Application of molecular genetics in the clinical management of breast cancer

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20th Annual Controversies and Problems in Surgery
Disclosure

Director and shareholder of Gknowmix (Pty) Ltd. –
developed a database tool for research translation
Precision Medicine

• The ability to identify subgroups that differ in their
  • genetic susceptibility to cancer development
  • response to anti-cancer treatment

Today’s medicine challenge: One size doesn’t fit all

Patients are different

Medicines are not differentiated

~ 30% of patients do not benefit from medicines¹ (100,000 deaths and 2.2 million nonfatal events from ADR in the US in 1994)

¹ JAMA 1998, 279: 1200

Source: Bayer HealthCare Diagnostics and Burrell & Company
Will Genomically Informed Cancer Care Be Better for Patients?

What does this profile mean in terms of my cancer care?

Discuss Your Profile Here

Customized Care

Artwork by Joanne Kelly © 2008.
Many genetic tests available

Target Group

But risk not determined by genetics alone

Treatment Options
### Our Experience

*Shift in clinical paradigms from treating cancers of a specific type to treating cancers with specific genetic alterations*

<table>
<thead>
<tr>
<th>TEST NAME</th>
<th>TEST CRITERIA</th>
<th>TEST BENEFIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA Test &amp; exome sequencing</td>
<td>Strong family history Early onset of cancer</td>
<td>Determine risk of 2\textsuperscript{nd} (bilateral) cancer Pre-symptomatic diagnosis for cancer prevention in at-risk relatives</td>
</tr>
<tr>
<td>MammaPrint &amp; BLuePrint</td>
<td>Stage I-II Nodes 0-3 Tumour size ≤5cm ER/PR-positive HER2 –negative No adjuvant treatment</td>
<td>Safe avoidance of chemotherapy in patients with early-stage breast cancer Predict drug response based on functional pathways of intrinsic subtypes: Luminal A&amp;B, HER2-enriched and basal</td>
</tr>
<tr>
<td>OncoDEEP &amp; Trace</td>
<td>Drug resistance Metastasis</td>
<td>Gene targeted treatment based on individualised tumour DNA sequencing</td>
</tr>
</tbody>
</table>
Insurance companies may not request a genetic test.

(Kotze et al. 2005, SA Fam Pract 2005;47: 38-40)
Moving from single to multi-gene genetic tests
Microarray covers all critical cancer pathways

- **LOW RISK**
  - 97% chance of survival after 10 years and **87%** chance to be metastasis free after 10 years without adjuvant treatment

- **HIGH RISK**
  - less than 50% chance of survival after 10 years and less than **44%** chance to be metastasis free after 10 years without adjuvant treatment
Molecular signatures are becoming increasingly important for anticipating the prognosis of individual patients ('prognostic' biomarkers) or for predicting how individual patients will respond to specific treatments ('predictive' biomarkers, more generally called 'treatment-effect modifiers'). A voluminous literature of >150 000 papers documenting thousands of claimed biomarkers has been produced in medicine of which fewer than 100 have been validated for routine clinical practice [1]. Indeed, <20 prognostic or predictive biomarkers are recognized with variable levels of evidence in the 2014 European Society of Medical Oncology (ESMO) clinical practice guidelines for lung, breast, colon and prostate cancer [2].

In early breast cancer, while several clinical prediction models exist based on clinical and pathological (CP) characteristics, such as age, tumor size, nodal status, tumor grade, estrogen receptor, at least six different gene signatures are commercially available (OncoType DX, MammaPrint, Genomic Grade Index, PAM50, Breast Cancer Index and EndoPredict). The concordance of predicted risk categories of the different gene signatures for individual patients is moderate [3, 4], as illustrated by recent OPTIMA study which evaluated—among others—the two well-known Mammaprint (low/high) and OncoType Dx (<23 versus >25) on 302 patients in a head-to-head comparison and found a low level of agreement, i.e. a kappa value of 0.40 (95% CI 0.30–0.49) [5]. Of course, even when repeating the same assay twice on a single tumor sample, the stringent degree of concordance would be expected but unlikely to this extent. This has led to a pretty awkward situation where the treatment decision for adjuvant chemotherapy does not depend anymore on the clinician but on the genomic test ordered. Furthermore, according to a European consensus panel, none of these tests reached the highest level of evidence [6] and according to an Evaluation of Genomic Applications in Practice and Prevention (EGAPP) panel, there was only indirect evidence that Oncotype Dx could predict benefit from chemotherapy [7], while an ASCO panel in the United States gave a strong recommendation with high level of evidence that Oncotype Dx may be used to guide decisions on adjuvant systemic chemotherapy for node-negative (N0) ER-positive (ER+), HER2-negative (HER-) breast cancer [8]. This divergence may result from the degree of subjectivity in evidence evaluation or from a different vision of what type of evidence is needed for a gene signature to be clinically useful. In this commentary, we focus on prognostic and predictive gene expression signatures in breast cancer to highlight the difficult path from the laboratory to the clinic, but the concepts are applicable to other omics data.

