UUMSAC Application 1163:

Final Decision Analytic Protocol (DAP) to guide the assessment of HER2 testing in advanced gastric cancer

October 2011

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is the decision analytic protocol that will be used to guide the evidence-based assessment of HER2 testing in advanced gastric cancer. This protocol has been finalised after inviting relevant stakeholders to provide input and has been developed using the widely accepted "PICO" approach.

The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients – specification of the characteristics of the population or patients in whom the intervention is intended to be used;
Intervention – specification of the proposed intervention;
Comparator – specification of the therapy most likely to be replaced or added to by the proposed intervention; and
Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention.

Purpose of the application

In February 2011, an application from Roche Products Pty Limited was received by the Department of Health and Ageing requesting a Medicare Benefits Schedule (MBS) listing for HER2 testing in advanced adenocarcinoma of the stomach or gastro-oesophageal junction –henceforth described as gastric cancer. This application relates to a test already funded on the MBS (immunohistochemistry to detect over-expression of the human epidermal growth factor receptor 2 [HER2]) as well as a new test (*in-situ* hybridisation for detection of amplification of the HER2 gene).

Adelaide Health Technology Assessment (AHTA), School of Population Health and Clinical Practice, University of Adelaide, as part of its contract with the Department of Health and Ageing, has developed this decision analytic protocol with input from the Applicant, other stakeholders and the PASC members. This protocol will guide the assessment of the safety, effectiveness and cost-effectiveness of HER2 testing in gastric cancer patients, in order to inform MSAC's decision-making regarding public funding of the HER2 test/s which determine patient eligibility for access to trastuzumab treatment.

Background

Current arrangements for public reimbursement

Immunohistochemistry (IHC) for the detection of oestrogen, progesterone and HER2 are currently listed on the MBS (see Table 1 for relevant item number and descriptor). This item number is currently not restricted by patient indication.

In contrast, there are currently no arrangements for the public reimbursement of *in situ* hybridisation (ISH) in advanced gastric cancer. Roche Products Pty Limited currently fund HER2 testing by ISH in IHC (0, 1+ and 2+) equivocal patients with advanced gastric cancer. This determines the eligibility of patients for its trastuzumab (Herceptin) patient access program. Testing is provided by five reference laboratories in Australia (SydPath, St Vincent's Hospital, NSW; Pathology Queensland, Princess Alexandra Hospital, QLD; Department of Pathology, Peter MacCallum Cancer Centre, VIC; SA Pathology, SA; and PathWest QeII Medical Centre, WA) and is available to private and public patients.

The only data available regarding the utilisation of HER2 testing relate primarily to the use of IHC in breast cancer. Currently, IHC testing is Medicare-funded for breast cancer and the MBS descriptor also allows testing for oestrogen or progesterone receptors (Table 1).

Table 1 Current MBS item descriptor for IHC testing

Category 6 – Pathology services
MBS 72848 Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 of the following antibodies - oestrogen, progesterone and cerb- B2 (HER2) Fee: $75.00 (Item is subject to rule 13 – If more than 1 of the services mentioned in items 72846, 72847, 72848; 72849 and 72850 or 73059, 73060, 73061, 73064 and 73065 are performed in a single patient episode, a medicare benefit is payable only for the item performed that has the highest scheduled fee.)

In breast cancer, ISH testing is provided and funded by Roche Products Pty Limited and is required to determine HER2 status and thus eligibility for Pharmaceutical Benefits Scheme (PBS)-subsidised treatment with trastuzumab (Herceptin), a monoclonal antibody that binds selectively to the HER2 protein and inhibits uncontrolled cellular (tumour) growth. IHC testing (through MBS item 72848) complements ISH testing to determine eligibility for the Herceptin program.

The utilisation of MBS item 72848 indicates that between July 2009 and June 2010 there were 6,438 services claimed (Table 2). The majority of these are likely to be in women with breast cancer as suggested by the breakdown of item utilisation by sex. These data are reflective of IHC testing in the private healthcare setting and do not reflect the testing that occurs in the public healthcare system.

Table 2 Medicare item utilisation between July 2009 and June 2010

Item number and subgroup	Services
72848 – Total	6,438
Women	6,278
Men	160

It is estimated that there are approximately 2,000 cases of incident gastric cancer per year in Australia (AIHW & AACR 2010). Based on data from the NSW Central Cancer Registry between 2004 and 2008, 26.1% of patients have localised disease at the time of diagnosis, while 29.8% have regional lymph node involvement, and 28.4% have distant metastases[1]. Given that a late stage diagnosis is the norm, it could be expected that the use of IHC testing will increase should trastuzumab receive public funding for this additional clinical indication ie advanced gastric cancer. Currently there is no reason to test for HER2 status in gastric cancer patients (other than for those patients who wish to access trastuzumab

[1] NSW Central Cancer Registry 2004-2008. Accessed - August 2011. http://www.statistics.cancerinstitute.org.au/prodout/top20_extent/top20_extent_lhnres_incid_2004-2008_NSW_P.htm

through the Roche patient access program) but should trastuzumab be publicly funded this situation will change.

It is expected that the extent of confirmatory ISH testing in gastric cancer will vary depending on the additional clinical and cost benefit that it produces over and above the IHC test result – various clinical scenarios will be explored as part of the proposed assessment of HER2 testing.

Regulatory status

In vitro diagnostic medical devices (IVDs) are, in general, pathology tests and related instrumentation used to carry out testing on human samples, where the results are intended to assist in clinical diagnosis or in making decisions concerning clinical management (Therapeutic Goods Administration 2009).

Manufacturers of Class 2, Class 3 and Class 4 commercial IVDs must hold certification from a regulatory body to show compliance with a suitable conformity assessment procedure (Therapeutic Goods Administration 2009).

There are several kits available in Australia to determine HER2 status (Table 3), which have differing resource implications. The classification of these kits range between *in vitro* diagnostic (IVDs) Class 2 and 3.

Class 2 IVDs are those that detect the presence of, or exposure to, infectious agents that are not easily propagated in the Australian population or that cause self-limiting diseases. Class 2 IVDs that present a moderate individual risk include those which provide results that are not intended to be used as the sole determinant in a diagnostic situation, or where an erroneous result rarely puts the individual in immediate danger (Therapeutic Goods Administration 2009).

Class 3 IVDs are devices which present a moderate public health risk, or a high individual risk and include those used for selection of patients for selective therapy and management, or for disease staging, or in the diagnosis of cancer including cancer staging, where initial therapeutic decisions will be made based on the outcome of the test results, for example, personalised medicine (Therapeutic Goods Administration 2009).

In terms of using HER2 testing to selectively determine access to trastuzumab therapy, these test kits and any in-house IVDs would be considered as Class 3 IVDs.

Table 3 Regulatory status of HER2 testing in Australia

Testing method	Test kit / antibody or DNA probe	Sponsor	ARTG number	Approved indication
IHC	HercepTest™	Dako	76270	Not included on record[a]
	Roche Diagnostics Ventana anti-Her-2/neu (4B5) primary antibody	Roche Diagnostics Australia	In Progress	N/A
	Roche Diagnostics Confirm anti-Her-2 neu	Roche Diagnostics Australia	Exempt	N/A
FISH	HER2 FISH PharmDx™	Dako	76270	Not included on record[a]
	PathVysion kit	Abbott Molecular	23280	Not included on record[a]
CISH	SPOT-Light® HER2 CISH kit	Invitrogen	132070	For *in vitro* diagnostic use only
SISH	ultraView SISH detection kit	Roche Diagnostics Australia	174896	Class II IVD - intended to be used alone or in combination with other IVDs to perform various tissue related histology and cytology-related tests and procedures
	INFORM HER2 DNA single probe	Roche Diagnostics Australia	180933	Class III IVD - DNA IVD probes intended to be used in genetic testing to provide information about acquired genetic alterations, which may include chromosomal alterations, mutations and/or alterations in gene expression, and which may be used to characterise haematological or solid tumour malignancies and/or provide prognostic information.
	ultraView Alk Phos Red ISH Detection kit	Roche Diagnostics Australia	174896	Class II IVD - intended to be used alone or in combination with other IVDs to perform various tissue related histology and cytology-related tests and procedures
	INFORM Chromosome 17 single probe	Roche Diagnostics Australia	176103	Class II IVD - Various products intended to be used alone or in combination with other IVDs to perform various human genetics-related tests (e.g *In Situ* Hybridisation)
	ultraView SISH DNP detection kit	Roche Diagnostics Australia	174896	Class II IVD - intended to be used alone or in combination with other IVDs to perform various tissue related histology and cytology-related tests and procedures
	Ultraview Red ISH DIG Detection kit	Roche Diagnostics Australia	174896	Class II IVD - intended to be used alone or in combination with other IVDs to perform various tissue related histology and cytology-related tests and procedures
	INFORM HER2 Dual ISH DNA probe cocktail	Roche Diagnostics Australia	180933	Class III IVD - DNA IVD probes intended to be used in genetic testing to provide information about acquired genetic alterations, which may include chromosomal alterations, mutations and/or alterations in gene expression, and which may be used to characterise haematological or solid tumour malignancies and/or provide prognostic information.

