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The cost impact of unselective vs selective MammaPrint testing in early-stage breast cancer in Southern Africa

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ABSTRACT

Background: MammaPrint (MP) has been applied in South Africa (SA) for decision-making in early-stage hormone receptor-positive breast cancer since 2006. The cost-impact of MP in SA has not been assessed.
Aim: To assess different MP testing strategies for cost-minimization in early-stage breast carcinoma using a funder perspective.
Methods: Clinico-pathologic information was extracted from a prospectively collected database. Clinical risk stratification was done using Adjuvant Online! (AOL) and the Predict V2.1 algorithm (www.predict.nhs.uk). An unselected MP testing strategy was compared to a selective strategy, testing only clinically high risk (cHigh) patients. Excluding human epidermal growth factor receptor-2 positive tumours, the costs for chemotherapy treatment and MP using funding data were used to evaluate the financial impact of these strategies.
Results: In 583 patients with 601 tumours, 52% were clinically low risk (cLow) (AOL) while the average Predict 10-year survival with chemotherapy was 2.9%. MP correlated strongly with Predict and 318 (60%) patients were MP low risk. Unselective testing allowed omission of chemotherapy in 44 (8.4%) patients but escalated cost by 57.7%. Using a selective testing strategy, only 251 would be tested, de-escalating treatment in 138 (55%) and reducing cost by 19.5%. Considering a Predict value up to 3.2% as cHigh, cost would be up to 7.3% ($p = 0.0467$) lower with a selective testing strategy.
Conclusion: MP allowed reduction in the use of adjuvant chemotherapy. Unselective use of MP increases overall costs. A selective testing strategy through clinical risk stratification using AOL/Predict results in substantial cost saving.

1. Introduction

Genomic analysis of breast tumours has promised more individualised treatment [1] and have been shown to reduce uncertainty when making clinical decisions [2], but cost and accessibility have remained a barrier for many patients worldwide. Online tools such as Adjuvant Online! (AOL) and Predict (www.predict.nhs.uk) have facilitated more objective decision-making [3,4] and guidelines have attempted to use standard pathological features as a surrogate for molecular subtyping [5] but they correlate poorly with the true genomic subtype [6,7].

MammaPrint (Agendia, NL) (MP) is an RNA-based, 70-gene microarray which has been prospectively validated [8,9] and has the benefit of producing a binary result which is independent of the standard clinico-pathological features of the cancer [10]. Currently available Level 1 A data supports safely omitting chemotherapy in clinically high-risk (cHigh) patients using MP [9,11].

Since 2006, MP has been available in South Africa and is the only assay with prospectively collected and published data from this region [7,12–14]. While 93% of international breast cancer experts

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recommend genomic assays [15], the cost remains prohibitive in South Africa, limiting its use.

MammaPrint is considered cost-effective in several countries, including the United States [16], the Netherlands [17–20], Spain [21] and Japan [22] based on studies utilizing a Markov model comparing indiscriminate MP screening with a clinical treatment strategy [23,24].

The South African Health System is divided into Private and Public healthcare settings. The private sector is funded largely by medical aid schemes (MAS). These provide voluntary health care insurance to 15% of the population [25] while accounting for 44% of the total health expenditure according to the World Health Organization Global Health Expenditure database. While international guidelines including those from the National Comprehensive Cancer Network (NCCN) [26] and The American Society of Clinical Oncology (ASCO) [27] are generally used in all sectors, MAS employ independent healthcare management companies to act as intermediaries between providers and funders to ensure adherence to protocols.

With poor economic growth in the Southern African region and the impact of the recent SARS-Cov-2 pandemic, the cost of European tests such as MP have steadily increased. Conversely, the cost of many cytotoxic agents has decreased due to pharmaceutical companies developing alternative funding strategies for developing countries, such as the availability of generics, centralised procurement and dispensing [28].

It is therefore important to evaluate different cost minimization strategies when using MP in South Africa.

2. Methods

This study was performed in accordance with the ethical standards laid out in the 1964 Declaration of Helsinki. Ethics approval was granted by the Health and Research Ethics Committee of the University of Stellenbosch (reference number N09/06/166, subproject 8213).

