MSAC Application 1821

Testing for Chromogranin A in patients with neuroendocrine neoplasms

PICO Set

Population

Describe the population in which the proposed health technology is intended to be used:

The proposed health technology, serum chromogranin A (CgA) monitoring, is intended for patients with well differentiated neuroendocrine neoplasms (NENs) who have advanced/metastatic disease and are undergoing ongoing surveillance during treatment or follow-up, where there is a clinical need to monitor for disease progression or recurrence.[1] The technology is primarily intended for patients in whom CgA is clinically "trackable" (i.e. elevated at baseline and/or previously shown to correlate with tumour activity for that individual) so that serial measurements can be interpreted as a longitudinal marker of progression.

NENs are a heterogeneous group of cancers with varying prognoses. These include well and moderately differentiated tumours (NETs; grade 1–2) and poorly differentiated neuroendocrine carcinomas (NECs; grade 3).[1, 2] They most commonly arise in gastro-entero-pancreatic (GEP) sites (small intestine, rectum, pancreas) and lung, and may be described clinically as functional (hormone-secreting) vs non-functional.

The symptoms of NENs range from mass effect (abdominal pain, obstruction, bleeding, cough/wheeze) to hormone syndromes (flushing/diarrhoea in carcinoid syndrome; episodic hypoglycaemia in insulinoma), and natural history is stage- and grade-dependent. Localised disease is often amendable to total resection and has excellent outcomes (>90% 5-year survival in some GEP-NEN series), while metastatic and/or high-grade disease has markedly poorer survival, with strong variation by site (e.g. 5-year survival ~88% for rectal NEN vs ~53% for pancreatic NEN).[3]

Historical data indicate the incidence of NENs is increasing (**Figure 1**). The most recent age-standardised incidence rate reported by the Australian Institute of Health and Welfare (AIHW) was around 19 per 100,000 in 2021, noting that the eligible population is a subset of these.[4] The prevalence of NENs is high as many are indolent and chronic, contributing to a substantial survivorship population. NENs are typically diagnosed in later life, with a median age at diagnosis of 57, though all age groups are affected.[5]

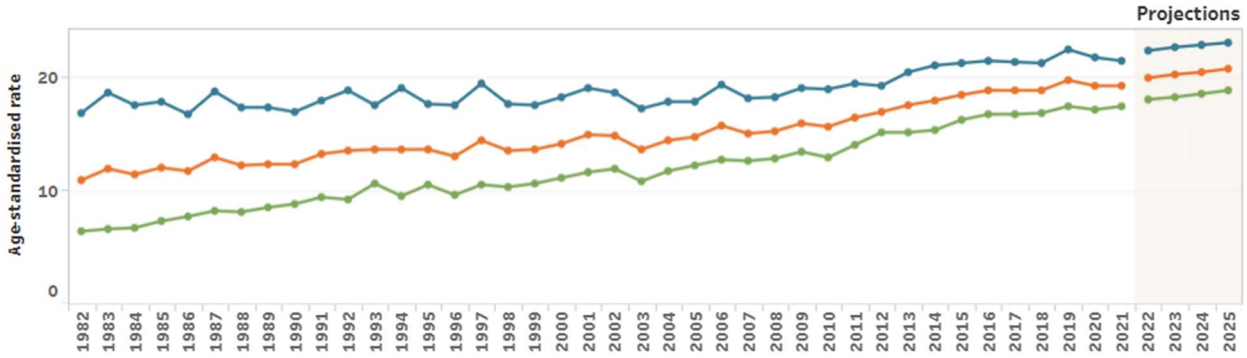

Figure 1 Age-standardised (2025 Australian population) incidence rate for NENs by sex, 1982 to 2025

Source: AIHW[4]

Specify any characteristics of patients with, or suspected of having, the medical condition, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian healthcare system in the lead up to being considered eligible for the technology:

The proposed patient population includes those with a confirmed diagnosis of a well-differentiated NEN (most commonly gastro-entero-pancreatic NEN) who have advanced/metastatic disease. CgA testing in these patients is used the purposes of ongoing disease surveillance and/or monitoring treatment response (i.e. for patients on active systemic therapy, post–liver-directed therapy, or on observation for stable metastatic disease).[1, 6]

The diagnostic pathway for NENs commonly starts in primary care with history and clinical examination, baseline blood tests and anatomical imaging (e.g. ultrasound, X-ray, CT), with endoscopy/colonoscopy or bronchoscopy guided by suspected site; tumour markers such as CgA and urinary 5-HIAA may be ordered but are interpreted cautiously pre-diagnosis due to the risk of false positives caused by confounding factors (e.g. PPIs, renal impairment).[6] If a NEN is suspected based on preliminary investigations, patients are referred for specialist assessment to confirm the diagnosis and stage. This is typically done using targeted biochemistry, CT/MRI and functional imaging where indicated (e.g. ^{68}Ga-DOTATATE PET/CT, ^{18}F-FDG PET), and histopathology (grade/differentiation), ideally reviewed by an experienced NEN pathologist.[6]

Management is individualised via multidisciplinary team (MDT) care, ranging from curative surgery to surveillance, with systemic options including somatostatin analogues, peptide receptor radionuclide therapy (PRRT) in selected metastatic patients, targeted therapies (e.g. everolimus), chemotherapy mainly for higher-grade disease, and liver-directed therapies for liver-dominant metastases.[6]

Provide a rationale for the specifics of the eligible population:

Measurement of CgA can be useful for evaluation of response to treatment if elevated, and to detect progression and recurrence at an early stage.[7] CgA is elevated in 60-100% of patients with NENs, including midgut NENs (both functioning and non-functioning), pancreatic NENs (both functioning and non-functioning), and phaeochromocytomas.[1] However, the specificity of CgA testing may be lower in midgut NENs, and it is not a reliable measure for gastrinomas or in patients on proton pump inhibitors (PPIs).[1] We acknowledge the COSA guidelines note that CgA monitoring may be also be used in patients with completely resected disease;[1] however, this population is not recommended for CgA monitoring as part of this application in order to maintain a targeted scope for the proposed MBS items, based on the indications with the greatest clinical utility.

