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BACKGROUND

Molecular profiling is a scientific approach that compare different types of samples (tissues, body fluid, etc) at a molecular level (DNA, mRNA or protein) on a global scale. The molecular profiling assay is a genomic technology for predicting individual patient's prognosis by interpreting the expression pattern of a panel of specific tumour-related genes. The transcription of specific set of genes is used as a surrogate marker for metastatic potential. The pattern of gene expression and the specific gene expression threshold levels are able to identify tumours with a more aggressive biology. Thereby it will quantify the risk of recurrence more accurately and the oncologist may plan for either less or more aggressive treatment. In early-stage breast cancer, the advances in molecular biology and pharmacology aids in better understanding of breast cancer and enables the design of effective therapy to target the cancer more efficiently. The molecular profiling assays aim to improve the use of chemotherapy in breast cancer by improving the categorisation of patients in accordance with risk and the identification of those patients who will gain most benefit from chemotherapy. There are several commercially available molecular profiling assays including Oncotype DX, Prosigna (Predictor Analysis of Microarray 50 [PAM 50]), EndoPredict and MammaPrint. This assessment was requested by a Senior Consultant Breast & Endocrine Surgery from Hospital Kuala Lumpur due to increasing demands from patients and clinicians to use gene assays profiling as part of the management of early breast cancer. However, in-depth knowledge of the different assays, their usefulness, and cost-effectiveness is not readily available for a sound decision making process by clinicians for the individual patient(s).

POLICY QUESTIONS

Is molecular profiling assay as part of early breast cancer management, beneficial to predict the recurrence risk of early breast cancer?

Should the molecular profiling assay be part of early breast cancer management in Ministry of Health (MOH)?

OBJECTIVE

To assess the relative effectiveness and safety of different types of molecular profiling and subsequent management in breast cancer.
(As a result of this, decision to give or not to give chemotherapy will determine patient outcomes such as mortality, and quality of life [QoL]).

To assess the economic implication, social, ethical, and organisational aspects related to molecular profiling of early breast cancer.

METHODS

Literature search was developed by the main author and *Information Specialist* who searched for published articles pertaining to molecular profiling assays in breast cancer. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub

Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to June 2022, EBM Reviews - Health Technology Assessment (4th Quarter 2016), EBM Reviews - Cochrane Database of Systematic Review (2005 to January 2022), EBM Reviews - Cochrane Central Register of Controlled Trials (June 2022), and EBM Reviews - NHS Economic Evaluation Database (4th Quarter 2016). Parallel searches were run in PubMed, US FDA and INAHTA database. Search was limited to articles in English and in human.

RESULTS AND CONCLUSION:

Part A: Systematic Review

A total of **297** records were identified through the Ovid interface and PubMed while **2** were identified from other sources (references of retrieved articles). Following the removal of **138** duplicates and irrelevant titles, **161** titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, **50** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the **50** full text articles, **16** full text articles were included. The 16 studies consisted of **three** systematic reviews (SRs), **seven** retrospective cohorts, and **six** economic evaluation studies (consisted of one SR, one budget impact analysis and four cost-effectiveness studies). Three prospective cohort studies on Oncotype DX test and MammaPrint (TAILORx, RxPONDER and MINDACT) were already discussed in the included SRs and will not individually reported in this assessment.

Effectiveness

Individual Findings

Oncotype DX – Recurrence Score (RS)

The Oncotype DX test showed an excellent prognostic ability in patients with HR+/HER2- N0 breast cancer. One of the included studies showed a statistically significant difference in the six-years distant recurrence free survival (DRFS) rate of 94.4%, 96.9% and 85.1% between low-, intermediate- and high-genomic risk groups respectively ($p < 0.001$). The five-year overall survival (OS) difference between the groups to the Recurrence Score (RS) classification was 99% for low- and intermediate-risk and 92%-94% for high-risk population. RS was correlated with the effect of chemotherapy in the three risk groups in terms of 10-years DRFS which was significantly increased in the high-risk group receiving chemotherapy compared to the low-RS group.