[a] these devices were listed on the ARTG prior to the introduction of the regulatory framework for in-vitro diagnostic medical devices; IHC = immunohistochemistry; N/A = not applicable; FISH = fluorescence *in situ* hybridisation; CISH = chromogenic *in situ* hybridisation; SISH = silver *in situ* hybridisation

Intervention

Description

Adenocarcinoma of the stomach, or gastric cancer (including cancer of the gastro-oesophageal junction), is often diagnosed at a late stage of the disease. For cases of gastric cancer diagnosed between 1998 and 2004, the five year relative survival was approximately 25% (AIHW & AACR 2010). For early localised, non-metastatic cancer complete surgical resection may be curative (Songun et al 2010; De Vita et al 2010). However, data from the NSW Central Cancer Register (1980-2003) suggest that even those with localised disease at the time of diagnosis have only a 53.3% survival rate at five years. For those with cancer that has spread to regional lymph nodes at the time of diagnosis, five year survival is 29.5%, whereas for those with distant metastases, five year survival is only 7%. [2] Most improvement in survival from gastric cancer occurs within five years of the diagnosis, with a plateau in survival thereafter (Tracey et al 2007).

The sponsor has proposed that HER2 testing is performed on tissue samples from patients with advanced gastric cancer (equivalent to stage III and IV) in order to be able to access trastuzumab therapy. Table 4 and Table 5 together define the categories in the TNM staging system. Clinical advice suggests that patients with inoperable locally advanced or metastatic gastric cancer should be eligible for HER2 testing, irrespective of staging, because of the available treatment options. Some locally advanced stage III cancers can be treated surgically; and surgical treatment is first line therapy because it is potentially curative.

[2] Noting that survival has been improving in each diagnostic period since 1980 and so recent survival data are likely to be better than these results which have been averaged across a 24 year period.

Table 4 TNM staging of gastric cancer

Primary tumour (T)		Regional lymph node (N)		Distant metastasis (M)	
TX	Primary tumour cannot be assessed	NX	Regional lymph node(s) cannot be assessed	MX	Distant metastasis cannot be assessed
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	M0	No distant metastasis
Tis	Carcinoma *in situ*: intraepithelial tumour without invasion of the lamina propria	N1	Metastasis in 1–6 regional lymph nodes	M1	Distant metastasis
T1	Tumour invades lamina propria or submucosa	N2	Metastasis in 7–15 regional lymph nodes		
T2	Tumour invades muscularis propria or subserosa	N3	Metastasis in >15 regional lymph nodes		
T2a	Tumour invades muscularis propria				
T2b	Tumour invades subserosa				
T3	Tumour penetrates serosa (visceral peritoneum) without invasion of adjacent structures				
T4	Tumour invades adjacent structures.				

Source: (Okines et al 2010)

Table 5 American Joint Committee on Cancer stage grouping

Stage grouping	T stage	N stage	M stage
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2a/b	N0	M0
Stage II	T1	N2	M0
	T2a/b	N1	M0
	T3	N0	M0
Stage IIIA	T2a/b	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T3	N2	M0
Stage IV	T4	N1–3	M0
	T1–3	N3	M0
	Any T	Any N	M1

Source: (Okines et al 2010); orange shading denotes proposed eligibility for HER2 testing

The HER2 protein is a transmembrane tyrosine kinase receptor and part of the epidermal growth factor receptor family (Jorgensen 2010). Activation of the receptor results in rapid cell growth, differentiation, survival and migration (Gravalos & Jimeno 2008). Gene amplification and over-expression of this receptor in patients with gastric cancer was first reported in 1986 (Fukushige et al 1986; Sakai et al 1986). There has been debate regarding the prognostic effect of HER2 expression in gastric cancer with early studies failing to find an association with outcome, along with a recently reported large study (Grabsch et al 2010; Sasano et al 1993; Tateishi et al 1992). Conversely, other studies have found negative (Gravalos & Jimeno 2008) or positive (Yoon et al 2011) prognostic effects of the biomarker, this variation may – in part – be due to the level of HER2 expression present in the population being studied.

In patients with advanced gastric cancer, who have not been previously treated, suitability for treatment with trastuzumab may be determined by assessment of the presence of HER2 (either detection of gene amplification or protein over-expression) in the biopsy of tumour tissue and resection samples. Over-expression and amplification can be detected by IHC and ISH, respectively.

IHC is performed on formalin-fixed, paraffin-embedded tumour samples and detects the presence of the HER2 receptor in the cellular membrane using a specific antibody for the HER2 protein. Antibodies which have bound to the receptor are then detected by another subsequent antigen-antibody reaction. Visualisation of these immunogenic reactions occurs as a result of labelling the secondary antibody with either dyes or enzymes which are involved in chromogenic reactions. HER2 positivity is based on the staining patterns seen in the biopsy and surgical samples (Table 6).

Table 6 Scoring of IHC staining pattern in tumour biopsy samples

Staining intensity score	Staining pattern	HER2 over-expression assessment
0	No reactivity or membranous reactivity in < 10% of tumour cells.	Negative
1+	Faint/barely perceptible membranous reactivity in > 10% of tumour cells; cells are reactive only in part of their membrane.	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in > 10% of tumour cells.	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in > 10% of tumour cells. Biopsy (not surgery) samples with cohesive IHC 3+ clones are considered positive irrespective of percentage of tumour cells stained.	Positive

Source: (Hofmann et al 2008); IHC = immunohistochemistry

Detection of amplification of the HER2 gene is performed with ISH which detects copies of the HER2 gene within the cells using specific labelled probes that are detectable with bright-field methodology (chromogenic [CISH] or silver [SISH]) or by fluorescent

microscopy (FISH). Different types of probes are available and these determine the method of visualisation; including CISH, SISH or FISH. If amplification is occurring, there will be increased copies of the gene detected in the cells. Determination of gene amplification can be determined by the ratio of HER2 gene copy number to control gene copy number as well as the absolute HER2 gene copy number (Rüschoff et al, 2010). Discordance between CISH and FISH with low-level amplification has been observed in breast cancer samples (Penault-Llorca et al 2009), however, only one study was identified that assessed the concordance rate between CISH and FISH in gastric cancer, which reported a perfect correlation between the two (Yan et al 2010). Further research on the comparative test performance (and costs) of the different ISH testing methods to detect HER2 gene amplification in gastric cancer tumour samples is needed.

Delivery of the intervention

According to calculations based on incidence and mortality data from 1998 to 2007, the incidence and mortality of stomach cancer in Australia was estimated to be 2,000 and 1,100 persons in 2010 respectively (AIHW & AACR 2010).

The NSW Cancer Registry (2004-2008) reports that, at the time of diagnosis, 58.3% of cases have either regional lymph node involvement or distant metastases. In the absence of combined incidence and prevalence data reporting on the proportion of those who are either diagnosed or have progressed to inoperable locally advanced or metastatic gastric cancer, it is assumed that this percentage may approximate the population suitable for receiving IHC with/without ISH testing to determine HER2 status. The expected utilisation of IHC and ISH testing to determine HER2 status is therefore 1,166 per year. It is unclear how many tumour samples would require retesting due to a sample that was not evaluable.

Table 7 Stomach cancer in NSW between 2004 and 2008 by extent of disease

Extent of disease at diagnosis	Cases diagnosed between 2004 and 2008 in NSW
Total	3,275
Localised	854 (26.1%)
Regional lymph node involvement	977 (29.8%)
Distant metastases	931 (28.4%)
Unknown	513 (15.7%)

Source: NSW Central Cancer Registry 2004-2008. [Accessed, August 2011].
http://www.statistics.cancerinstitute.org.au/prodout/top20_extent/top20_extent_lhnres_incid_2004-2008_NSW_P.htm

Biopsy samples are routinely taken as part of clinical practice in establishing a gastric cancer diagnosis and for tumour staging. Assuming there is adequate tumour material, the original biopsy sample would also be used for HER2 testing. MESP and PASC members suggest that the most appropriate testing algorithm is yet to be established due to issues regarding heterogeneity in sample staining, false positives and negatives and (dis)agreement between IHC and ISH. Consequently, different testing strategies should be explored to determine the optimal use of the two tests to determine eligibility for

trastuzumab treatment. It is also suggested that ISH should only be performed by an accredited reference laboratory with specific expertise in ISH and preferably with respect to HER2 testing in gastric cancer.

Biopsy and surgical samples are stored for a period of at least ten years for subsequent testing according to the National Guidelines for Tissues Storage; many centres and institutions would keep samples indefinitely. If repeat testing is necessary, due to initial results that are not evaluable, it is unlikely that additional biopsies would be required because stored samples would be sufficient to enable new material for testing. Similarly, once HER2 status of the tumour is determined, no further testing would be required.

Prerequisites

Ordering of HER2 testing should be restricted to surgeons, gastroenterologists or oncologists once a diagnosis of inoperable locally advanced or metastatic gastric cancer has been established.

Delivery of the intervention and reporting of the results would be provided by a pathologist with knowledge and expertise in testing for gastric cancer and IHC and/or ISH testing. As a consequence, billing of the intervention would be done by the pathologist.

IHC testing should be performed in a National Association of Testing Authorities accredited laboratory. The low volume of cases and range of unique gastric cancer-specific issues (such as heterogeneity of expression within tumour samples) ideally would require laboratory participation in the Royal College of Pathologists of Australasia quality assurance program. Given the heterogeneity of receptor expression in tissue samples, experts recommend that ISH is performed with access to the IHC test/slide to guide the direction of reading (where possible).

