 70-gene both HIGH risk
N=1806

Use Clin-Path risk to decide Chemo or not
Use 70-gene risk to decide Chemo or not

N=2187
MINDACT RESULTS

• Complex trial, heterogeneous pop (10% TNBC, 9.5% HER2 pos; 21% pN1)
• Insufficient power to compare randomised groups
• Primary EP = 95% chance of 5-yr DDFS >92% for genomic low/ clin high no chemo group: **achieved**

• Genomic low/ clin high risk 5yr DMFS Δ chemo vs not = 1.5%
• Genomic high/ clin low risk 5yr DMFS Δ chemo vs not = 0.8%
• All chemo vs not p NS

• Error in risk assessment affected 16% genomic high/ clin low

Cardoso 2016 NEJM 375:717
TAILORx & RxPONDER SCHEMA

**TAILORx:** pN0, ER-pos Her2-neg Breast Cancer

- Register Specimen banking
- **Oncotype DX® Assay** → unblinded
- **RS <11**
  - **Endocrine Rx Registry**
- **RS 11-25:** Randomize
  - Endocrine Rx vs Chemo + Endocrine Rx
- **RS >25**
  - Chemo + Endocrine Rx

**RxPONDER:** pN1, ER-pos Her2-neg Breast Cancer

- Register Specimen banking
- **Oncotype DX® Assay** → unblinded
- **RS 0-25:** Randomize
  - Endocrine Rx vs Chemo + Endocrine Rx
- **RS >25**
  - Chemo + Endocrine Rx

Onco type DX® Assay Register Specimen banking
TAILORx (RCT) & RxPONDER

• TAILORx randomised study (RS 11-25) chemo + endocrine therapy vs endocrine therapy
  • ? Will report 2018 – median f.u. c.10 years
  • Majority (75%+ ?) NPI score <3.4 (low-risk)
  • Very low event rate – analysis planned for 2015
  • Most late events (>5yrs) not influenced by chemo

• RxPONDER randomised study (RS 0-25)
  • Same design & issues as TAILORx randomised study
  • ? Will report 2020
OPTIMA MAIN STUDY DESIGN

1° Outcome = Non-inferiority of IDFS (Δ=-3%)
Cost effectiveness evaluation of test-directed treatment

key 2° Outcome = Non-inferiority of IDFS in low-risk patients (Δ=-3.5%)

Sample size = 4500 patients (+ OPTIMA prelim)  Recruitment period = 46 months
commenced Jan 2017

Female or Male
age ≥40
post 1° excision
ER pos, HER2 neg
pN1-2/ pN1mi & pT≥20
/pN0 & pT ≥30

Option 1
(control)

Option 2
(research)

R

treatment
assigned by score

high score
ROR ≥61

ROR<61

low score

blinded to randomisation

chemo. → endocrine

chemo. → endocrine

endocrine

chemo.

Prosigna

Estimated 65% of tumours are Prosigna low-score
CONCLUSIONS

• The totality of information supports the clinical utility of the molecular signatures (The Emperor is clothed)
  • The best evidence is for prognosis in node-negative disease
  • Limited evidence supports prognostic use in pN1 disease
  • Reliable prognostic tests for pN1 disease require stage information
  • Because of the contribution of nodal status to risk, the tests have limited utility for pN1 disease
  • Current data suggest that the tests may predict chemotherapy sensitivity
• The diversity of the tests and the validation studies is problematic
• If there is a best test we do not know which it is
MOVING FORWARDS

- Re-calibrating test output would assist clinician & patient decision-making
  - 5 & 10 year DDFS
  - 10 year BCSS
- The development of user-friendly risk assessment tools would be a major advance
  - Incorporation of results into PREDICT / AoL would be a major advance
  - This presents formidable obstacles
- More regulation is required for the diagnostics industry
Chemotherapy pre-specified from a menu of regimens stratified by efficacy.

Chemotherapy allocation blinded to avoid potential bias in chemo administration.

Endocrine therapy: standard
- AI for post-menopausal,
- tam for men
- OS + tam/AI for pre-menopausal at trial entry

Adjuvant bisphosphonates recommended for all.

Patients may join other studies – e.g. AddAsprin
• 300 patient feasibility study for OPTIMA
• Establish acceptability of randomisation to patients & clinicians.
• Evaluate the performance and health-economics of alternative multi-parameter tests
ASSUMPTIONS UNDERPINNING OPTIMA

• Multi-parameter assays predict chemotherapy sensitivity

• Tumour stage is prognostic for all patients irrespective of multi-parameter assay score

• Advanced stage patients with poor prognosis will not benefit from chemotherapy if the tumour has a low multi-parameter assay score

  • Example – few patients multi-node positive low molecular grade tumours will benefit from chemotherapy
1. To establish a method of selecting patients with hormone sensitive primary breast cancer who are likely to benefit or not benefit from post-operative chemotherapy.

2. To establish the cost-effectiveness of alternative test-guided treatment strategies compared to standard practise.
Main Inclusion Criteria
• “Adequate surgery”
• Age ≥40
• ER-pos HER2-neg (local lab)
• pN1-2/ pN1mi & T≥20mm / pN0 & T≥30mm
• Fit for chemotherapy

Main Exclusion Criteria
• Advanced stage – pN3/ IM node involvement
• Neoadjuvant therapy
• Previous IBC – surgically treated DCIS permitted
Feasibility study for OPTIMA – completed recruitment summer 2014 (412 patients)

Used Oncotype DX as primary discriminator

Integral pathology study and economic analysis conducted on 313 patients/tumours designed to select MPA for main study

Qualitative Recruitment Study (MRC Conduct II Hub)
## Kappa Stats for Agreement Between Tests (by Risk Category)

<table>
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<tr>
<th>Kappa statistic (95% confidence interval)</th>
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<th>IHC4-AQUA (Low/Low-Mid)</th>
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