Are there any prerequisite tests?

No

Are the prerequisite tests MBS funded?

N/A

Provide details to fund the prerequisite tests:

N/A

Intervention

Name of the proposed health technology:

Chromogranin A (CgA) testing.

Describe the key components and clinical steps involved in delivering the proposed health technology:

Delivering serial CgA monitoring involves establishing a baseline in an eligible patient with confirmed metastatic NEN (preferably when clinically stable and before/early in a treatment or surveillance phase), ensuring consistent pre-analytical conditions (same assay where possible, documented reference range), and arranging repeat venous blood collections. The requesting clinician specifies the indication (surveillance/response monitoring), and the pathology provider performs the immunoassay, quality control, and reporting with the result, reference range, and any relevant interpretive notes.

Circulating CgA can be measured using several immunoassay platforms, including radioimmunoassay (RIA), immunoradiometric assay (IRMA) and enzyme-linked immunosorbent assay (ELISA).[8] Older first-generation assays are no longer used routinely, and second generation assays are used in Australian practice. Because results can vary by method and there are no universal standards or a single accepted "best" technique (though some reports favour RIA analytically), laboratories typically select assays based on feasibility and operational considerations, reinforcing the importance of using the same method repeatedly when monitoring trends over time.[8]

Clinically, results are interpreted longitudinally rather than as a single value. The treating clinician reviews symptoms, treatment status, and potential confounders (notably PPI use, renal impairment, concurrent illness), and may repeat testing after addressing reversible causes if an unexpected rise occurs. A sustained, clinically meaningful increase in serum CgA typically triggers earlier specialist review and confirmatory imaging (CT/MRI ± somatostatin-receptor imaging when management-changing), while stable CgA alongside stable clinical status and CT/MRI may support maintaining routine follow-up intervals and deferring functional imaging (PET) until these more expensive scans likely to change management.[1]

Identify how the proposed technology achieves the intended patient outcomes:

CgA is a protein released by neuroendocrine cells, which are hormone-secreting cells found throughout the body. NENs (benign and malignant), including carcinoid tumours, insulinomas, small cell lung cancer and neuroblastoma, are associated with increased concentrations of CgA, whereas they are not always associated with increases in the hormones expected to be secreted from the tissues they originate. For this reason, CgA acts as a tumour-agnostic biomarker for NEN activity, increasing its utility beyond specific primary sites.

CgA monitoring achieves intended outcomes by adding a repeatable, low-burden longitudinal signal to routine follow-up in metastatic NENs, enabling earlier detection of increasing disease activity than symptom- and imaging-based monitoring alone, thereby supporting the assessment of treatment response and prognosis. Longitudinal data show that rising CgA during follow-up is associated with radiologic progression/recurrence, so a sustained, clinically meaningful rise can trigger earlier specialist review and confirmatory imaging (CT/MRI ± somatostatin-receptor imaging), leading to timelier treatment optimisation/escalation and potential benefits in symptom control and avoidance of late complications.[9, 10] Conversely, stable CgA alongside stable clinical status and CT/MRI may support deferring high-cost functional imaging (PET) to management-changing decision points; this is particularly important for patients that live in rural and remote areas where access to PET is significantly more limited.

As noted previously, it is important to acknowledge that because CgA is a non-specific neuroendocrine secretory protein, it can also be elevated by common non-tumour factors (notably PPIs, gastritis, renal/hepatic impairment, inflammatory bowel disease, glucocorticoids and rheumatoid factor).[1, 11] Therefore, results must be interpreted in context and ideally trended using a consistent assay. Due to these confounding factors, clinicians typically review medications/comorbidities and may repeat testing after addressing reversible causes before attributing changes in CgA results to tumour activity. Major confounders can be managed (e.g. review/withhold PPI where clinically safe; interpret cautiously with renal impairment).

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

N/A

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

Yes

Provide details and explain:

The main indication for which for CgA monitoring is proposed is patients with metastatic disease, who are being observed following treatment. In these patients, testing is recommended every 3 months initially, and then less frequently once stable.[1] In line with this guidance, a limitation of up to 4 tests per patient per calendar year is appropriate, noting that most patients will require fewer tests.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

Testing will be provided by Approved Pathology Practitioners (APPs) in line with other tests on the MBS Pathology Services Table.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

N/A

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

Requesting would be limited to specialist or consultant physicians practicing as oncologists, endocrinologists, or gastroenterologists. This restriction helps ensure CgA is used in the appropriate population (metastatic, well differentiated NEN), interpreted in clinical context (including confounders such as PPI use and renal impairment), and linked to a management plan for confirmatory imaging and treatment review where necessary.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

Yes

Provide details and explain:

Testing will be delivered only by APPs with appropriate scope of practice in NATA Accredited Pathology Laboratories by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Services Table.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

☐ Consulting rooms
☐ Day surgery centre
☐ Emergency Department
☒ Inpatient private hospital
☒ Inpatient public hospital
☒ Laboratory
☒ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

In the context of CgA monitoring for metastatic NENs, the proposed health technology would be delivered primarily in the outpatient setting, as most patients are managed through specialist clinics (medical oncology, endocrinology, gastroenterology) with pathology collection occurring via community or hospital-based outpatient collection centres. A smaller subset of tests may be performed for inpatients, but this would be uncommon and would typically occur when the patient is admitted for management of complications of advanced disease or treatment, with CgA collected opportunistically alongside other routine blood tests.