As part of a quality use of medicines initiative prior to the PBS listing of trastuzumab for early breast cancer, reference laboratories were established to assist pathologists in performing HER2 testing and ensure reproducibility of results. Pathologists underwent ISH certification training resulting in certified ISH reference laboratories. Currently, 27 laboratories are certified to conduct ISH testing in Australia for breast cancer. The ISH testing program is available to any laboratory that can demonstrate the required quality and concordance of results with an existing validated ISH assay (FISH, CISH or SISH), can perform a minimum number of tests per year and has established links with a multidisciplinary team.

Information provided by the Sponsor indicates that a similar program has been established for HER2 testing in advanced gastric cancer. An expert panel of a core group of pathologists, experienced in conducting HER2 testing, has been established to share their expertise in breast cancer testing, and apply this experience to gastric cancer, taking account of the differences between the two testing approaches.

Co-administered and associated interventions

HER2 testing is a co-dependent technology with the purpose of identifying patients with inoperable locally advanced or metastatic gastric cancer who are likely to benefit from treatment with trastuzumab. Patients who test positive for HER2 would receive the regimen tested in the ToGA trial (Bang et al 2010), namely trastuzumab by intravenous infusion at a dose of 8 mg/kg on day 1 of the first chemotherapy cycle, followed by 6 mg/kg every 3 weeks until disease progression or unacceptable toxicity.

Trastuzumab is currently being considered by the Pharmaceutical Benefits Advisory Committee (PBAC) for listing on the PBS for the treatment of HER2 positive patients with advanced (equivalent to stage III or IV) gastric cancer. Trastuzumab has been available through the PBS and the Herceptin Program, for early and late stage breast cancer respectively. In the setting of advanced gastric cancer, trastuzumab may be delivered in either an inpatient or outpatient setting and is TGA-approved to be co-administered in addition to cisplatin and a fluoropyrimidine (ie either 5-fluorouracil or capecitabine). The vast majority (93%) of patients are over 50 years of age at the time of diagnosis (Tracey et al 2010). Given that trastuzumab treatment increases the risk of cardiac adverse events, at least one baseline assessment of left ventricular ejection fraction with echocardiography, or a gated heart pool scan, is warranted.

Listing proposed and options for MSAC consideration

Proposed MBS listing

The current and proposed MBS item descriptors and fees are provided in Table 8.

Table 8 Proposed MBS item descriptor for HER2 testing in advanced gastric cancer

Category 6 – Pathology services
MBS 72848 (*current MBS item*) Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 of the following antibodies - oestrogen, progesterone and cerb- B2 (HER2). Fee: $75.00 If more than 1 of the services mentioned in items 72846, 72847, 72848; 72849 and 72850 or 73059, 73060, 73061, 73064 and 73065 are performed in a single patient episode, a medicare benefit is payable only for the item performed that has the highest scheduled fee.
MBS [item number] (***proposed MBS item***) A test of tumour tissue from a patient with inoperable, locally advanced or metastatic, gastric or gastro-oesophageal (GE) junction cancer, to determine if the requirements relating to amplification of c-erb-B2 (HER2) in biopsy material, by *in situ* hybridisation techniques, for access to trastuzumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $330.00

May only be used to test samples from patients who have not received prior chemotherapy for advanced gastric cancer and in whom HER2 protein expression has been examined by immunohistochemistry.

People with inoperable locally advanced or metastatic gastric cancer, including cancer of the gastro-oesophageal junction, who are eligible for trastuzumab treatment would be tested to determine HER2 status. HER2 testing would be restricted to patients who had not received prior chemotherapy for the treatment of their metastatic gastric cancer.

The proposed use of HER2 testing described above is consistent with the TGA-approved indication for trastuzumab.

Clinical place for proposed intervention

HER2 testing would be used to identify a subgroup of patients with inoperable locally advanced or metastatic gastric cancer who would likely benefit from treatment with trastuzumab. In the current management of advanced gastric cancer, all patients receive palliative chemotherapy without determination of HER2 status. Given the paucity of data for using HER2 testing for gastric cancer, there is uncertainty around the appropriate testing scenario to be used in current Australian practice.

The key assessment of HER2 testing for gastric cancer, to date, has been in the ToGA trial (Bang et al., 2010). All of the patients in the ToGA trial received both IHC and ISH tests (represented in Figure 1 below). Patients were eligible from randomisation to receive either trastuzumab in addition to chemotherapy, or chemotherapy alone, if their tumour samples were scored as 3+ on immunohistochemistry or if they were FISH positive (Bang et al 2010). A small number of patients with IHC3+/FISH- in the ToGA trial was treated as HER2 positive (represented in Figure 2 below), although clinical advice suggests that these patients would be treated as HER2 negative in Australian clinical practice.

The use of IHC and ISH testing for HER2 positivity in advanced gastric cancer is complicated by concerns regarding the concordance of interpretation of IHC results across laboratories, as described in the GaTHER study (Kumarasinghe et al 2011), and consequently disquiet regarding variation in testing methodologies/performance among laboratories performing IHC, perhaps related to the heterogeneity of gastric cancer tumour samples. Further, there are concerns regarding the role of chromosome 17 polysomy in HER2 positivity, as this cannot be detected using IHC testing and the presence of this marker may indicate non-response to HER2-targeted therapy (Varshney et al, 2004; Downey et al, 2010).

Given these concerns, and that IHC test results may also guide ISH testing to a particular locus, the base case proposed clinical algorithm (Figure 1) advocates ISH testing for all biopsy and resection samples after IHC in order to confirm the presence/absence of HER2 positivity. IHC and ISH testing of the same sample in the same laboratory may improve the

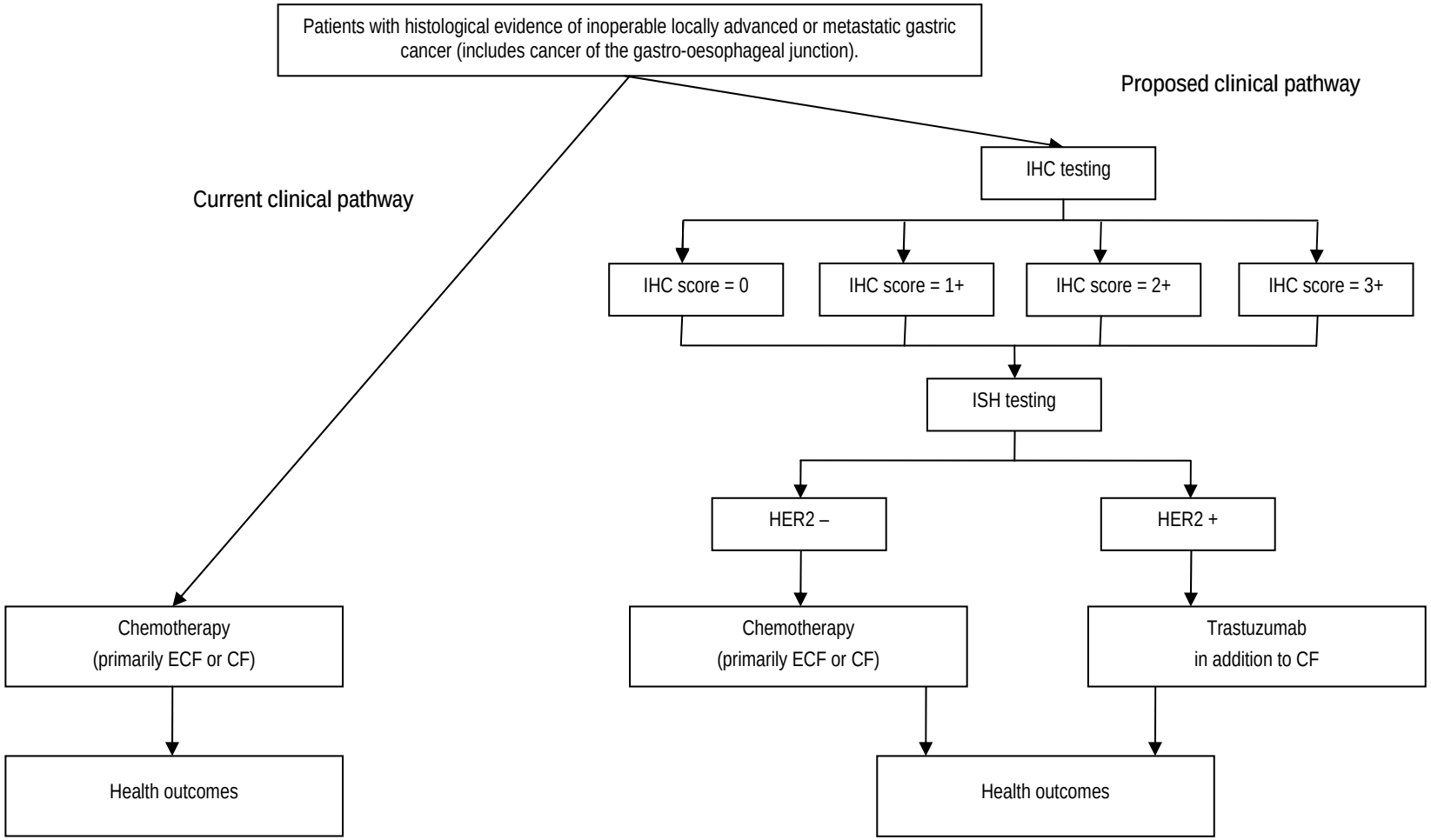
test performance. Apart from being a very conservative testing strategy, this algorithm would allow the reliability of IHC and ISH testing in inoperable locally advanced and metastatic gastric cancer to be established in Australia, ie if a small number of reference laboratories undertaking ISH testing for advanced gastric cancer record concordance with the initial IHC result, a re-assessment of the appropriate HER2 testing scenario could be undertaken in the future.

