Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1376.1 – 70 gene signature (MammaPrint) for use in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit

Applicant: **Genome Investigation Pty Ltd**

Date of MSAC consideration: **MSAC 82nd Meeting, 29-30 July 2021**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

A focussed application requesting a new Medicare Benefits Schedule (MBS) listing of a 70 gene signature test (MammaPrint®) was received from Genome Investigation Pty Ltd by the Department of Health in response to the stakeholder meeting held on 21 June 2021 by the Royal College of Pathologists of Australasia (RCPA), Cancer Australia, and the Australian Government Department of Health.

2. MSAC's advice to the Minister on GEP tests

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding for any of the three gene expression profiling (GEP) tests in early breast cancer. MSAC accepted that the tests provided some modest prognostic information, however no applicant provided sufficient evidence for additional prognostic value beyond current standard of care, and thus the economic and financial basis for funding could not be determined. MSAC confirmed that it did not accept predictive value had been adequately demonstrated for any GEP test, and recalled its recent conclusion of worse cancer outcomes with an applicant's proposed predictive use of one GEP test. MSAC advised that the financial implications were uncertain but would likely be high.

In the absence of randomised trial evidence demonstrating predictive value, MSAC advised that any future application for Medicare Benefits Schedule (MBS) listing of a GEP test would need to provide evidence that it meets the following parameters: an appropriate regulatory and quality assurance framework, an appropriate nomination of clinical place aligned with sufficiently robust clinical evidence of incremental prognostic value, an adequate justification of cost per test, and an acceptable total net financial cost to government.

Consumer summary

Medicare Benefits Schedule (MBS) funding was requested for three different gene expression profiling (GEP) tests in early breast cancer, by three different applicants: MammaPrint® (by Genome Investigation Pty. Ltd.), EndoPredict® (by Myriad Genetics Pty. Ltd.) and Prosigna® (by Veracyte Inc.). These three applicants lodged 'focused applications' in response to a stakeholder meeting held on 21 June 2021 by the Royal College of Pathologists of Australasia (RCPA), Cancer Australia, and the Australian Government Department of Health. At this meeting the Department invited 'focused applications' to MSAC addressing a few specified matters.

These GEP tests can be used by patients who have early breast cancer, to give them an estimate of their likely future risk of cancer recurrence after surgery (prognostic value). However, some applicants also claimed that their test can be used to predict which patients can safely avoid chemotherapy after surgery (predictive value).

MSAC accepted that these GEP tests do have some modest prognostic value, when used in conjunction with other information that clinicians and patients can use to estimate the risk of cancer recurrence. However, MSAC needed evidence of the extent of the added prognostic value of each GEP test, beyond that of other information that clinicians and patients can use to estimate the risk of cancer recurrence. This is needed so that MSAC could judge whether each GEP test represents good value for money.

MSAC did not accept that these GEP tests should be used to guide treatment decisions (i.e. to have predictive value); as there was insufficient evidence that these GEP tests can be used to safely identify patients who can avoid chemotherapy. MSAC recalled from its March/April 2021 meeting that the evidence for MammaPrint® showed that avoiding chemotherapy based on its test results can in fact be harmful and result in worse cancer outcomes.

MSAC provided a framework of evidence requirements that each applicant would have to meet in any future application for public funding for its GEP test, if predictive value is not demonstrated. This includes appropriate regulation of the test in Australia, clinical evidence that supports the clinical place proposed for the testing (including showing that the GEP test has extra prognostic value over other information), a proposed fee that reflects this extra prognostic value, and an acceptable total net cost of this testing to government.

MSAC's advice to the Commonwealth Minister of Health

MSAC did not support funding MammaPrint®, EndoPredict® or Prosigna®, because it did not consider any of these GEP tests had been shown to be comparatively safe, effective or cost-effective. MSAC was particularly concerned about the potential harms of using a GEP test to decide to avoid chemotherapy. MSAC advised that it needed more information from each applicant, including about the prognostic value each test adds to other available information.