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes

Provide additional details on the proposed health technology to be rendered outside of Australia:

N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian healthcare system). This includes identifying healthcare resources that are needed to be delivered at the same time as the comparator service:

For the proposed population, the appropriate comparator is current practice without serial CgA monitoring ("no CgA monitoring"), in which disease status is assessed using clinical review plus scheduled imaging, with selective use of other biochemistry depending on tumour functionality and symptoms.

In routine Australian practice, metastatic NEN follow-up relies on regular clinician visits (usually specialist-led) for symptom review, treatment toxicity assessment, and physical examination, combined with planned cross-sectional imaging, typically CT or MRI at defined intervals (often ~3–12 monthly depending on grade, site, burden and treatment), to assess stability versus progression.[1] When CT/MRI is equivocal, when there is clinical suspicion of progression, or when results are likely to alter management, patients may undergo somatostatin-receptor imaging (e.g. ^{68}Ga DOTA-peptide PET/CT) and, in selected higher-grade cases, ^{18}F-FDG PET.[1]

While imperfect, CgA remains the most accessible and widely used biochemical marker for NENs, and is superior in performance to alternatives like pancreastatin or neuron-specific enolase, which are either less validated or less available in Australia.[12] These additional markers are not commonly used in practice in Australia, and are therefore not considered to be relevant comparator tests to CgA testing.

List any existing MBS item numbers that are relevant for the nominated comparators:

N/A

Provide a rationale for why this is a comparator:

See response above.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

☐ None (used with the comparator)

☐ Displaced (comparator will likely be used following the proposed technology in some patients)
☐ Partial (in some cases, the proposed technology will replace the use of the comparator, but not all)
☒ Full (subjects who receive the proposed intervention will not receive the comparator)

Outline and explain the extent to which the current comparator is expected to be substituted:

All eligible patients that do not currently have access to biomarker testing would be expected to uptake CgA monitoring if available on the MBS. Real-world uptake typically falls below these expectations.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☒ Health harms
☐ Resources
☐ Value of knowing

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

CgA is a valuable biomarker for predicting relapse and assessing prognosis in patients with metastatic NENs, as it correlates with tumour burden, stage, and treatment response.[13, 14] The predictive and prognostic value of CgA for monitoring treatment response and relapse in patients with NENs is well-supported by clinical evidence.

CgA levels are useful for early detection of recurrence post-treatment. In patients with completely resected disease, an increase in CgA levels can precede clinical and radiological evidence of relapse by several months. For instance, an increase in CgA values can anticipate clinical and objective disease recurrence after a period of 9-12 months.[13] Additionally, a ≥40% increase in CgA levels during follow-up is associated with a higher probability of tumour progression or recurrence.[14]

Baseline CgA levels correlate with tumour burden, stage, and grade, making it a valuable prognostic marker. Higher baseline CgA levels are associated with more advanced disease stages and poorer overall survival (OS). For example, patients with higher baseline CgA levels had significantly worse OS after adjusting for other factors.[14] Furthermore, a decrease in CgA levels post-treatment is positively correlated with improved survival rates.[13]

Serial measurements of CgA can help assess treatment efficacy and disease progression. Changes in CgA levels, such as normalisation or a ≥30% decrease, suggest a positive therapeutic response.[14] Conversely, patients with serum CgA levels higher than 95 ng/mL have significantly shorter survival compared to those with lower levels.[14]

Proposed MBS items

How is the technology/service funded at present? (e.g., research funding; State-based funding; self-funded by patients; no funding or payments):

Currently, CgA monitoring is funded predominantly on an out-of-pocket basis, with patients typically paying between $45 to $80 per test depending on the provider, with some patients undergoing up to four tests per year as part of disease surveillance. These funding arrangements create inequitable access to testing; uptake is contingent on a patient's capacity to pay, and/or their proximity to services willing to absorb costs, which can disproportionately disadvantage people on lower incomes, those in regional and remote areas, and patients requiring more frequent monitoring due to clinical complexity. As a result, access is inconsistent across jurisdictions and providers.

Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:

MBS item number (where used as a template for the proposed item)	N/A
Category number	P2
Category description	Chemical
Proposed item descriptor	Quantitation of chromogranin A (CgA) for a patient with a well differentiated neuroendocrine tumour, performed to establish a baseline and for serial monitoring of disease activity, to assist in identifying relapse/progression and in assessing response to treatment, where the patient has known metastatic disease, and the service is requested by a specialist or consultant physician. Maximum 4 tests per year.
Proposed MBS fee	$65.00 **Benefit**: 75%=$48.75 85%=$55.25
Indicate the overall cost per patient of providing the proposed health technology	$65.00
Please specify any anticipated out of pocket expenses	$0
Provide any further details and explain	Draft practice notes: 1. CgA is not a measure of tumour bulk for gastrinomas, therefore other hormonal markers need to be measured. It is also not a useful measure for patients on proton pump inhibitors,

	and if appropriate, attempts should be made to measure it where this drug therapy can be interrupted.[1] 2. Antibody-derived assays are variable and hence patient's samples should be measured in the same lab consistently.[1]