Table 1. Evidence-based criteria for a prognostic gene signature in the path from the laboratory to clinical practice

<table>
<thead>
<tr>
<th>No.</th>
<th>Concept</th>
<th>Elaboration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Proof of concept</td>
<td>Do signature levels differ substantially between patients with and without outcome?</td>
</tr>
<tr>
<td>2</td>
<td>Analytical validity</td>
<td>Signature’s ability to accurately and reliably measure the genotype of interest between and within laboratories</td>
</tr>
<tr>
<td>3</td>
<td>Clinical validity</td>
<td>Does the signature predict risk of outcome in multiple external cohorts or nested case-control/cohort studies?</td>
</tr>
<tr>
<td>4</td>
<td>Incremental value</td>
<td>Does the signature add enough information to established clinico-pathological prognostic markers or provide a more reproducible measurement of one of them?</td>
</tr>
<tr>
<td>5</td>
<td>Clinical impact</td>
<td>Does the signature change predicted risk sufficiently to change recommended therapy?</td>
</tr>
<tr>
<td>6</td>
<td>Clinical utility</td>
<td>Does use of the signature improve clinical outcome, especially when prospectively used for treatment decisions in a randomized controlled trial?</td>
</tr>
<tr>
<td>7</td>
<td>Cost-effectiveness</td>
<td>Does use of the signature improve clinical outcome sufficiently to justify the additional costs of testing and treatment?</td>
</tr>
</tbody>
</table>
“At present, most oncologists make recommendations for adjuvant chemotherapy after considering common clinical and biological criteria such as patient’s age, and the stage and grade, as well as the hormonal receptor and HER2 status of his or her tumor,” said Martine Piccart, MD, PhD, head of the Medicine Department at the Jules Bordet Institute in Brussels, Belgium, and co-founder and chair of the Breast International Group (BIG). “The MINDACT trial results provide level 1A evidence that using MammaPrint could change clinical practice by substantially de-escalating the use of adjuvant chemotherapy and sparing many patients an aggressive treatment they will not benefit from.”
MINDACT
Chemotherapy Benefit Prediction

- Clinically high risk patients with a MammaPrint low risk profile -
  Including 48% 1-3LN+
  - distant metastasis free survival (DMFS) at 5 years of 94.7% without chemotherapy

- Intention-to-treat analysis
  - no statistically significant difference in DMFS between those randomized to chemotherapy vs no chemotherapy

- Noted a small numerical difference of 1.5%
  - did not meet statistical significance, but even if real, is below the threshold of benefit for chemotherapy

- Compared to DMFS, other endpoints such as DFS and OS
  - not indicative of the utility of a molecular assay designed to predict risk of metastatic disease
MINDACT

- **CLow + MPLow - 97.6%**
- **Discordant - 95%**
- **Chigh + MPHigh - 90.6%**

**Table:**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low clinical and genomic risk</td>
<td>2745</td>
</tr>
<tr>
<td>Low clinical, high genomic risk</td>
<td>592</td>
</tr>
<tr>
<td>High clinical, low genomic risk</td>
<td>1550</td>
</tr>
<tr>
<td>High clinical and genomic risk</td>
<td>1806</td>
</tr>
</tbody>
</table>

*Figure 3. Survival without Distant Metastasis in the Four Risk Groups.*

*C = Clinical risk, MP = MammaPrint genomic risk*
Application of advanced molecular technology in the diagnosis and management of genetic disorders in South Africa

M J Kotze, PhD

Division of Chemical Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University and the National Health Laboratory Service, Tygerberg Hospital, Cape Town, South Africa