2.1. Data collection

Clinical and pathological data on all patients referred for MP testing since 2007 are collected in a central database. MammaPrint is currently indicated for oestrogen receptor (ER)/progesterone receptor (PR) positive, human epidermal growth factor receptor 2 (HER2) negative tumours of up to 5 cm with up to 3 nodes involved [12,29]; however, it was initially applied to all subtypes of breast cancer and thus some HER2 positive or ER/PR negative patients have been tested at the discretion of the treating oncologist. Anonymized records of 642 tumour samples referred from private oncology units in South Africa and Namibia between Jan 2007 and November 2020 were extracted including fresh and formalin fixed paraffin embedded core biopsies and/or excision specimens. Of these, 41 entries were excluded due to incomplete data entries. For the purpose of this study, HER2 status was assigned as per the ASCO 2013 Guidelines, which was the classification guideline in effect for most of the records collected in the dataset and in previous publications [7,12–14]. It should be noted that data on treatment decisions and outcomes was not available.

2.2. Clinical prognostication

For comparison to other trials such as MINDACT (Microarray In Node negative Disease may Avoid ChemoTherapy), the same modified AOL criteria were used to classify tumours as being cHigh or clinically low-risk (cLow) (Table 13 of the supplementary material of the MINDACT trial [8]).

Because AOL is no longer available, Predict v2.1 was used as an alternative for calculating 10-year survival benefit for a 3rd generation chemotherapy regimen (with endocrine therapy, where applicable) [30]. This gave a continuum of values above which patients would be classified as cHigh. The algorithm uses a Ki67 level of 10% as the cut-off between positive and negative [30].

2.3. Testing strategies evaluated

Two testing models were evaluated. In both scenarios it is assumed that chemotherapy was used in all gHigh tumours:

1) Unselective testing where all ER/PR positive, HER2 negative tumours are submitted for MP and chemotherapy is given to all MPHigh cases.
2) Selective testing where only tumours considered cHigh based on AOL or Predict is submitted to MP testing, omitting chemotherapy in MPLow cases.

In the event of multiple tumours per patient, treatment decisions were based on the lesion with the worst clinical and/or genomic risk.

2.4. Cost analysis

Since MP is only available to some patients covered by MAS, and these companies are only responsible for the primary treatment costs, this study adopted a funder perspective. All monetary values used in this article are presented in ZAR (South African Rands).

2.5. Patients with HER2 positive tumours were excluded from all cost calculations

The Independent Clinical Oncology Network (ICON) is a managed healthcare company involved in authorizing treatment plans for a large component of the private oncology market in South Africa [31]. They have formal chemotherapy protocols based on NCCN [26] and ASCO Clinical Practice Guidelines [32]. ICON provided the average cost for adjuvant therapy regimens requested as well as the supporting drugs used in 4119 early breast cancer patients by affiliated oncologists throughout South Africa for the period of 2018–2020. The average cost per patient for 2020 was used in all calculations. Although the cost of MP changed over time, the current cost of MP was used for analysis as this will make the results applicable to use in the current economic setting.

2.6. Data processing and statistics

Patient age, tumour size, nodal involvement, ER, PR and HER2 status by immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) were reviewed and the MP result extracted for each record. Patient age was calculated to the date of specimen collection/surgery. Data processing was performed using MS Excel. Statistical analyses were performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium) [33]. MedCalc's Test for one proportion uses the z-test for calculating the p-value and the Clopper-Pearson confidence interval for the observed proportion of %MPLow.

3. Results

3.1. Characteristics of study participants and tumours

Complete records of 583 patients with 601 tumours were available. Sixteen patients had more than one tumour of which two

had three tumours. Table 1 contains the demographics of the study population.

3.2. HER2 positive tumours

Sixty (10%) tumours were HER2 positive of which 25 (4.2%) were MPLow, indicating potential inaccuracy in HER2 reporting based on ASCO 2013 criteria. These were excluded from further cost analysis.

3.3. Clinical risk: modified AOL

Applying the MINDACT criteria, clinical risk assignments were determined for the data records and presented in Table 2. Notably, 52% of tumours were cLow which implies that MP was used to potentially escalate therapy in 94 (17.5%) of patients while 138 (26.2%) patients with 143 tumours could be spared chemotherapy.

3.4. Clinical risk: Predict

The average 10-year survival benefit for chemotherapy was 2.9% (0.1–14.5%) with 69% of cases having a predicted benefit of <3% for chemotherapy. Fig. 1 shows the distribution of the data based on the Predict 10-year survival advantage. There was a correlation between the Predict value for ER/PR positive, HER2 negative tumours and the MP risk with a Pearson Product-Moment Correlation Coefficient (R^2) = 0.9382.

