MSAC Public Summary Document

Application No. 1342.1 - Gene expression profiling of 21 genes in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit

Sponsor/Applicant/s: **Genomic Health Inc**

Date of MSAC consideration: **MSAC 61st Meeting, 3-4 April 2014**

1. Purpose of application

The original application was submitted in November 2012 by Genomic Health Inc. and requested the Medicare Benefits Schedule (MBS) listing for a 21-gene expression profiling test (Oncotype DX®) in a subset of early breast cancer patients with node negative or up to 3 positive nodes oestrogen receptor-positive (ER+) or progesterone receptor-positive (PR+) and human epidermal growth factor receptor 2-negative (HER2-) disease.

2. Background

The application has been previously considered by MSAC in November 2013, which advised the Minister that MSAC did not support public funding.

Following MSAC's consideration, a re-application addressing MSAC's concerns was submitted by the applicant in February 2014.

3. Prerequisites to implementation of any funding advice

The proposed 21-gene expression profiling test is not subject to regulation by the Australian Therapeutic Goods Administration (TGA) as it is conducted in a single laboratory located in California in the United States of America (USA). It is registered only in the USA.

The California-based Genomic Health laboratory is certified to perform the proposed 21-gene expression profiling test by the United States' Centers for Medicare and Medical Service (CMS), is accredited by the College of American Pathologists (CAP) under the USA Clinical Laboratory Improvement Amendment (CLIA) of 1988, and operates in accordance with USA federal and state laws.

4. Proposal for public funding

The original application proposed the following MBS item descriptor.

Proposed MBS item descriptor

MBS [item number] Pathology Group P7 Genetics
Gene expression profiling of tumour samples (surgical resection preferably or core biopsy) by reverse-transcriptase polymerase chain reaction (RT-PCR) technique for 21 genes in breast cancer tissue. May only be used to test samples from patients with the following characteristics as determined by the referring clinician: • early breast cancer (stages I-II) • suitable for hormone therapy • suitable for adjuvant chemotherapy • ECOG performance status 0-2 and As determined by an Australian pathology laboratory • invasive tumour >2mm • node negative or 1-3 positive nodes • oestrogen positive or progesterone positive as determined by immunohistochemistry • HER2 negative as determined by immunohistochemistry and/or in situ hybridisation May only be used once per new primary breast cancer diagnosis Fee: $4,200

The original application proposed an MBS fee of $4,200 to cover the costs of collecting and preparing the sample (performed in Australia), shipping the sample overseas, performing the test in the USA laboratory, reporting the results and returning the sample to Australia.

The re-application proposed a hidden **(redacted)**% reduction in the cost of the test to $**(redacted)**from that proposed initially ($4,200). This reduction would be achieved by **(redacted)**. The re-application acknowledged that arrangements would need to be agreed to allow for this.

MSAC observed that the decision of whether to accept the applicant's proposal for a hidden pricing arrangement behind the published fee **(redacted)**was a policy matter for the government. However, MSAC noted ESC advice that a similar arrangement is known to exist in England and that hidden prices are also used in the Pharmaceutical Benefits Scheme (PBS). MSAC therefore agreed with ESC in advising that, should this offer be accepted and implemented, the existence of hidden prices should not be kept confidential, even if its details are kept confidential.

5. Summary of Consumer/Consultant Feedback

Feedback from consumers and professional bodies broadly supported testing because knowledge of the susceptibilities of a patient's breast cancer to chemotherapy and /or endocrine therapy allows more informed decision making regarding the risks and benefits of treatment.
It was also noted that, for women with a recurrence score which indicates chemotherapy is not required, there are advantages in avoiding a toxic treatment and its associated side effects that may ultimately be of no benefit to them.

The original cost of the test ($4,200) was consistently raised as being out of reach for most women; therefore it was considered that listing the test would make access more equitable. It was acknowledged that whilst the test is not perfect, it is an important tool to assist women in making decisions regarding their treatment.

6. Proposed intervention's place in clinical management

The intervention would be used in the clinical setting as an adjunct to current clinical practice rather than replacing any part of it.

The application stated that there is no change in the treatment algorithm between the current and proposed pathways for patients in Australia diagnosed with breast cancer. The pathway reflects the assessment of all patients diagnosed with breast cancer up to the point of surgery.

It was proposed that the proposed 21-gene expression profiling test be funded as an adjunctive test following surgery for a subgroup of patients who are classified as stage I or II, ER+ or PR+ and HER2– with 0-3 positive lymph nodes.