Understanding the molecular characteristics of both tumour and host genetics is critical to establishing their relationship with drug response and epigenetic processes underlying the development of cancer and many other chronic diseases. Nearly 100 genes have been identified that, if mutated, will convert a normal breast cell into a breast cancer cell. The influence of germline mutations on tumour pathology is particularly strong between mutations in the BRCA1 gene and the basal-type breast cancer. This subtype usually tests negative for ER, progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2), and is, therefore, called triple-negative breast cancer (TNBC). ER, PR and HER2 status provide useful parameters for selecting patients eligible for transcriptional genotyping, as evidenced in SA breast cancer patients released for microarray analysis. Pohl et al. demonstrated a change in chemotherapy treatment in 52% of SA patients with early-stage breast cancer by using a newly developed microarray pre-screen algorithm to facilitate risk assessment beyond standard pathology and clinical prediction models.

While detection of germline mutations in the BRCA1/2 genes is associated with a high risk for local or contralateral recurrence of breast cancer, microarray-based assessment of tumour genetics determines risk of distant recurrence (70-gene profile); and simultaneously enables subtyping of breast cancer into four treatment groups (80-gene profile): Luminal A, Luminal B, HER2-enriched and the basal-type. Owing to the ability of microarrays to distinguish between HER2-positive breast cancer of the Luminal B and HER2-enriched subtypes, our testing algorithm has now been extended to help resolve equivocal, borderline and contradictory pathology results prior to selection of patients for trastuzumab therapy. The...
Comparative Effectiveness Study using FFPE in SA patients

Original article

Incorporating microarray assessment of HER2 status in clinical practice supports individualised therapy in early-stage breast cancer

Kathleen A. Grant a, b, Fredrieka M. Pienaar c, Karen Brundyn d, Gillaume Swart d, George S. Gericke e, Etienne J. Myburgh f, Colleen A. Wright a, g, Justus P. Apfelstaedt h, Maritha J. Kotze a, i

ABSTRACT

Accurate determination of human epidermal growth factor receptor-2 (HER2) status is essential for optimal selection of breast cancer patients for gene targeted therapy. The analytical performance of microarray analysis using TargetPrint for assessment of HER2 status was evaluated in 138 breast tumours, including 41 fresh and 97 formalin-fixed paraffin embedded (FFPE) specimens. Reflex testing using immunohistochemistry/in situ hybridization (IHC/ISH) in four discordant cases confirmed the TargetPrint results, achieving 100% agreement regardless of whether fresh tissue or FFPE specimens were used. One equivocal IHC/ISH case was classified as HER2-positive based on the microarray result. The proven clinical utility in resolving equivocal and borderline cases justifies modification of the testing algorithm under these circumstances, to obtain a definitive positive or negative test result with the use of microarrays. Determination of HER2 status across three assay platforms facilitated improved quality assurance and led to a higher level of confidence on which to base treatment decisions.
# Breast cancer subtypes

<table>
<thead>
<tr>
<th>SUBTYPE</th>
<th>PREVALENCE (approximate)</th>
<th>MOST COMMON IHC PROFILES FOR EACH SUBTYPE *</th>
<th>DNA MUTATIONS IDENTIFIED BY NEXT GENERATION SEQUENCING</th>
<th>MICROARRAY PROFILING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>40%</td>
<td>ER+ and/or PR+, HER2-, low Ki67</td>
<td>PIK3CA (49%)</td>
<td>Distinguish patients with Luminal A and Luminal B subtypes as they are treated differently in relation to hormone and chemotherapy</td>
</tr>
<tr>
<td>Luminal B</td>
<td>20%</td>
<td>ER+ and/or PR+, HER2+ (or HER2-), high Ki67</td>
<td>TP53 (32%)</td>
<td>Identification of basal-like subgroup important for selection of specific systemic therapy regimen</td>
</tr>
<tr>
<td>Basal-like</td>
<td>15-20%</td>
<td>ER-, PR-, HER2-</td>
<td>TP53 (84%)</td>
<td>Patients with the HER2-enriched subtype respond better to trastuzumab than HER2-positive cases identified with standard IHC/FISH</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>10-15%</td>
<td>ER-, PR-, HER2+</td>
<td>TP53 (75%)</td>
<td></td>
</tr>
</tbody>
</table>

*Not all tumours will have these features within the subtypes, originally discovered with use of microarray analysis (Perou et al. 2000)*
Clinical Overestimation of HER2 Positivity in Early Estrogen and Progesterone Receptor–Positive Breast Cancer and the Value of Molecular Subtyping Using BluePrint