Three other potential clinical algorithms for determining HER2 positivity are proposed as requiring investigation during the assessment of HER2 testing for MSAC. Two clinical algorithms reflect the suggestion that ISH testing might only be used for equivocal IHC test results (Figure 2 and Figure 3), while the remaining algorithm is consistent with the biological plausibility argument that – given HER2 testing is a co-dependent technology - trastuzumab effectiveness will be greatest in patients with tumour samples exhibiting high levels of HER2 protein expression (as opposed to gene amplification only) (Figure 4). The plausible IHC thresholds for proceeding to ISH testing are therefore: any grade of IHC (Figure 1); IHC grade 0, 1+ or 2+ (Figure 2); and IHC grade 2+ (Figure 3).

Other clinical management algorithms could be envisaged that varied IHC or ISH testing strategies, as well as eligibility for trastuzumab. It would be helpful for MSAC's assessment if the full range of testing scenarios was explored.

In the clinical algorithms (below), the left side explains current practice with regard to the management of patients; and the right side explains the proposed use of HER2 testing. The difference between the algorithms is the introduction of HER2 testing and the subsequent change in management in those patients who are found to be HER2 positive. Consequently, HER2 testing would be introduced to satisfy a previously unmet clinical need for the subgroup of patients who might benefit from the addition of trastuzumab to current chemotherapy.

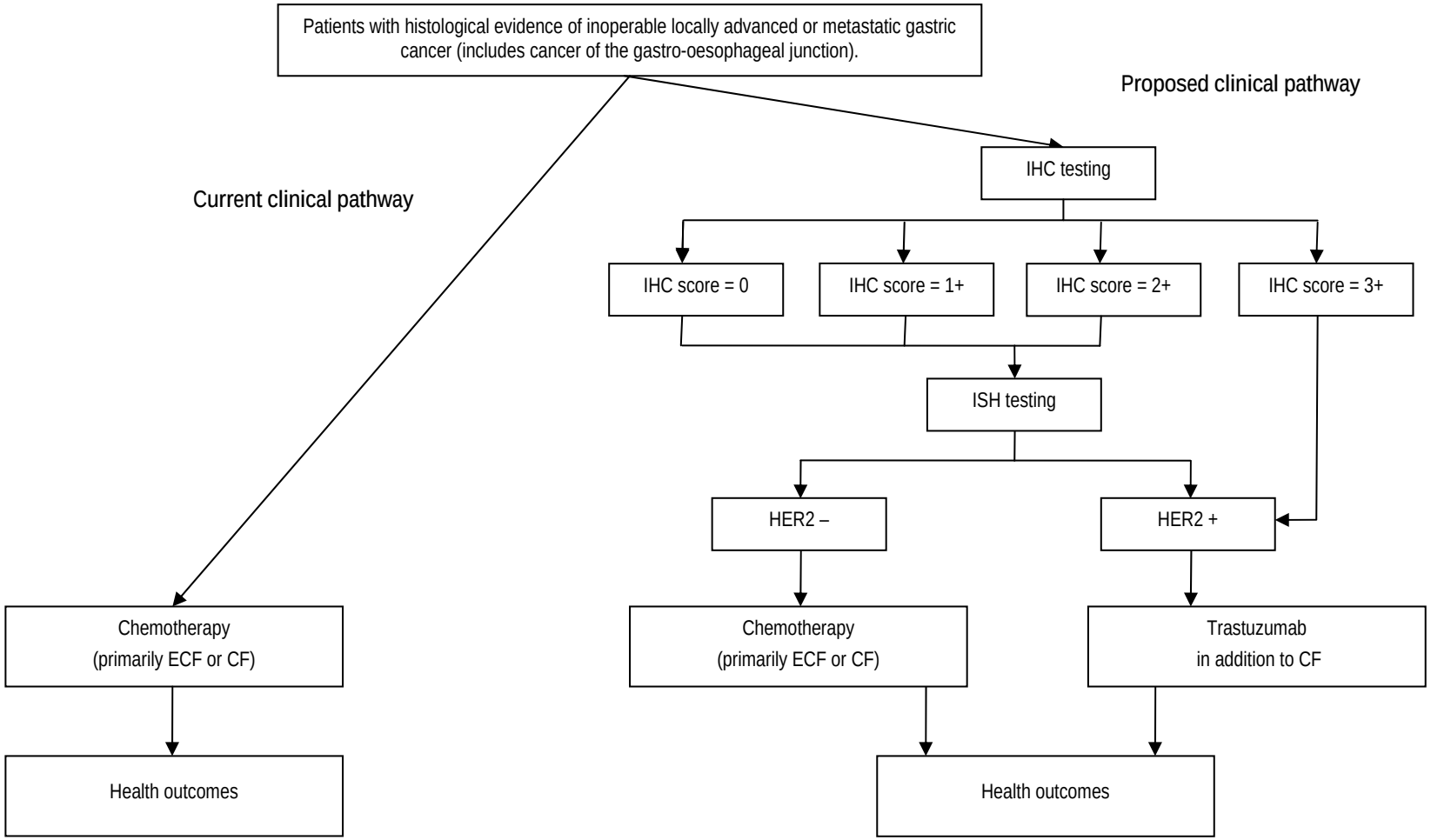
Figure 1 Management algorithm for use of HER2 testing in advanced gastric cancer – scenario 1



Note: Eligibility for trastuzumab is dependent on all samples receiving two tests.

IHC = immunohistochemistry; ISH = *in situ* hybridisation; ECF = epirubicin plus cisplatin plus a fluoropyrimidine (capecitabine or 5-FU); CF = cisplatin plus a fluoropyrimidine (capecitabine or 5-FU); 5-FU = 5-fluorouracil

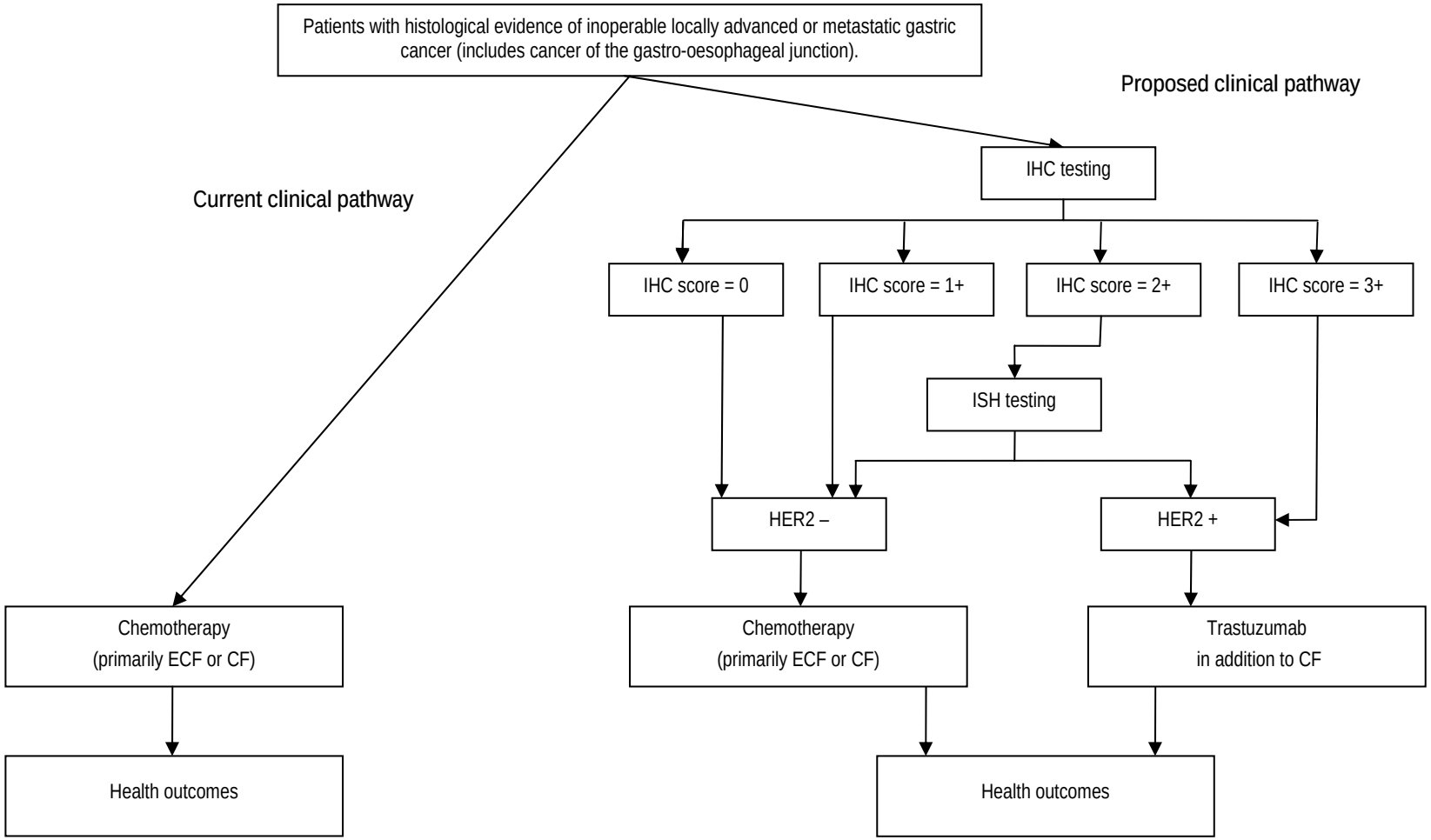
Figure 2 Management algorithm for use of HER2 testing in advanced gastric cancer – scenario 2



Note: Eligibility for trastuzumab is dependent on all samples receiving two tests, with exception of samples graded IHC3+.