3.5. Cost of unselected MP testing

All patients in this study underwent MP testing. Based on the assumption that all cHigh patients would have received chemotherapy but, due to MP, only MPHigh tumours were offered chemotherapy, the impact of MP would be an escalation of therapy in cLow tumours with MPHigh result, while de-escalating therapy in cHigh patients with MPLow result. Data presented in Table 2, reveals that 44 (8.4%) fewer patients would have received chemotherapy. The total cost impact of this is presented in Table 3 showing that despite treating fewer patients, the additional cost of MP escalates total cost by 15.25mil ZAR (57.7%).

3.6. Cost of a de-escalation strategy using MINDACT modified AOL

If the same study population were considered, but MP was only performed on those deemed clinically high risk while excluding HER2+ cases, it would have resulted in performing only 257 MP assays (52% fewer tests) and de-escalation in 138 (55%) cHigh patients with 143 tumours. This would result in a net saving of 5.22mil ZAR (19.5%) in this cohort.

3.7. Breakeven Cost Ratio (BCR)

For the cost of MP (MPCost) to be offset by the savings in treatment (RxCost) the following should apply:

RxCost x %cHigh = MPCost + RxCost x %MPHigh

In an unselected testing model, the %cHigh varies constantly, but in a selective testing model where only cHigh patients are submitted for MP and when considering that %MPHigh is equal to 1-%MPLow then:

RxCost = MPCost + RxCost − RxCost x %MPLow which is simplified to:

$$\%MPLow = \frac{MPCost}{RxCost}.$$

The breakeven point occurs when the %MPLow equals the ratio between MPCost and RxCost defined the Breakeven Cost Ratio or BCR.

During 2020 the average cost for a single MP analysis was 38 007 ZAR. The average cost to funders for chemotherapy and

Table 1
Patient and tumour demographics.

Median Age at tumour collection in years (range) n = 583 (min-max)		53	(24–80)
Median tumour size in millimetres (range) n = 601 (min-max)		17.2	(0.5–70[a])
Histological type and grade of differentiation		n = 601	%
Infiltrating Ductal (n = 512)	Grade 1	118	20%
	Grade 2	297	49%
	Grade 3	97	16%
Lobular		68	11%
Other Types		21	3%
Biological Typing			
ER/PR	Positive	596	99%
	Negative	5	1%
HER2	Positive	60	10%
	Negative	470	78%
	Equivocal/Unknown	71	12%
Ki67	≤10%	113	19%
	>10%	270	45%
	Unknown	218	36%
Nodal status		n = 601	%
Nodes 0		389	65%
	N1itc	11	2%
	N1mi	55	9%
Nodes 1		93	15%
Nodes 2		27	4%
Nodes 3		20	3%
Nodes 4+		6	1%
MammaPrint genomic risk		n = 601	%
Low Risk (MPLow)		358	60%
High Risk (MPHigh)		243	40%

[a] Some tumours were ill defined and consisted of small tumour nests over an extended area. The widest distance between tumour cells were used in these cases.

Table 2
MammaPrint comparison to Clinical Risk using MINDACT modified AOL excluding HER2 positive tumours.

Clinical Risk:			Genomic Risk:	Impact of Genomic Risk to Treatment Decision	Patients	
Modified AOL per MINDACT			MammaPrint		n	%
cLow	274	52%	MPHigh	Escalated	94	18%
			MPLow	Unchanged	180	34%
cHigh	251	48%	MPHigh	Unchanged	113	22%
			MPLow	De-escalated	138	26%
				Total:	**525**	**100%**