Within HR+/HER2- N1 breast cancer subgroup, the six-years DRFS with Oncotype DX-Recurrence score were 92.3%, 85.2%, and 71.3% in low-, intermediate and high-genomic risk groups respectively. The interaction between RS and clinical benefit of chemotherapy in the lymph node positive subgroup was significant for the first five-years after treatment.

The included studies also reported that the Oncotype DX test led to changes in treatment recommendations. The percentage of changes recommendations in most of the included studies ranges between 21% to 74% in either escalation or de-escalation of chemotherapy. Specifically, the de-escalation of chemotherapy to no chemotherapy ranged between 6.1% to 74%.

MammaPrint

When compared with clinical parameters-only assessment, MammaPrint reclassified the risk category of patients with good

clinical prognostic factors to either low-risk or high-risk patients. In addition, MammaPrint also significantly predict the chemotherapy outcome and prognostic value in both LN- and LN+ tumours.
Addition of MammaPrint assay test result to the clinical-pathological assessment, led to changes in treatment recommendations. The overall changes were between 18% to 40%, with decision from chemotherapy to no chemotherapy ranges between 2% and 32%.

EndoPredict – EP score and EPclin
In LN+ breast cancer of pre-menopausal women, the EndoPredict test reported a distant metastasis free survival (DMFS) at 10-years at 93% in low-risk group compared to 67% in high-risk group ($p<0.0001$).

Prosigna/PAM50 – Risk of Recurrence (ROR)
The included studies reported that the Prosigna discriminated between low-risk and high-risk patients very well.

Correlation and Concordance between Assays
There was no prospective head to head trial comparing each of the assays retrieved. Only a few studies looked at the correlation and concordance between the available assays. These studies were included in this HTA report. Overall, each molecular profiling assay had either very week correlation or no correlation among each other.

Oncotype DX versus MammaPrint
Oncotype DX was initially utilised among stage I node negative but later included node positive patients in the RxPONDER study. Both assays were associated with a significant decrease rate of chemotherapy administration with profiling versus without molecular profiling test (24.5% versus 37.2%; $p < 0.001$).

Oncotype DX versus EndoPredict
There was positive Pearson correlation between EndoPredict and Oncotype DX, $r = 0.65$ with 76% concordance between risk categories. However, this study had only a small sample size, $n = 34$ hence the results have to be interpreted with caution.

Oncotype DX versus Prosigna
Based on Spearman correlation coefficient, Oncotype DX and Prosigna had very weak positive correlation ($r_s = 0.08$). Both assays also showed weak correlation when applied to post-menopausal women; $r_s = 0.276$, $p = 0.013$.

MammaPrint versus EndoPredict
Although MammaPrint to EPclin showed significant association in the overall population (included all risk cases), both assays failed to show a significant association amongst the high-risk subgroup ($p = 0.294$, $\kappa = 0.15$, 95% CI -0.089 – 0.39).

Molecular Profiling Assays versus Clinical-Pathological Model
This study found that patients with larger tumour size (>20mm), Allred PR expression of 0-4 and higher-grade tumours (grade III) had higher likelihood ratio (LR) of high-genomic risk; odds ratio 3.84, 95% CI 1.84 – 6.98 ($p < 0.001$), odds ratio 3.46; 95% CI 1.76 – 6.82 ($p < 0.001$) and odds ratio7.24; 95% CI 3.82- 13.70 ($p < 0.001$), respectively. This confirms the ineligibility of grade 3 tumours to be tested with genomic assays.

SAFETY

No safety issue related to molecular profiling assays in breast cancer was retrieved.

ORGANISATIONAL

There were two guidelines related to the use of molecular profiling in management of early-stage breast cancer retrieved. The most recent guideline was published in 2022 by Ontario Health (Cancer Care Ontario) Health Program in Evidence-Based Care (PEBC) in Canada and another guideline was published in 2018 by the National Institute for Health and Care Excellence (NICE) in the United Kingdom. The Ontario guideline was intended for clinician and policymakers who are involved in the diagnosis and treatment of breast cancer. As for NICE guideline, molecular profiling is used to guide adjuvant chemotherapy decision in early breast cancer. Generally, both guidelines recommended the used of molecular profiling as an option to guide systemic therapy or chemotherapy decision in patients with ER+ HER2-ve early-stage breast cancer.