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

The diagnosis of NENs typically begins in primary care with a clinical history and examination, followed by baseline blood tests (e.g. full blood count, B12/iron studies, liver and renal function, thyroid function, calcium, cholesterol and CRP) and initial anatomical imaging such as ultrasound, chest X-ray and/or CT, with referral for endoscopy/colonoscopy or bronchoscopy guided by suspected site and imaging findings. Tumour markers such as CgA and 24-hour urinary 5-HIAA may be considered but are interpreted cautiously pre-diagnosis due to the risk of false positives (e.g. PPI use and renal impairment affecting CgA).[6]

Once a NEN is suspected, specialist work-up to confirm the diagnosis and stage relies on biochemical assessment (including CgA where appropriate and targeted hormone tests guided by symptoms), staging imaging with both anatomical modalities (CT/MRI) and functional imaging where indicated (e.g. ^{68}Ga-DOTATATE PET/CT or ^{18}F-FDG PET), and histopathology to establish grade, ideally reviewed by a pathologist experienced in diagnosing NENs.[6]

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

N/A

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

As noted previously, CgA monitoring is used in conjunction with other investigations to monitor disease progression and treatment response. Metastatic NEN follow-up relies on regular clinician visits (usually specialist-led) for symptom review, treatment toxicity

assessment, and physical examination, combined with planned cross-sectional imaging, typically CT or MRI at defined intervals (often ~3–12 monthly depending on grade, site, burden and treatment), to assess stability and progression.[1] When CT/MRI is equivocal, when there is clinical suspicion of progression, or when results are likely to alter management, patients may undergo somatostatin-receptor imaging (e.g. ^{68}Ga DOTA-peptide PET/CT) and, in selected higher-grade cases, ^{18}F-FDG PET.[1] Collectively, these represent the standard of care in the absence of CgA (the comparator).

Explain what other healthcare resources are used in conjunction with the comparator health technology:

See above.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

N/A

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the proposed health technology:

Treatment of NENs is individualised and typically planned through a specialist MDT, with intent ranging from curative to disease control and symptom palliation. Options include surgery (curative where feasible, or debulking/palliative in selected cases) and, for some low-grade, asymptomatic, stable disease, active surveillance ("watch and wait"). Systemic management may include somatostatin analogues (SSAs) for anti-secretory and anti-proliferative benefit, peptide receptor radionuclide therapy (PRRT) for appropriately selected metastatic patients (typically with somatostatin receptor expression on molecular imaging and often after progression on SSAs) plus targeted therapies such as everolimus (and other agents depending on site/subtype). Chemotherapy is generally reserved for NEC and/or higher-grade, unresectable or advanced NENs (with careful selection by grade and primary site), and liver-directed therapies (e.g., hepatic artery embolisation/chemoembolisation or radioembolisation) may be used for liver-dominant metastatic disease.[6]

A sustained or clinically meaningful increase in CgA (e.g. ≥50% rise to >100 ng/mL),[9] particularly if accompanied by new or worsening symptoms, may prompt escalation to confirmatory testing, rather than an immediate treatment change based on solely on the CgA result. This involves specialist review and imaging (e.g. CT chest/abdomen/pelvis and/or MRI targeted to dominant disease sites). Additional biochemistry may be requested in parallel (repeat CgA, 5-HIAA, or selected hormone assays guided by symptoms) to contextualise findings and support differential diagnosis.

Where there is suspicion of progression, uncertainty on anatomical imaging, or a need to determine eligibility for subsequent therapies, functional imaging may be used to inform treatment-planning. This usually means somatostatin receptor imaging (^{68}Ga-DOTATATE PET/CT, or octreotide-based imaging where PET is not available) to characterise receptor

expression and disease extent; FDG-PET may be incorporated when higher-grade biology is suspected or to evaluate heterogeneous disease behaviour. These investigations support both confirmation of progression and selection of appropriate next-line management.

Management actions are then driven by the combined clinical picture (symptoms, imaging, biomarker trends, and tumour biology) rather than CgA in isolation. If progression is confirmed, treatment options may include optimisation or change of systemic therapy (e.g. adjustment of somatostatin analogues, targeted therapies such as everolimus, or chemotherapy in selected higher-grade scenarios), or consideration of PRRT where receptor imaging supports suitability. If progression is not confirmed, patients generally return to routine surveillance, with CgA monitoring continuing as an adjunct that can trigger earlier reassessment if trends change.

CgA can be a useful adjunct biomarker for some patients with metastatic NENs, particularly where frequent imaging is difficult to access, by providing a low-burden longitudinal signal that may prompt earlier specialist review and appropriately targeted imaging when a sustained rise suggests possible progression. In particular, it is a useful biomarker for patients that live in rural and remote areas with limited access to imaging due to its high specificity, as it can safely reduce the necessity for follow-up imaging, including expensive PET scans.[9]

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the comparator health technology:

In the comparator pathway, patients with metastatic NENs continue routine specialist-led follow-up based on symptoms, physical examination, treatment review, and scheduled imaging rather than serial biomarker monitoring. Required healthcare resources include regular specialist appointments, planned CT or MRI, and selective use of functional imaging such as ^68Ga-DOTA-peptide PET/CT or, in selected higher-grade cases, ^18F-FDG PET where progression is suspected or imaging is equivocal. If progression is confirmed, management is escalated through the usual MDT-led treatment pathway, which may include somatostatin analogues, PRRT, targeted therapy, chemotherapy, liver-directed therapy, or supportive care according to tumour biology and prior treatment.