IHC = immunohistochemistry; ISH = *in situ* hybridisation; ECF = epirubicin plus cisplatin plus a fluoropyrimidine (capecitabine or 5-FU); CF = cisplatin plus a fluoropyrimidine (capecitabine or 5-FU); 5-FU = 5-fluorouracil

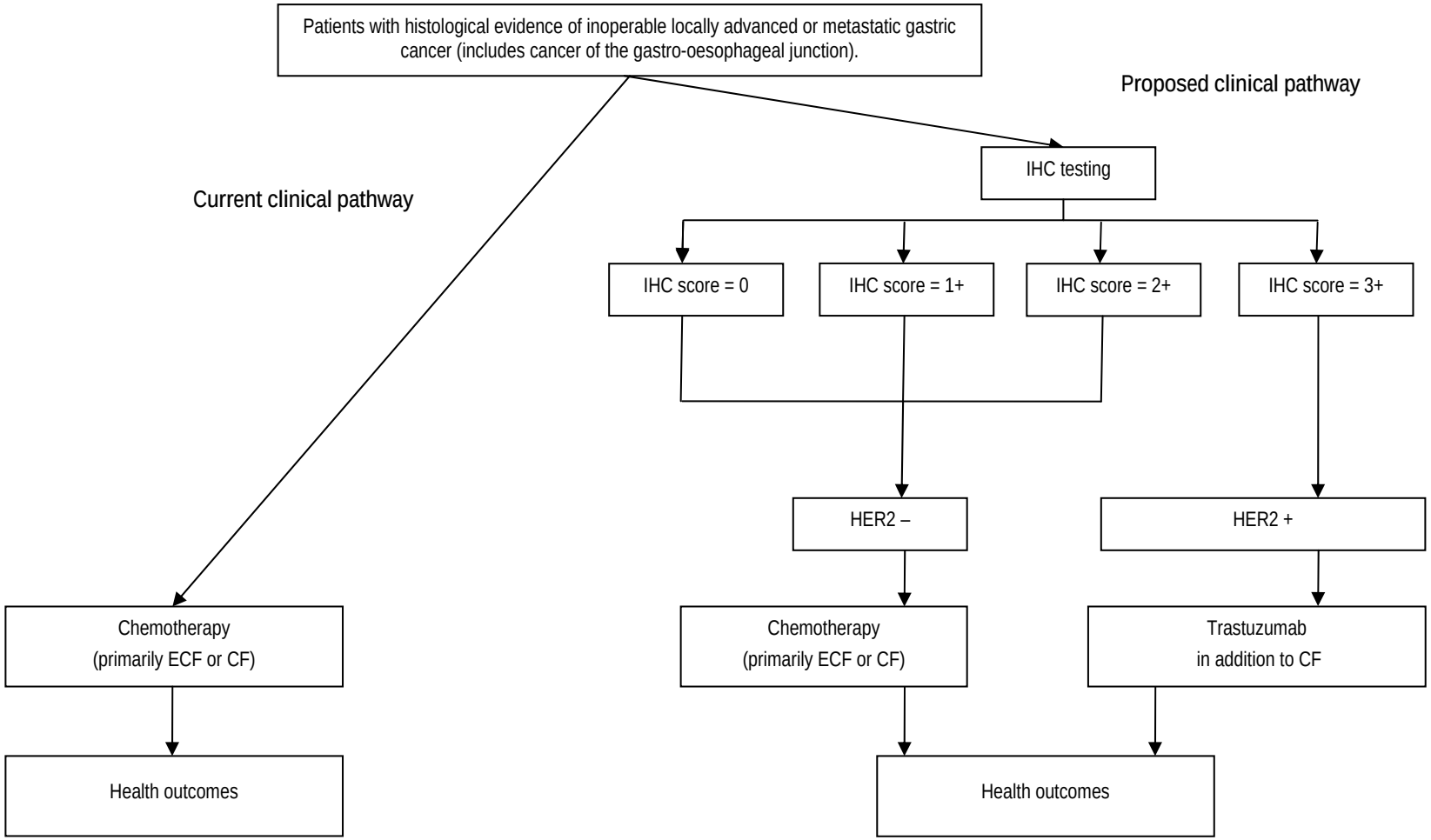
Figure 3 Management algorithm for use of HER2 testing in advanced gastric cancer – scenario 3



Note: Eligibility for trastuzumab is dependent on having an IHC2+ result confirmed by ISH or of having an IHC3+ result.

IHC = immunohistochemistry; ISH = *in situ* hybridisation; ECF = epirubicin plus cisplatin plus a fluoropyrimidine (capecitabine or 5-FU); CF = cisplatin plus a fluoropyrimidine (capecitabine or 5-FU); 5-FU = 5-fluorouracil

Figure 4 Management algorithm for use of HER2 testing in advanced gastric cancer – scenario 4



Note: Eligibility for trastuzumab is dependent on being IHC3+. ISH testing is not required.

IHC = immunohistochemistry; ISH = *in situ* hybridisation; ECF = epirubicin plus cisplatin plus a fluoropyrimidine (capecitabine or 5-FU); CF = cisplatin plus a fluoropyrimidine (capecitabine or 5-FU); 5-FU = 5-fluorouracil

Comparator

The comparator for this assessment will be usual care without testing to determine HER2 status. Consequently all patients with inoperable locally advanced or metastatic gastric cancer in the comparator arm would receive standard chemotherapy regardless of their HER2 status. There are no MBS item descriptors for usual care without testing to determine HER2 status. There are however, MBS items which cover the provision of chemotherapy, although these would also be relevant to the intervention arm.

Standard chemotherapy for inoperable locally advanced or metastatic gastric cancer in Australia primarily consists of one of two chemotherapy regimens:

- epirubicin, cisplatin and a fluoropyrimidine (5-FU or capecitabine) (ECF); or
- cisplatin and a fluoropyrimidine (CF).

Of note, there is no current standard approach to the dosing of cisplatin and 5-FU, with modifications including variable doses of cisplatin and various administration strategies (ie giving all of the dose on a single day or giving divided doses over 2 days). Clinical advice suggests that a minority of patients may also receive a fluoropyrimidine alone if they cannot tolerate stronger chemotherapy.[3]

When trastuzumab is used in combination with the CF regimen, the cisplatin and fluoropyrimidine is dosed differently than when CF is provided in isolation or when it is provided in combination with epirubicin.

Outcomes for safety and effectiveness evaluation

A comparison of test outcomes across proposed test options and strategies is necessary, in each case including consideration of the adequacy of samples for laboratory assessment.

The health outcomes, upon which the comparative clinical performance of HER2 testing versus usual care will be measured, are listed below:

Effectiveness

Primary outcomes: Overall survival; quality of life; progression free survival.

Secondary outcomes: Response rate (complete response or partial response according to RECIST criteria); duration of response; rate of stable disease; rate of disease progression; time to progression.

[3] This regimen would not qualify as a comparator as these patients would not be eligible for trastuzumab (which must be administered in addition to *both* cisplatin and a fluoropyrimidine).

Safety

Psychological and physical harms from testing. Any adverse events related to a change in treatment including tolerability; toxicity (particularly cardiovascular adverse events); and neutropaenia.

Summary of the PICO to be used for the assessment of evidence (systematic review)

Table 9 provides a summary of the PICO used to:

(1) define the question for public funding,

(2) select the evidence to assess the safety and effectiveness of HER2 testing, and

(3) provide the evidence-based inputs for any decision-analytic modelling to determine the cost-effectiveness of HER2 testing.

Table 9 Summary of PICO to define research questions that assessment will investigate

Patients	Intervention	Comparator	Reference Standard	Outcomes to be assessed
Patients with inoperable locally advanced or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior chemotherapy for their disease, and who have a WHO performance status of 2 or less.	*Direct evidence*			
	HER2 testing (IHC, ISH and combinations thereof to be defined) with usual care in test negative or untested patients and trastuzumab combined with chemotherapy in test positive patients	Usual care without HER2 testing	N/A	Safety Psychological and physical harms from testing. Any adverse events related to a change in treatment including tolerability; toxicity; and neutropaenia. Effectiveness *Direct evidence*[a] Primary outcomes: Overall survival; quality of life; progression free survival Secondary outcomes: Response rate (complete response or partial response according to RECIST criteria); duration of response; rate of stable disease; rate of disease progression; time to progression.
	Linked evidence[a]			*Outcomes as above, plus* *Other factors*[a] Adequacy of test samples according to test method Re-testing rate according to test method Concordance/agreement between IHC and ISH HER2 tests Comparative test performance and costs of the different ISH testing methods

Research Question

Is HER2 testing (immunohistochemistry ± *in situ* hybridisation), followed by usual care in test negative patients or untested patients, or by trastuzumab combined with chemotherapy in test positive patients, safe, effective and cost-effective compared to usual care alone without HER2 testing in advanced gastric cancer?