SOCIAL

Generally, not many patients are aware about molecular profiling assays and their utility in breast cancer management. However, after being introduced and having a personal experience with the assays, most of the patients expressed higher confidence with the final treatment recommendations.

ECONOMIC EVALUATIONS

One SR on economic evaluations of Oncotype DX reported that Oncotype DX had an ICER of ≤$100,000 per QALY. The SR also evaluated the probability of industrial funded studies which might influence the outcome of the economic evaluations. Fortunately, in both industrial funded or non-funded studies, the Oncotype DX test was associated with cost-saving, with favourable ICERs of US$900 versus US$3,100 per QALY. In another SR, if patient's outcome is being considered, any use of molecular profiling assays was cost effective in 90% of the economic evaluation studies, regardless of the type of assays used. On the other hand, when comparing N- and N+ breast cancer, the estimated QALYs gained was larger in N- (on average 0.24 versus 0.07 QALYs) than N+ patients. In Germany, the Oncotype DX was cost saving with no negative impact on mortality when compared with EndoPredict and MammaPrint; as the average saving per patient was 2,500€ and 1,936€ when compared to EndoPredict and MammaPrint respectively. Meanwhile, the Canadian public healthcare system view that, the addition of molecular profiling assays into clinicopathological predictors to guide chemotherapy decision was cost-effective. In the UK study, Prosigna was deemed the preferred assay for further research. However, in the sensitivity analysis, Oncotype DX was the favoured assay on the basis of its expected cost-effectiveness followed by Prosigna. In Spain, Oncotype DX and MammaPrint played a significant role in treatment management of patients with early-stage breast cancer and both assays were cost-saving and highly cost-effective at national health care system and societal perspective; 13,920€ (95% CI 11,697€ - 12,218€) and 32,793€ (95% CI 28,432€ - 37,827€), respectively. In Turkey, the Oncotype DX was found to be cost-effective at national health care perspective with improvement in QoL and may be introduced for routine clinical practice among early breast cancer

patients. The ICERs was estimated to be $7,207.9 per QALY gained and 5,720.6 per LY gained for Oncotype DX versus current clinical practice in Turkey.

Part B: Economic Evaluation

Objectives

The general objective of this economic evaluation was to assess the cost benefit of using new molecular profiling assays in guiding decision making on chemotherapy treatment for early HR-positive HER2-negative breast cancer patients.

The specific objectives were to estimate the savings associated with the usage of new molecular profiling assays compared to conventional clinical risk prognostic tools in decision making on chemotherapy for HR-positive HER2-negative node negative (N0) as well as node positive (N1-3) in early breast cancer patients; and to estimate the budget implicated for the population that would benefit from the cost savings.

Methods

A decision tree model was developed with Microsoft 365 Excel Workbook® to estimate the costs and benefit of using molecular profiling assays for chemotherapy guidance in early HR-positive HER2-negative breast cancer compared with using conventional non-genetic risk prognostic tools (St Gallens classification, PREDICT online, Adjuvant! Online) alone. The perspective taken was from the Ministry of Health perspective.

The population included in the simulation cohort were the HR-positive, HER2- negative early breast cancer with either LN- negative (No node involvement) or LN-positive (one to three node involvement) who have undergone surgery.

Based on the systematic review and meta-analysis conducted in this HTA report earlier, molecular profiling assays (regardless the type of assays) was cost effective in 90% of economic evaluation studies, with estimated QALYs gained larger in the node-negative group. Regardless of lymph node status, Oncotype DX and MammaPrint was able to predict the potential benefit to be seen with omission or administration of chemotherapy. For the purpose of this cost benefit analysis, the Oncotype DX and MammaPrint tests were simulated in the model as the locally available interventional gene expression profile assays, and the comparator was the conventional non-genetic risk prognostic tools.

The short-term outcome was measured as cost benefit from chemotherapy averted.

Model Structure

The model structure was constructed following a literature review, and consultation with an expert committee which consisted of multidisciplinary experts namely clinical oncologists, breast and endocrine surgeons, pathologists, radiologists, health economists, public health physicians and pharmacists. This economic evaluation was designed from the Ministry of Health (MOH) perspective.