Describe and explain any differences in the healthcare resources used after the proposed health technology vs. the comparator health technology:

The difference in resource use between the intervention and comparator is not that CgA mandates new categories of care per se, but that it can shift the timing and frequency of existing investigations. With CgA monitoring, a sustained rise (or discordance with symptoms) more often triggers earlier, otherwise unscheduled imaging (CT/MRI) and, in some cases, additional functional imaging (somatostatin receptor imaging) to confirm or refute progression.

In the comparator pathway, escalation to imaging is more commonly driven by symptoms, physical findings, or routine scheduled scans, which may delay reassessment in patients whose disease is progressing biochemically before it becomes clinically apparent. Therefore, the downstream node following CgA monitoring and no CgA

monitoring in Figure 2 is the same, noting that the main difference from a modelling perspective will be in the proportions of patients that have evidence of disease progression based on whether CgA is tested.

Resource use therefore depends on test performance and how strictly clinicians apply an algorithm that requires corroboration between test results. CgA may increase short-term diagnostic activity (repeat blood tests, earlier scans) while potentially reducing downstream resource intensity in some patients if earlier confirmation enables timelier optimisation of therapy, avoiding late presentation with complications (e.g. emergency admissions, urgent imaging, unplanned procedures).

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

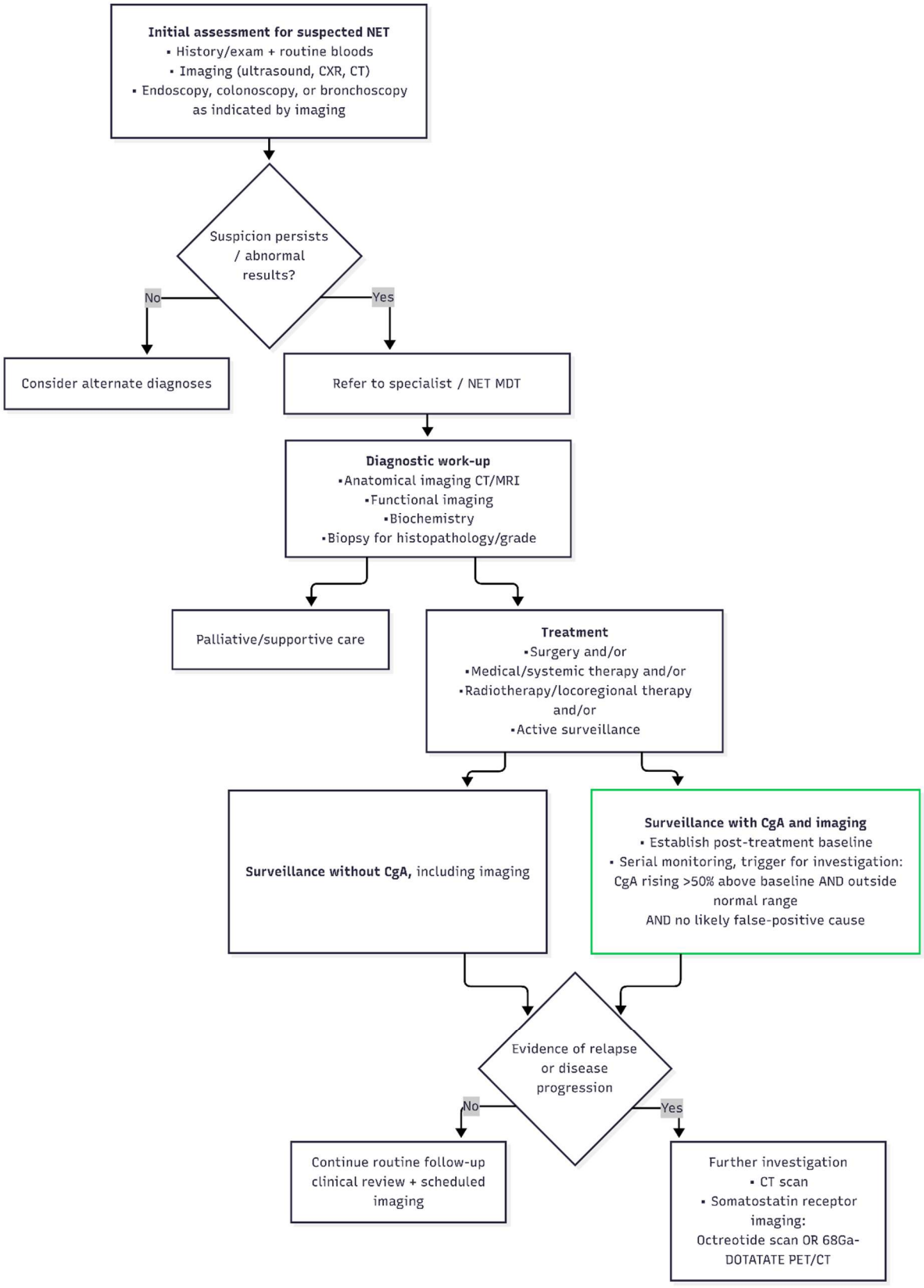

Figure 2 Clinical management algorithm of patients with metastatic NEN, with CGA monitoring (green box) and without.

Source: Based on the Optimal care pathway for people with neuroendocrine tumours.[6]

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:

Compared with no biomarker testing, serial CgA monitoring in patients with metastatic NENs who have a trackable (elevated) baseline provides an accessible longitudinal signal of increasing disease activity that can prompt earlier clinical review and confirmatory investigation (CT/MRI and, where appropriate, somatostatin-receptor imaging), thereby supporting timelier treatment reassessment or escalation.