Purpose
Human epidermal growth factor receptor 2 (HER2) positivity is an important prognostic and predictive indicator in breast cancer. HER2 status is determined by immunohistochemistry and fluorescent in situ hybridization (FISH), which are potentially inaccurate techniques as the result of several technical factors, polysomy of chromosome 17, and amplification or overexpression of CEP17 (centromeric probe for chromosome 17) and/or HER2. In South Africa, HER2-positive tumors are excluded from a MammaPrint (MP; Agendia BV, Amsterdam, Netherlands) pretest algorithm. Clinical HER2 status has been reported to correlate poorly with molecular subtype. The aim of this study was to investigate the correlation of clinical HER2 status with BluePrint (BP) molecular subtyping.
NEW DEVELOPMENT

Next generation sequencing combined with Immunohistochemistry (IHC)

Development of bladder cancer in a patient with a low-risk MammaPrint profile.....

Rare variants in BRCA2 and CHEK2 are associated with the risk of urinary tract cancers

OncoDEEP&TRACE
The sample and the data from sequencing were good to provide us with reliable data for this blood sample. We identified the TP53 potentially damaging variant (M237I) at 7.79%. This variant has already been detected in the solid biopsy (see solid biopsy for conclusion on this variant). Moreover, we didn't identify any CNV (copy number variation) in this sample.
Combining diagnostic BRCA mutation screening with CYP2D6 pharmacogenomics

CYP2D6 genotyping and use of antidepressants in breast cancer patients: test development for clinical application

Nicole van der Merwe · Christianne S. H. Bouwens · Rika Pienaar · Lize van der Merwe · Yandiswa Y. Yako · Dieter H. Geiger · Maritha J. Kotze

Table 4 Breast cancer patients with a medical history of depression analysed during the implementation phase of the study

<table>
<thead>
<tr>
<th>Sample</th>
<th>Age</th>
<th>CYP2D6*4</th>
<th>Antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>48</td>
<td>Wild-type</td>
<td>Not provided</td>
</tr>
<tr>
<td>B</td>
<td>58</td>
<td>Wild-type</td>
<td>Wellbutrin</td>
</tr>
<tr>
<td>C</td>
<td>47</td>
<td>Wild-type</td>
<td>Not provided</td>
</tr>
<tr>
<td>D</td>
<td>54</td>
<td>Wild-type</td>
<td>Zoloft, Wellbutrin</td>
</tr>
<tr>
<td>E</td>
<td>45</td>
<td>Wild-type</td>
<td>Cipralex</td>
</tr>
<tr>
<td>F</td>
<td>60</td>
<td>Heterozygous</td>
<td>Not provided</td>
</tr>
<tr>
<td>G</td>
<td>46</td>
<td>Wild-type</td>
<td>Not provided</td>
</tr>
<tr>
<td>H</td>
<td>59</td>
<td>Heterozygous</td>
<td>Not provided</td>
</tr>
<tr>
<td>I</td>
<td>68</td>
<td>Heterozygous</td>
<td>Cipramil, Cipralex, Wellbutrin</td>
</tr>
<tr>
<td>J</td>
<td>57</td>
<td>Heterozygous</td>
<td>Not provided</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample</th>
<th>Age</th>
<th>Ethnic group</th>
<th>ER status</th>
<th>BRCA mutation positive</th>
<th>CYP2D6*4</th>
</tr>
</thead>
<tbody>
<tr>
<td>77</td>
<td>41</td>
<td>Caucasian</td>
<td>Negative</td>
<td>BRCA1</td>
<td>Wild-type</td>
</tr>
<tr>
<td>140</td>
<td>52</td>
<td>Caucasian</td>
<td>Positive</td>
<td>BRCA1</td>
<td>Homozygous</td>
</tr>
<tr>
<td>22</td>
<td>48</td>
<td>Caucasian</td>
<td>Positive</td>
<td>BRCA2</td>
<td>Homozygous</td>
</tr>
<tr>
<td>23</td>
<td>45</td>
<td>Coloured</td>
<td>NA</td>
<td>BRCA2</td>
<td>Wild-type</td>
</tr>
<tr>
<td>38</td>
<td>63</td>
<td>Caucasian</td>
<td>NA</td>
<td>BRCA2</td>
<td>Wild-type</td>
</tr>
<tr>
<td>66</td>
<td>63</td>
<td>Coloured</td>
<td>NA</td>
<td>BRCA2</td>
<td>Wild-type</td>
</tr>
</tbody>
</table>
Tamoxifen
- The clinician should not use CYP2D6 polymorphisms to guide adjuvant endocrine therapy selection.