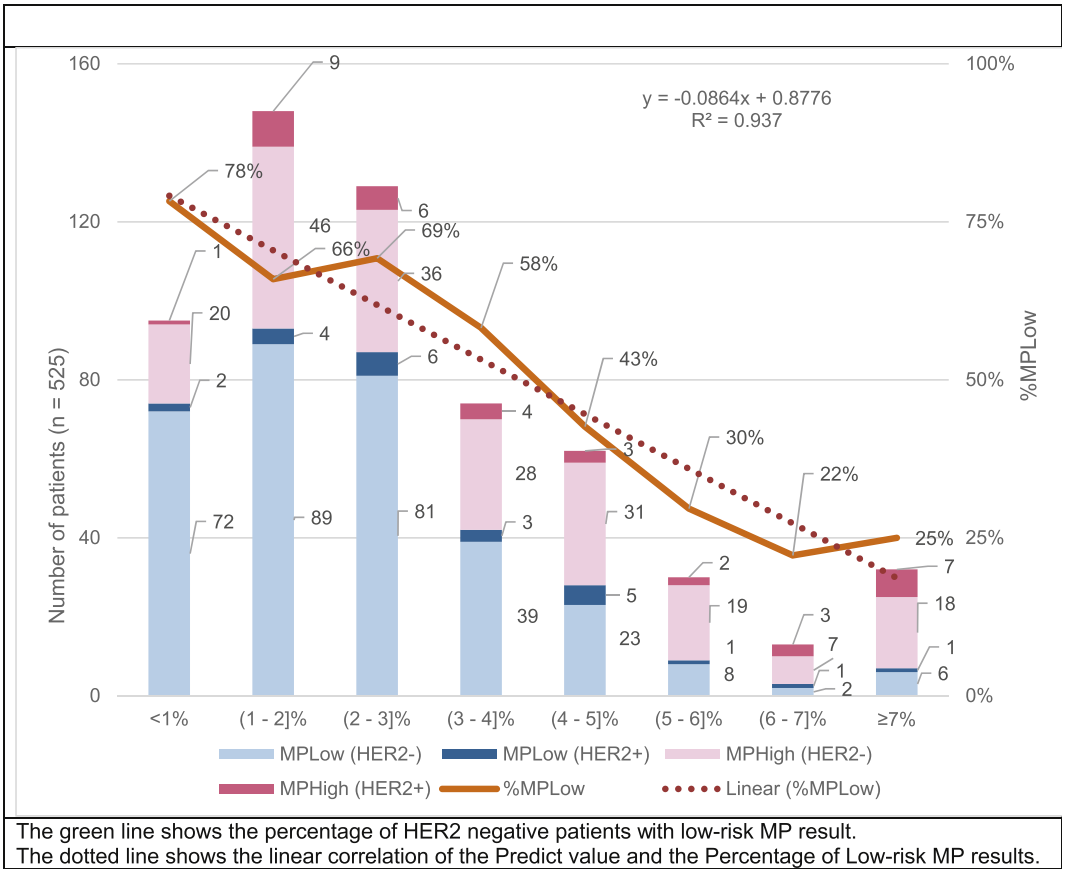


Fig. 1. MammaPrint comparison to Clinical Risk using Predict.

Table 3
Cost comparison of clinical decision-making vs MP comparing different testing models.

Strategy Followed	Number of tumours tested with MP (excl HER2)	Number of patients treated.	Total Cost (ZAR)	Difference (%)
Clinical decision making	N/A	251	26 851 227.00	
Unselected Testing Model	525	207	42 097 914.00	↑57.7%
De-escalation model	251	113	21 628 158.00	↓19.5%

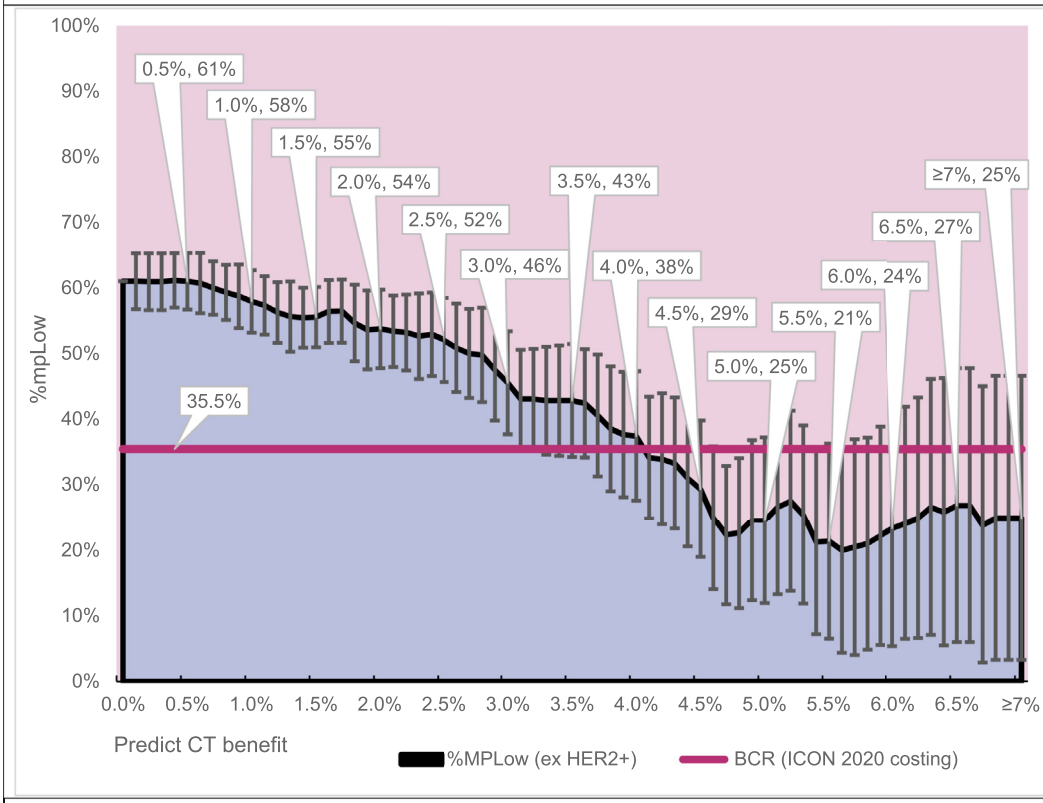
supportive medication was 106 977 ZAR per patient (Source: ICON) and this gives a BCR value of 0.355 (35.5%) indicating MP would be cost saving if ≥ 35.5% patients are spared chemotherapy by its use.