The test results would be used to guide the use of adjuvant chemotherapy in addition to existing prognostic approaches based on tumour staging, histological features and lymph node involvement.

Expert opinion sought on the time to commence adjuvant chemotherapy after surgery indicated that treatment usually commenced within 3-6 weeks after surgery. The results of the proposed 21-gene expression profiling test would be available within two weeks of the sample being sent to the Genomic Health laboratory in the USA, therefore there was no anticipated delay for treatment to commence. There would be a need for repeat testing in less than 10% of cases.

The algorithm considered all patients with early breast cancer (stage I-II) who undergo primary surgical resection.

7. Comparator

MSAC previously accepted usual care, defined as traditional clinical judgement based on clinical (for example, age, menopausal status), pathological (tumour size, tumour grade) and molecular (ER, PR, HER2) parameters to estimate the risk of recurrence by combining them in informal or formal algorithms, as the appropriate main comparator. The re-application retained this comparator.

8. Comparative safety

The original application presented no comparative safety data but noted "Given this is a gene expression test on tissue that was removed during surgery for breast cancer (i.e. not specifically for the test), there are no relevant safety issues."

As this test is not registered with TGA, there is no control in Australia in relation to quality assurance and quality control issues.

MSAC previously noted that although the test is procedurally safe because it relies on samples already taken for other purposes, there is a degree of risk in the misallocation of patients to risk categories, which would affect the outcomes of the therapy subsequently selected.

There was nil change to the comparative safety in the re-application.

9.   Comparative effectiveness

The re-application stated that the original application presented MSAC with two prospective studies supporting the predictive validity of the proposed 21-gene expression profiling test (Paik et al. 2006 and Albain et al. 2010).

The re-application indicated that, the Paik (2006) and Albain (2010) prospective data are sufficient to determine the predictive ability of the proposed 21-gene expression profiling test. The results are shown in the table below.

Table 1: Hazard ratio for disease free survival of chemotherapy and hormonal therapy versus hormonal therapy by risk subgroup defined by recurrence score from the proposed 21-gene expression profiling test

Recurrence score subgroup	Node negative (Figure 3, Paik et al., 2006)	Node positive (Figure 5, Albain et al., 2010)
Low recurrence score	1.31 (0.46, 3.78)	1.02 (0.54, 1.93)
Intermediate recurrence score	0.61 (0.24, 1.59)	0.72 (0.39, 1.31)
High recurrence score	0.26 (0.13, 0.53)	0.59 (0.35, 1.01)

The re-application also indicated that, waiting for the results from the three pending trials OPTIMA, TAILORx and RxPONDER would not help MSAC answer the question on the predictive ability of the test over and above the prospective data which has already been presented. The re-application also noted that there are no other new prospective data available in the foreseeable future.

The re-application stated that, based on the strength and quality of evidence supporting the predictive validity of the proposed 21-gene expression profiling test, the test has been specifically recommended as a predictive tool to inform chemotherapy decisions in a number of international breast cancer guidelines (Harris et al., 2007; NCCN, 2011; Aebi et al., 2010; Gnant et al., 2011; and Goldhirsch et al., 2013).

10.   Economic evaluation

The re-application amended the original economic evaluation presented as a cost-utility analysis to address the three proposed changes in the re-application. These were:
- a reduced fee through a confidential agreement with the Commonwealth
- examining the effect of removing the predictive ability of the proposed 21-gene expression profiling test in intermediate and high risk subgroups on the ICER
- adjusting HT recurrence rates to reflect lower rates observed with anastrozole as opposed to tamoxifen.

The respecified base case was also provided to include corrections of minor data entry errors. In the response to ESC advice submitted previously, these ICERs were $18,496 and $2,538 for the node-negative and node-positive patient groups respectively. The results in the node-positive population were noted in the reapplication to appear quite sensitive to this variable because the costs were so close to neutrality in the base case.

The re-application proposed reducing cost to the Commonwealth through a confidential rebate of $**(redacted)**/test rendered whilst keeping the published schedule fee as $4,200. This is a model similar to that used under the PBS however, as the MBS framework is different, the proposal would require further discussions to implement.

11.   Financial/budgetary impacts

The re-application summarised the net financial impact to government expenditure expected from a "Medicare-like" funding of the proposed 21-gene expression profiling test. The calculations incorporated the rebates proposed above with the expected utilisation of the test unchanged from the original application.