Model Estimation

The epidemiological and disease-related data were obtained from local sources of data whenever available, or literature review when local data was not available. The proportion of patients in each risk

level is taken from literature review, while the cost of treatment was from local institution data. The hypothetical cohort was derived from mixed local registry data and literature review.

Results and Conclusion

From the decision analytic modelling that has been conducted, for a hypothetical cohort of 3,500 patients simulated, usage of Oncotype DX was cost saving in the intermediate risk of recurrence group, in both lymph node positive and lymph node negative patients. In LN-negative cohort, there is an estimated cost savings of MYR 10,703,458.56 for those with intermediate risk of recurrence, and in the LN-positive cohort, there was an estimated cost savings of MYR 4,447,623.36 in those profiled as having intermediate risk of recurrence. However, incremental cost was valued at MYR 17,341,739.76 in the LN-negative cohort and MYR 7,540,934.88 in the LN-positive cohort. An overall incremental cost of MYR 24,882,674.64 was estimated if a blanket testing of all eligible patient population was performed.

For the cohort of 3,500 patients simulated, usage of MammaPrint gave an overall incremental cost of MYR 67,395,212.24 in LN-negative patients and MYR 28,869,914.40 in LN-positive patients. This resulted in an overall incremental cost of MYR 96,265,126.64 if all eligible 3,500 were tested with MammaPrint regardless of LN status and risk stratification.

In conclusion, both Oncotype DX and MammaPrint incurred incremental cost if they are utilized to test the whole eligible patient population. However, cost savings of approximately MYR 15,151,081.92 can be achieved with the usage of Oncotype DX in both intermediate risk of recurrence LN-negative group and LN-positive group of 880 patients averting chemotherapy. Therefore, maximal cost savings and potential benefits in averting chemotherapy and chemotherapy complications may be achieved if targeted testing was performed using Oncotype DX in the intermediate risk of recurrence group. The budget implications to procure Oncotype DX assays for 1,574 patients would be MYR 23,610,000.00.

CONCLUSION

Molecular profiling assays are significantly effective in prognosticating between low-risk and high-risk of recurrence among patients with HR+/HER2-ve early-stage breast cancer. However, further assessment is required in terms of predicting of chemotherapy benefit, Oncotype DX and MammaPrint are able to predict the chemotherapy benefit regardless of lymph-nodes status. Individual prospective assays are available but there are not head to head prospective study to compare between the assays. Retrospective study looking at the association and correlations between the assays are limited in number and has small sample size (<100). Each assay had poor to weak association with each other and should not be used interchangeably. Overall, LN- and low-risk early breast cancer patients might benefit more from molecular profiling assays. Economically wise, the molecular profiling assays were cost-effective compared to conventional method and Oncotype DX was the most commonly used.

In economic evaluation, both Oncotype DX and MammaPrint incurred incremental cost if utilized for testing the whole eligible population. However, cost savings of approximately MYR 15,151,081.92 can be

seen with usage of Oncotype DX in both intermediate risk of recurrence LN-negative and LN-positive breast cancer patients with 880 patients who averted chemotherapy. Therefore, maximal cost savings and potential benefits in averted chemotherapy with its complications may be achieved if targeted testing was performed using Oncotype DX in the intermediate risk of recurrence group. The budget implications to procure Oncotype DX assays for 1,574 patients would be MYR 23,610,000.00.

The sensitivity analysis showed that overall cost savings can be achieved if the price of Oncotype DX is reduced to 50% of the quoted price, giving a total accrued cost savings of MYR 1,367,325.36. If price negotiation can be done, a minimum reduction of 50% of the Oncotype DX price may potentially offer eligible population greater access to Oncotype DX assay regardless of LN status or risk. The budget required for procurement of Oncotype DX assay for 3,500 patients with reduction to 50% of the quoted price is MYR 26,250,000.00

POLICY RECOMMENDATION

Molecular profiling assays has a role in discriminating recurrence risk in HR+/HER2- early-stage breast cancer patients. Oncotype DX may be recommended in management of HR+/HER2- early breast cancer with the maximal potential benefit in the intermediate risk of recurrence group with purchasing price negotiation.