3.8. Cost effect of a de-escalation strategy using Predict

Fig. 2 depicts a similar de-escalation strategy employing Predict, considering all patients above a specified threshold value to be cHigh. For any threshold up to 3.5%, MP would result in a significant cost saving. At a Predict threshold value of 3.2%, 59 (42.1%) fewer patients would require chemotherapy with a total cost saving of 1 262 286 ZAR (7.3%) ($p < 0.0467$), (refer Table S3). Evidenced by the correlation between the Predict benefit and the %MPHigh (Fig. 1), selecting a higher Predict threshold is unlikely to result in significant cost saving as can be observed in the widening 95%-Confidence intervals (95%-CI).

4. Discussion

MammaPrint remains an expensive assay in South Africa and as price pressures mount in healthcare, the pragmatic implementation of cost saving strategies become increasingly relevant. When



The cost effect of using Predict to determine the threshold above which patients are considered cHigh, thus considering chemotherapy and MP testing to allow de-escalation in MPLow group (Blue Shaded area). The 95%-Confidence Intervals are shown. Labels at 0.5% intervals, indicate the threshold based on Predict Value and %MPLow for all cases above this point. The BCR calculated on current costs is shown.

**Refer Table S3 for purposes for more detailed information.*

Fig. 2. Cost effectiveness of different Predict threshold values for MP testing.

initially implemented into the South African health system, a pre-screen algorithm was proposed to guide safe and cost-effective use. Initial publications suggested a substantial impact on treatment decision making using MP [12–14]. In 2016, Pohl et al. published South African data on 109 tumours where MP was performed [13]. Of these, 56% were cLow using AOL and treatment was escalated for 19 patients. Since then, prospective results from the MINDACT trial have confirmed the prognostic validity and predictive utility of MP in de-escalating therapy in cHigh patients [8,9]. Although referrals have increased since publication of the MINDACT data, current results indicates a bias remains toward referring clinically low-risk patients with 52% considered cLow using AOL criteria and 65.8% as having a Predict survival benefit of less than 3%. This is consistent with recent publication of the IMPACT trial by Soliman et al. where the majority (77.5%) of the patients were cLow [34]. Some reasons for this might be the fee-for-service structure or the concern over litigation due to perceived undertreatment, but these remain speculative. Currently guideline 1.7, published by ASCO on the use of biomarkers, advises against the use of MP in cLow patients [29].

When MP is used unselectively as reflected in this dataset and presuming treatment escalation based on a MPHigh result in cLow patients, it would result in a significant cost escalation, thus creating a financial burden which cannot be offset by savings in treatment cost. Figures published in 2013 by Retèl et al. [19] using prospective data from the microarRAy-prognoSTics-in-breast-cancER (RASTER) study, reported that total health care costs per patient were: €26,786 when using MP vs €29,187 for clinical prognostication based on AOL despite an unselective testing model. This might be partly due to their adoption of a healthcare perspective and therefore including the cost of relapse and death. This was outside the scope of this study, making direct comparison difficult. The diversity of the South African healthcare environment also presents challenges to health economic assessment and direct comparison to European studies [35]. Furthermore, the lack of measured outcomes in this study limits accurate assessment of these extended healthcare costs. It is, however, clear that utilizing a de-escalation strategy would result in fewer MP tests, and significant saving of 19.5% in direct costs.