Rising CgA during follow-up is associated with recurrence/progression and can prompt further investigation before new symptoms become apparent (after accounting for confounding factors such as PPI treatment), or the next scheduled scan.[14, 15] In doing so, management changes (e.g. systemic therapy adjustment or locoregional control) may be enacted sooner, potentially improving symptom control, avoiding progression-related complications, and preserving quality of life. This is supported by evidence of the test's performance (pooled sensitivity ~74.6%, specificity ~84.7%).[16, 17] The tests higher specificity but lower sensitivity for RECIST-defined progression supports its utility for triage rather than as a stand-alone test.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

A requestor would seek to use serial CgA rather than no biomarker testing because it provides a low-burden, repeatable adjunct marker that can be trended between imaging timepoints to help detect changing disease activity in patients with metastatic NEN. Used alongside routine clinical review and scheduled CT/MRI (and functional imaging when indicated), longitudinal CgA results can signal probable progression or relapse earlier, prompting earlier reassessment and confirmatory imaging rather than waiting for symptoms or the next planned scan. By its nature, it is a particularly useful and valued biomarker for patients that live in rural and remote areas, who have limited access to imaging services.

Identify how the proposed technology achieves the intended patient outcomes:

See previous response.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management?	Yes
A change in health outcome?	Yes
Other benefits?	No

Please provide a rationale, and information on other benefits if relevant:

N/A

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

CgA monitoring will increase short-term costs to the MBS because it is used adjunctively. It adds a recurring pathology episode (collection, assay, reporting) and clinician time to interpret longitudinal trends and exclude confounders (e.g. PPI use, renal impairment), with occasional repeat testing. Downstream, CgA may bring forward confirmatory imaging (CT/MRI and, where appropriate, somatostatin-receptor PET/CT) when progression is suspected; however, by providing a widely accessible longitudinal signal with relatively high specificity in follow-up settings, CgA may also help avoid high-cost PET use when results are stable and concordant with stable clinical status.[17]

If your application is in relation to a specific radiopharmaceutical(s) or a set of radiopharmaceuticals, identify whether your clinical claim is dependent on the evidence base of the radiopharmaceutical(s) for which MBS funding is being requested. If your clinical claim is dependent on the evidence base of another radiopharmaceutical product(s), a claim of clinical noninferiority between the radiopharmaceutical products is also required.

N/A

Estimated utilisation

Estimate the prevalence and/or incidence of the proposed population:

Data from the AIHW indicate there were 4,832 new cases of NENs diagnosed in 2021 (18.8 per 100,000, crude rate), and 21,794 prevalent cases of people living with NENs that were diagnosed since 2012.[4] A Victorian audit of NENs from 1982-2019 reported 58% of all NENs were well-differentiated.[18] It is unclear how many of these are likely to have had metastatic disease, as TNM stage was not collected in the NEN dataset for this audit.[18] Applying this percentage to the recent AIHW data yields an estimated 2,802 new cases, and 12,640 prevalence cases in the proposed population, noting that this is likely to be an over-estimate as it does not confirm if these patients had metastatic disease, or if they had a previously resected tumour (and would not be considered in the eligible population).

Provide the percentage uptake of the proposed health technology by the proposed population:

Year 1 estimated uptake(%): 70%

Year 2 estimated uptake(%): 80%

Year 3 estimated uptake(%): 90%

Year 4 estimated uptake(%): 90%

Estimate the number of patients who will utilise the proposed technology for the first full year:

10,809

Optionally, provide details:

This estimate is based on the epidemiological estimate for prevalent + incident cases of well-differentiated NENs, multiplied by the expected uptake (which often lags behind the availability of a new MBS item). We note, again, that this is likely an overestimate.

Will the technology be needed more than once per patient?

Yes.

Over what duration will the health technology or service be provided for a patient? (preferably a number of years):

Lifelong, typically 1-15+ years based on survival data.

Optionally, provide details:

For metastatic NENs, follow-up is generally ongoing/lifelong due to the chronic nature of the condition, and recurrence/progression can occur late in the disease. Of well-differentiated NENs reported in the Victorian audit, the 5-year survival was 86% (95% CI 84-88) and median overall survival was 15.5 years (14.5-NR).[18] It is unclear how generalisable these data are to other States and Territories in the country, particularly those with greater geographical distances that limit access to imaging and other follow-up services compared to Victoria.

What frequency will the health technology or service be required by the patient over the duration? (range, preferably on an annual basis):

1-4 per year

Optionally, provide details:

As noted previously, testing is recommended 3-monthly initially, and then less frequently once stable.[1] Based on available data from labs that currently conduct CgA monitoring in practice, only 7% of patients receive twice-yearly CgA testing, and even fewer patients have more than two CgA tests per year. This may reflect the cost barriers to testing.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',

#	Study	Title	Abstract	Link	Date
1	Meng et al. 2024[9]	Circulating Chromogranin A as a Surveillance Biomarker in Patients with Carcinoids—The CASPAR Study	Prospective multicenter blinded observational validation study of an automated immunofluorescence chromogranin A assay in 153 gastroenteropancreatic NET patients, using RECIST 1.1 on CT/MRI as reference. A positive test was ≥50% rise to >100 ng/mL. Specificity was 93.4% and sensitivity 34.4%; PPV 57.9%, NPV 84.3%, AUC 0.73. CgA may inform the frequency of imaging in appropriately selected, asymptomatic patients within standard intervals.	PMID 39453770	Oct 2024
2	Yu et al. 2021[10]	Use of Chromogranin A for Monitoring Patients With Pancreatic Neuroendocrine Neoplasms	Retrospective post-therapy cohort of 77 pancreatic neuroendocrine neoplasm patients (101 Ga-68 DOTA-peptide PET events, 2017–2020) measuring serum chromogranin A by ELISA. Against PET-based response criteria, CgA cutoffs 52.39 and 60.18 ng/mL detected active and metastatic disease (77.8%/80.7%, 73.9%/73.1% sensitivity/specificity). Serial changes predicted remission/progression in 18 pairs.	PMID 34347728	July 2021