[a] Direct evidence, as described in the PICO table above, can be employed when there are trials available (on all inoperable locally advanced or metastatic gastric cancer patients) that compare a management strategy that involves HER2 testing with a management strategy that does not involve HER2 testing and the differential impact on patient-relevant clinical outcomes is measured. When this type of information is lacking, a linked evidence approach may be employed (ie linking evidence assessing diagnostic accuracy of the HER2 test/s, to evidence of a change in management as a consequence of testing, and then to the effect of that change in management eg trastuzumab therapy on patient health outcomes). However, when a reference standard is lacking, a standard linked evidence approach is not usually feasible as diagnostic accuracy cannot be determined with any certainty.

Section B of the "Information requests for co-dependent technologies" table (http://www.health.gov.au/internet/hta/publishing.nsf/Content/whats-new) outlines some strategies for linking evidence in the absence of a reference standard, including systematically reviewing data on the prognostic effect of HER2 status in advanced gastric cancer, constructing a reference standard against which test accuracy can be measured, and/or determining concordance or agreement between the results of different HER2 tests. Should these forms of evidence be used, and a linked evidence approach undertaken, the PICO to address each type of evidence linkage would need to be pre-specified and a research question constructed. The outcomes listed above could therefore be supplemented by additional information in order to fulfil the linked evidence information requests.

WHO = World Health Organization; IHC = immunohistochemistry; ISH = *in situ* hybridisation; N/A = not applicable; RECIST = Response Evaluation Criteria in Solid Tumours

Clinical claim

The application claims that the use of HER2 testing, to identify patients with HER2 positive advanced gastric cancer for treatment with trastuzumab, indirectly results in a clinically relevant and statistically significant improvement in overall survival, progression-free survival, response rates, time to progression, duration of response and clinical benefit rate in a disease with a uniformly poor prognosis. The application claims that HER2 testing and treatment with trastuzumab are safe and well tolerated.

It is claimed that trastuzumab, when used in combination with standard chemotherapy for the treatment of patients with HER2 positive advanced gastric cancer, is significantly more effective than standard chemotherapy alone and is no worse than standard chemotherapy in terms of comparative safety.

These claims suggest that HER2 testing, to identify patients who would benefit from trastuzumab, would result in superior health outcomes for individuals found to be HER2 positive. Relative to the comparator of usual care without HER2 testing, HER2 testing followed by trastuzumab in HER2 positive patients and usual care in HER2 negative or untested patients would therefore be considered non-inferior in terms of safety and superior in terms of effectiveness. As such, the type of economic evaluation required is a cost-effectiveness analysis or cost-utility analysis (green shading in Table 10). Should superiority in health outcomes be unable to be demonstrated due to a lack of evidence, an economic evaluation would not be required, as HER2 testing and treatment with trastuzumab would be more expensive than the comparator, for no demonstrable health benefit. MSAC is unlikely to recommend subsidy of HER2 testing under these conditions.

Table 10 Classification of an intervention for determination of economic evaluation to be presented

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="4">Comparative effectiveness versus comparator</td></tr>
<tr><td colspan="2">Superior</td><td>Non-inferior</td><td colspan="2">Inferior</td></tr>
<tr><td rowspan="6">Comparative safety versus comparator</td><td rowspan="3">Superior</td><td colspan="2" rowspan="3">CEA/CUA</td><td rowspan="3">CEA/CUA</td><td>Net clinical benefit</td><td>CEA/CUA</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
<tr><td>Non-inferior</td><td colspan="2">CEA/CUA</td><td>CEA/CUA*</td><td colspan="2">None^</td></tr>
<tr><td rowspan="3">Inferior</td><td>Net clinical benefit</td><td>CEA/CUA</td><td rowspan="3">None^</td><td colspan="2" rowspan="3">None^</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
</table>

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost comparison analysis. Cost comparison analysis should only be presented when there is a lack of evidence indicating superiority and the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes for economic evaluation

The Applicant claims that there is a statistically significant benefit in terms of overall survival, progression-free survival, response rates, time to progression, duration of response and clinical benefit rate for patients who are eligible for trastuzumab-based therapy. Therefore, the health outcomes for the economic evaluation should be life-years gained and quality-adjusted life-years gained over a three year and/or life-time time horizon.

Health care resources

As diagnosis and staging of inoperable locally advanced or metastatic gastric cancer will occur in both comparative arms, ie with or without HER2 testing, costs and resource use associated with these will not be needed in the economic evaluation of HER2 testing.

A list of the resources that would need to be considered in the economic analysis is provided in Table 11. The amount of resources and cost of resources will vary according to which of the clinical algorithms are being costed (eg scenarios 1-4).

Table 11 List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS/PBS Schedule Fee	Safety nets[a]	Other govt budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population: HER2 testing										
Immunohisto-chemistry (IHC)	Medical oncologist / gastro-enterologist	Outpatient	100%	1	MBS item number 72848 $75.00					$75.00
Re-testing			% to be based on trial evidence or clinical opinion							TBD
In situ hybridisation (ISH)[b]		Outpatient			Proposed MBS item number $330.00					
Scenario 1(base case)			100%	1						$330.00
Scenario 2			% to be based on trial evidence or clinical opinion	1						TBD
Scenario 3				1						TBD

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS/PBS Schedule Fee	Safety nets[a]	Other govt budget	Private health insurer	Patient	Total cost
Scenario 4				0						$0.00
Resources provided to deliver proposed intervention: Proposed drug (trastuzumab) + co-administered chemotherapy (cisplatin + a fluoropyrimidine)										
Trastuzumab 150mg vial 60mg vial	Medical oncologist	Outpatient/ inpatient	HER2 positivity rate (patients eligible for HCF)	No of vials/ patient[c]	Cost/vial c-in-c c-in-c					TBD
Cisplatin 10mg vial 50mg vial 100mg vial	Medical oncologist	Outpatient/ inpatient		No of vials/ patient[c]	Cost/vial $11.35 $19.67 $39.78					TBD
5-Fu 1000mg vial 500mg vial					$48.22 $54.80					
OR Capecitabine 150mg tablet 500mg tablet				No of packs/ patient	Cost/pack $123.93 $695.17					

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS/PBS Schedule Fee	Safety nets[a]	Other govt budget	Private health insurer	Patient	Total cost
Chemotherapy administration costs										
Drug administration cost for 1 to 6 hour infusion in outpatient setting	Medical oncologist	Outpatient	% to be based on health service usage data or clinical opinion	Number of infusions/ patient[d]	Cost/ infusion MBS item number 13918 $94.20					TBD
Full day hospital admission for chemotherapy in a public hospital setting (excluding average pharmacy cost component)		Outpatient	% to be based on health service usage data or clinical opinion	Number of infusions/ patient[d]	Cost/ infusion $516					TBD
Full day hospital admission for chemotherapy in a private hospital setting (excluding average pharmacy cost component)		Inpatient	% to be based on health service usage data or clinical opinion	Number of infusions/ patient[d]	Cost/ infusion $310					TBD
Resources provided in association with proposed intervention: Costs associated with cardiac monitoring for patients receiving trastuzumab										
Echocardiogram		Outpatient	% to be based on trial evidence or clinical opinion	Number of procedures/ patient	Cost/ procedure MBS item number 55113 $230.65					TBD
Multiple gated acquisition scans (MUGA)		Outpatient		Number of procedures/ patient	Cost/ procedure MBS item number 61313 $303.35					TBD
Twelve-lead electro-cardiography		Outpatient		Number of procedures/ patient	Cost/ procedure MBS item number 11700 $30.05					TBD
Resources provided in association with proposed intervention: Costs associated with treating adverse events (other than cardiac monitoring) for patients receiving trastuzumab										
Will depend on adverse events										TBD

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS/PBS Schedule Fee	Safety nets[a]	Other govt budget	Private health insurer	Patient	Total cost
associated with trastuzumab usage										
Resources provided to deliver CF in clinical practice:										
Cisplatin 10mg vial 100mg vial	Medical oncologist	Outpatient/ inpatient	% of patients on doublet chemo-therapy (CF) 30% total pop'n (based on clinical advice)	No of vials/ patient[c]	Cost/vial $11.35 $39.78					TBD
5-fluorouracil 1000mg vial 500mg vial OR Capecitabine 150mg tablet 500mg tablet		Outpatient/ inpatient			$48.22 $54.80 Cost/pack $123.93 $695.17					TBD
Chemotherapy administration costs (CF)										
Drug administration cost for 1 to 6 hour infusion. an outpatient setting	Medical oncologist	Day patient	% to be based on health service usage data or clinical opinion	Number of infusions/ patient[d]	Cost/ infusion MBS item number 13918 $94.20					TBD
Full day hospital admission for chemotherapy in a public hospital setting (excluding average pharmacy cost component)[e]		Day patient	% to be based on health service usage data or clinical opinion	Number of infusions/ patient[d]	Cost/ infusion $516					TBD
Full day hospital admission for chemotherapy in a private hospital setting (excluding average pharmacy cost component)[e]		Day patient	% to be based on health service usage data or clinical opinion	Number of infusions/ patient[d]	Cost/ infusion $310					TBD
Resources provided to deliver ECF in clinical practice:										
Epirubicin 10mg vial 20mg vial 50mg vial	Medical oncologist	Outpatient/ inpatient	% of patients on triplet chemo-therapy (ECF) 60% total pop'n (based on clinical	No of vials/ patient[c]	Cost/vial $176.30 $322.50 $773.06					TBD
Cisplatin 10mg vial 100mg vial		Outpatient/ inpatient		No of vials/ patient[c]	Cost/vial $11.35 $39.78					TBD
5-fluorouracil		Outpatient/		No of vials/	Cost/vial					TBD