3. Summary of consideration and rationale for MSAC's advice for GEP tests

MSAC noted that on 21 June 2021 a stakeholder meeting was held by the RCPA, Cancer Australia, and the Australian Government Department of Health, with attendees also

including representatives from consumers, clinicians, pathologists and each of the four GEP test applicants to MSAC. At this meeting the Department invited 'focused applications' to MSAC addressing a few specified matters. MSAC noted that each focused application received requested MBS funding of one of three GEP tests in early breast cancer – EndoPredict® (from Myriad Genetics), MammaPrint® (from Genome Investigation) and Prosigna® (from Veracyte). MSAC noted that the applicant for Oncotype DX® had elected not to lodge a focused application.

MSAC noted the supportive public consultation feedback from the Australian Society for Breast Disease and Breast Surgeons of Australia and New Zealand. However, MSAC noted the authors of the support letters stated they intended to use GEP tests to assist with adjuvant chemotherapy decisions and "sparing" some women from chemotherapy, i.e. predictive rather than prognostic use.

MSAC accepted that GEP tests are being used in clinical practice and supported in clinical practice guidelines, for early breast cancer, and also increasingly for other cancer types. MSAC noted that, based on this acceptance of clinical use, arguments for listing were also based on equity of access issues, but considered that these arguments needed to be considered in the context of MSAC's previously expressed concerns about the comparative safety, comparative effectiveness and comparative cost-effectiveness of the GEP tests.

MSAC noted that all these GEP tests – including Oncotype DX® – have been previously considered by MSAC and none have been supported for public funding to date. MSAC recalled its previous conclusions that none of the GEP tests had satisfactorily demonstrated predictive value (clinical utility: improved health outcomes from changing treatment decisions based on different test results). MSAC considered that each of the three proposed GEP tests is likely have some modest prognostic value, but that it was unclear what incremental prognostic value each GEP has over other information that clinicians and patients can use to estimate the risk of cancer recurrence for early breast cancer patients, and against other GEP tests.

MSAC reaffirmed that it did not accept any applicant's claim that its GEP test has predictive value; MSAC considered that the evidence presented to date did not demonstrate that GEPs can accurately predict which women can safely avoid chemotherapy. MSAC remained concerned that some women have worse outcomes when chemotherapy is avoided based on GEP test results, and that these GEP tests will be used to guide clinical management, which could result in poorer cancer outcomes. Given the consistency of the consultation feedback that patients and clinicians wanted to use these GEP tests for their perceived predictive value, MSAC expressed reservations about the appropriateness of supporting any MBS listing based on prognostic value, knowing that this could result in poorer cancer outcomes for patients when used for this other unsupported purpose.

MSAC remained concerned about the high costs of the tests and the resulting likely high incremental cost-effectiveness ratios (ICERs) based on previous applications. MSAC considered that each applicant must address this in any future application by either justifying the high cost of its test by providing more data on incremental prognostic value that could result in a lower ICER, or proposing and justifying a lower fee for the test.

MSAC also suggested that consideration might need to be given to ensuring an upper limit on the budget impact of any funding via a risk-sharing arrangement. However, MSAC acknowledged that this would require the government to introduce the necessary policy

framework. Expenditure caps would also be difficult to determine because of the uncertainty in the definition of the eligible population for testing and in the likely uptake rates of testing.

MSAC advised that the following parameters must be addressed to enable MSAC to consider whether to support MBS funding for a GEP test in early breast cancer, in the absence of robust evidence supporting predictive value:

- The GEP test must be approved by the Therapeutic Goods Administration (TGA), be performed in an Australian laboratory accredited by the National Association of Testing Authorities (NATA) according to National Pathology Accreditation Advisory Council (NPAAC) standards, with the GEP test forming part of the accredited testing repertoire of the laboratory.
- There must be an appropriate quality assurance program (QAP) in place. MSAC considered this is a highly complex matter for GEP tests, as, unlike other genetic testing programs, each has their own suite of genes and algorithms used to calculate risk scores. MSAC advised it is therefore not possible to have a single QAP for multiple GEP tests.
- There must be an appropriate clinical place for the GEP test, including acceptable prognostic value (clinical validity), acceptable incremental prognostic value (compared with routine clinic-pathologic prognostic methods and compared with other GEP test options provided in Australia). Preferably, there should also be acceptable clinical utility that leads to improved patient care. Improved patient care might be achieved by avoiding unnecessary treatments, or supporting the addition of more treatment(s) when required, or by re-classifying patients differently compared with routine risk prediction methods. These improved patient outcomes should result in less harm and better cancer-related outcomes.
- Clinical evidence must be provided to align with the GEP test's proposed clinical place, noting the current MSAC guidelines for assessment reports, including the importance of presenting development and validation datasets, the concepts of incremental (prognostic) clinical validity and preferably (predictive) clinical utility, and considering results of relevant randomised controlled trials (RCTs) to date. MSAC considered that additional evidence would need to be provided to demonstrate at least incremental prognostic value, and noted the PROGRESS framework as relevant for assessing such evidence.
- The GEP test must have an acceptable fee based on acceptable incremental cost-effectiveness and net budget impact. This includes quantifying and valuing any estimated improvement in health outcomes that are contingent on improvements in care and/or prognostic confidence. MSAC considered that the fees proposed in each of the focused applications would likely result in unacceptably high ICERs per quality-adjusted life year based on previous applications. Thus, MSAC considered the proposed fees to be too high, unless an applicant can satisfactorily demonstrate that its GEP generates sufficient clinical utility. In the absence of improved health outcomes, then the basis for the proposed fee should be limited to the incremental costs of production of the test, as with any other pathology test.
- The GEP test must have an acceptable budget impact, based on robust estimates of the expected utilisation rates of testing for the proposed eligible population. MSAC considered that should more than one GEP test be MBS funded, there would be a risk of requesting more than one GEP test per patient (based on recently published research[1]),

[1] Bartlett, JMS et al. (2021) Comparative survival analysis of multiparametric tests—when molecular tests disagree—A TEAM Pathology study. *NPJ Breast Cancer* **7:**90.

which could lead to additional cost and discordant results leading to overall diminishing incremental prognostic value.

- Funded access to a GEP test would also need to be restricted to those patients who are most likely to benefit – MSAC advised an MBS-listing mechanism would be needed to limit use to such patients, such as a capped number of funded services per early breast cancer diagnosis. MSAC also advised it would require a better-defined population proposed to have access to the GEP test.
- As such "intermediate risk" should be better defined to minimise wasteful testing of patients adequately identified for appropriate treatment as being clearly either low risk or high risk. As a GEP test's greatest value will be for women at intermediate risk of future cancer recurrence, MSAC considered that adopting a more concrete definition of "intermediate risk" using a universally accepted scoring system would be helpful. In this context, MSAC noted that the National Institute for Health and Care Excellence (NICE; UK) guidelines restrict use of GEP tests to ER-positive, HER2-negative and lymph node-negative early breast cancer patients who are at intermediate risk of distant recurrence based on a validated tool, such as PREDICT or the Nottingham Prognostic Index.

MSAC advised a "generic" MBS listing that would not specify any branded GEP test option might mitigate risk and simplify administrative arrangements in an evolving setting, for example by allowing future GEP test options to be added, or by allowing existing GEP test options to change in terms of their methods of testing, genes assessed, and/or algorithms combining and reporting the individual gene results. However, MSAC noted a key difficulty with a generic MBS item would be that the three considered GEP tests have different prognostic values and thus will have different incremental prognostic values. MSAC also noted difficulties for clinicians in choosing which GEP test would be appropriate for each patient, as the three considered GEP tests assess different genes (with some overlap). In addition, given these differences in the GEP tests, it would not possible to develop a single quality assurance program covering more than one GEP test. Thus MSAC foreshadowed that support for MBS funding would be unlikely to allow a diagnosed patient to have multiple tests, whether using the same or a different GEP test.

4. Summary of consideration and rationale for MSAC's advice for MammaPrint®

MSAC noted that the applicant for MammaPrint® referred to two RCTs as providing supportive clinical trial evidence: MINDACT and TAILORx (the latter MSAC considered was not directly relevant because it involved Oncotype DX®, a different GEP test). The applicant asserted that MammaPrint® has prognostic and predictive benefits, primarily based on the results of the MINDACT trial. The applicant stated that its proposed fee of US$4200 (currently A$5000) is appropriate and non-negotiable due to the large number of genes reviewed, the corporate costs and the reagents needed. MSAC noted that the MBS is not intended to reimburse corporate research and development costs. MSAC also noted NPAAC's advice that the MammaPrint® GEP test did not have an external QAP in place, making it difficult to validate the test.