#	Study	Title	Abstract	Link	Date
3	Tsai et al. 2021[14]	The Prognostic and Predictive Role of Chromogranin A in Gastroenteropancreatic Neuroendocrine Tumors – A Single-Center Experience	Retrospective single-centre cohort of 102 grade 1/2 gastroenteropancreatic NET patients with baseline (n=60) and/or serial (n=94) serum chromogranin A. Higher baseline CgA associated with more advanced stage and worse overall survival after adjustment (HR 13.52). During follow-up, ≥40% CgA rise predicted progression/recurrence (adjusted OR 5.04), supporting CgA as a monitoring biomarker.	PMID 34868938	Nov 2021
4	Fuksiewicz et al. 2018[19]	Prognostic value of chromogranin A in patients with GET/NET in the pancreas and the small intestine	Observational study measured pre-treatment serum chromogranin A (CgA) in 131 patients with digestive neuroendocrine neoplasms (pancreas, small intestine/caecum, caecum/appendix/colon). CgA was not elevated in appendix/colon vs controls. Higher CgA associated with nodal/distant metastases, liver involvement, and active disease; in pancreatic NET, CgA correlated with grade/Ki67 but did not predict PFS/OS. In small intestine/caecum NET, elevated CgA independently predicted worse PFS and OS.	PMID 29724794	Jun 2018
5	Rossi et al. 2018[16]	Chromogranin A in the Follow-up of Gastroenteropancreatic Neuroendocrine Neoplasms: Is It Really Game Over? A Systematic Review and Meta-analysis	Systematic review and meta-analysis of eight studies (previous 10 years) evaluating serial CgA for follow-up of gastroenteropancreatic neuroendocrine neoplasms. Across studies, sensitivity ranged 46–100% and specificity 68–90%. Pooled estimates showed overall accuracy 84%, sensitivity 74.6% and specificity 84.7% for detecting recurrence/progression, supporting use mainly when baseline CgA is elevated.	PMID 30325865	Nov 2018

#	Study	Title	Abstract	Link	Date
6	Han et al. 2015[20]	The value of serum chromogranin A as a predictor of tumor burden, therapeutic response, and nomogram-based survival in well-moderate nonfunctional pancreatic neuroendocrine tumors with liver metastases	Prospective cohort of 51 well/moderately differentiated nonfunctional pancreatic NET patients with liver metastases, plus 134 other NETs and 125 controls, measured serum chromogranin A using ELISA at baseline and after therapy. CgA change tracked RECIST response (P<0.001). Rising CgA predicted worse PFS; baseline >2.5×ULN predicted poor OS.	PMID 25822862	May 2015
7	Rossi et al. 2015[21]	Chromogranin A as a predictor of radiological disease progression in neuroendocrine tumours	Retrospective cohort from a NET database including 152 metastatic NET patients (91 midgut, 61 pancreatic) with RECIST 1.1–defined radiological progression. Plasma chromogranin A (radioimmunoassay) was compared 12 and 6 months pre-progression and at progression. CgA showed an overall upward trend at 6 months, with signal mainly in pancreatic NETs and grade 1 tumors; changes were not evident in midgut NETs. CgA has predictive value 6 months prior to RP for PNETs and G1 tumours.	PMID 26207246	Jun 2015
8	Chou et al. 2014[22]	Plasma chromogranin A levels predict survival and tumor response in patients with advanced gastroenteropancreatic neuroendocrine tumors	Retrospective post-recruitment study of 60 Asian patients with advanced gastro-entero-pancreatic NETs treated April 2010–April 2013 assessed plasma chromogranin A (CgA) for prognostic and predictive value. Favourable overall survival was independently associated with ECOG 0–1, WHO grade 1–2, single-organ metastasis, and baseline CgA <2×ULN. A >17% ΔCgA distinguished partial response/stable disease from progression (sensitivity 91.2%, specificity 82.9%).	PMID 25275071	2014

#	Study	Title	Abstract	Link	Date
9	Arnold et al. 2008[23]	Plasma chromogranin A as marker for survival in patients with metastatic endocrine gastroenteropancreatic tumors	Cohort of 344 patients with metastatic, well-differentiated neuroendocrine tumours evaluated the prognostic value of plasma CgA; 102 had radiologic hepatic tumour-burden correlation. Higher log10 CgA predicted shorter survival (HR 2.14, 95% CI 1.75–2.62; P<0.001). CgA correlated with hepatic tumour burden (Spearman ρ=0.57; P<0.001) but not extrahepatic load. Sudden CgA rises paralleled rapid progression and poor survival.	PMID 18547872	Jul 2008

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

	Type of study design	Title	Abstract	Link	Date
1.	Prospective cohort study	Evaluation of Neuroendocrine Differentiation as a Potential Mechanism of Tumor Recurrence Following Radiotherapy	118 recruited men receiving definitive or salvage radiotherapy ± androgen deprivation for localized prostate adenocarcinoma will under serial serum chromogranin A (CgA) testing pre-, during, and post-treatment to determine whether post-therapy CgA rises (as a marker of neuroendocrine differentiation) correlate with Gleason score and predict biochemical recurrence.	NCT03017794	Estimated study completion December 2027