The re-application also indicated that the test would attract a Medicare benefit of 85% and the patient out of pocket cost would be capped. The Department noted that, as the sample for the test will in most cases have been taken during hospitalisation, it would attract a Medicare benefit of 75% with no cap on the patients out of pocket cost (MBS rule G.10.1). MSAC remained concerned about the high out-of-pocket costs for patients, now estimated at $1,050 per test, assuming that only the MBS fee is charged.

The application estimated that there would be 1,789 services in Year 1, increasing to 3,882 services in Year 5. These were considered to be likely underestimates in relation to both the numbers of eligible patients and the rate of uptake for the test.

The re-application estimated that in the first year of funding, the net expenditure on the proposed 21-gene expression profiling test after rebates was estimated to be approximately $6 million. By year five, net expenditure on the proposed 21-gene expression profiling test is expected to be approximately $13million.

After accounting for cost savings due to lower use of chemotherapy and other health care services, the re-application noted that the net financial impact of the proposed 21-gene expression profiling test to government expenditure is expected to be approximately $4 million in the first year of funding to $9 million in the fifth year of funding.

12.   Other significant factors

Nil.

13.   Summary of consideration and rationale for MSAC's advice

MSAC reviewed the responses provided in the re-application to the four main concerns listed in its November 2013 advice to the Minister. MSAC noted that no new evidence was provided in the reapplication.

Prospective data on predictive value beyond prognostic value and thus clinical utility

MSAC noted that the three ongoing randomised trials involving the proposed 21-gene expression profiling test are not scheduled to produce results for several years. TAILORx (in node-negative patients) and RxPONDER (in node-positive patients) were designed to further investigate the usefulness of the test for patients with less than a revised "high" recurrence score threshold (ie after excluding patients with a recurrence score of 25 and above rather than 31 and above). OPTIMA was designed to compare outcomes between (a) treating all eligible low-risk node-positive patients with chemotherapy + hormone therapy and (b) treating these patients with hormone therapy and using the result of the proposed test to guide the decision as to whether to add chemotherapy.

MSAC reconsidered the primary evidence in the previous application as summarised in Table 1 and corresponding Kaplan-Meier curves for the subgroup analyses. The committee noted that the recurrence score cut points (18 and 31) emphasised in the original application were prespecified for both re-analyses of completed randomised trials which examined the proposed test. Tests for

interaction between recurrence score and additional chemotherapy treatment effect on disease-free survival were statistically significant (P=0.038 for the likelihood ratio test for interaction in Paik et al, 2006; and P=0.029 for the first five years of follow-up [P=0,053 overall] in Albain et al, 2010). However, the need to retrospectively rely on re-analysing only a subgroup of the original intent-to-treat populations, ie only those who had samples which could be subjected to the proposed test (651/2299 = 28% for Paik et al., 2006 and 367/1477 = 25% for Albain et al., 2010), introduced a risk of bias. Overall, MSAC accepted that this evidence indicates that the proposed test is detecting a signal by consistently predicting additional benefit from adding chemotherapy to hormone therapy in the prespecified high risk group, but less consistently predicting no additional benefit from adding chemotherapy in the prespecified intermediate or low risk groups.

MSAC remained concerned that this weak evidence of moderate predictive value did not readily translate into clinical utility. MSAC disagreed with the applicant that uptake of the proposed test by clinicians constituted evidence of clinical utility, because uptake is a matter of implementation, not a characteristic of test performance. MSAC emphasised that clinical utility related initially to whether results from the test changed clinical decision-making and ultimately to whether these changed decisions improved health outcomes (and avoided unnecessary use of health care resources).

MSAC remained concerned about the basis for estimating the extent to which the results of the proposed test would change therapy decisions beyond surgery and hormone therapy (ie whether to add chemotherapy when otherwise it would not have been added, or whether to not add chemotherapy when otherwise it would have been added). This concern was exacerbated by changing the thresholds for risk categorisation for the ongoing trials without a clear rationale, and the pre-MSAC response that the recurrence score reported via its continuous scale rather than in any risk categorisation might be more influential on changing chemotherapy decisions. MSAC considered that varying the approach to interpreting the recurrence score is likely to vary the clinical utility results.