MSAC recalled from its March/April 2021 consideration that, compared with the intention to treat analysis, relying on MammaPrint® to avoid chemotherapy in the more appropriate per protocol analysis resulted in worse cancer outcomes, based on results assessed after both 5 and 8 years of follow-up. MSAC considered that the time-to-event curves appear to be diverging, and that the point estimates of the hazard ratios were consistent with superiority

for chemotherapy (with moderate certainty). MSAC noted that the associated confidence intervals did not cross zero for distant metastasis-free survival (DMFS) or for disease-free survival, and that the point estimate for overall survival was -0.01. Thus, MSAC concluded that using MammaPrint® for predictive purposes (specifically to make a treatment decision to avoid chemotherapy) would result in inferior cancer outcomes for some patients.

5. Background

MSAC Application 1376 was considered by PASC at its April and August 2014 meetings but did not progress to ESC or MSAC. In November 2016, the MSAC Executive recommended that the application should be submitted as a new application under the MSAC reform process, via the standard pathway.

Application 1376.1 was considered by MSAC at its March 2018. MSAC did not support public funding for a diagnostic microarray to measure the expression of 70 genes in breast cancer tissue (MammaPrint; hereafter the 70 gene signature test). MSAC considered the results of the key supporting trial (MINDACT) and noted that, on average, there was a consistent pattern of poorer breast cancer outcomes when chemotherapy was withheld in high clinical risk patients on the basis of a finding of low genomic risk using the 70 gene signature test. As a result, MSAC had little confidence that the 70 gene signature test could be used to justify withholding chemotherapy in such patients without negatively impacting upon important outcomes, including overall survival. MSAC was concerned that, overall, use of the 70 gene signature test to inform treatment decisions about whether to not add adjuvant chemotherapy to hormone therapy would lead to inferior breast cancer outcomes compared with current clinical care).

The applicant subsequently requested that MSAC revisit several statements in the March 2018 MSAC Public Summary Document (PSD) for Application 1376.1 and to note the 8-year follow-up data from the MINDACT study. This was considered by MSAC at its March-April 2021. After considering the updated clinical data, MSAC affirmed that the previous minutes of its March 2018 meeting require no change, including in relation to the accuracy of its description of the previously published results of the MINDACT trial. MSAC also advised that the extended follow-up results from this trial (8 years) further strengthened MSAC's previous conclusions and advice, with the results more unfavourable towards MammaPrint at 8 years than at 5 years. That is, withholding adjuvant chemotherapy in patients with early breast cancer using MammaPrint to identify those with low genomic risk (who would normally be given adjuvant chemotherapy because of high clinical risk) probably leads to worse cancer outcomes such as recurrent disease and distant metastases. (Public Summary Document [PSD], Application 1376.1, March 2018 and March/April 2021)

On 21 June 2021, the Royal College of Pathologists of Australasia (RCPA), together with the Department of Health and Cancer Australia, hosted a stakeholder meeting to discuss options for publicly funded access to gene expression profiling (GEP) tests in Australia. The outcome of this stakeholder meeting was that GEP test providers were invited to lodge focussed applications to support the prognostic value of GEP tests; the focussed application should also address Therapeutic Goods Administration (TGA) registration, the Department's proposed Medicare Benefits Schedule (MBS) item fee consistent with prognostic value, and provide a proposed MBS item descriptor.

Focussed applications were received for EndoPredict from Myriad Genetics Pty Ltd, MammaPrint from Genome Investigation Pty Ltd and Prosigna from Veracyte, Inc.

6. Applicant's comments on MSAC's Public Summary Document

Earlier this year, Piccart et al published their 8 year MINDACT follow up (Piccart et al Lancet Oncol 2021 March 12; 1-13) including subgroup analyses of women older and younger than 50 years of age. The Applicant will apply to MSAC to seek funding for MammaPrint testing in Australia for eligible women older than 50 years of age.

7. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website