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS/PBS Schedule Fee	Safety nets[a]	Other govt budget	Private health insurer	Patient	Total cost
		inpatient	advice)	patient[c]						
1000mg vial					$48.22					
500mg vial					$54.80					
OR					Cost/pack					
Capecitabine										
150mg tablet					$123.93					
500mg tablet					$695.17					
Chemotherapy administration costs (ECF)										
Drug administration cost for 1 to 6 hour infusion. an outpatient setting	Medical oncologist	Day patient		Number of infusions/ patient[d]	Cost/ infusion MBS item number 13918 $94.20					TBD
Full day hospital admission for chemotherapy in a public hospital setting (excluding average pharmacy cost component)[e]		Day patient		Number of infusions/ patient[d]	Cost/ infusion $516					TBD
Full day hospital admission for chemotherapy in a private hospital setting (excluding average pharmacy cost component)[e]		Day patient		Number of infusions/ patient[d]	Cost/ infusion $310					TBD

CF = cisplatin + a fluoropyrimidine; ECF = epirubicin + cisplatin + a fluoropyrimidine; HCF = trastuzumab + cisplatin + a fluoropyrimidine
TBD = to be determined based on the assumption provided regarding the proportion of patients receiving the resource.
c-in-c = commercial in confidence

[a] Include costs relating to both the standard and extended safety net.
[b] Page 24 of the PASC Information Form notes that unit cost of ISH testing includes pathologists, laboratory, reagent, controlled and uncontrolled overheads and Quality Assurance Program costs and a repeat testing rate of 10%.
[c] Estimate from the product of number of vials per infusion and number of infusions per patient.
[d] Estimate using the component drug with the highest number of infusions.
[e] Average cost from the National Hospital Cost Data Collection, AR-DRG version 5.3, Round 13 (2008-09)

Proposed structure of economic evaluation (decision analysis)

Many decision analyses could be envisaged that vary IHC or ISH testing strategies, as well as eligibility for trastuzumab. It would be helpful for MSAC's assessment if the full range of testing scenarios was explored in the economic modelling.

However, the decision analyses provided below (Figure 5, Figure 6,

Figure 7,

Figure 8) should be included in the assessment. These decision analyses allow provision for the use of linked evidence, ie by breaking down the outcomes into true positives and false positives (the latter designated a 'true negative' on the basis of a gold standard), and true negatives and false negatives (the latter designated a 'true positive' on the basis of the same gold standard). However, in the event that there is acceptable direct trial evidence of the impact of HER2 testing and targeted treatment on health outcomes, these arms can be collapsed so that health outcomes from a positive test result are provided and health outcomes from a negative test result are provided (as the effect of any false positives and negatives will then be effectively included in the health outcome measure). However, should the test method in the direct evidence differ from what is being proposed for use in Australia, then additional evidence would need to be provided regarding the test performance and costs of these other testing methods, as well as their likely impact on health outcomes.

The decision analyses provided below reflect the proposed alternative clinical management algorithms incorporating HER2 testing for inoperable locally advanced or metastatic gastric cancer that could be used in Australia.

Figure 5 Decision tree representing the decision options of using HER2 testing to guide treatment in inoperable locally advanced or metastatic gastric cancer – Scenario 1 (base case)

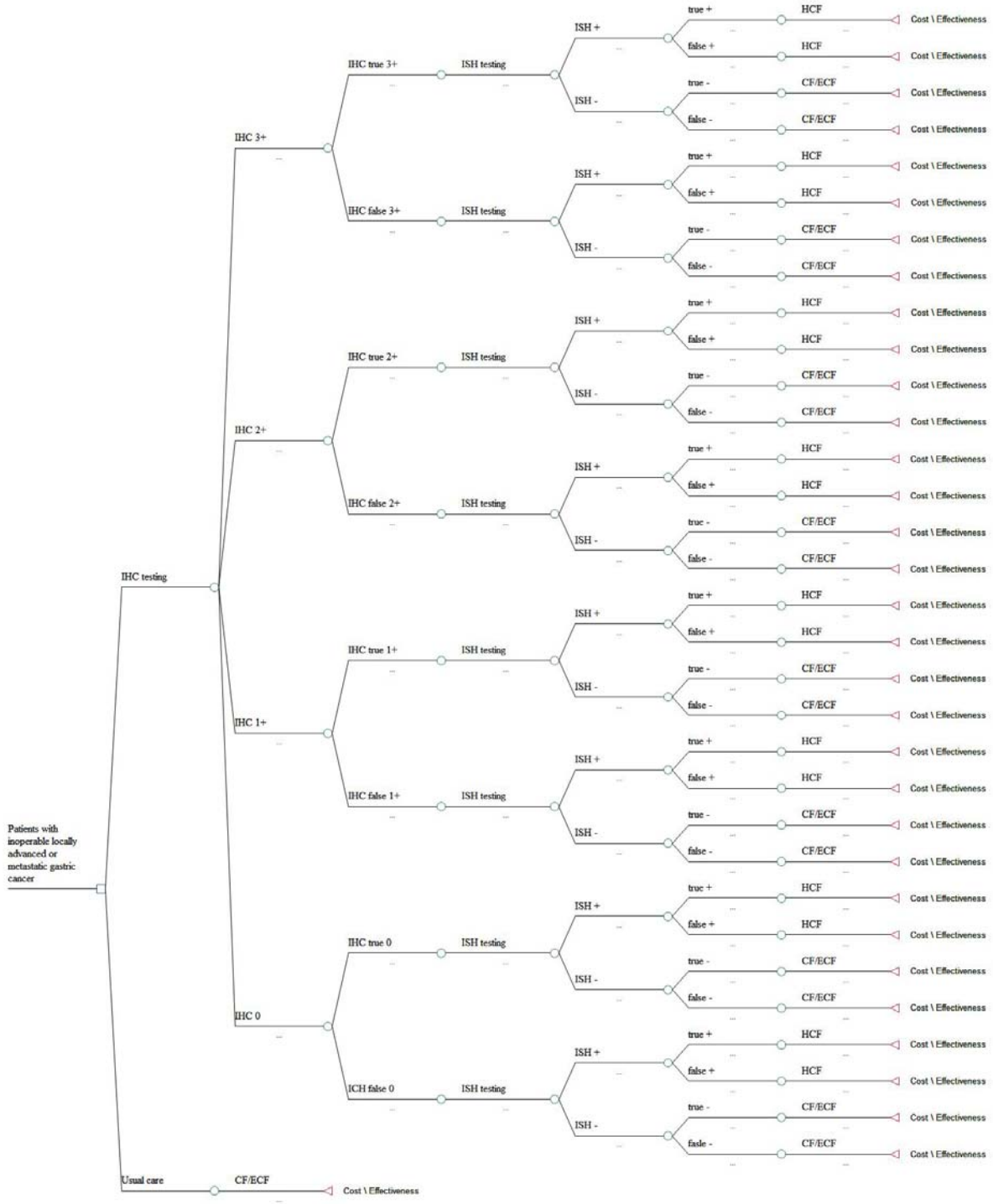


Figure 6 Decision tree representing the decision options of using HER2 testing to guide treatment in inoperable locally advanced or metastatic advanced gastric cancer – Scenario 2