MSAC's concerns with clinical utility affected its interpretation of the modelled economic evaluation. Although the differentiation of the effect of adding chemotherapy to hormone therapy is numerically greater for node-negative than node-positive patients, the modelled economic evaluation has, paradoxically, a more favourable outcome for node-positive patients than node-negative patients. MSAC considered that this appeared to be affected by both the larger overall baseline risk in node-positive patients resulting in a larger absolute effect of adding chemotherapy in the high risk population (>31 recurrence score), and the relatively large proportion of patients for whom cost offsets are achieved by changing the decision from adding chemotherapy to not adding chemotherapy. In other words, as acknowledged by the applicant, the driver of the more favourable node-positive economic evaluation is the reduction in use of chemotherapy in lower risk patients. In this regard, MSAC noted that this particular group forms the basis of the ongoing OPTIMA trial, which is designed to show whether not adding chemotherapy on the basis a result from the proposed test would result in poorer health outcomes for these patients. In relation to node-negative patients, MSAC continued to regard the results of the economic evaluation as being uncertain, but noted that the multi-way sensitivity analysis yielded an incremental cost of $63,883 per QALY gained, which was unacceptably high in these circumstances.

Further data regarding the gains in patient health outcomes

MSAC reiterated its doubts about the extent to which health outcomes would change as a result of modelled changes to therapy decisions. These arose for two reasons. First, the therapies and the way they were delivered in the trials which provided the basis for the primary evidence in the previous application did not represent contemporary therapeutic

regimens. Second, without a strong biological basis for the relationship between risk categorisations from the proposed test and absolute differences in treatment effects from changing therapy options, the magnitude of the health outcome gains predicted by the model remains uncertain.

MSAC noted that the re-application provided sensitivity analyses of the modelled economic evaluation to use anastrozole as more contemporary hormone therapy rather than tamoxifen, which appropriately reduced the incremental health outcomes of adding chemotherapy. However, the reapplication did not provide sensitivity analyses to represent the effect of using contemporary chemotherapy. MSAC also noted that the ongoing trials are using more contemporary therapeutic regimens overall, which may provide useful information on this issue in the future.

MSAC noted that the applicant acknowledged the challenge of developing therapy-specific evidence, but then submitted a model which relied on a claim that the effect is broadly applicable, despite the recognised lack of evidence. In this regard, MSAC observed that there is a major difference between a panel of expert clinicians agreeing that a test "could" be utilised (eg Goldhirsch et al., 2013), and the government committing to fund a test that would be utilised by a broader range of clinicians.

MSAC noted that the re-application provided a series of sensitivity analyses which modified some of the clinical and economic claims with respect to the proposed test, specifically to "remove the predictive ability of Oncotype DX® in intermediate and high risk patients" and to adjust the hormone therapy recurrence rates to "reflect lower rates observed with anastrozole as opposed to tamoxifen". MSAC considered that the reapplication's proposal, for modelling purposes, to pool the intermediate and high risk categories whilst keeping the low risk category separate conflicted with both MSAC's conclusion that the high risk category has a distinct predictive profile compared to the other two categories, and also the exclusion of the high risk category from the ongoing randomised trials for the same reason.

MSAC also considered the series of concerns raised by ESC in interpreting these analyses. Although the pre-MSAC response from the applicant indicated that some of these concerns arose from errors in the table presenting the basis of the new analyses rather than within the modelling itself, MSAC agreed with the ESC advice that, before considering the sensitivity analyses presented in the reapplication in any substantive way, there would first need to be independent verification of the calculations, review of the biological plausibility of the new assumptions, and checking of how these assumptions are applied to produce the new sensitivity analyses.

Comparative data with other predictive tests

MSAC noted that a key limitation of the available evidence related to the variability in "normal care", as demonstrated by the variability in the number needed to test inputs to the model. Normal care includes access to a range of clinical and test information, including HER2, oestrogen receptor status and progesterone receptor status and increasingly Ki-67. MSAC was concerned that these cheap and readily available sources of information were already appropriately influential on therapeutic decision making and it was important to ascertain the additional benefit (in terms of health outcomes and use of other health care resources) of adding the result of the proposed test to this array of information in order to judge whether this justifies the cost of the proposed test.

MSAC acknowledged that the IHC-4 test and its algorithms were less well developed than the proposed test and does not yet constitute "usual care", but it provided an example of how

clinicians are already using a range of tools to guide therapy decision making, and it is this current practice or "usual care" that forms the comparator against which the claimed improvements and extra test cost needs to be assessed. In this context, MSAC also noted both the recent exchange of letters in Annals of Oncology, supplied by the applicant in response to a late MSAC request, on the effect of HER2 negative status on the predictive power of the proposed test; and also the fact that the proposed item descriptor for the proposed test requires eligible patients to be HER2 negative.