Clinical interpretation of literature review
- The ability of polymorphisms in CYP2D6 to predict tamoxifen benefit has been extensively studied (47-50). The results of these pharmacogenomics studies have been controversial, with more recent studies being negative.
- At this point, data do not support the use of this marker to select patients who may or may not benefit from tamoxifen therapy.
Pathology-supported Genetic Testing

M. J. Kotze et al.

- Presenting symptomatology or family history of illness
  - Questionnaire-based evaluation and database generation for test validation using an ethically approved protocol
- Pathology
- Identification of disease subtype
- Biochemistry
  - Identification of novel biomarkers for targeted treatment
- Genetics
  - High-penetrance causative mutations
  - Low-penetrance functional polymorphisms
  - Investigation of genetically uncharacterized patients
- Therapeutic intervention
  - Decreasing cumulative NCD risk
  - Evaluation of treatment failure/severe drug-related side effects
- Whole exome or genome sequencing
Exome Sequencing Pre-screen Algorithm

Kotze MJ, SAMJ 2016

<table>
<thead>
<tr>
<th>Disease pathway analysis</th>
<th>Family medical history and genetic susceptibility</th>
<th>Environmental factors and treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical risk profile</td>
<td>Contribution of genetic variants implicated in the dysfunctional regulation of key metabolic pathways across the disease spectrum to clinical presentation</td>
<td>Consideration of lifestyle intervention that may ameliorate risk for expression of disease-associated phenotypes in genetically susceptible individuals</td>
</tr>
<tr>
<td>Pathology test results</td>
<td>Pathological indicators (biochemistry, histology) which may reflect gene-environment interactions as biological intermediates</td>
<td>Monitoring of relevant pathological indicators/biochemical test results in relation to treatment response and side-effect profile</td>
</tr>
</tbody>
</table>
Mutation penetrance determines the need for relevant clinical information obtained with the questionnaire for clinical interpretation of the genetic results.

Report used by doctor to explain to patient why a particular medical diagnosis exists, or areas of risk that may occur should particular clinical or lifestyle risk factors not be addressed.
In a learning health care system, research influences practice and practice influences research.

**EVALUATE**
Collect data and analyze results to show what works and what doesn’t.

**ADJUST**
Use evidence to influence continual improvement.

**IMPLEMENT**
Apply plan in pilot and control settings.

**DESIGN**
Design care and evaluation based on evidence generated here and elsewhere.

**DISSEMINATE**
Share results to improve care for everyone.

**INTERNAL AND EXTERNAL SCAN**
Identify problems and potentially innovative solutions.

Building a Genomics Database Resource
Acknowledgements:

A multi-disciplinary team
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Dear Valued Healthcare Partner,

The recent publication of the MINDACT trial in the *New England Journal of Medicine* represents another important milestone in the field of molecular diagnostics and underscores the importance of integrating genomic tests into clinical practice.

However, the results of MINDACT only support the prognostic capability of MammaPrint® and do not provide evidence that MammaPrint can predict chemotherapy benefit.

Specifically, in women designated as low-risk by MammaPrint and high-risk by clinical factors, improved disease-free survival was observed among those randomized to receive chemotherapy. This suggests that physicians and patients who use MammaPrint results may not choose potentially curative therapy. Conversely, women designated as high-risk by MammaPrint and low-risk by clinical factors had no discernible benefit of chemotherapy and therefore use of MammaPrint for these patients may result in unnecessary treatment and toxicity.

At Genomic Health we remain steadfast in ensuring our marketing claims are supported by rigorous scientific evidence. Our Oncotype DX® assay for invasive breast cancer remains the only test with level 1 evidence for predicting chemotherapy benefit. Specifically, multiple studies have demonstrated that women with high Oncotype DX scores are those who benefit from chemotherapy. With strong evidence predicting chemotherapy benefit and prospective outcomes in over 50,000 patients, it is clear that Oncotype DX remains the only test that can provide you the confidence that your patients will receive the care they deserve.