With the discontinuation of AOL, other online tools such as Predict have become widely used in South Africa. Our study is the first to report a correlation between Predict chemotherapy benefit and MammaPrint, showing a Correlation Coefficient (R2) of 0.937. The consistency of this finding might be influenced by the progressively smaller number of cases with higher Predict values. If Predict is used to identify cHigh cases above a specified threshold,

our data suggests that any threshold up to 3.2% would be cost saving ($p < 0.05$). Guidelines from the Cambridge Breast Unit (UK) suggest that chemotherapy should be considered at ≥3% [36] although many clinicians would consider a lower threshold. Regardless, it would seem sensible to use any institutional guideline for the use of Predict and adapt that as a threshold for MP testing, resulting in cost-minimization. Making use of the BER, the de-escalation percentage needed to achieve cost-minimization can easily be calculated on an institutional basis.

This study used industry supplied cost data reflecting a variety of chemotherapy regimens employed by clinicians. For comparison, if a regimen of dose dense doxorubicin/cyclophosphamide (DDAC) is used followed by weekly Paclitaxel, cost could be as much as 136 068 ZAR whereas DDAC followed by bi-weekly Paclitaxel would be 91 888 ZAR. Both options have been confirmed in a meta-analysis by the Early Breast Cancer Trialists Collaborative Group to reduce disease recurrence, breast cancer specific- and overall mortality at 10 years when compared to conventional dosing intervals [37] and is adopted into the NCCN guidelines [26].

This study was limited by several factors. The sensitivity of the model to its input variables is an important consideration. As chemotherapy cost and the MP test price changes over time it may affect the cost analysis. The current dataset is also determined by historic referral patterns for MP and a future de-escalation strategy might influence the demographics thus affecting future analyses. We did not model the effect of disease recurrence, long-term treatment related effects nor intercurrent expenses, which patients incur. Consequently, the effective cost impact of chemotherapy may have been underestimated. These issues could be further resolved by a Markov simulation approach in a future study. Most of the cases also underwent the Blueprint, 80-gene molecular subtyping assay with reclassification of many of the ER/PR/HER2 positive tumours into MPLow tumours which might influence the use of anti-HER2 therapy with the associated cost involved [13,14]. The potential role for MP to identify ultra-low risk patients where endocrine therapy may be omitted, was also not considered [38].

5. Conclusion

MP remains a valuable assay in reducing the requirement for cytotoxic chemotherapy in early-stage breast cancer. The current referral pattern is biased towards clinically low-risk patients and if applied in a non-selective manner, results in cost escalation. In accordance with international guidelines [29], we would strongly advise that referral for MP testing be limited to patients deemed clinical high risk with the intention of identifying those where chemotherapy may be omitted. Such a de-escalation model would allow substantial cost saving. Expansion of the South African central MP database to include outcomes data would allow better evaluation of the clinical and financial impact of MP and the development of funding policies and referral guidelines [39].

Author contributions

The first two authors contributed equally to this study. JJ de Jager performed data processing, conceptualisation of the BCR metric, compilation of the manuscript and obtained ethics approval for the cost benefit analysis. E Myburgh evaluated the clinical relevance of the equations provided as part of overall conceptualisation of the study, interpretation of the data within a clinical context and compilation of the final manuscript. KA Grant obtained ethics approval for maintenance of the database co-developed by MJ Kotze as the study coordinator. E Murray was involved at inception of the study, assessed costing, and contributed written work in this regard with continued editorial input including the final document. M de Klerk contributed to the development of the study protocol for ethics approval and student supervision for a Master of Business Administration degree obtained by JJ de Jager in 2019. All authors approved the final version of the manuscript using an extended data set following an external audit.

Data availability statement

Patient data is confidential and protected by South African law in accordance with the Protection of Personal Information Act of 2013.

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Declaration of competing interest

JJ de Jager is employed in the chemical active pharmaceutical ingredient (API) manufacturing industry. However, he has no influences associated with pharmaceutical (chemotherapeutic) agents related to the treatment of breast cancer. Prof MJ Kotze is a non-executive director and shareholder of Gknowmix (Pty) Ltd., that has developed a database tool for research translation under the auspices of the South African Medical Research Council. The other authors have no affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.05.010.

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