MSAC noted that the re-application questioned the analytical robustness of the IHC-4 test. In this regard, MSAC recalled that it had specifically queried the metric used to assess the analytical reproducibility of the proposed test, and noted that the re-application did not respond to this issue or to the clinical correlate, i.e. the probability of a patient being assigned to a different risk category on re-testing. MSAC further noted that the re-application dismissed some data relating to the IHC-4 test on the grounds that its utility may be cohort-specific, but did not apply this criterion to its own proposed test.

<u>High cost of the proposed test to the government and the consumer</u>

MSAC noted that the out-of-pocket payment would be $1,050 for the proposed test if funded by the government as proposed by the applicant. This would constitute a substantial cost for patients for a publicly funded medical service, even if a proportion of patients would have this cost absorbed by private health insurance.

MSAC also noted that the proposed rebating arrangement to government would reduce the overall cost of the proposed test to government. However, MSAC noted that the re-application did not respond to MSAC's November 2013 concern about the potential for the test to be requested for other patients with early breast cancer beyond those identified by the proposed item descriptor without clear clinical justification for the increased costs.

<u>Other issues</u>

MSAC reiterated its concern about the reliance on a single laboratory performing the test located in the United States outside Australian standards maintained through the Therapeutic Goods Administration (TGA) or the National Association of Testing Authorities (NATA) and its questioning of the need to develop new arrangements to publicly fund a test that is available only outside Australia with the potential for delay in results and lack of local quality assurance.

MSAC discussed whether there was another way forward for the application whilst awaiting new data from the ongoing trials in lower risk patients. MSAC's main concerns remained:
- quantifying the incremental clinical utility of the proposed test over other methods to assimilate similar information used by clinicians now and in the likely near future
- needing to be more confident that clinicians would follow the guidance provided by the result of the proposed test when deciding whether to add chemotherapy to hormone therapy
- needing to confirm whether this clinical decision making would continue to be influenced by other information
- needing to confirm whether this clinical decision making would be influenced by variations in the way the result of the proposed test is conveyed (eg as the recurrence score, or as falling within one of the three categories of risk with their varying thresholds)
- not knowing who set the thresholds for the categories of risk at various times (eg owner of the proposed test, clinical trial investigators)

- not knowing what the evidentiary basis was for setting the original thresholds for the categories of risk and what the subsequent evidentiary basis was for varying them in the different circumstances of the ongoing randomised trials.

14. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of gene expression profiling of 21 genes in breast cancer to quantify the risk of disease recurrence and predict the need for adjuvant chemotherapy, MSAC did not support public funding because of limitations identified in the performance, clinical utility, cost-utility, and utilisation of the test.

In conveying this advice, MSAC recognised the desire for patients and clinicians to have greater clarity in predicting risk of recurrence and response to therapy options before making decisions regarding chemotherapy. Nonetheless, given the limitations identified above, MSAC was not prepared to support public funding.

MSAC considered that any further reapplication should be made via ESC and would require external evaluation.

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

Genomic Health and Specialised Therapeutics Australia are disappointed with the MSAC decision not to recommend the reimbursement of Oncotype DX breast cancer test in Australia. The evidence to support the clinical effectiveness and cost effectiveness of Oncotype DX providing information beyond traditional measures, is available from multiple well designed and controlled clinical studies and supported from the multiple independent review committees, such as St Gallen's, ESMO, ASCO, NCCN. Oncotype DX is the only genomic test with clinical evidence to predict the likelihood of chemotherapy benefit in invasive breast cancer. More than 440,000 Oncotype DX tests have been ordered by more than 19,000 physicians in over 70 countries since the test became available in 2004. In the past 12 months, over 300 Australian women have received Oncotype DX at considerable personal cost. The MSAC decision also goes against decisions made in other countries of the Commonwealth where the test is reimbursed. Indeed, Canada, Ireland and more recently the UK have all agreed to reimburse the test for eligible patients. We will continue to work with Australian physicians and other stakeholders to secure access for Australian patients as we believe that patients are best served when their treatment decisions are based on evidence and on the biology of disease.

16. Linkages to other documents

Further information is available on the MSAC Website at: www.msac.gov.au.