References

1.Cancer Council Australia. COSA Neuroendocrine Neoplasms (NENs) Guidelines 2023 [Available from: https://app.magicapp.org/#/guideline/jlAbxL.
2.Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010;39(6):707–12.
3.Wu P, He D, Chang H, Zhang X. Epidemiologic trends of and factors associated with overall survival in patients with neuroendocrine tumors over the last two decades in the USA. Endocr Connect. 2023;12(12).
4.AIHW. Cancer data in Australia 2026 [Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/summary-dashboard.
5.Wyld D, Wan MH, Moore J, Dunn N, Youl P. Epidemiological trends of neuroendocrine tumours over three decades in Queensland, Australia. Cancer Epidemiol. 2019;63:101598.
6.Cancer Council Victoria and Commonwealth Government. Optimal care pathway for people with neuroendocrine tumours. Cancer Council Victoria, Melbourne; 2022.
7.Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2016;103(2):153–71.
8.Int. CL. Chromogranin A as a biomarker for the detection of neuroendocrine tumours 2020 [Available from: https://clinlabint.com/chromogranin-a-as-a-biomarker-for-the-detection-of-neuroendocrine-tumours/.
9.Meng QH, Halfdanarson TR, Bornhorst JA, Jann H, Shaheen S, Shi RZ, et al. Circulating Chromogranin A as a Surveillance Biomarker in Patients with Carcinoids-The CASPAR Study. Clin Cancer Res. 2024;30(24):5559–67.
10.Yu F, Fu J, Zhang C, Wu W, Ai S, Yao X, et al. Use of Chromogranin A for Monitoring Patients With Pancreatic Neuroendocrine Neoplasms. Pancreas. 2021;50(6):882–9.
11.Koffas A, Giakoustidis A, Papaefthymiou A, Bangeas P, Giakoustidis D, Papadopoulos VN, et al. Diagnostic work-up and advancement in the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. Front Surg. 2023;10:1064145.
12.Loree JM, Chan D, Lim J, Stuart H, Fidelman N, Koea J, et al. Biomarkers to Inform Prognosis and Treatment for Unresectable or Metastatic GEP-NENs. JAMA Oncol. 2024;10(12):1707–20.
13.Massironi S, Rossi RE, Casazza G, Conte D, Ciafardini C, Galeazzi M, et al. Chromogranin A in diagnosing and monitoring patients with gastroenteropancreatic neuroendocrine neoplasms: a large series from a single institution. Neuroendocrinology. 2014;100(2-3):240–9.
14.Tsai H-J, Hsiao C-F, Chang JS, Chen L-T, Chao Y-J, Yen C-J, et al. The Prognostic and Predictive Role of Chromogranin A in Gastroenteropancreatic Neuroendocrine Tumors – A Single-Center Experience. Frontiers in Oncology. 2021;Volume 11 - 2021.
15.Chatani PD, Aversa JG, McDonald JD, Khan TM, Keutgen XM, Nilubol N. Preoperative serum chromogranin-a is predictive of survival in locoregional jejuno-ileal small bowel neuroendocrine tumors. Surgery. 2021;170(1):106–13.
16.Rossi RE, Ciafardini C, Sciola V, Conte D, Massironi S. Chromogranin A in the Follow-up of Gastroenteropancreatic Neuroendocrine Neoplasms: Is It Really Game Over? A Systematic Review and Meta-analysis. Pancreas. 2018;47(10):1249–55.
17.Meng QH, Halfdanarson TR, Bornhorst JA, Jann H, Shaheen S, Shi RZ, et al. Circulating Chromogranin A as a Surveillance Biomarker in Patients with Carcinoids—The CASPAR Study. Clinical Cancer Research. 2024;30(24):5559–67.

18.Michael M, Thursfield V, te Marvelde L, Kong G, Hicks RJ. Incidence, prevalence, and survival trends for neuroendocrine neoplasms in Victoria, Australia, from 1982 to 2019: Based on site, grade, and region. Asia-Pacific Journal of Clinical Oncology. 2022;18(5):e306–e17.
19.Fuksiewicz M, Kowalska M, Kolasińska-Ćwikła A, Ćwikła JB, Sawicki Ł, Roszkowska-Purska K, et al. Prognostic value of chromogranin A in patients with GET/NEN in the pancreas and the small intestine. Endocr Connect. 2018;7(6):803–10.
20.Han X, Zhang C, Tang M, Xu X, Liu L, Ji Y, et al. The value of serum chromogranin A as a predictor of tumor burden, therapeutic response, and nomogram-based survival in well-moderate nonfunctional pancreatic neuroendocrine tumors with liver metastases. Eur J Gastroenterol Hepatol. 2015;27(5):527–35.
21.Rossi RE, Garcia-Hernandez J, Meyer T, Thirlwell C, Watkins J, Martin NG, et al. Chromogranin A as a predictor of radiological disease progression in neuroendocrine tumours. Ann Transl Med. 2015;3(9):118.
22.Chou WC, Chen JS, Hung YS, Hsu JT, Chen TC, Sun CF, et al. Plasma chromogranin A levels predict survival and tumor response in patients with advanced gastroenteropancreatic neuroendocrine tumors. Anticancer Res. 2014;34(10):5661–9.
23.Arnold R, Wilke A, Rinke A, Mayer C, Kann PH, Klose KJ, et al. Plasma chromogranin A as marker for survival in patients with metastatic endocrine gastroenteropancreatic tumors. Clin Gastroenterol Hepatol. 2008;6(7):820–7.