Agenda Responds to “Clinical Insights on MINDACT”

Phillip G. Febbo, MD
Chief Medical Officer
Genomic Health, Inc.

October 4, 2016
Despite the misleading letter the MINDACT trial did indeed meet its objectives.

Unequivocally establishing level 1A evidence for the clinical utility of the MammaPrint 70-gene assay.

Largest prospective, randomized controlled trial of its kind published in a peer-reviewed journal.

To date MammaPrint is the only breast cancer recurrence assay to achieve this highest level of evidence.
In contrast to MINDACT (MammaPrint) the TAILORx has failed, up to now, to report on its primary objective of the randomized Oncotype Dx RS between 11-25.

TAILORx identifies patients who do not benefit from adjuvant chemotherapy in only 16 percent of those enrolled with RS of 10 or less.

Nearly 70% had a mid-range score of 11 to 25, with no evidence to date whether whether this subset of women can be spared chemotherapy.
Risky and uncertain

• No clear and consistent prospective evidence available regarding the risk of distant relapse above the Oncotype Dx RS=10
  o de-escalation of treatment using the 21-gene assay risky and uncertain in the majority of patients undergoing Oncotype Dx testing

• What is the exact cutoff in the Oncotype Dx Recurrence Score that determines if a patient is at low risk of recurrence? Is it 10? 11? 18? or 25?
  o contributing no precision to “Precision Medicine” as the test requires that physicians return to reliance upon only clinical-pathological criteria

• Thousands of oncologists and patients continues to rely on Oncotype Dx with RS scores of 11-25
Chemotherapy yes or no?

• Most challenging decision in the presence of high risk clinical features that would otherwise indicate the need for chemotherapy to prevent metastatic recurrence
  o only the HIGHEST level of evidence can provide the confidence that withholding treatment for these patients is safe

• MammaPrint has achieved this through MINDACT
  o showing no clinically meaningful benefit of chemotherapy in MammaPrint Low Risk patients

• As the only assay that has specifically sought out to answer this question, it is the only assay that has consistently proven
  o its ability to identify these patients, and safely spare patients from overtreatment.
MammaPrint Pre-screen Algorithm (MPA) reduces chemotherapy in patients with early-stage breast cancer

K A Grant,1,2 Nat Dip Med Tech, NHD, M Tech; J P Apfelstaedt,2 Dr Med, M Med (Surg), FCS (SA), MBA; C Wright,2,4 Nat Dip Med Tech, MB ChB, M Med, F C Path, F R C Path, FIAC, PhD; E Myburgh,5,5 MB ChB, FCS (SA), M Med (Surg); R Pienaar,6 MB ChB, M Med, Rad T; M de Klerk,7 MB ChB, M Fam Med, MBA, DCH; M J Kotze,2 B Sc, B Sc (Hons), M Sc, PhD

Background. Clinical and pathological parameters may overestimate the need for chemotherapy in patients with early-stage breast cancer. More accurate determination of the risk of distant recurrence is now possible with use of genetic tests, such as the 70-gene MammaPrint profile.

Objectives. A health technology assessment performed by a medical insurer in 2009 introduced a set of test eligibility criteria – the MammaPrint Pre-screen Algorithm (MPA) – applied in this study to determine the clinical usefulness of a pathology-supported genetic testing strategy, aimed at the reduction of healthcare costs.

Methods. An implementation study was designed to take advantage of the fact that the 70-gene profile excludes analysis of hormone receptor and human epidermal growth factor receptor 2 (HER2) status, which form part of the MPA based partly on immunohistochemistry routinely performed in all breast cancer patients. The study population consisted of 104 South African women with early-stage breast carcinoma referred for MammaPrint. For the MammaPrint test, RNA was extracted from 60 fresh tumours (in 58 patients) and 46 formalin-fixed, paraffin-embedded (FFPE) tissue samples.

Results. When applying the MPA for selection of patients eligible for MammaPrint testing, 95 of the 104 patients qualified. In this subgroup 62% (59/95) were classified as low risk. Similar distribution patterns for risk classification were obtained for RNA extracted from fresh tumours v. FFPE tissue samples.

Conclusions. The 70-gene profile classifies approximately 40% of early-stage breast cancer patients as low-risk compared with 15% using conventional criteria. In comparison, more than 60% were shown to be low risk with use of the MPA validated in this study as an appropriate strategy to prevent chemotherapy overtreatment in patients with early-stage breast cancer.