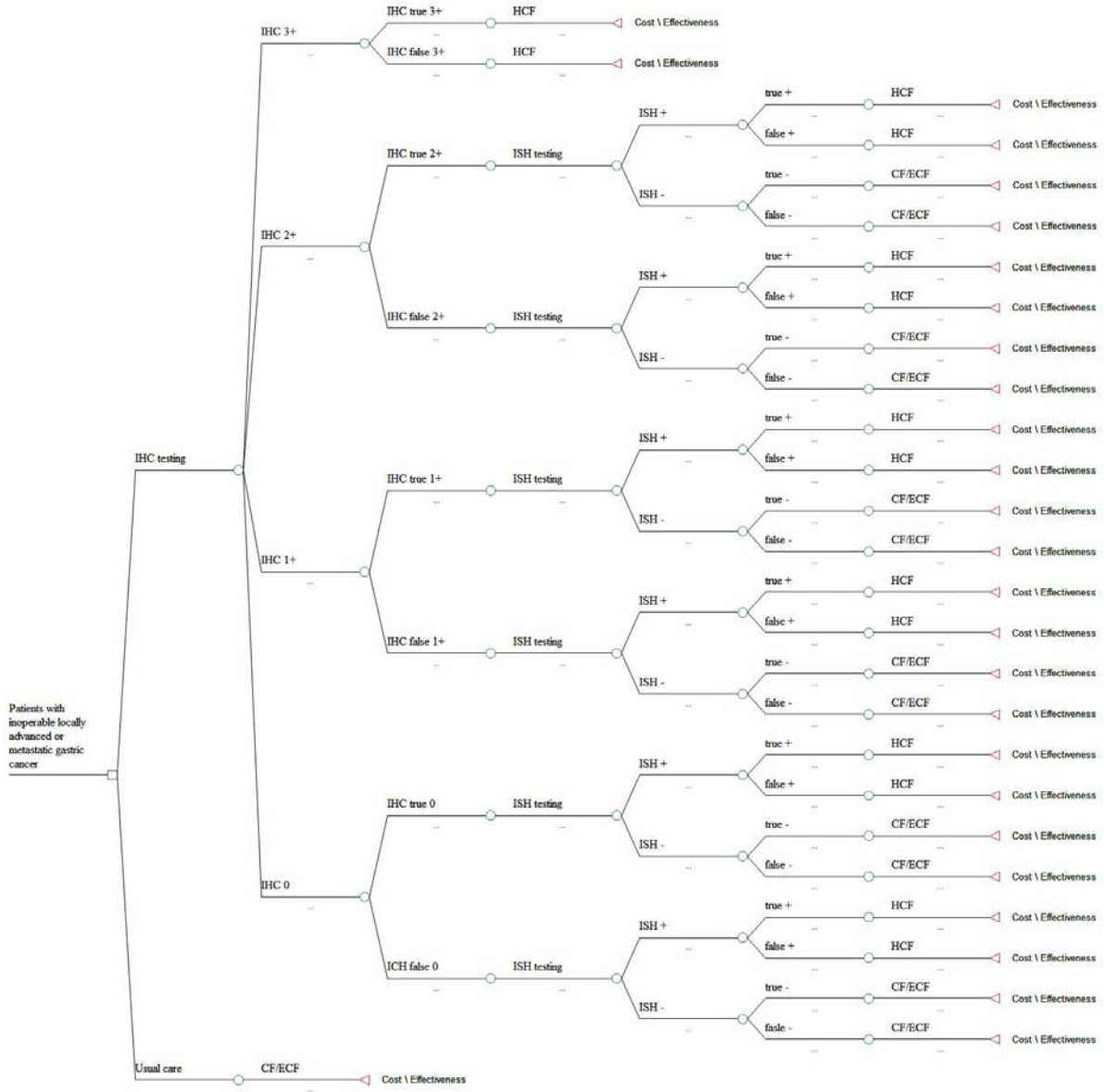


Figure 7 Decision tree representing the decision options of using HER2 testing to guide treatment in inoperable locally advanced or metastatic gastric cancer – Scenario 3

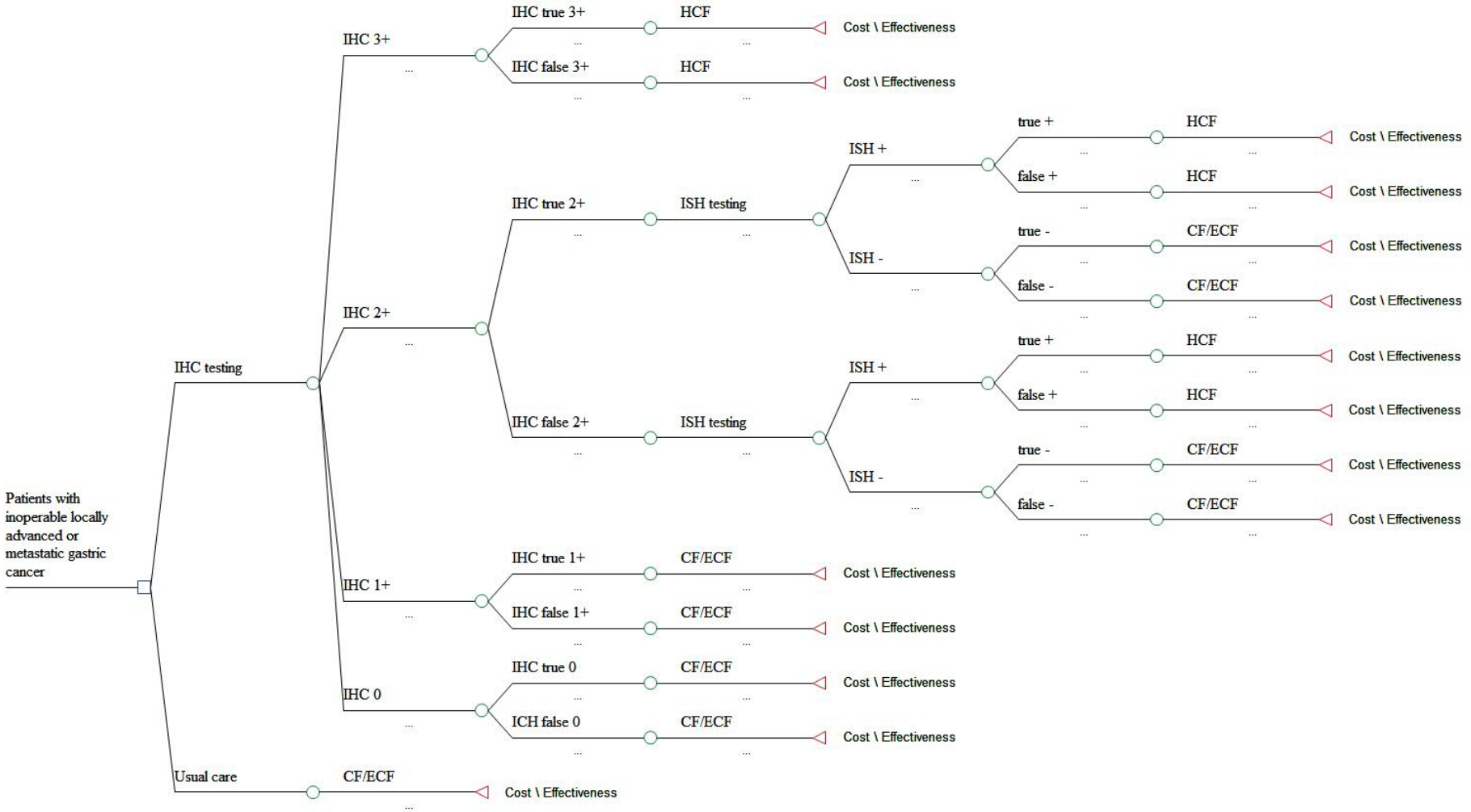
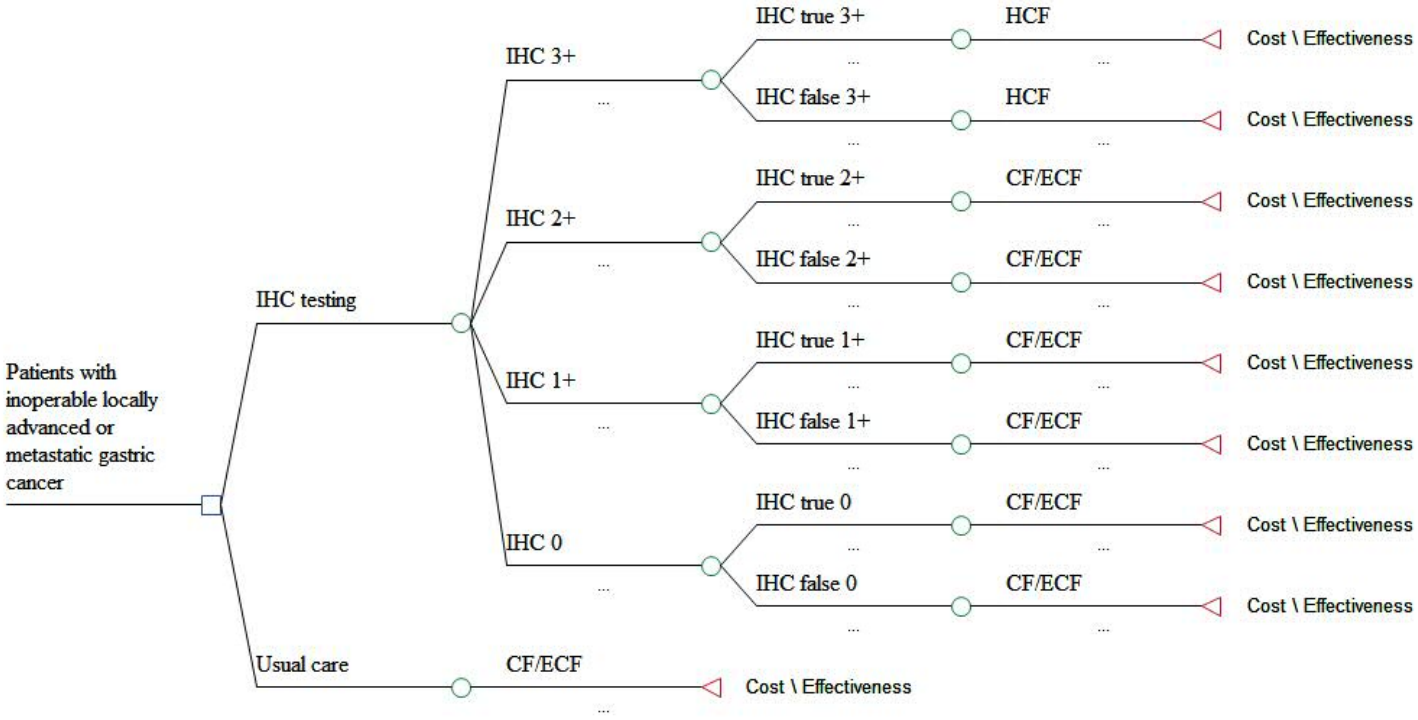


Figure 8 Decision tree representing the decision options of using HER2 testing to guide treatment in inoperable locally advanced or metastatic gastric cancer – Scenario 4



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